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FLUORINE EFFECTS ON STRUCTURAL, PHYSICAL, BIOLOGICAL, AND AGROCHEMICAL PROPERTIES OF ORGANOFLUORINE COMPOUNDS

LAVRAS-MG
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EFEITOS DO FLÚOR SOBRE PROPRIEDADES ESTRUTURAIS, FÍSICAS, BIOLÓGICAS E AGROQUÍMICAS DE COMPOSTOS ORGANOFLUORADOS

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RESUMO

Estereoquímica é uma importante área da química orgânica, pois a estrutura das moléculas rege propriedades biológicas, físico-químicas e espectroscópicas, além da reatividade dos compostos orgânicos. O isomerismo conformacional, um aspecto da análise conformacional e, consequentemente, da estereoquímica, é regido por fatores clássicos (estéricos e eletrostáticos) e não clássicos (deslocalização eletrônica). Conhecer esses fatores permite o controle conformacional de compostos orgânicos, de modo a otimizar condições reacionais, respostas biológicas e propriedades de materiais. O átomo de flúor possui características estruturais peculiares e também induz efeitos conformacionais já bem estabelecidos, como o efeito *gauche*. A introdução do átomo de flúor em uma molécula é, portanto, uma estratégia única de controle conformacional e os organofluorados são uma classe de compostos orgânicos com aplicações em várias áreas da ciência. Neste trabalho, explorou-se, teórica e experimentalmente, a influência de átomos de flúor sobre as características químicas, físicas e biológicas de alguns sistemas, dado que esse elemento pode ser usado para o aprimoramento de propriedades desejadas em sistemas de interesse. O trabalho foi dividido em duas partes. 1ª) Impacto nas características estereoeletrônicas e controle conformacional: estudo do efeito *gauche* em 2-halofluoroetanos e 2-haloetanóis, expandindo para compostos contendo átomo de iodo, dado que efeitos conformacionais para sistemas contendo este elemento não são amplamente explorados. Além disso, o átomo de flúor pode estabelecer efeito *gauche* eletrostático com o átomo de fósforo, à semelhança do que tem sido observado em sais sulfônicos, por isso, um estudo de moléculas β-fluoroetil-fosforadas também foi realizado. 2ª) Impacto em propriedades biológicas: foi avaliado o efeito da substituição de átomos de cloro por átomos de flúor em pesticidas organoclorados de uso na agricultura, visto que a ligação C−F gera características desejadas (maior polaridade, ligação geralmente mais estável e menor potencial de bioacumulação). Além disso, foi analisada a influência de efeitos estereoeletrônicos sobre a conformação e coeficiente de partição sangue/gás — um importante parâmetro utilizado para previsão da absorção de fármacos pelo organismo — de anestésicos inalatórios fluorados; sabe-se que características estereoeletrônicas são diretamente relacionadas ao momento dipolar, e este, por sua vez, responsável pela permeação através da membrana celular. Cálculos teóricos foram conduzidos com base nos métodos pós Hartree-Fock (MP2) e teoria do funcional de densidade (DFT). Difração de raio-X também foi empregada. Na segunda parte, a técnica de docking foi empregada para predição de energias e modos de interação de ligantes e proteínas. Foi possível observar que a presença de átomos de flúor permite modular as preferências conformacionais de compostos e, além disso, o flúor promove o efeito *gauche* eletrostático quando está vicinal a átomos de fósforo parcialmente carregados. Ainda na segunda parte, uma importante observação é que a substituição bioisostérica de cloro por flúor aumenta as características desejáveis em compostos com aplicação imediata, como pesticidas, devido à maior polaridade e estabilidade da ligação C−F comparada à ligação C−Cl, bem como à diminuição da lipofilicidade, parâmetro que indica o potencial de bioacumulação nos organismos. Finalmente, foi demonstrada a dependência do coeficiente de partição de anestésicos fluorados com momento dipolar dos confôrmeros mais estáveis das moléculas.

Palavras-chave: Química Computacional. Modulação Conformacional. Efeitos Conformacionais. Moléculas de Alta Performance. Sistemas Biológicos.

ABSTRACT

Stereochemistry is an important area of organic chemistry since the molecular structure rules biological, physicochemical, and spectroscopic properties, besides the reactivity of organic compounds. The conformational isomerism, an aspect of conformational analysis and, therefore, of the stereochemistry field, is ruled by classical (steric and electrostatic) and nonclassical effects (electron delocalization). The knowledge of these factors allows for the conformational control of organic compounds to optimize reaction conditions, biological responses, and material properties. The fluorine atom has unique structural and induces well-known conformational effects, such as the *gauche* effect. Therefore, the fluorine introduction in a molecule is a pivotal strategy for conformational control, and the organofluorine is a chemical class with application in a variety of science fields. In this work, we exploited the impact on chemical, physical and biological characteristics at the molecular level caused by the introduction of fluorine atoms, both theoretically and experimentally, since this element can be used to improve key features in specific systems. This work is divided into two parts. 1st) Impact on stereoelectronic features and conformational control: a study of the *gauche* effect in 2-halofluoroethanes and 2-haloethanols, expanding to iodine compounds, since conformational effects involving iodine have not been explored in details. In addition, the fluorine atom can establish an electrostatic *gauche* effect with phosphorus, similar to that found in β-fluoroethyl sulfonium motifs. For this reason, some β-fluoroethyl-phosphorus compounds were also studied. 2nd) Impact on biological properties: the replacement of chlorine with fluorine atoms in pesticide molecules with agricultural application was evaluated, since C–F bonds bring desirable features (more polar and, generally, stable bonds, with a lesser propensity to bioaccumulation). Also, inhalational fluorinated anesthetics were further studied to gain insight into the influence of stereoelectronic effects on the conformation and, subsequently, in the gas/blood partition coefficient of these compounds — it is known that the partition coefficient is an important parameter used to predict drug absorption through the body. Stereoelectronic features are directly related to the molecular dipolar moment, which is responsible for the permeation of the drugs throughout the cell membrane. Theoretical calculations based on the post Hartree-Fock method (MP2) and density functional theory (DFT) were performed. X-ray diffraction was also used. In the second part, the docking technique was carried out to predict energies and binding modes of ligand-protein interactions. It was observed that the fluorine atom modulates the conformational preferences of organic compounds. In addition, fluorine provides an electrostatic *gauche* effect when it is in a vicinal position to a partially charged phosphorus atom. Also in the second part, an important finding is that the bioisosteric replacement of chlorine with fluorine improves desirable features in compounds with an application, such as pesticides. This is due to the higher polarity and stability of the C–F bond compared to C–Cl, besides the decrease in lipophilicity, a parameter used as an indication of bioaccumulation in the body. Finally, we demonstrated the dependence of the partition coefficient and dipolar moment of the most stable conformers of volatile fluorinated anesthetics.

Keywords: Computational Chemistry. Conformational Modulation. Conformational Effects. High-performance Molecules. Biological Systems.

LIST OF FIGURES

SUMMARY

FIRST PART

1 Introduction

The tridimensional features of a molecule within the stereochemistry field play a central role in organic chemistry since they explain macroscopic properties, reactivity, biological responses, and others (DESLONGCHAMPS, 1975; EVIDENTE; ANDOLFI; CIMMINO, 2011; HIRST *et al.*, 2004). The stereochemistry is divided into some branch fields, and among them is the conformational analysis. In conformational analysis, molecules are studied under the point of view of single bond rotations, in which each step in the rotation around a single bond gives a different shape in space, named conformation. Its stability is attributed to classical – steric and electrostatic – or non-classical effects – electron delocalization. Over the years, the importance of molecular conformation and its impact in miscellaneous areas of science, *e.g.* synthesis, catalysis, materials, and pharmaceutics have become clear (LAI *et al.*, 2015; MOITESSIER; ENGLEBIENNE; CHAPLEUR, 2005; TANG *et al.*, 2010; ZHANG *et al.*, 2014; ZIMMER; SPARR; GILMOUR, 2011). Therefore, a deep knowledge of conformational stabilities and the factors that rule the conformational preferences are fundamental.

The recent development in conformational analysis and computational chemistry has allowed us to understand the driving effects ruling the molecular shape and provide means to control the molecular conformation and modulate the molecular properties for a given purpose. A classic example relates to the *t*-butyl group. The well-understood conformational isomerism of monosubstituted cyclohexanes is practically represented by two main conformers: the equatorial and axial (Figure 1). Interestingly, when the substituent group is *t*-butyl, the equatorial conformer is highly preferred with a $\Delta G = 4.9$ kcal mol^{-1} (ANTÚNEZ; JUARISTI, 1996; ELIEL, 1965). The reason for such a preference is explained in classical terms – steric repulsion is smaller when *t*-butyl group adopts the equatorial position. This effect is well known, and the *t*-butyl is used as a lock group in six-membered rings. Conformational modulation can also be done by electrostatic features, in which opposite charges attract each other, and identical charges repel one another (Figure 2). However, after the findings by Pophristic and Goodman (2001), it becomes clear that electron delocalization (a non-classic factor) is also important in some systems. When the preference for certain conformations cannot be fully explained by classical terms, some assumptions for conformational effects arise, such as the *anomeric*, *rabbit-ear*, and *gauche* effects, see Figure 3 (GOODMAN; GU;

POPHRISTIC, 2005; HUTCHINS; KOPP; ELIEL, 1968; WOLFE; WHANGBO; MITCHELL, 1979). The last one is one of the focuses of this thesis.

Figure 1 — Conformational equilibrium of monosubstituted six-membered rings (upper) and preference for equatorial conformation when R = *t*-Bu group (lower).
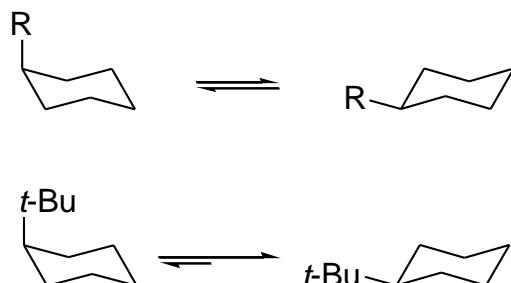
Source: from the Author (2022)

Figure 2 — Conformational equilibria dictated by electrostatic interactions.
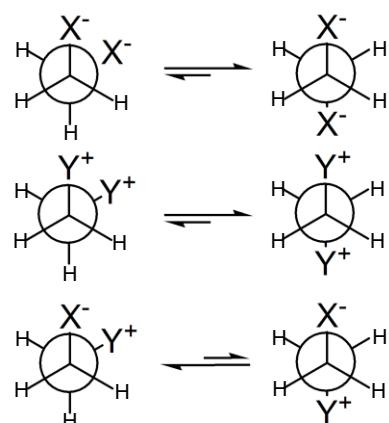
Legend: X = negatively charged group and Y = positively charged group.

Source: from the Author (2022)

Figure 3 — The preference for the *syn*-axial conformer (*Rabbit-ear* effect representation on the left bottom). The preference for axial conformer (*Anomeric* effect representation on the right upper).
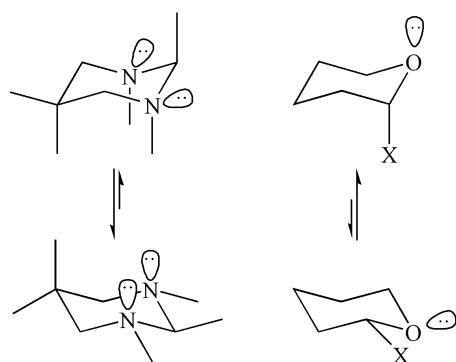
Source: from the Author (2022)

The *gauche* effect is "a tendency to adopt that structure which has the maximum number of *gauche* interactions between the adjacent electron pairs and/or polar bonds" (WOLFE, 1972). This counter-intuitive tendency can be observed in Figure 4, where electronegative X groups should repel each other, but the *gauche* conformation predominates. The *gauche* preference is attributed to antiperiplanar $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interactions (Figure 4) (RABLEN *et al.*, 1999; TAVASLI *et al.*, 2002). Fluorine is the benchmark atom leading the *gauche* preference because of the low-lying energy (good electron-accepting ability) of the σ^*_{C-F} orbital; furthermore, it has interesting features, such as high electronegativity, similar size to the hydrogen atom, highly polarized, and stable bonds with carbon (O'HAGAN, 2008). These features make fluorine an important tool in conformational modulation.

Figure 4 ― Conformational equilibrium of a 1,2-disubstituted ethane indicating the *gauche* effect, even being disfavored by classical parameters (top); stabilizing antiperiplanar $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interaction (bottom).
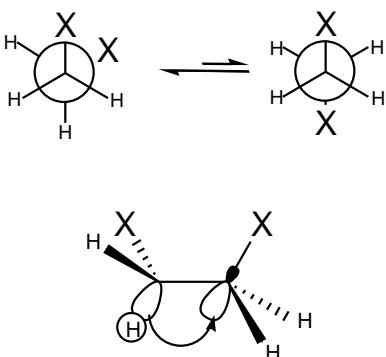
Source: from the Author (2022)

The fluorine *gauche* effect is well known in systems containing the X–C–C–F motif, where X is an electronegative group. Although the conformational behavior for X = F, Cl, Br, and I have been widely explored, the origin of the conformational preferences in these systems is still controversial (RAMASAMI, 2006; SHARGH; BOGGS, 2011; SILVA *et al.*, 2021; YOUNG; BORJEMSCAIA; WLADKOWSKI, 2005). Moreover, from the point of view of stereoelectronic effects, the behavior in systems where X = I is intriguing and may be useful, since organic compounds containing iodine atoms are present in many reactive molecules. Additionally, the σ^*_{C-I} orbital is lower in energy compared to the other halogens and, consequently, the most prone to act as an electron acceptor, which could lead to a strong $\sigma_{C-H} \rightarrow \sigma^*_{C-I}$ interaction. On the other hand, σ_{C-I} is the ablest to act as an electron-donating orbital (along with the halogen series), since it lies in the highest energy level (RAUK, 2004). The

competition between σ$_{C-H}$→σ*$_{C-I}$ (leading to the *gauche* conformer) and σ$_{C-I}$→σ*$_{C-F}$ (leading to the *anti* conformer) in an ethane fragment can be further exploited.

Electrostatics is another perspective of the fluorine *gauche* effect. Since fluorine bears a partial negative charge, it can attract positive sites and repel negative charges in its vicinity. This effect is observed, for example, in some systems where an ammonium or pyridinium group is present (Figure 5) (GOOSEMAN *et al.*, 2007). Attempts to observe the fluorine *gauche* effect involving compounds with an atom (sulfur) beyond the second row have been performed (ALEKSIC; STOJANOVIC; BARANAC-STOJANOVIC, 2015; THIEHOFF *et al.*, 2015; THIEHOFF *et al.*, 2016; THIEHOFF; REY; GILMOUR, 2017), but not all third-row elements are capable of leading fluorine to a preferred *gauche* position (ANDRADE; FREITAS, 2017). The electrostatic fluorine *gauche* effect with sulfur depends on the sulfur oxidation state; higher oxidation states ensure higher positive charges and more effective attraction (ALEKSIC; STOJANOVIC; BARANAC-STOJANOVIC, 2015). In this sense, phosphorus is another interesting atom occupying the third row of the Periodic Table, since it is present in many molecules with agrochemical, ionic liquid, and antimicrobial properties (BLUNDELL; LICENCE, 2014; ETO, 1997; XUE; XIAO; ZHANG, 2015). Similar to sulfur, phosphorus can experience different oxidation states, which allow for the study of the electrostatic fluorine *gauche* effect.

Figure 5 ― Electrostatic *gauche* effect between fluorine and a positively charged ammonium group.
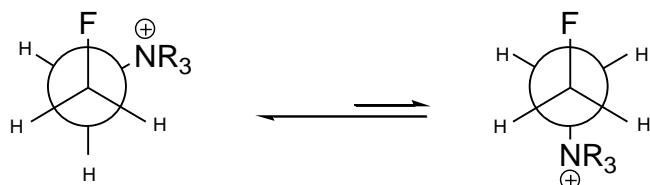
Source: from the Author (2022)

All of these demonstrate the potential of the fluorine atom as a conformational tool at the molecular level. The stereoelectronic effects caused by fluorine insertion can be used in conformational modulation to lead to a specific structure. However, the fluorine atom is not limited to structural features in molecules. In biological systems, fluorinated molecules represent 25-30% of therapeutics and agrochemicals licensed worldwide (FUJIWARA; O'HAGAN, 2014; O'HAGAN, 2010), also showing potential to cause biological responses.

In bioactive molecules, fluorine can provide deep changes. It is related to engaging in halogen bonds, which have been a source of stability of active molecules in the enzyme pocket. In addition, this specific interaction has been explored as a tool in drug discovery (MENDEZ *et al.*, 2017; RIEL *et al.*, 2019). Fluorine is the most electronegative atom in the Periodic Table and induces a high C—F bond polarity, then changing the ability of membrane permeation, increasing the molecular stability, and decreasing the bioaccumulation in fatty tissues. It can replace hydrogen atoms without significant steric consequences. Also, it can replace hydroxyl groups since its electronegativity is close to the oxygen and, therefore, it can similarly act as a hydrogen bond acceptor (O'HAGAN, 2008). All these features make fluorine an alternative group for replacement in therapeutics and agrochemistry.

Computational chemistry has long been used to evaluate the conformational equilibrium of small organic molecules, where more sophisticated methods can be applied and, consequently, more accurate results can be obtained. In addition, molecular modeling resources have evolved in such a way that uses in the biological response prediction have been significantly increasing (HILLISCH; HEINRICH; WILD, 2015; MANLY; LOUISE-MAY; HAMMER, 2001). Modern computational chemistry allows an efficient ligand-enzyme interaction prediction for a huge number of biological systems (AZEVEDO; DIAS, 2008). Consequently, preliminary theoretical studies before experimental analysis are a beneficial strategy to optimize the search for promising molecules, besides saving time and money *e.g.* in a drug development process.

For this reason, a theoretical study of the bioisosteric replacement of chlorine by fluorine atoms in organochlorine pesticides was evaluated herein. Organochlorines have been banned in many countries due to the potential to cause adverse effects on human and animal health. Organochlorine compounds can accumulate in fatty tissues and are likely to C—Cl bond cleavage (although this does not ensure toxicity) (EGELER *et al.*, 1997; LIANG *et al.*, 2017; PUIU *et al.*, 2019). The bioisosteric replacement could be successful because of the desirable features of fluorinated compounds mentioned above. Moreover, a theoretical study can avoid dispendious synthetic and experimental procedures before ensuring the bioisosteric replacement is a safe alternative.

Finally, a recent study found that the stereochemical dependence of molecular polarity determines the lipophilicity (log *P*) of organofluorine compounds (O'HAGAN; YOUNG, 2016). Consequently, stereoelectronic effects can directly influence the absorption and distribution of fluorinated drugs throughout the body (CONSTANTINESCU; LUNGU; LUNG,

2019). In this sense, the dependence on stereoelectronic effects and lipophilicity can be further exploited by taking some fluorinated compounds as model molecules. Inhalational fluorinated anesthetics are good systems to study the stereoelectronic effects on log P due to the stereoelectronic effects caused by fluorine and because of their well-known biological properties. It is well known that vicinal fluorine atoms tend to adopt the *gauche* conformation, and as a consequence, all C—F bonds are pointed out nearly in the same direction, which increases the neat molecular dipole moment (μ). Therefore, the most polar (and probably the most stable) conformer will present a small log P value, indicating a high concentration in the (aqueous) blood and poor absorption.

This work aims at improving the understanding of fluorine chemistry, from the point of view of structural, physical, biological and agrochemical perspectives.

2 Theoretical Framework

2.1 Conformational Analysis and Tools

2.1.1 Basic Concepts

Each step of a rotation around single bonds in a molecule yields different shapes, named conformations. Meanwhile, the conformation corresponding to an energy minimum in a potential energy curve is named conformer. It is known that even the rotation around the single bond for the simplest system ($H_3C–CH_3$) provides an infinite number of conformations. In this system, for example, there are two main conformations, the staggered and eclipsed structures (they represent the extremes – the energy minimum and maximum, respectively – in the potential energy curve). It is worth mentioning that the conformation is characterized by its dihedral angle of rotation (θ), which is the angle formed by four atoms and three bonds (Figure 6). While the system's complexity increases, the number of conformations and conformers can also increase. For instance, disubstituted ethanes $XH_2C–CH_2X$ (Figure 7, where $X = CH_3$) have four noticeable conformations, and among them are two conformers (the energy minima). However, not only acyclic molecules undergo rotation around single bonds and then present

conformations; a remarkable example refers to alicyclic six-membered rings, the most stable ring and widely found in natural systems, which show three main conformations (chair, boat, and twist-boat). The chair conformer is the most stable six-membered ring and, with few exceptions, this ring is exclusively in this form. During the conformational rotation in these systems, the substituents in the ring interconvert from axial to equatorial orientation, see Figure 8 (CLAYDEN; GREEVES; WARREN, 2012).

Figure 6 ― Dihedral angle θ formed by four atoms and three bonds.
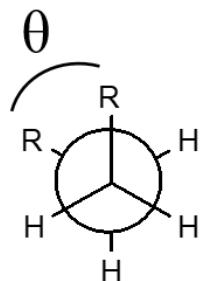
Source: from the Author (2022)

Figure 7 ― Potential energy curve for butane at the HF/3-21G level of theory.
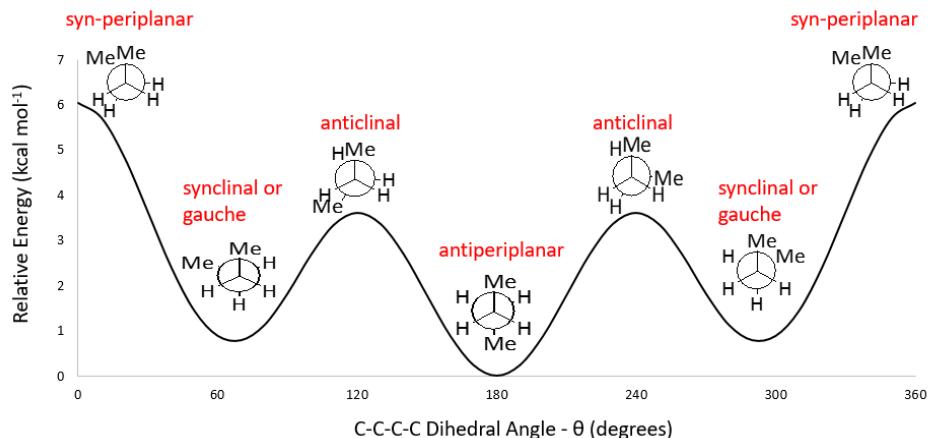
Legend: The main conformations – staggered as minimum and eclipsed as maximum – are highlighted in the potential curve.

Source: from the Author (2022)

Figure 8 ― Ring interconversion of cyclohexane showing the axial-equatorial interplay of hydrogens.
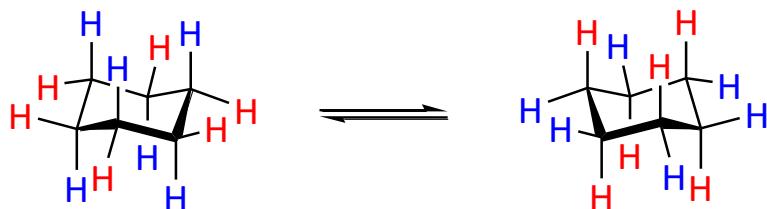
Source: from the Author (2022)

In the early stages of conformational analysis, the conformational equilibrium used to be rationalized in terms of classical interactions – steric and electrostatics. At that time, these concepts were sufficient to explain the conformational behavior of molecules. The preference for the equatorial form in monosubstituted six-membered rings, for example, was based on γ-*gauche* and 1,3-diaxial repulsion (Figure 9) (BARTON, 1953; ELIEL; WILEN, 1994; ORLOFF, 1954; OUELLETTE; RAWN, 2018). In acyclic compounds, the explanation is based on the same argument, *i.e.* the preference for staggered conformers in an *anti*-position to avoid steric and electrostatic (if the substituents have the same charge) repulsion or *gauche* preference if opposite charges are close to each other (TERUI *et al.*, 1974). However, some cases of conformational preferences could not be fully explained by the known classical terms. For example, the unexpected stability of the axial conformer in some α-substituted pyrans (WOLFE; WHANGBO; MITCHELL, 1979) and the preference for the *gauche* conformer in ethane fragments containing vicinal electronegative atoms or polar bonds (WOLFE, 1972). In these cases, a conformational effect is observed (conformational effect rises when classical terms alone are not sufficient to explain a given conformational behavior).

Figure 9 ― a) γ-*gauche* repulsion in a mosubstituted six-membered ring; b) 1,3-diaxial repulsion in a mosubstituted six-membered ring.
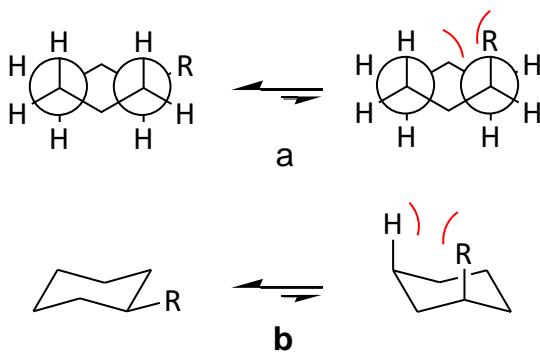
Source: from the Author (2022)

In conformational analysis, some conformational effects are widely known and, therefore, are named in special terms. These effects include the *rabbit-ear effect*, where unshared electron pairs on non-adjacent atoms are preferred in a *syn*-axial position, even being counter-intuitively stable by classical terms (HUTCHINS; KOPP; ELIEL, 1968), see Figure 3; *alpha effect*, which affects the nucleophilicity of atoms due to the presence of an alpha atom with lone pairs of electrons (REN; YAMATAKA, 2007); the *anomeric effect* gives unexpected stability for α-anomers in pyranoside rings (WOLFE, 1979). Another important conformational effect is the *gauche* effect, which is the tendency of electronegative atoms or polar bonds to adopt a *gauche* position, even being the least stable by classical terms. Such stability has been attributed to electronic delocalization, only possible because of the quantum nature of electrons. The electron delocalization from a filled to a low-lying energy orbital ($\sigma_{CH} \rightarrow \sigma^*_{CX}$), only possible in the *gauche* conformer, stabilizes the system (Figure 4).

One of the consequences of the *gauche* effect is the increase in the molecular dipolar moment, since the *gauche* polar bonds are pointed out almost in the same direction. It has an impact on biological responses, such as the absorption throughout the cell membrane, solubility in aqueous solution (*e.g.* the blood), and lower accumulation in fatty tissues (YANG; HINNER, 2015). In organic reactions, it has been proved that conformational effects can be used to optimize processes, for example, exploring the reverse anomeric effect (responsible for increasing the equatorial population in the axial-equatorial equilibrium of monosubstituted pyran-like rings) to increase the yield in the production of orthoester polymers. The formation of orthoester bonds in polymerization requires the α-substituent to adopt an equatorial position in pyran-like rings. However, these systems are known to experience the *anomeric* effect, which leads to a preference for the α-substituent in the axial position and, consequently, a low yield for this specific reaction is achieved. Li and co-workers (2015) overcome this limitation by taking advantage of the reverse *anomeric* effect, which favors the equatorial isomer for α-substituent, Figure 10. Therefore, it was possible to increase reaction rates and yield through conformational effects (Li *et al.*, 2015). Moreover, conformational isomerism has an impact also in organic catalysis. It is known that catalysts based on carbon chains have been developed and are consequently prone to experience conformational isomerism. Conformational modulation can decrease the free rotation to give rigid structures (ZIMMER; SPARR; GILMOUR, 2011). Therefore, a deep knowledge of conformational behavior and its causes is crucial in many areas. A rational way to induce or modulate conformation is valuable to optimize reactions, improve biological responses, and for materials development.

Figure 10 — Orthoester bond formation promoted by a nucleophile capable to establish the reverse anomeric effect.
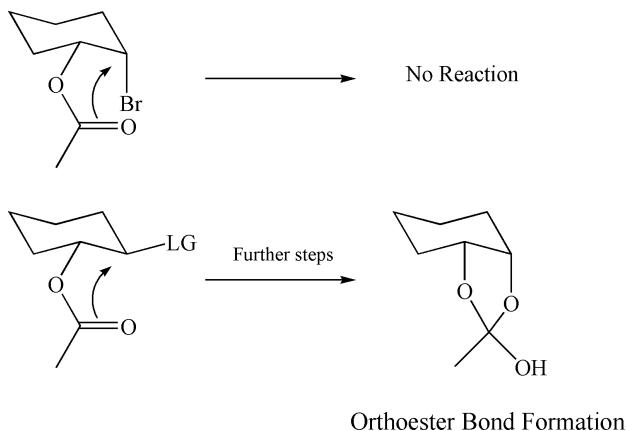
Source: from the Author (2022)

2.1.2 The Fluorine Chemistry

Fluorine is an element with unique properties in the Periodic Table since it is the most electronegative atom and has a small atomic radius (Van der Waals radius of 1.47 angstrom) (ROWLAND; TAYLOR, 1996). In organic chemistry, these features provide organic fluorinated compounds with useful applications and a profound structural impact. The fluorine's high electronegativity makes the C—F bond the most polar in organic chemistry, while the bond polarity is crucial in many aspects. For instance, the bond polarity determines the molecular dipolar moment, which is responsible for intermolecular interactions, thus directly affecting properties such as melting and boiling points and solubility. In biological terms, it is responsible for cell membrane absorption and body distribution.

Because fluorine is small, with dimension compared to the hydrogen atom, the C—F and C—H bonds are similar in steric terms (O'HAGAN 2008). However, this replacement brings high electrostatic consequences to a molecule, which is useful in the conformational analysis, since this helps to elucidate conformational effects without further steric implications (O'HAGAN, 2008, 2010). Another valuable replacement can be done by changing the hydroxyl group by fluorine atom – fluorine and oxygen have similar electronegativity. In addition, it is known that organic fluorine can act as a fairly good hydrogen acceptor but not as a hydrogen donor; this feature makes the fluorine replacement an essential conformational tool to evaluate the role of hydrogen bonds in conformational isomerism. Altogether, these characteristics of

fluorine cause also a deep impact on biological systems, thus allowing for the design of performance molecules.

The increasing number of pharmacological and agrochemical compounds containing fluorine indicates how important are the features attributed to fluorine atoms (FUJIWARA; O'HAGAN, 2014; O'HAGAN, 2010). However, fluorine chemistry is not limited only to biological systems. Fluorine-carbon bonds are also applied in materials science, such as in the development of polymers and liquids crystals (the C—F bond is highly stable and less prone to cleavage) (CAVALLO *et al.*, 2018; FANG *et al.*, 2020; MCKEEN, 2012).

Fluorine plays a central role as a conformational tool. Due to the high C—F bond polarity, the antibonding orbital (σ^*_{CF}) has relatively low energy, which allows it to act as an electron acceptor. This feature provides a remarkable conformational implication since the low-lying energy of the σ^*_{CF} orbital has been attributed as the main reason for the *gauche* stability in FCH_2CH_2F fragments (MIYAJIMA; KURITA; HIRANO, 1987; TAVASLI *et al.*, 2002). It is known that $\sigma_{CH} \rightarrow \sigma^*_{CF}$ interaction, only possible in the *gauche* conformer, is highly stabilizing (Figure 3). As mentioned above, the *gauche* form has a higher dipolar moment than the *anti* conformer, which directly affects the molecular properties.

The conformational effects caused by fluorine can be used for conformational control, leading to a specific conformer or diminishing the number of possible conformations. It allows for designing more effective biological molecules and catalysts based on the carbon chain (EVIDENTE; ANDOLFI; CIMMINO, 2011; ZIMMER; SPARR; GILMOUR, 2011).

In this work, the consequences of a bioisosteric replacement of chlorines by fluorines in some pesticides, namely the aldrin, dieldrin, lindane, α-chlordane, and β-chlordane pesticides were evaluated (Figure 11). While the need for food around the world increases, organochlorine pesticides have been banned because of their human and animal harm. The main harmful characteristic of organochlorines is the bioaccumulation/biomagnification in the food chain. Organochlorine pesticides act in the $GABA_A$ receptor, disrupting the chloride flux, which induces an over-excitation of the body and, consequently, respiratory failure (BLOOMQUIST; SODERLUND, 1985; FISHMAN; GIANUTSOS, 1985; POMES; RODRÍGUEZ-FARRÉ; SUÑOL, 1994). The bioaccumulation capacity of organochloride pesticides triggers high doses over the years and throughout the food chain. In this sense, the replacement of chlorine with fluorine atoms can improve the pesticides in some aspects, such as providing lower lipophilicity

(fluorine increases the molecular polarity compared to chlorine) and more stable bonds (C—F is more stable than C—Cl) (THEODORIDIS, 2006).

Figure 11 — Organochlorine pesticides (for X= Cl) and bioisosterically-replaced fluorinated derivatives (for X = F).
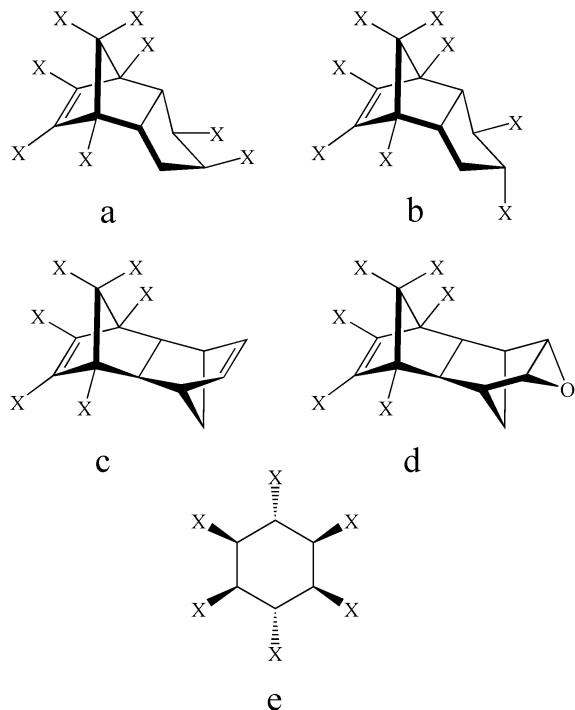
Legend: a) alpha chlordane or alpha fluordane; b) beta chlordane or beta fluordane; c) aldrin or F-aldrin; d) dieldrin or F-dieldrin; e) lindane or F-lindane

Source: from the Author (2022)

A theoretical study of fluorinated bioisosteres of organochlorines can open up a new sight in pesticides and agrochemical design. Accordingly, computational insight can be useful to avoid experimental costs before ensuring new molecules as good alternatives.

2.1.3 The Phosphorus Chemistry

The current number of phosphorus-containing compounds highlights the importance of this atom. The phosphorus atom is a ubiquitous element present in biological systems, such as nucleotide, DNA, enzyme cofactor, and macronutrients. Also, it is important in chemical reactions, like the Wittig and nucleophilic reactions (CLAYDEN; GREEVES; WARREN,

2012), and as a catalyst in some reactions (ASWIN *et al.*, 2014; GIMBERT *et al.*, 2005). Unfortunately, phosphorus compounds are also used as chemical weapons, such as sarin (an organophosphate). These molecules (organophosphates) are capable of inactivating the acetylcholinesterase enzyme, which is an important enzyme responsible for acetylcholine degradation. The accumulation of acetylcholine in the synaptic cleft causes continuous stimulation and respiratory failure (PETER; SUDARSAN; MORAN, 2014). In agrochemistry, phosphorus-containing compounds have a wide range of applications since organophosphates are alternatives to organochlorine pesticides. While organochlorine pesticides act in the GABA receptors, the organophosphate's mode of action is similar to those observed in humans, *i.e.* they act in the acetylcholinesterase enzyme of insects (FUKUTO, 1990). Recently, antimicrobial activity has been assigned to materials containing quaternary phosphonium salts (KANAZAWA; IKEDA; ENDO, 1994; XUE; XIAO; ZHANG, 2015). All these features demonstrate the broad use of phosphorus and its large applicability.

The phosphorus atom plays an important role in fundamental science. It is a third-row element of group 15 (5A) in the Periodic Table and, as a consequence, it shares similarities with the nitrogen atom – an atom extensively studied in conformational analysis, present in conformational effects, such as the *gauche* and *anomeric* effects (BOOTH; DIXON; KHEDHAIR, 1992; ERXLEBEN; KEDZIORA; URBAN, 2014; GOOSEMAN *et al.*, 2007). Stereoelectronic features of P can be further explored in the conformational analysis, since the σ^*_{CP} orbital has lower energy than the σ^*_{CN} orbital, which makes the C—P antibonding orbital a better electron pair receptor (pronounced hyperconjugation). At the same time, the phosphorus electron lone pair is more prone to be donated, since it lies on a higher energy level than the nitrogen lone pair. These characteristics make phosphorus a useful conformational tool to investigate conformational effects.

Recently, an effort has been made to extend the fluorine *gauche* effect to the third row of the Periodic Table. It was observed that vicinal fluorine and sulfur atoms experience the fluorine *gauche* effect, and electrostatics is the main stabilizing factor of the *gauche* conformation, although the observed $\sigma_{CH} \rightarrow \sigma^*_{CF}$ (see Figure 12) (ALEKSIC; STOJANOVIC; BARANAC-STOJANOVIC, 2015; THIEHOFF *et al.*, 2015). Accordingly, the *gauche* population increases as the sulfur atom becomes more positively charged (THIEHOFF *et al.*, 2016). This is crucial, since one allows to modulate the conformational population by changing the sulfur oxidation state. Santschi *et al.* (2016) have shown the potential of such modulation in organometallic systems.

Figure 12 ─ The *gauche* effect between fluorine and sulfur in a F–C–C–S motif.
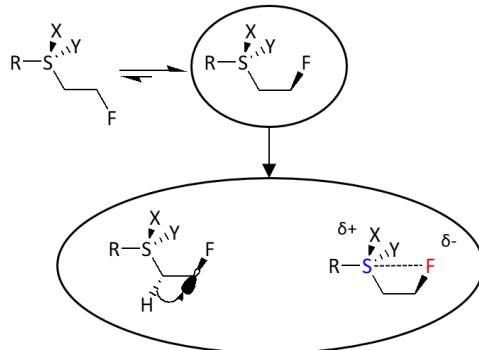
Legend: The hyperconjugation (bottom, at the left) and electrostatic contribution (bottom, at the right).

Source: from the Author (2022)

Phosphorus has been another third-row element to be recently studied in an attempt to induce a *gauche* effect, but β-fluorinated organophosphorus have not been shown to experience any fluorine *gauche* effect (ANDRADE; FREITAS, 2017). Then, not all third-row elements can experience such an effect. However, there is the possibility of inducing the fluorine-phosphorus *gauche* effect by modulating the charge on the phosphorus atom, since it has been demonstrated that the increase in the positive charge of the sulfur atom increases the *gauche* population. It is known that the phosphorus atom in a molecule can present more than one oxidation state, such as phosphine, phosphine oxide, and phosphonium salt.

In this work, the possibility of the appearance of a fluorine-phosphorus *gauche* effect was further explored, considering various phosphorus oxidation levels. Chair-like six-membered rings were the molecular models chosen to evaluate the *gauche* effect (Figure 13). These cyclic systems were proposed to simplify the conformational landscape, since rotation around single bonds in acyclic compounds could originate a variety of conformers rather than only the axial and equatorial conformers in the alicyclic compounds. From the outcomes of this analysis, the fluorine-phosphorus electrostatic *gauche* effect could be further evaluated to an acyclic compound: the (2-fluoroethyl)triphenylphosphonium cation.

Figure 13 — β-fluorinated organophosphorus models proposed for conformational studies.
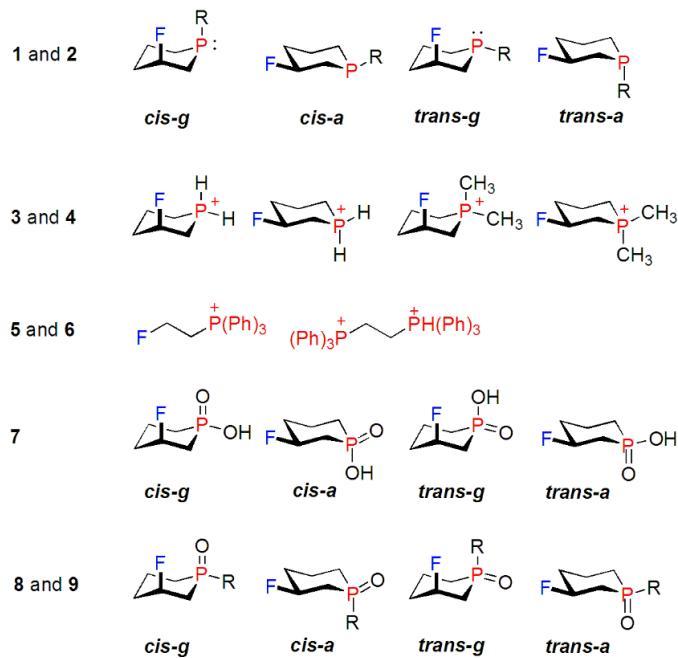
Legend: From top to bottom: chair conformations and isomers for the studied phosphines **1** (R = H) and **2** (R = Me), phosphonium cations **3** (R = H) and **4** (R = Me), (2-fluoroethyl)triphenylphosphonium (**5**) and (ethane-1,2-diyl)bis(triphenylphosphonium) (**6**) cations, phosphinic acid **7**, phosphine oxides **8** (R = H) and **9** (R = Me).

Source: *ChemPhysChem*, 23, (2022), e202100856

2.1.4 The Iodine Chemistry

The use of iodine atoms has been increasing over the years, since this halogen presents interesting features from the synthetic and stereoelectronic/structural points of view. Iodine is a large-sized halogen, easily polarizable, low in electronegativity, goes beyond the most common oxidation state of -1 (characteristic of halogens), then presenting hypervalent states, such as +3, +5, and +7 (ZHDANKIN, 2014). Hypervalent iodine compounds are oxidant agents used, for example, to convert alcohols into the corresponding carbonyl compounds and in the α-oxygenation of carbonyl compounds (MAITI; YADAV, 2001; MORIARTY *et al.*, 1987). In regular courses of organic chemistry, the iodine atom is wide explored as a leaving group in nucleophilic substitution reactions. It is known that C—I bond is the most prone to cleavage in the halogen series; one reason is the small overlap between iodine and a carbon atom, thus yielding a soft bond. Therefore, all these features make organoiodine compounds an important class to study.

The iodine atom in molecules ensures particular stereoelectronic effects, since the C—I bonding orbital (σ_{CI}) has the highest energy in the halogen series and, consequently, it can act as a good electron donor in delocalization effects. At the same time, the C—I antibonding orbital (σ^*_{CI}) is the lowest in energy along with the halogen series, which leads to a good electron acceptor (RAUK, 2004). It has been earlier mentioned that these interactions are important in conformational isomerism and can be exploited to elucidate conformational effects.

1,2-Dihaloethanes (XCH_2CH_2Y) have been extensively studied by experimental and theoretical methods. The 1,2-difluoro-, 1,2-dichloro- and 1,2-dibromoethane, for example, have been studied in all phases by vibrational spectroscopy and theoretical methods (BUTCHER; COHEN; ROUNDS, 1971; KLABOE; NIELSEN, 1960; MIZUSHIMA, 1954). Studies with two different halogens are also known; the conformational equilibria of 1-chloro-2-fluoroethane, 1-bromo-2-fluoroethane, and 1-iodo-2-fluoroethane have been determined by microwave spectroscopy (NIIDE, *et al.*, 1986; NIIDE; OHKOSHI, 1990). It is known that 1,2-difluoroethane is a benchmark molecule exhibiting the *gauche* effect. However, not all 1,2-dihaloethanes can adopt a preferential *gauche* conformation. This fact makes the XCH_2CH_2Y fragment a good model molecule to explore the conformational effects and their origins. Furthermore, the effects ruling the conformational equilibrium of FCH_2CH_2I it is not fully understood and, then, are worth to be explored.

In this work, we have studied 1,2-dihaloethanes and 2-haloethanols to gain insight into the role of the competing factors that rule the conformational equilibria in these motifs. Combining two different vicinal halogens, we can explore the steric and electrostatic features, besides the role of intramolecular hydrogen bonds (in the case of 2-haloethanols). Moreover, it has been widely mentioned that the $\sigma_{CH} \rightarrow \sigma^*_{CF}$ interaction is responsible for *gauche* stabilization in 1,2-difluoroethane due to the relatively low energy of the σ^*_{CF} orbital. Therefore, a $\sigma_{CH} \rightarrow \sigma^*_{CI}$ interaction is expected to be more stabilizing than that observed in fluorine, since the σ^*_{CI} orbital lies in a lower energy level than σ^*_{CF}. In this case, the *gauche* form of the iodine derivative could be more stable. However, the role of σ_{CI} as a good electron donor can lead to a $\sigma_{CI} \rightarrow \sigma^*_{CF}$ interaction in the *anti* position, which would decrease the *gauche* population (Figure 14). The competitive $\sigma_{CH} \rightarrow \sigma^*_{CI/F}$ (in *gauche* conformer) and $\sigma_{CI} \rightarrow \sigma^*_{CF}$ (in *anti* conformer) interactions can be further exploited to give insight into the role of delocalization in the fluorine *gauche* effect. For all these reasons, the study of ICH_2CH_2F is interesting, *i.e.* the smaller and the bigger halogen are vicinal, and a high number of competitive

interactions can be observed, such as steric effects (caused by the iodine volume), electrostatic and delocalization effects.

Figure 14 — Competition between two stabilizing stereoelectronic effects in 1-fluoro-2-iodoethane.
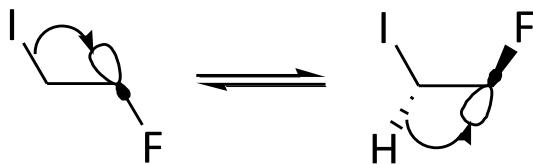
Legend: $\sigma_{CI} \rightarrow \sigma^*_{CF}$ (favoring the *anti* form) and $\sigma_{CH} \rightarrow \sigma^*_{CF}$ (favoring the *gauche* form) interactions.

Source: from the Author (2022)

2.2 Spectroscopic Methods for Conformational and Structural Determination

2.2.1 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) is a crucial tool in structural determination since it allows the detection of atomic nuclei, their vicinity, and even the electronic environment of atoms in molecules. NMR spectroscopy is only possible due to an intrinsic nuclear property named *spin* (*I*) that is a form of angular momentum. It can be 0, 1/2, 1, 3/2 … but only nuclei with $I \neq 0$ are active in NMR spectroscopy. Furthermore, the nuclear *spin* is associated to the nuclear magnetic moment (μ), if the elementary particle has mass, see Equation 1. In the presence of an external magnetic field (B_0), the magnetic vector of nuclei tends to become parallel to B_0. This tendency, combined with the rotational inertia of the nuclei, creates a precession movement with a given frequency (v_0), according to Figure 15 (GEROTHANASSIS *et al.*, 2002).

$$\mu = \gamma \, I \, \hbar \tag{1}$$

γ is the nucleus gyromagnetic ratio and $\hbar$ is a constant.

Figure 15 ─ The precession movement (represented by the blue curve) of a nucleus with magnetic moment (μ) submitted to an external magnetic field (B₀).
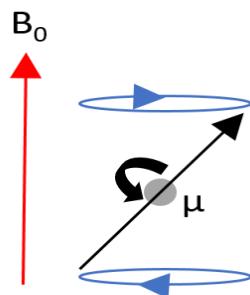
Source: from the Author (2022)

As a consequence of the quantum nature of nuclei, the nuclear magnetic moment vector can adopt only specific orientations (the stationary states), which are dependent on the *spin* and, consequently, nuclei-dependent (Equation 2).

Number of stationary states = $2I + 1$ (2)

Nuclei with $I = ½$ are particularly useful in NMR, since they show only two possible stationary states in the presence of B₀: aligned to an external magnetic field (lowest energy - α) or against it (highest energy - β). In addition, the energy difference associate to these states is dependent of the external magnetic field and two constants, see Equation 3 (ATKINS, 1998). Common atoms in organic chemistry have $I = ½$, such as ^{1}H, ^{13}C, ^{19}F, and ^{31}P. Therefore, this fact makes the NMR spectroscopy useful in organic chemistry.

$\Delta E = - \gamma \hbar B_0$ (3)

The acquisition of NMR spectra takes advantage of the spin magnetization *perpendicular*, instead of *along* B₀, since longitudinal magnetization measurement is impractical due to the small magnitude. The magnetic moment vector becomes parallel to B₀ when submitted to an external magnetic field. At this point, a negligible macroscopic magnetization is observed if the equilibrium is achieved. However, by incising electromagnetic radiation (radio frequency, *r.f*), the magnetic moment vector is rotated by $2/\pi$ radians around the x-axis. Consequently, the spin polarization is transferred from the z-axis to the y-axis. After turning off the *r.f* radiation, the spins of all active nuclei in the sample tend to return to a parallel position to B₀, Figure 16. Consequently, they decay after a time, and this movement provides an induced current that is measured and used to generate the NMR signal (LEVITT, 2008).

Figure 16 ― Longitudinal and transverse magnetization (upper) and transverse relaxation (lower).
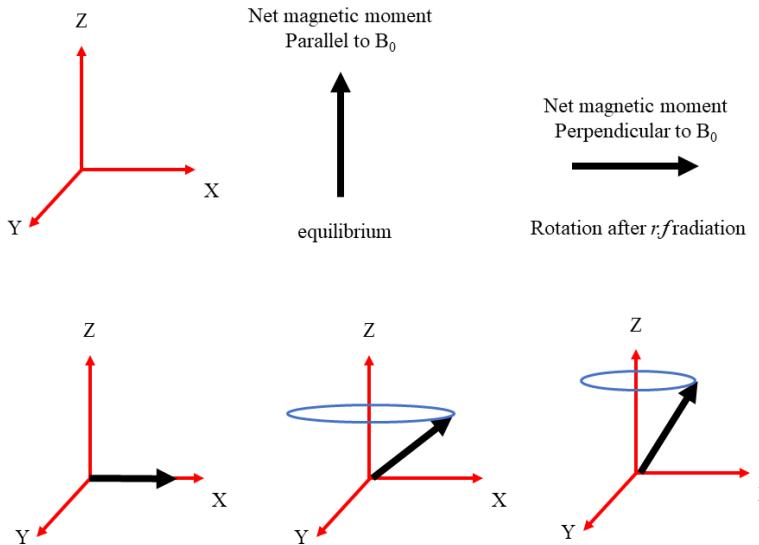
Legend: net magnetic moment that represents the summation of all nuclei magnetic moments in dark arrow, cartesian axes in red and the precession movement of net magnetic moment in blue.

Source: from the Author (2022)

One point rises due to Lenz's law; it is known that electrons are charged particles in movement and, as a consequence, they create their particular magnetic field ($B_{electron}$), in counterpart to B_0. This fact ensures a resulting magnetic field ($B_{effective}$), that represents the real magnetic field over the nuclei ($B_{effective} = B_0 - B_{electron}$). The nuclei are shielded, with few exceptions, from the resulting magnetic field created by electron motion, and the magnitude of the shielding is given by σB_0 (σ is the shielding or screening constant). This observation allows for the comprehension of the electronic environment (GEROTHANASSIS *et al.*, 2002; GÜNTHER, 1995; HARRIS, 1983).

In NMR spectroscopy, there are two main parameters. The first one is the chemical shift (δ), a consequence of the electronic shielding. This parameter is used to differentiate nuclei in a distinct magnetic environment, even for the same element. The presence of an electron cloud around the nuclei causes different resonance conditions (B_0 or ν) and, consequently, different NMR peaks in the spectra. The chemical shift is determined by comparing the shift of the nucleus of interest to a shift of a known nucleus that is attributed to zero, in general, tetramethylsilane (TMS) (HOFFMANN; FORSÉN; GESTBLOM, 1971).

The second NMR parameter is the coupling constant (J). The scalar coupling constant is responsible for information about the neighboring of the active atom. The signal multiplicity observed in the NMR spectra is a consequence of the nuclear spin coupling of atoms and indicates the number of active nuclei in its vicinity, $2nI + 1$ (in which n is the number of active atoms). In this sense, chemical shift and coupling constant make the NMR a powerful technique for structural elucidation.

In conformational analysis, the coupling constant is most usually explored since Karplus (1963) established a mathematical relationship between a conformational parameter (dihedral angle) and an NMR parameter ($^3J_{H,H}$ – the three-bond coupling between two hydrogens). Therefore, it is possible to gain conformational information using NMR spectroscopy. In the Karplus curve (Figure 17), it is possible to observe a local maximum and global maximum in $0°$ and $180°$, respectively. It is a consequence of a better orbital overlap involving the C–H bonds. A minimum is observed at $90°$, in which the overlap is poor. There are different relationships between coupling constant and dihedral angle, for example, for $^3J_{H,H}$, $^3J_{C,H}$, $^3J_{H,F}$.

Figure 17 — Relationship between coupling constant ($^3J_{H,H}$) and the H–C–C–H dihedral angle established by Martin Karplus.
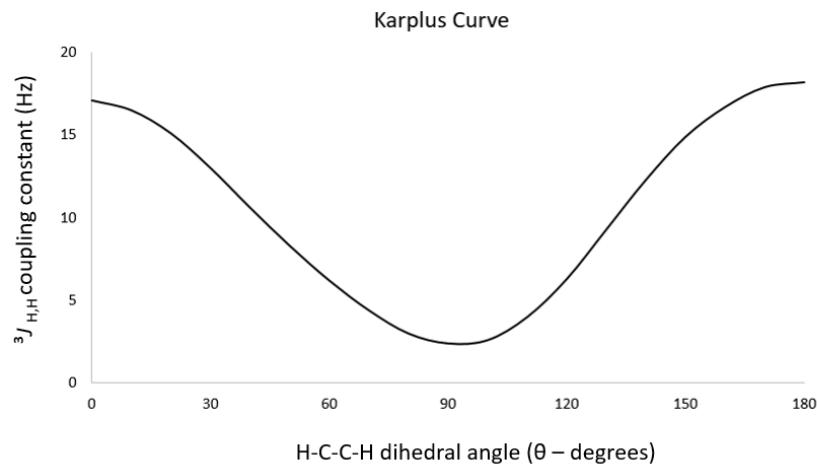
Legend: The plot was obtained for ethane at the HF/6-31G level of theory.

Source: from the Author (2022)

NMR spectroscopy has been widely employed in conformational studies. This technique allows for understanding the conformational isomerism for a wide variety of molecules, either cyclic or acyclic compounds (ENOMOTO-ROGERS *et al.*, 2016; TORMENA, 2016). Specifically, many studies of ethane-like fragments have been conducted using NMR

techniques (ABRAHAM; GATTI, 1969; HAMMAN, *et al.*, 1983). For flexible molecules in which the conformational interconversion is faster than the NMR time scale, the signals observed in spectra correspond to an average for the conformers, see Equation 4. If the interconversion is slow, the conformers have separate signals for each of them.

$$J_{obs} = n_A \times J_A + n_B \times J_B \tag{4}$$

in which J_{obs} is the coupling constant observed in the NMR spectra, J_A and J_B are the coupling constants of conformers A and B, respectively, and n_A and n_B are the mole ratio of A and B, respectively.

2.2.2 X-Ray Crystallography

X-ray is a well-known electromagnetic radiation, with a wavelength in the order of 1 angstrom (10^{-8} cm). The energetic X-ray interacts with the inner electrons of an atom beyond the valence interaction present in techniques like infrared and ultraviolet. Due to this property, X-ray spectroscopy is used to determine the elementary composition in complex matrices, since each element has particular lines of X-ray emission (GOLDSTEIN; SLEMMONS; CANAVAN, 1996; KIM; BROWN; RYTUBA, 2000). However, the use of X-rays is far beyond elementary determination and quantification. Currently, chemical structures have been reliably determined by X-ray crystallography, a technique in which X-ray radiation is diffracted by the sample.

Amongst the mentioned spectroscopic methods, X-ray crystallography is the most powerful in structural elucidation – even an arrangement around a chiral center is possible to determine. Its principle is based on the ability of crystalline compounds to diffract X-rays. Diffraction is only possible when the irradiated wavelength is close to the interatomic distances in the sample, typically in crystals (1 to 3 angstroms), and from the resulting diffraction pattern is possible to obtain the spatial arrangement (KRISHNAN; RUPP, 2012; PICKNETT; BRENNER, 2001). The main limitation in X-ray crystallography is the necessity of samples to be crystalline; subsequently, the structural accuracy is dependent on the crystal quality.

Currently, X-ray crystallography is widely employed to determine tridimensional structures in material sciences and biological macromolecules, such as proteins and nucleic acids (HUSSAIN; SARACCO; RUSSO, 2012; ILARI; SAVINO, 2008). Moreover, small

molecules have also been determined by this technique, thus contributing to conformational elucidation. Ceylan *et al.* (2011) obtained the single-crystal X-ray of (2-hydroxyethyl)-triphenylphosphonium chloride salt, a similar compound to the ones envisaged in this work.

2.3 Quantum Mechanics Computational Methods

2.3.1 Methods Based on Wavefunction

Computational chemistry is a tool within the theoretical chemistry scope, in which mathematical equations, combined with fundamental laws, are solved to understand chemical problems (JENSEN, 2007). Since the advent of electronic computers (1950), computational methods have increased. Its popularity comes mainly from the quantum mechanics theory, which states that all systems have particle and wave behavior. The wave-like features are pronounced in small systems, such as electrons. In this sense, a complete understanding of molecules, bonds, and electron interactions requires an account of this feature. The resolution of such complex equations is possible because of modern computers.

The well-known Schrödinger equation, Equation 5, plays a central role in modern quantum mechanics, since it allows to determine the system's wave function – in quantum mechanics, each system has a wave function, and by the wave function, it is possible to extract much information about the system, such as the energy, momentum, magnetic responses, and others (ALCÁCER, 2007). A problem arising from the Schrödinger equation is that an analytical resolution is only possible for the hydrogen atom, the simplest system.

$$\hat{H}\Psi = E\Psi \tag{5}$$

The Hamiltonian operator ($\hat{H}$) is composed of kinetic (K) and potential (V) energy terms. In addition, the potential term is the contribution of nucleus-electron attraction (V_{ne}), nucleus-nucleus repulsion (V_{nn}), and electron-electron repulsion (V_{ee}), according to Equation 6. The kinetic and potential nucleus-electron attraction terms have a well-known formulation, since they are based on classical equations. Moreover, the potential nucleus-nucleus repulsion component is simplified by the Born-Oppenheimer approximation. In this sense, the most problematic term is the electronic repulsion, which appears for systems with more than one

electron; a complete variable separation is not possible, as required to solve differential equations (JENSEN, 2007).

$$\hat{H} = K + V_{nn} + V_{ne} + V_{ee} \tag{6}$$

In an attempt to overcome this problem, many approximations have been adopted; consequently, many computational methods have emerged. The simplest method created to solve the many-body problems was named the Hartree-Fock method, in which a pseudo-one-particle is admitted. In this model, each electron is considered to be independent, and each one is described by its wave function (φi) and has a given energy (ε_i) (the Hamiltonian operator is h_i). Equation 7 describes the Schrödinger equation for each electron (ECHENIQUE; ALONSO, 2007; SLATER, 1951).

$$h_i\varphi_i = \varepsilon_i\varphi_i \tag{7}$$

The system's Hamiltonian is given by the sum of all electrons Hamiltonian ($H = h_1 + h_2 + \ldots h_n$), the system energy is the sum of all electrons energy ($E = \varepsilon_1 + \varepsilon_2 + \ldots \varepsilon_n$), and the total wave function is given by the product of the electronic wave functions ($\Psi = \varphi_1\varphi_2\ldots\varphi_n$). In a process called self-consistent field, the equation converges to the lowest energy, and the Ψ is achieved to the best system's wave function. Although the electron-electron repulsion is taken into account, only an average result is considered. Consequently, a poor description of V_{ee} is given. Several different methods based on the Hartree-Fock theory have been developed to improve the electron-electron interaction accounting, which is known as post-Hartree-Fock methods (JENSEN, 2007).

There are many post-Hartree-Fock methods in which the electron-electron correlation is considered, but a specific method used in this work is the Moller-Plesset (MP), which will be further discussed.

MP methods are based on the Perturbation theory, where the Hamiltonian operator is the sum of a known unperturbed Hamiltonian ($\hat{H}_0$ – given by the HF theory) and a small perturbation H', Equation 8 (CREMER, 2011).

$$\hat{H} = \hat{H}_0 + \lambda\hat{H}' \tag{8}$$

The λ parameter indicates the strength of perturbation. As the perturbation can vary from zero to a finite number, then the energy and wave function can be written as a Taylor expansion in powers of λ. As follow:

$$E = \lambda^0 E_0 + \lambda^1 E_1 + \lambda^2 E_2 + \dots$$

$$\Psi = \lambda^0 \Psi_0 + \lambda^1 \Psi_1 + \lambda^2 \Psi_2 + \dots$$

The zeroth-order represents the Hartree-Fock theory. The electron correlation starts in the second-order (MP2). The MP2 method is the most economical method, which accounts for 80-90% of the correlation energy. However, it is computationally expensive for large systems (JENSEN, 2007).

The relatively low cost of MP2 method makes this method useful and a diverse number of papers have been published in different science fields (GÓMEZ; PACIOS, 2005; SAGARA, 2005).

2.3.2 Methods Based on Electron Density

Further improvement in quantum mechanics, in particular in minimizing computational effort, was achieved after Hohenberg and Kohn proved E. B. Wilson's arguments. Hohenberg and Kohn showed that the energy ground state is fully determined by the electronic density (ρ) (HOHENBERG; KOHN, 1964). In addition, by the integration over the electronic density, it is possible to obtain the number of electrons, the nucleus position, and the nuclear charge (JENSEN, 2007).

In the simplest wave function method (HF) to many-body systems, each electron is solved in three spatial coordinates (x,y,z), and as a consequence, the system with N electrons has 3N variables. In counterpart, the electronic density always has three coordinates, independently of the number of electrons. This fact is an improvement in terms of computational cost (CRAMER, 2004).

The density functional theory is based on the existence of a functional that links the system's energy and its electronic density. Although the clear relationship between energy and electronic density, there is a lack of knowledge of the exact form of the functional. Currently, the functional is based on the wavefunction equation (by analogy), which is also divided into kinetic ($T[\rho]$), potential nucleus-electron ($E_{ne}[\rho]$) and potential electron-electron repulsion ($E_{ee}[\rho]$), and the nucleus-nucleus interaction is approximated by Born-Oppenheimer (Equation 9).

$$E[\rho] = T[\rho] + E_{ne}[\rho] + E_{ee}[\rho] \tag{9}$$

The $\hat{E}_{ee}[\rho]$ is divided into two terms: the first is the coulomb functional ($J[\rho]$), based on classic equations, and the second corresponds to the exchange ($K[\rho]$) functional, which includes the quantum features (Equation 10). The main challenge in functional development lies in the exchange/correlation of functional.

$$E[\rho] = T[\rho] + E_{ne}[\rho] + J[\rho] + K[\rho] \tag{10}$$

Kohn and Sham proposed that the kinetic term could be almost entirely described by HF kinetic energy (99%) and the remaining energy included in the exchange functional. Now, with Kohn-Sham's assumptions, Equation 10 takes the form of Equation 11 (KOHN; SHAM, 1965).

$$E_{DFT}[\rho] = T_{HF}[\rho] + E_{ne}[\rho] + J[\rho] + E_{XC}[\rho] \tag{11}$$

The $E_{XC}[\rho]$ includes the kinetic and potential exchange/correlation energy. All development in DFT lies in $E_{XC}[\rho]$ functional design. Modern DFT functional can recover almost 100% of the exchange/correlation energy. However, there is no universal functional capable of describing every system. Deep knowledge about a specific case is crucial to developing a reliable theoretical study.

A particular functional widely used in organic molecules is the B3LYP. This functional has been demonstrated to properly reproduce thermodynamic parameters and geometrical structures (BECKE, 1993). A problem with DFT functional is the absence of long-range interactions, since the energy is dependent on electronic density, and the density decreases rapidly with the distance. However, corrections to include dispersion effects can be found (GRIMME *et al.*, 2010; GRIMME; EHRLICH; GOERIGK, 2011). In B3LYP, corrections to long-range interactions are made by including HF terms in the functional, yielding *e.g.* the B3LYP-D3 and B3LYP-D3BJ methods. Other functionals capable of recovering long-range interactions are also available, such as ωB97XD and CAM-B3LYP (CHAI; HEAD-GORDON, 2008; YANAI; TEW; HANDY, 2004).

In this sense, DFT can represent a large number of systems, including dispersion, long-range and relativistic effects. Furthermore, DFT is computationally cheaper than wave function methods and has been applied for different studies, such as materials, biological molecules, thermodynamic properties, and reactions (BAUERFELDT; ARBILLA; SILVA, 2005;

HERRERA; SERRA; D'AMICO, 2017; NEUGEBAUER; HICKEL, 2013; RAUGEI; GERVASIO; CARLONI, 2006).

2.4 Molecular Mechanics Methods

Computational methods based on Newtonian mechanics rather than those based on the Schrödinger equation are known as classical mechanics methods or molecular mechanics methods (MM). In this type of method, the wave nature of the system is not considered, and the particles are rather punctual with positive (nucleus) or negative (electron) charges. For this reason, the Coulomb interactions of these particles are most important for the system. Although the solution to classical equations is known, the computer is required due to the high number of particles involved and, consequently, the high number of equations (JENSEN, 2007).

MM methods are capable of predicting geometric arrangement, relative energies, and many other molecular properties. However, classical concepts are used to describe the system (atoms and bonds are considered balls and springs, respectively). Consequently, the quantum aspects are neglected, and bond information should be explicitly provided. In MM methods, the energy is dependent on many molecular terms, such as bond stretching, bond bending, bond torsion, electrostatic, and Van der Waals interaction (ALLINGER, 1976). All these terms are combined in a Force Field (FF); the difference among the diverse FF available is the type of parameterization used. Equation 12 gives the usual FF energy components.

$$E_{FF} = E_{str} + E_{bend} + E_{tor} + E_{VDW} + E_{el} + E_{cross} \tag{12}$$

in which E_{FF} corresponds to the system's energy, calculated by a given FF. E_{str} is the relative energy of bond stretching and shortening. E_{bend} is the energy to deform the angle (θ) between three atoms and two bonds. E_{tor} is the torsion energy of the angle (ω) between four atoms and three bonds. E_{VDW} is the energy relative to the Van der Waals interactions. E_{el} refers to the electrostatic interactions, and finally, E_{cross} is used to cover the coupling of the five earlier interactions (Figure 18).

Figure 18 ― Interactions considered in a molecule by a Force Field.
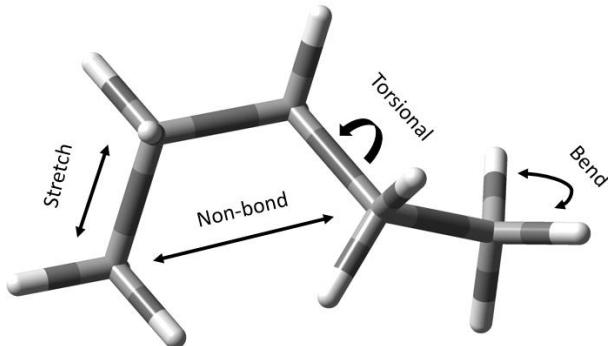
Source: from the Author (2022)

The solution for a given FF without time evolution gives the system's energy for a given geometry. The process can be done for a set of structures, and the relative energy is found. However, there are solutions for FF with time evolution, since Newtonian mechanics is deterministic, and the equations can be integrated over time. Consequently, it is possible to predict the structure at a given moment or for some time. In this case, the method is known as molecular dynamics. Solutions without time evolution can be useful to predict the enzyme-substrate interaction, such as in docking studies, while dynamics solutions can predict the stability of *e.g.* an enzyme-substrate complex.

2.4.1 Docking

Docking is a computational technique based on the MM method that allows the prediction of possible interaction modes between a small molecule (substrate, which can cause biological response) and a protein, in particular, with the protein's binding pocket (PAGADALA; SYED; TUSZYNSKI, 2017). The method is based on the key-and-lock model, in which a substrate fits in the enzyme´s active site. The small molecule can adopt different conformations, which have different binding energies.

The docking study can be conducted basically in three ways: 1) rigid docking, where the substrate is allowed to change, and the active site is forbidden to move, and the energy is computed; 2) semi-flexible, where the small molecule has a free movement and some residues

in the binding site are allowed to move; 3) flexible, where both substrate and active site residues can freely move (MENG *et al.*, 2011).

There are different programs capable of running docking calculations. They generally vary in the FF applied, but the main focus is to find the most-likely bioconformations and the intermolecular interactions governing the induced fit, such as hydrogen bonds, Van der Waals, electrostatic and hydrophobic interactions.

Docking is a useful technique in the development of new compounds with therapeutical activity. Also, this technique allows us to understand the specific ways of coupling between enzyme and substrate and then to rationalize the most affected regions in an enzyme site related to a biological process. These features make the docking procedure a powerful technique in drug/agrochemical discovery and development (DE RUYCK *et al.*, 2016; FAN; FU; ZHANG, 2019).

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SECOND PART

Stereoelectronic Impact of the Fluorine Atom

The fluorine *gauche* effect and a comparison with other halogens in 2-halofluoroethanes and 2-haloethanols

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Abstract: While the *gauche* effect in 1,2-difluoroethane is widely known as being due to hyperconjugative interactions between σ_{CH} electron-donating orbitals and σ^*_{CF} electron-accepting orbitals, the corresponding 1,2-dichloro, 1,2-dibromo and 1,2-diiodo derivatives are preferentially in the *anti* conformation. 2-Halofluoroethanes ($F-CH_2-CH_2-X$) combine a small halogen (fluorine) and a vicinal low-lying energy antibonding orbital (σ^*_{CX}) that activates a stabilizing antiperiplanar $\sigma_{CH} \rightarrow \sigma^*_{CX}$ electron delocalization, which can induce the *gauche* effect. On the other hand, σ_{CX} orbitals are good electron donors to σ^*_{CF}, that would favor an "*anti* effect", in addition to traditional interpretations based on steric and electrostatic repulsion. Therefore, a balance of steric, dipolar and hyperconjugative effects drive the conformational equilibrium of these compounds – hyperconjugation was found to explain the *gauche* effect in some cases, whilst Lewis-type interactions determine the *anti* preference in others. The *gauche* effect takes place in a polar solvent, but not for 1-fluoro-2-iodoethane. According to NMR three-bond spin-spin coupling constants, the *gauche* population increases when fluorine is replaced by a hydroxyl group (except for 2-fluoroethanol relative to 1,2-difluoroethane), but this is not primarily due to intramolecular hydrogen bond.

Introduction

1,2-Difluoroethane is a benchmark compound exhibiting the *gauche* effect (Figure 1),[1] that has *a tendency to adopt that structure which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds*.[1a] This behavior is counterintuitive if only traditional steric and electrostatic interactions are taken into consideration, because these repulsive interactions would lead to a preference for the *anti* conformation. In turn, the *gauche* effect in *e.g.* 1,2-difluoroethane can be accounted for stabilizing antiperiplanar hyperconjugative interactions between σ_{CH} electron-donating orbitals and σ^*_{CF} electron-accepting orbitals, which are allowed in the *gauche* conformation. However, it is well-known that σ^*_{CX} antibonding orbitals (X = Cl, Br and I) lie at a lower energy level than σ^*_{CF} due to a dominance of the interaction matrix element (overlap dependence, which decreases rapidly across the series X = F, Cl, Br, I) and, based on the energy splitting of the donor and acceptor orbitals, $\sigma_{CH} \rightarrow \sigma^*_{CX}$ hyperconjugative interactions are anticipated to be more stabilizing than $\sigma_{CH} \rightarrow \sigma^*_{CF}$ electron delocalization.[2] On the other hand, earlier studies demonstrated that conformers of 1,2-dihaloethanes (halo = Cl, Br and I) are preferentially in

the *anti* conformation, because steric effect between *gauche* halogens overrides hyperconjugative interactions and also due to stabilizing $\sigma_{CX} \rightarrow \sigma^*_{CX}$ interactions in the *anti* conformer.[3]
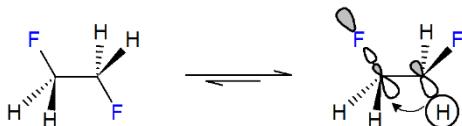
Figure 1. *Gauche* effect in 1,2-difluoroethane due to $\sigma_{CH} \rightarrow \sigma^*_{CF}$ hyperconjugation.

This work reports a spectroscopic (NMR) and theoretical conformational study of 2-halofluoroethanes, which have both small and large halogens, as well as bonding and antibonding orbitals with different electron-donating/accepting capabilities, in order to probe the role of steric and hyperconjugative interactions on the conformational equilibrium of these compounds. Although simple, these compounds display structural properties that can be useful to explore: they are 1,2-disubstituted ethanes and organofluorine compounds, whose framework is widely found in pharmaceutical, agrochemical, and material sciences.[4] Thus, conformational modulation through stereoelectronic interactions, such as the fluorine *gauche* effect, may be harnessed for the design of performance molecules.

1-Bromo- and 1-chloro-2-fluoroethanes have been found to be preferentially *anti* in the gas phase, and mainly *gauche* in a liquid, solid or solution.[5] The reasons for these behaviors are unclear, though. In addition, only the *gauche* form for 1-fluoro-2-iodoethane has been observed through microwave spectroscopy;[6] actually, 1-fluoro-2-iodoethane appears to be the most interesting case within this series of compounds, since its conformational equilibrium has not been determined in solution yet and it contains both the largest of these halogens and the best electron-accepting/donating orbital for hyperconjugation. Moreover, replacement of the fluorine substituent by a hydroxyl group provides information about the role of a possible OH···X intramolecular hydrogen bond[7] on the conformational equilibrium compared to the fluorine *gauche* effect. Previous work on these systems[7i] did not account for Lewis-type analysis to evaluate the contributions from hyperconjugation, H-bond and steric/electrostatic interactions to the conformational equilibrium. The large *gauche* preference in protonated 2-fluoroethylamine and 2-fluoroethanol has been attributed either to an intramolecular F···H bond or to an electrostatic $F \cdots O^+/N^+$ interaction.[8]

Results and Discussion

Ab initio calculations for the 2-halofluoroethanes in the gas phase indicate that the *gauche* effect takes place only for 1,2-difluoroethane (Table 1), despite the less stabilizing σ_{CH} → σ^*_{CF} interaction compared to σ_{CH} → σ^*_{CX} hyperconjugation (Table 2). Thacker and Popelier explained the fluorine *gauche* effect in 1,2-difluoroethane in terms of a 1,3 F⋯C electrostatic polarization interaction;[9] however, this interpretation is not supported by geometric parameters obtained for the optimized structures of *gauche* ($\angle_{CCF}$ = 110.3º and $d_{F1⋯C2}$ = 2.375 Å) and *anti* ($\angle_{CCF}$ = 107.9º and $d_{F1⋯C2}$ = 2.352 Å) 1,2-difluoroethane, nor by the well-known statement that intramolecular interactions with organic fluorine forming five-membered rings or less are not stable.[10] The behavior of other 2-halofluoroethanes compared to 1,2-difluoroethane can be explained on the basis of a traditional repulsion model, because the *gauche* conformer becomes sterically disfavored as the halogen at C2 increases in size. Moreover, the second-order perturbation analysis of donor-acceptor interactions in the natural bond orbitals (NBOs) (Table 2) indicates that the σ_{CX} → σ^*_{CF} interaction, which is active in the *anti* conformation, is highly stabilizing and even overcomes the σ_{CH} → σ^*_{CF} interaction in **FI**. These orbital interaction energies are affected by an orbital overlap component [represented by the element of the Fock matrix describing the donor-acceptor interactions – $F(i,j)$] and by the energy splitting of the donor and acceptor orbitals (ε_i – ε_j). Despite the $F(\sigma_{CH},\sigma^*_{CF/CI})$ values for the *gauche* conformation of **FF** and **FI** are similar, the energy gap $\varepsilon_{\sigma CH}$ – $\varepsilon_{\sigma*CI}$ is smaller than $\varepsilon_{\sigma CH}$ – $\varepsilon_{\sigma*CF}$, thus enhancing the orbital interaction energy in **FI** (Supporting Information). On the other hand, both $F(\sigma_{CX},\sigma^*_{CF})$ and $\varepsilon_{\sigma CX}$ – $\varepsilon_{\sigma*CF}$ terms indicate a more effective orbital interaction in *anti* **FI** than in *anti* **FF**. Overall, the non-Lewis-type interactions owing to electron delocalization favor the *gauche* conformation in all 2-halofluoroethanes, whilst Lewis-type interactions, namely steric plus electrostatic effects, disfavor this conformer by a larger amount, except for **FF** (Table 2). Thus, the conformational equilibrium of 2-halofluoroethanes appears to be similar to that of X–CH_2–CH_2–X.[3] However, electrostatic components mask the role of steric and stabilizing orbital interactions; the latter intramolecular interactions are not strongly affected by the environment, while the former significantly change with the medium.[11]

The relative importance of dipolar interactions on the conformer energies can be evaluated by analyzing the solvent effect on the conformational equilibrium, since the repulsion originated from the interaction between the local dipoles C–X and C–F bonds attenuates as the solvent polarity increases. Indeed, in an environment where steric and hyperconjugative effects

override electrostatic interactions, the *gauche* population increases in comparison to the gas phase and the *gauche* effect appears when hyperconjugation is the dominating factor (see Lewis and non-Lewis energies obtained using solvation models in Supporting Information). The *gauche* effect does not appear for **FI** though, even considering the highly polar solvent DMSO (according to an implicit solvation model – Table 1 and Figure 2); because the *anti* conformation of **FI** remains stabilized by a $\sigma_{CI} \rightarrow \sigma^*_{CF}$ interaction, the overall non-Lewis contribution that still favors the *gauche* conformation is counterbalanced by the Lewis-type contributions (nearly reduced to steric effects in DMSO) that destabilizes this conformation.

Table 1. Relative conformational standard Gibbs free energies (in kcal mol^{-1}) and conformer populations (%, in parenthesis) for the studied 2-halofluoroethanes and 2-haloethanols in the gas phase and implicit solvents, obtained at the MP2/6-311++g(d,p) level (def2 TZVP was used for bromine and iodine atoms, and ECP was included to the iodine atom).
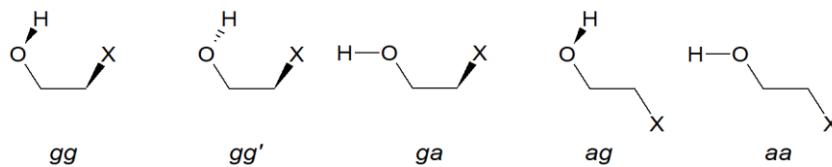
Cpd.	Structure	Conf.	ΔG^0_{gas}	ΔG^0_{CHCl3}	ΔG^0_{DMSO}
FF	F–CH$_2$–CH$_2$–F	g	0.00 (78)	0.00 (94)	0.00 (97)
		a	0.74 (22)	1.61 (6)	2.09 (3)
FC	F–CH$_2$–CH$_2$–Cl	g	0.50 (30)	0.00 (63)	0.00 (78)
		a	0.00 (70)	0.31 (37)	0.74 (22)
FB	F–CH$_2$–CH$_2$–Br	g	0.87 (19)	0.03 (49)	0.00 (66)
		a	0.00 (81)	0.00 (51)	0.40 (34)
FI	F–CH$_2$–CH$_2$–I	g	1.20 (12)	0.51 (30)	0.12 (45)
		a	0.00 (88)	0.00 (70)	0.00 (55)
OF	HO–CH$_2$–CH$_2$–F	gg	0.00 (84)	0.00 (62)	0.00 (44)
		gg′	2.33 (2)	1.16 (9)	0.55 (17)
		ga	1.46 (7)	0.58 (23)	0.16 (35)
		ag	2.22 (2)	1.89 (3)	1.77 (2)
		aa	1.70 (5)	1.72 (3)	1.77 (2)
OC	HO–CH$_2$–CH$_2$–Cl	gg	0.00 (71)	0.00 (51)	0.00 (36)
		gg′	2.26 (2)	1.25 (6)	0.59 (13)
		ga	1.34 (7)	0.49 (22)	0.04 (34)
		ag	1.36 (7)	0.90 (11)	0.78 (10)
		aa	1.03 (13)	0.96 (10)	0.98 (7)
OB	HO–CH$_2$–CH$_2$–Br	gg	0.00 (75)	0.00 (61)	0.00 (46)
		gg′	2.58 (1)	1.59 (4)	0.85 (11)
		ga	1.59 (5)	0.90 (13)	0.40 (23)
		ag	1.41 (7)	1.02 (11)	0.82 (12)
		aa	1.11 (12)	1.03 (11)	1.03 (8)
OI	HO–CH$_2$–CH$_2$–I	gg	0.00 (65)	0.00 (48)	0.00 (38)
		gg′	2.29 (1)	1.24 (6)	0.68 (12)
		ga	1.41 (6)	0.75 (14)	0.36 (20)
		ag	1.00 (12)	0.63 (17)	0.43 (18)
		Aa	0.81 (16)	0.68 (15)	0.66 (12)

Table 2. Lewis (L) and non-Lewis (NL) contributions to the full electronic conformational energies of 2-halofluoroethanes and 2-haloethanols, and important electron delocalization interactions obtained by NBO analysis (data in kcal mol^{-1}, for the gas phase molecules).

Cpd	Conf.	ΔE_{FULL}	ΔE_{L}	ΔE_{NL}	$\sigma_{CH}\rightarrow$ $\sigma^*_{CF/CO}$	$\sigma_{CH}\rightarrow$ σ^*_{CX}	$\sigma_{CF/CO}\rightarrow$ σ^*_{CH}	$\sigma_{CX}\rightarrow$ σ^*_{CH}	$\sigma_{CH}\rightarrow$ σ^*_{CH}	$\sigma_{CF/CO}\rightarrow$ σ^*_{CX}	$\sigma_{CX}\rightarrow$ $\sigma^*_{CF/CO}$
FF	g	0.00	7.08	-7.08	4.56	4.56	0.67	0.67	4.44	-	-
	a	0.80	0.80	0.00	1.08	1.08	-	-	8.16	1.50	1.50
FC	g	0.56	3.75	-3.19	4.41	5.32	0.83	1.39	4.81	-	-
	a	0.00	0.00	0.00	1.22	-	-	-	9.14	1.81	2.91
FB	g	0.88	3.71	-2.83	4.33	6.06	0.87	1.73	4.87	-	-
	a	0.00	0.00	0.00	1.20	-	-	-	9.34	2.15	3.77
FI	g	1.17	2.85	-1.68	4.34	6.22	0.91	2.19	4.94	-	-
	a	0.00	0.00	0.00	1.24	-	-	-	9.62	2.23	4.88
OF	gg	0.00	6.26	-6.26	4.02	4.68	0.82	0.84	4.78	-	-
	gg'	2.56	12.70	-10.10	4.49	4.83	0.71	0.71	4.87	-	-
	ga	2.10	7.36	-5.26	3.79	4.59	0.87	0.73	4.55	-	-
	ag	2.40	5.59	-3.19	-	1.07	-	-	8.77	1.68	1.44
	aa	2.17	2.17	0.00	-	1.10	-	-	8.60	1.90	1.35
OC	gg	0.00	5.82	-5.82	4.02	5.52	0.92	1.59	5.04	-	-
	gg'	2.70	9.51	-6.81	4.36	5.65	0.82	1.40	5.18	-	-
	ga	2.27	4.51	-2.24	3.59	5.45	1.04	1.44	4.93	-	-
	ag	1.49	4.47	-2.98	-	-	-	-	9.64	2.04	2.72
	aa	1.51	1.51	0.00	-	-	-	-	9.54	2.35	2.51
OB	gg	0.00	6.35	-6.35	3.92	6.31	0.97	1.87	5.09	-	-
	gg'	2.71	9.22	-6.51	4.28	6.45	0.87	1.69	5.25	-	-
	ga	2.38	4.46	-2.08	3.60	6.19	1.12	1.77	5.01	-	-
	ag	1.31	4.23	-2.92	-	-	-	-	9.80	2.39	3.41
	aa	1.51	1.51	0.00	-	-	-	-	9.70	2.75	3.18
OI	gg	0.00	6.46	-6.46	3.95	6.62	0.98	2.27	5.12	-	-
	gg'	2.33	7.76	-5.43	4.26	6.63	0.90	2.13	5.29	-	-
	ga	2.05	3.40	-1.35	3.57	6.40	1.14	2.23	5.09	-	-
	ag	0.84	3.80	-2.96	-	-	-	-	10.07	2.51	4.31
	aa	1.20	1.20	0.00	-	-	-	-	9.94	2.89	3.97

Replacement of fluorine in 2-halofluoroethanes with a hydroxyl group gives rise to 2-haloethanols, whose X−C−C−OH fragment can experience either an intramolecular hydrogen bond[18] or the *gauche* effect, since the C−F and C−O bonds have similar properties regarding polarity and orbital energy levels. However, rotation around the C−O bond originates additional conformers owing to the hydroxyl group orientation either at *gauche* or *anti* positions relative to the C−C bond. In all cases, the potential energy surfaces of Figure 3 indicate that the *gg* conformer, whose O−H bond is directed towards the halogen, is significantly more stable than the others in the gas phase. Despite some spectroscopic evidence that this behavior can be due to an intramolecular hydrogen bond OH⋯X (stronger when X = F),[12,13] others indicate that such interaction may not be an attractive contact[14] and that H-bond properties cannot be generally considered to originate from the strong inductive effect of fluorine.[15]

From Table 1, the *gauche* preference in 2-haloethanols increases according to **OI** < **OB** ≈ **OC** < **OF**, which is consistent with expectations from both H-bond (stronger H-bond for OH⋯F) and *gauche* effect perspectives. Regardless whether H-bond determines the conformational equilibrium of *trans*-2-halocyclohexanols or not, their infrared O−H and C−O stretching vibrations show that these bonds are abnormally weaker in the fluorine derivative

than in the other halohydrins (indicating a more effective OH···F engagement).[12a] However, the electron delocalization $n_X \rightarrow \sigma^*_{O-H}$ obtained from NBO analysis, which is a hyperconjugative rather than electrostatic approach for the H-bond, is active in 2-chloro-, 2-bromo- and 2-iodoethanol (ranging from 0.6 to 1.4 kcal mol^{-1} stabilizing in this order), but not in 2-fluoroethanol. It is worth mentioning that an electrostatic OH···F H-bond is not necessarily more stabilizing than 0.6–1.4 kcal mol^{-1}, since a repulsive through-space $n_X \rightarrow \sigma_{O-H}$ interaction accompanies the two-electron/two-orbital interaction, and the hyperconjugative H-bond should be therefore dictated by a balance between the attractive and repulsive orbital contributions. Accordingly, if H-bond influences the conformational equilibrium in 2-haloethanols, it is predominantly electrostatic in nature. This is confirmed by the strong solvent dependence of the conformations in 2-haloethanols (Table 1) – a decrease of the *gg* population from the gas phase to implicit DMSO solvent is observed. Nevertheless, an O···X electrostatic repulsion in the *gg´* conformation also attenuates as the solvent polarity increases, thus shifting the conformational equilibrium from *gg* to *gg´*. It is not obvious if the hydrogen of the hydroxyl group in 2-haloethanols is directed towards the halogen to achieve a stabilizing H-bond or to avoid destabilizing O···X lone pair repulsive interactions. These interactions have been found to be comparable in strength elsewhere,[16] while H-bond seems to be absent in a series of aliphatic fluoroalcohols in solution.[17]
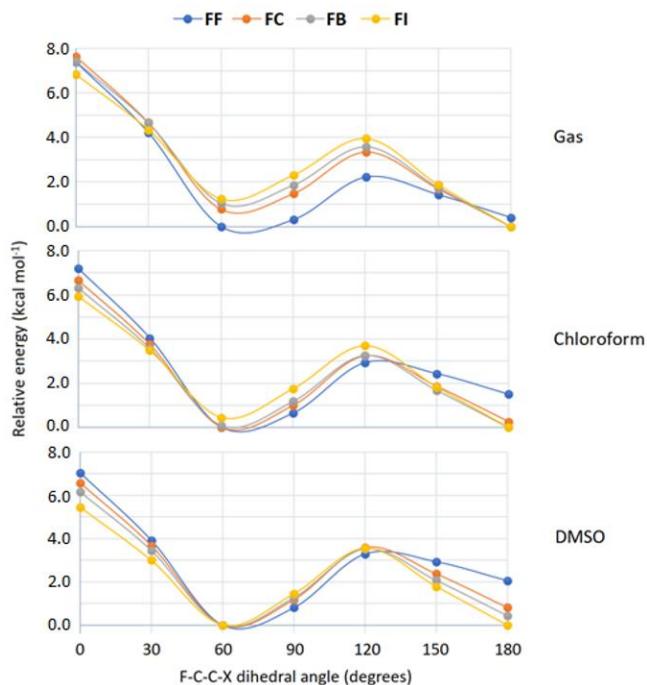
Figure 2. Potential energy curves for 2-halofluoroethanes in gas phase and implicit solvents (PCM). **FF** = 1,2-difluoroethane; **FC** = 1-chloro-2-fluoroethane; **FB** = 1-bromo-2-fluoroethane; **FI** = 1-fluoro-2-iodoethane.
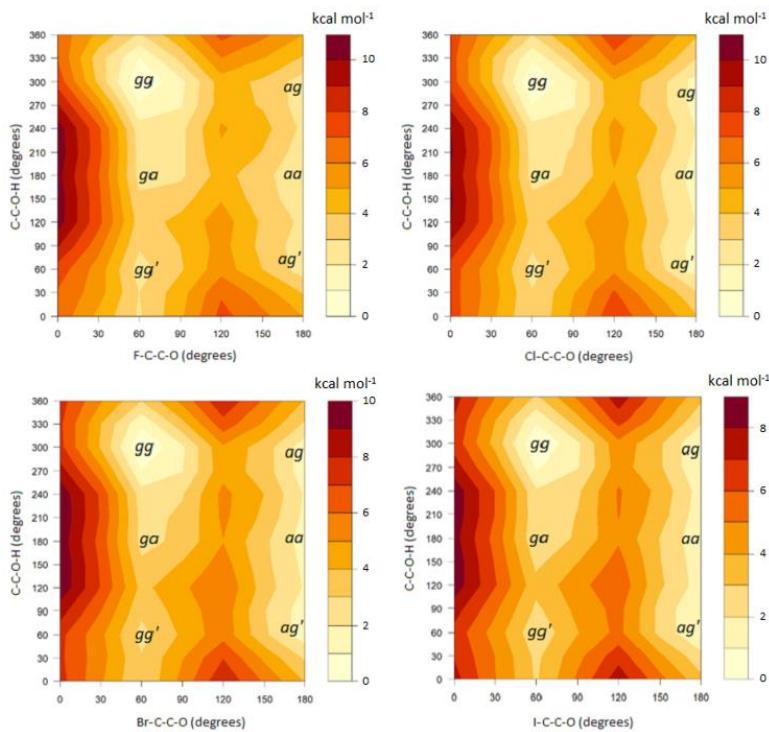
Figure 3. Potential energy surfaces for 2-haloethanols in gas phase (rotation around the X−C−C−O and C−C−O−H torsion angles).

It has been claimed that NBO overestimates the role of hyperconjugation on the rotation barrier of ethane;[18] therefore, experimental evidence supporting the theoretical outcomes would be useful to better understand the interactions governing the conformational equilibrium of the studied compounds. A comparison between the conformational behavior of 2-haloethanols and the corresponding 2-halofluoroethanes gives insight into the role of H-bond to the conformer stabilization of the halohydrins. While the *gauche* population is larger in 2-haloethanols than in 2-halofluoroethanes when the halogen refers to Cl, Br and I, the opposite behavior is observed comparing the fluorinated derivatives **FF** and **OF** (in solution). This behavior can be experimentally observed using NMR three-bond spin-spin coupling constants (SSCC´s) and taking into account the Karplus relationship for the H−C−C−H/F dihedral angle; the two-bond SSCC´s appear to be of little diagnostic value (Table 3). Because the experimental *J* values yield an average measure at room temperature, intrinsic SSCC values for each conformer can be calculated theoretically (Supporting Information) to gain insight into approximate conformer populations, according to Eqs. 1 and 2.

$$N_g + N_a = 1 \tag{1}$$

$$^3J_{\text{obs}} = (N_g \times {}^3J_g) + (N_a \times {}^3J_a) \tag{2}$$

where N_g and N_a are the mole ratios of *gauche* and *anti* conformers, respectively, $^3J_{\text{obs}}$ corresponds to the experimental $^3J_{\text{H,H}}$ (obtained from the literature in different solvents), and ^3J_g and ^3J_a are the intrinsic $^3J_{\text{H,H}}$ values theoretically obtained for the gas phase *gauche* and *anti* conformers (averaged by the calculated populations in the case of 2-haloethanols, where three *g* and two *a* conformations can exist), respectively (calculated $^3J_{\text{H,H}}$ values did not change significantly with the medium).

Table 3. Experimental coupling constants (Hz) for the studied 1,2-disubstituted ethanes.

Name	$^3J_{\text{HH}}$	$^3J_{\text{HF}}$	$^2J_{\text{HF}}$
FF	1.5 and 5.7 (avg. 3.6)[a]	30.8[a]	47.9[a]
FC	5.7,[b] 6.6[c]	23,[b] 20.9[c]	47,[b] 47.4[c]
FB	4.9,[b] 5.9[d]	18,[b] 21.0[d]	46,[b] 47.0[d]
FI	6.7[b,e]	18.6[b,e]	46.9[b,e]
OF	4.2[f,g]	30.2,[f] 28.2[g]	47.9,[f] 48.0[g]
OC	5.0[h]		
OB	5.0[i]		
OI	5.9[j]		

[a] Solvent data not available.[19]
[b] Solvent data not available.[20]
[c] In CDCl$_3$. https://www.chemicalbook.com/SpectrumEN_762-50-5_1HNMR.htm.
[d] In CDCl$_3$. https://www.sigmaaldrich.com/spectra/fnmr/FNMR008541.PDF.
[e] In C$_6$D$_6$.[21]
[f] In CDCl$_3$. https://www.sigmaaldrich.com/spectra/fnmr/FNMR001832.PDF.
[g] In C$_6$Cl$_{12}$.[17]
[h] In CDCl$_3$. https://www.sigmaaldrich.com/spectra/fnmr/FNMR002360.PDF.
[i] In CDCl$_3$. https://www.sigmaaldrich.com/spectra/fnmr/FNMR009498.PDF.
[j] In CDCl$_3$. https://www.sigmaaldrich.com/spectra/fnmr/FNMR002123.PDF.

From the experimental SSCC values available in the literature (Table 3), regardless of measurement uncertainties and the different solvents used to obtain the $^3J_{\text{HH}}$ values, the general trend observed for 2-halofluoroethanes indicates that the *gauche* population increases nearly according to **FI** (33%) < **FC** (36-57%) < **FB** (61-86%) < **FF** (89%). In addition, $^3J_{\text{HH}}$ values are smaller in halohydrins than in 2-halofluoroethanes, except for **OF** relative to **FF**. Accordingly, because $^3J_{\text{HH}}$ and $^3J_{\text{HF}}$ have an opposite trend, $^3J_{\text{HF}}$ in **OF** is smaller than in **FF**. Consequently, the experimentally obtained *gauche* population in **FF** (89%) is larger than that of **OF** (81%); therefore, it is not an OH⋯F intramolecular hydrogen bond that stabilizes the *gauche* **OF** in solution, but rather the hyperconjugative *gauche* effect caused by $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CO}}$ and $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CF}}$ interactions. According to calculations, the *gg* conformation (in which the O–H bond is directed

towards the halogen) in 2-haloethanols is largely more stable than *gg´* and *ga* (where an oxygen electron lone-pair is directed towards the halogen) in the gas phase, but the corresponding energy difference substantially decreases as the solvent polarity increases. This is consistent with a reduced Lewis-type energy in *gg´* and *ga* in implicit solvents (Supporting Information), while small changes in this term are observed for *gg* going from the gas phase to solution. Thus, H-bond does not seem to dictate the conformational equilibrium of 2-haloethanols.

Conclusions

2-Halofluoroethanes (except **FF**) do not experience the *gauche* effect in the gas phase, since repulsive interactions in the *gauche* conformer override stabilizing $\sigma_{CH} \rightarrow \sigma^*_{CF}$ (weaker) and $\sigma_{CH} \rightarrow \sigma^*_{CX}$ (stronger) hyperconjugative interactions, rather than because $\sigma_{CX} \rightarrow \sigma^*_{CF}$ interaction in the *anti* conformation would be importantly stabilizing. Such interaction is particularly stabilizing in 1-fluoro-2-iodoethane, which is predominantly *anti* both in the gas phase and solution. However, repulsive Lewis-type interactions in the *gauche* conformation at least cancel out the overall stabilizing non-Lewis interactions of this conformation even in a highly polar medium. Because the *gauche* population increases in solution, since dipolar repulsion in the *gauche* conformer attenuates as the solvent polarity increases, the *gauche* effect just dominates in solution for the chlorine and bromine derivatives, as supported by NMR three-bond spin-spin coupling constants; 1,2-difluoroethane is widely known to exhibit a strong *gauche* effect. Replacement of fluorine in 2-halofluoroethanes by a hydroxyl group leads to an increase of the *gauche* population in the resulting 2-haloethanol, tentatively because the hydroxyl hydrogen directed towards the halogen in a *gauche* conformer yields a smaller Lewis-type energy than a direct O⋯F contact; therefore, intramolecular hydrogen bond in solution should not be the driving effect of the conformational equilibrium in these cases.

Computational Section

Potential energy surfaces (PES) for 2-halofluoroethanes (F–C–C–X dihedral rotation) and 2-haloethanols (X–C–C–O and C–C–O–H rotations) were built by scanning the corresponding dihedral angles in steps of 30º, according to calculations at the B3LYP/6-311++(d,p) level of theory.[22] The def2 TZVP basis set[23] was used for bromine and iodine atoms (for iodine, ECP was used), to account for heavy atom effects and in agreement to earlier studies about systems containing bromine and iodine atoms.[24] The energy minima were fully

optimized and the frequencies for the corresponding geometries were computed at the MP2/6-311++(d,p) level of theory[25] (def2 TZVP for bromine and iodine atoms). Natural Bonds Orbitals (NBO) analysis was carried out at the B3LYP/6-311++(d,p) level (def2 TZVP for bromine and iodine atoms) to obtain stabilizing orbital interaction energies, as well as the Lewis and non-Lewis contributions to the full electronic energy. Finally, spin-spin coupling constants were calculated at the same level of theory. Calculations were performed in the Gaussian 09 program,[26] while the def2 TZVP basis set was obtained from the EMSL Basis Set Exchange (http://bse.pnl.gov/).[27]

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Theoretical and X-ray evidence of electrostatic phosphonium *anti* and *gauche* effects

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Abstract: Sulfur, not phosphorus, is the only known third-row element capable of experiencing an electrostatic *gauche* effect with fluorine. Some six-membered rings containing an endocyclic phosphorus atom and a β-fluorine substituent that can interconvert to axial (*gauche* relative to phosphorus) and equatorial positions were then analysed. While phosphines do not establish an electrostatic attraction between fluorine and phosphorus, some oxidised forms exhibit surprising stability for the sterically disfavoured axial orientation. Because the nature of this behavior was not obvious, since an intramolecular hydrogen bond can appear, a phosphonium derivative was further studied and its axial conformation was found to be highly stable. A preference for the *gauche* arrangement appears even for the acyclic and sterically hindered (2-fluoroethyl)triphenylphosphonium cation. On the other hand, (ethane-1,2-diyl)bis(phosphonium) cations are exclusively in *anti* conformation due to an (+/+)-electrostatic repulsion between the positively charged phosphonium groups.

Introduction

The conformational control of functionalised organic compounds is of interest to the pharmaceutical, material, agrochemical, and a variety of other application fields. One of the high-appearance approaches to modulate the conformation of organofluorine compounds is the so-called fluorine *gauche* effect.[1] 1,2-Difluoroethane is the benchmark compound that exhibits such effect because its *gauche* conformation is surprisingly more stable than the *anti* conformation.[2] This effect comes originally from an antiperiplanar stereoelectronic interaction between an electron-rich bonding orbital and the low-lying antibonding orbital of a C–F bond in a 2-substituted fluoroethane motif (substituent = electron-withdrawing group), which corresponds to the $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugative interaction in 1,2-difluoroethane (Figure 1).[3] The negligible steric impact of the small fluorine atom also contributes to the *gauche* effect.[4] The fluorine *gauche* effect is responsible for the helical structure of long-chain perfluorinated alkanes[5] and it is ubiquitous in biological chemistry, because conformation plays a key role in biological activity, for instance, and organofluorine compounds comprise about 20-30% of the marketed/licensed pharmaceuticals and herbicides worldwide.[6-9]
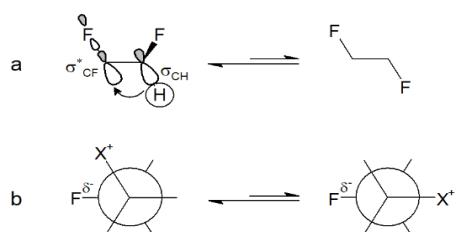
Figure 1. a) Hyperconjugative, and b) electrostatic fluorine *gauche* effects.

Despite the well-known role of donor-acceptor orbital interactions in describing the fluorine *gauche* effect,[10] an electrostatic rationale appeared later to explain the preferred *gauche* conformation in 2-(+)substituted fluoroethane moieties.[11] This is because the C–F bond is the most polar bond in organic chemistry[12] and, therefore, the partially negative fluorine atom can interact with positive sites, such as ammonium and pyridinium cations.[11,13-16] Such interaction has been found to be highly stabilising, allowing its application in a variety of biological systems, such as in fluorinated derivatives of GABA and NMDA.[17,18]

The so-called electrostatic fluorine *gauche* effect has been recently extended to include sulfur as an interacting heteroatom.[19-22] The sulfur atom in sulfoxides, sulfones, and thionium salts is partially positive, thus allowing for a Coulombic interaction with *gauche* fluorine.[19-22] In addition, the complexation of sulfides with a metal center induces a *gauche* preference along the S–C–C–F motif as a result of the electrostatic interaction mentioned above, thus providing interesting perspectives into the organometallics chemistry.[23] On the other hand, it has been shown that not all period 3 elements are capable to attract a fluorine atom through the electrostatic *gauche* effect only by modulating their oxidation state. This is the case of some β-fluorinated organophosphorus compounds, which adopt a preferential *anti* conformation, unless an intramolecular hydrogen bond in the *gauche* conformation takes place, such as in phosphinic and phosphonic acid derivatives.[24]

Nevertheless, the conformational equilibrium in β-fluorinated organophosphorus compounds could be better explored, since the conformations of compounds containing a phosphorus element with a formal positive charge have not been thoroughly studied, despite its wide range of applications, such as in Wittig olefination, catalysis, ionic liquids, and drug delivery.[25] Also, rotation around unhindered $C(sp^3)$–$C(sp^3)$ bonds in acyclic compounds has been currently evaluated, yielding a pool of conformers that hampers a straightforward analysis.[24] In this sense, the ability of an endocyclic phosphorus atom with different oxidation

states in a six-membered ring to induce an axial (*gauche*) fluorine was evaluated herein through high-level *ab initio* and density functional theory calculations. A sterically hindered acyclic β-fluorinated phosphonium compound was also studied to evaluate the limits of the electrostatic *gauche* effect.

On one hand, it is difficult to unambiguously distinguish the concept of dipolar repulsion between two negatively charged groups from Pauli repulsion; on the other hand, the nature of the interaction between two positive sites is most likely electrostatic. However, to the best of our knowledge, the effect of (+/+)-electrostatic repulsion on bond rotation, at least involving non-metal elements, has not been explored in conformational studies. Because diphosphonium cations have been employed as bactericidal compounds elsewhere and their conformation may play a critical role in bioactivity mechanisms,[26] an analysis of the interactions between two vicinal phosphonium groups bonded in a two-carbon unit aiming at observing an electrostatic *anti* effect was also provided.

Results and Discussion

An earlier study demonstrated that β-fluorinated phosphines and their respective oxidized forms do not exhibit an electrostatic fluorine *gauche* effect,[24] although a similar effect is observed with the third-row element sulfur.[19-23] Nevertheless, a detailed evaluation of phosphorus-containing six-membered rings would be valuable, as the chair interconversion yields only a few sets of stable conformers, and the analysis of the stabilizing conformational effects is, therefore, anticipated to be straightforward and accurate. Indeed, phosphine **1** (Figure 2) presents four stable stereoisomers (two pairs of conformers), with a preferential equatorial orientation for the fluorine substituent and an axial position for the P–H bond (Table 1). The second most stable structure also bears an axial P–H bond, indicating that the phosphorus lone pair of electrons is axially disfavoured. Thus, classical steric diaxial repulsion rules the energetics in **1**. The picture changes for **2**, since *2-trans-a* and *2-cis-a* are similarly stable in the gas-phase, indicating that the equatorial fluorine is preferred, while the phosphorus lone pair and the methyl group probably have comparable steric hindrance.

Because a *gauche* preference cannot be observed in the phosphines, we attached a different group at the phosphorus atom to evaluate its ionic form. A fluorine-phosphorus *gauche* preference is clear and conclusive for the phosphonium cations **3** and **4**, as the axial conformer in both compounds corresponds to the single stable form in the gas phase. To ensure that this

axial preference can be asserted as the *gauche* effect, we compared these rings with fluorocyclohexane and 3-fluoro-1,1-dimethyl-cyclohexane. Similar to other monosubstituted cyclohexanes, fluorocyclohexane and 3-fluoro-1,1-dimethyl-cyclohexane are preferred in the equatorial conformation (0.19 and 0.61 kcal mol^{-1} more stable than the axial conformer, respectively), which agrees with a previous report.[27] Therefore, the behavior found in their phosphorus analogs **3** and **4** can be characterized as a strong *gauche* effect. This is probably due to the positively charged phosphorus (QTAIM atomic charges q_P = +1.8 and +1.9, respectively) interacting with the negatively charged axial fluorine (q_F = -0.5), since the C-counterpart in fluorocyclohexane and 3-fluoro-1,1-dimethyl-cyclohexane is nearly neutral (q_C = +0.1 and +0.2, respectively). Considering the conformational energies of **3** and **4** relative to fluorocyclohexane and 3-fluoro-1,1-dimethyl-cyclohexane, it follows that the extension of the *gauche* effect in these systems ($\Delta\Delta E_{eq-ax}$) is *ca.* 3.6 kcal mol^{-1} in **3** and 3.9 kcal mol^{-1} in **4**.

To search for the role of hyperconjugation as the origin of the *gauche* effect in **3** and **4**, our NBO analyses (Supporting Information) demonstrated that the $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ interaction in the axial conformer is indeed stabilizing, but of similar magnitude to the corresponding interaction in axial fluoro-cyclohexane and 3-fluoro-1,1-dimethyl-cyclohexane (5.1-5.6 kcal mol^{-1}). Therefore, this contribution is not the primary source for the *gauche* preference in the phosphonium cations. In turn, the electrostatic fluorine *gauche* effect is known for systems containing N–C–C–F and S–C–C–F moieties, so the proposal of a P–C–C–F electrostatic *gauche* effect is a logical extension to those earlier found.[28-30]

Additional evidence to reinforce the electrostatic nature of the phosphorus-fluorine *gauche* effect for compounds containing a positively charged atom is the strong decrease in the *gauche* preference of **3** and **4** in an implicit polar medium (DMSO). Also, a comparison between the P···F$_{ax}$ distances in phosphines and phosphonium cations indicates a significant ring puckering in the latter as a result of the attractive Coulombic interaction; the P···F$_{ax}$ distance shortens from 3.258 Å in ***1-cis-g*** and 3.366 Å in ***2-cis-g*** to 2.970 Å in axial **3** and 3.096 Å in axial **4**, respectively. This finding appears to extend generally, because the conformational energy for the acyclic and sterically hindered (2-fluoroethyl)triphenylphosphonium cation (**5**) is consistent with those of the cyclic analogs.

A quantum theory of atoms in molecules (QTAIM) analysis was performed to check for a possible hydrogen bond between the axial fluorine and (P)H (**3**) or (P)CH$_3$ (**4**) hydrogens, but a bond path was found only for the latter (Supporting Information). QTAIM has been applied to conformational analysis[31] and, for some organophosphorus compounds, hydrogen bond-

type contributions (C−H···X−P, X = O and S) have shown to activate the anomeric effect.[32] According to Koch and Popelier, a few criteria have to be observed to characterize hydrogen bonds using QTAIM.[33] The first one states that a bond-critical point (BCP) and a bond path should be present. In this sense, only the molecules with R = CH$_3$ are capable of experiencing such interaction (Supporting Information). Furthermore, local properties over the BCP, such as charge density (ρ) and the Laplacian of ρ ($\nabla^2\rho$), have to be one order of magnitude smaller than those observed for covalent bonds and higher than zero ($\nabla^2\rho > 0$), respectively. Analysis of other parameters based on integrated properties is additionally required. The decrease in the hydrogen volume (V(H)), energy(E(H)), dipolar moment (μ(H)), and charge (q(H)) are expected for the hydrogen involved in a hydrogen bond, if compared with hydrogen that not experience such interaction. These data were computed, and the CH$_3$ hydrogens were compared. The parameters match the established conditions (see the Supporting Information), and a hydrogen bond is present in a few compounds. Despite such stabilization, hydrogen bond should not be responsible for the *gauche* effect in **4**, since both phosphine (**2**) and their phosphonium cation (**4**) experience this interaction.
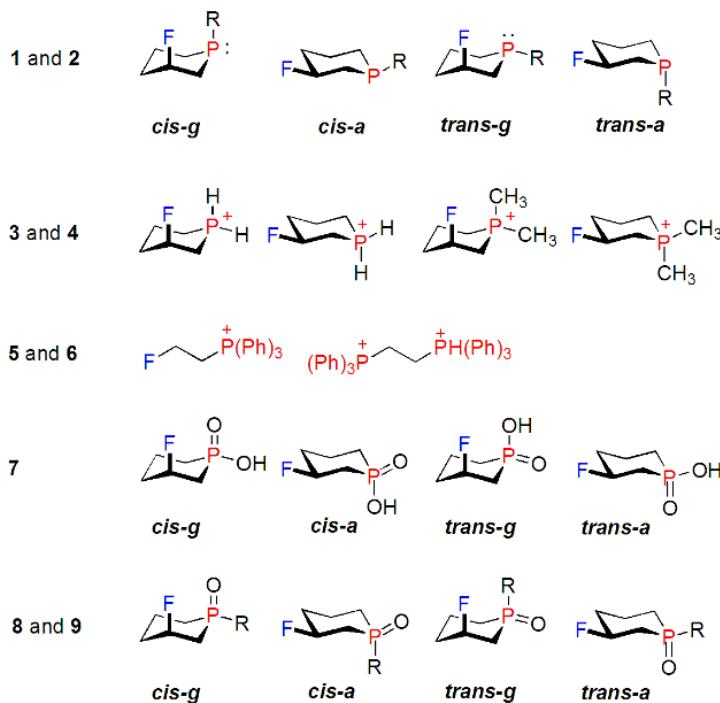
Figure 2. From top to bottom: chair conformations and isomers for the studied phosphines **1** (R = H) and **2** (R = Me), phosphonium cations **3** (R = H) and **4** (R = Me), (2-fluoroethyl)triphenylphosphonium (**5**) and (ethane-1,2-diyl)bis(triphenylphosphonium) (**6**) cations, phosphinic acid **7**, phosphine oxides **8** (R = H) and **9** (R = Me).

Table 1. Relative Gibbs free energies (in kcal mol^{-1}) for the studied compounds in the gas phase and implicit DMSO (IEFPCM), obtained at the B3LYP-D3BJ/6-311++g(d,p) level.

Compound[a]	Gas phase	Implicit DMSO
1-cis-g	1.25	1.37
1-cis-a	2.35	2.48
1-trans-g	3.72	3.46
1-trans-a	0.00	0.00
2-cis-g	0.98	1.48
2-cis-a	0.28	0.49
2-trans-g	1.74	1.52
2-trans-a	0.00	0.00
3$_{eq\text{-}ax}$	3.41	0.57
4$_{eq\text{-}ax}$	3.25	0.91
5$_{anti\text{-}gauche}$	1.90	0.39
7-cis-g_s	2.82	1.12
7-cis-g_a	7.74	2.65
7-cis-g_s'	-	1.03
7-cis-a_s	0.00	-
7-cis-a_g	-	0.00
7-cis-a_g'	-	0.18
7-trans-g_s	1.30	-
7-trans-g_g	-	1.00
7-trans-g_a	2.55	0.47
7-trans-g_g'	-	0.65
7-trans-g_s'	1.94	-
7-trans-a_s	0.66	0.71
7-trans-a_a	4.94	2.03
7-trans-a_s'	-	0.53
8-cis-g	2.72	1.48
8-cis-a	0.10	0.00
8-trans-g	0.00	0.22
8-trans-a	0.08	0.64
9-cis-g	3.35	1.34
9-cis-a	0.64	0.00
9-trans-g	0.42	0.51
9-trans-a	0.00	0.11

[a] *3*$_{eq\text{-}ax}$ and *4*$_{eq\text{-}ax}$ correspond to the energy difference between the equatorial and axial conformers. *5*$_{anti\text{-}gauche}$ is the energy difference between the *anti* and *gauche* conformers of **5**. The last letter in the names of stereoisomers **7** represents the hydroxyl orientation (*syn*, *anti*, or *gauche*). Compound **6** does not appear because there is only a single (*anti*) conformer.

To further understand the role of electrostatic interactions in the conformational equilibrium of the phosphonium cations, the rotational profiles of 2-fluoro-ethylphosphonium ($H_3P^+-CH_2-CH_2-F$, **PF**) and (ethane-1,2-diyl)bis(phosphonium) ($H_3P^+-CH_2-CH_2-PH_3^+$, **PP**) cations can be compared to that of butane, whose energy minima are located at staggered conformations due to steric and hyperconjugative considerations.[34-36] While butane is widely known to be preferentially in the *anti* conformation, **PF** is clearly more stable in the *gauche* orientation, both in the gas phase and polar solution (Figure 3). This emphasises the pivotal role of the electrostatic *gauche* effect in **PF**. Surprisingly, only a single conformer is observed for

PP corresponding to a staggered *anti* geometry in the gas phase, since the *gauche* conformer appears as a high-energy minimum only in solution (Figure 3). Noticeably, the QTAIM atom charges on **P** and **F** in these compounds are positive and negative, respectively, as well for the cyclic compounds (Figure S1, Supporting Information).
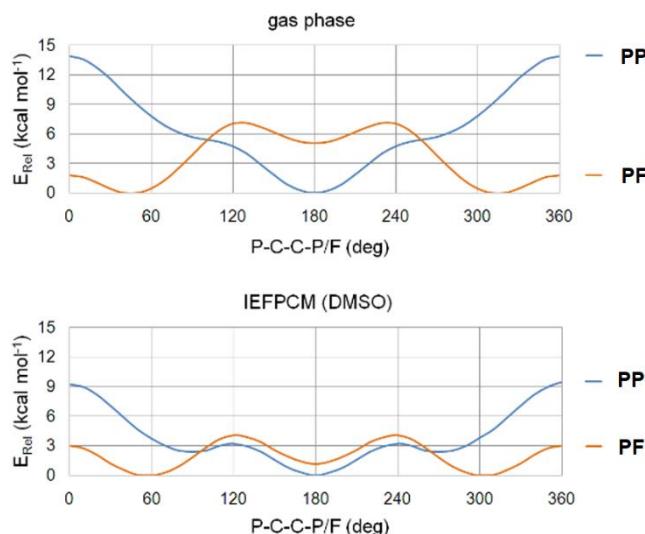
Figure 3. Rotational curves for **PF** and **PP** in the gas phase and implicit solvent (DMSO).

Vicinal electron-withdrawing groups – thus bearing negatively charged sites – repel each other due to electrostatic repulsion between the electron densities of the two substituents and to the Pauli repulsion between occupied closed-shell orbitals of both substituents.[37] In turn, the contribution to the conformational behavior in **PP** appears to be predominantly due to the repulsion between the nuclei of the substituents, which would give rise to an "(+/+)-electrostatic *anti* effect". To obtain experimental evidence for the so-called "(+/+)-electrostatic *anti* effect", the (ethane-1,2-diyl)bis(triphenylphosphonium) salt (**6**) was prepared and its single-crystal X-ray structure was obtained (Figure 4). The P−C−C−P dihedral angle in **6** was found to be *anticlinal* (*ca.* 135°), as expected from repulsive steric and electrostatic considerations, as well as to allow for a π-stacking interaction. Similarly, an *anti* arrangement along the P−P−P−P dihedral angle in 2,3-diphosphino-1,4-diphosphonium cations has also been observed,[38] as well as in $(C_{38}H_{34}P_2)MgBr_4$ powders useful for scintillation-based X-ray detection (P−C−C−P dihedral angle = 166.96°).[39]

Figure 4. Single crystal structure of (ethane-1,2-diyl)bis(triphenylphosphonium) iodide (**6**) with a $\phi_{P-C-C-P}$ dihedral angle of 134.8(3)$^{\circ}$.

A comprehensive analysis on the nature of the *gauche* and *anti* effects in **PF** and **PP** can be performed using quantum-chemical calculations for natural energy decomposition analysis (NEDA).[40] The interaction energy (E_{int}) between two open-shell fragments ($\bullet CH_2PH_3$ and $\bullet CH_2X$, X = F for **PF**, and PH_3 for **PP**) can be decomposed into electrical (E_{EL}), charge transfer (E_{CT}), and core (E_{core}) components. The rotational profile of these energies demonstrates that the E_{EL} and E_{CT} terms are stabilising, whereas the core repulsion is certainly destabilising (Figure 5). However, the E_{CT} term finds two minima with very similar energy for **PF**: a broad one at about 60° (*gauche*) and another minimum at 180° (*anti*). On the other hand, the stabilisation due to E_{EL} continuously decreases with $\phi_{P-C-C-F}$ going from 0° to 180°. Consequently, the *gauche* effect in **PF** appears to be dominated by the electrical term (comprised of electrostatic – E_{ES}, polarization – E_{pol}, and energy penalty of polarization – E_{SE} contributions), while the core repulsion neither favours nor disfavours the *gauche* conformer relative to the *anti*. In turn, E_{int} follows the trend observed for E_{EL} in **PP**, *i.e.* its rotational energy profile is dictated by the electrical term, which is more favoured in the *anti* conformer (Figure 5b). Because the electrostatic component rules the E_{EL} term (Figure 5c), the *anti* effect observed in **PP** can be unequivocally assigned to an (+/+)-electrostatic *anti* effect.
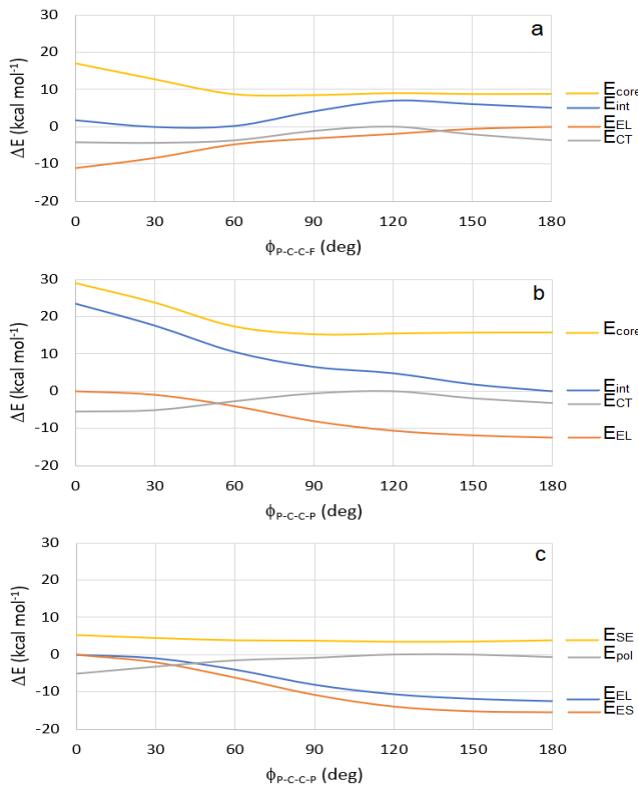
Figure 5. Natural energy decomposition analysis for rigid rotation (C−C distance fixed at the equilibrium distances of the *gauche* and *anti* conformers of **PF** and **PP,** respectively) of the $\phi_{P\text{-}C\text{-}C\text{-}F/P}$ dihedral angle of **PF** and **PP**. a) E_{int} and its components for **PF**; b) E_{int} and its components for **PP**; c) E_{EL} and its components for **PP**.

To further extend our knowledge about the newly established electrostatic fluorine-phosphorus *gauche* effect, a series of oxidised phosphorus compounds (**7**-**9**) was investigated. It has been demonstrated that phosphine oxides and derived acids do not show a sufficiently stabilising $P^{\delta+}\cdots F^{\delta-}$ electrostatic attraction in the *gauche* structure; the *gauche* preference appears to be rather due to F$\cdots$H–O hydrogen bond.[24] However, because the acid is easily dissociated in solution, such an interaction should be absent. Similar behavior is observed in the six-membered ring **7** (Figure 6); conformers with equatorial fluorine are the lowest-energy structures when the H–O–P=O dihedral angle is *synperiplanar*, independently of the P=O orientation (either axial or equatorial). A non-*synperiplanar* orientation along the H–O–P=O dihedral angle is favoured only for **7-trans-g**, where an F$\cdots$H–O hydrogen bond may be present in the gas phase. Yet, this is not the most stable structure for **7**, which is rather the *synperiplanar* structure of **7-cis-a** bearing both the highly polar C–F and P=O bonds in the equatorial position.
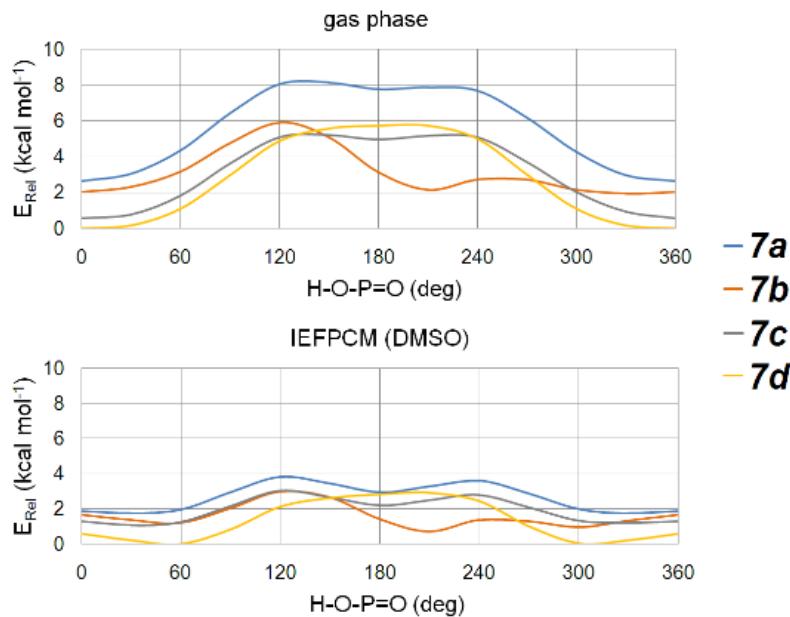
Figure 6. Potential energy surfaces accounting for the rotation around the P–OH bond in **3**.

The phosphine oxide **8** adopts a preferential axial orientation for the fluorine substituent (structure **8-trans-g**); however, according to an energy scale earlier reported,[10] an energy difference of *ca.* 0.1 kcal mol^{-1} does not indicate a "clearly *gauche* preference". It is worth mentioning that **8-cis-g** is anticipated to be destabilised by a dipolar repulsion between the axial C–F and P=O bonds. In addition, because of a possible long-range F···H–P hydrogen bond in **8-trans-g**, the electrostatic phosphorus-fluorine *gauche* effect in **8** cannot be asserted as being the single source of *gauche* stabilisation. Thus, a bulkier group attached to the phosphorus atom was considered with the aim at avoiding dubious interpretation on the ruling interactions of the structural energies, yielding compound **9**; accordingly, the relative stability of **9-trans-g** decreases if compared to **9-trans-g** and an *anti* preference takes place. Nevertheless, an *anti* structure **9-trans-a** is lower in energy than **9-trans-g** by only a small value, which can be due to a weak F···H–C hydrogen bond in the latter. This is confirmed by QTAIM analysis, in which a bond path between the interacting atoms reveals the electrostatic character of such a hydrogen bond (Supporting Information), as discussed earlier. It is worth mentioning that in phosphine oxides **8-trans-g** and **9-trans-g**, whose phosphorus atom bears a partially positive charge, the respective distances are 3.195 Å and 3.278 Å, higher than those found in the phosphonium cations **3** and **4**. Consequently, the preferred fluorine in the axial position cannot be asserted as being due to an electrostatic F···P interaction.

Conclusion

Although not all β-fluorinated organophosphorus compounds experience the electrostatic phosphorus-fluorine *gauche* effect, phosphonium analogs adopt a *gauche* conformation as the sharply most stable structure both in the gas phase and polar solution. The electrostatic phosphorus-fluorine *gauche* effect is not the dominant effect of the preferential *gauche* structure in six-membered rings containing pentavalent phosphorus; whereas phosphinic acids experience intramolecular hydrogen bond, the short $P{\cdots}F_{ax}$ distance in phosphine oxides compared to that found in the respective phosphines does not clearly explain the *gauche* effect. Whereas dipolar repulsion between negatively charged vicinal groups is known to move these groups away, then usually leading to an *anti* conformation, the electrostatic repulsion between the positively charged phosphonium groups also appeared to be an efficient mechanism for conformational control. In overall terms, the electrostatic fluorine *gauche* effect extends to phosphorus as a period 3 heteroatom, while vicinal phosphonium groups in an ethane moiety provide the newly revealed (+/+)-electrostatic *anti* effect.

Experimental

Computational. The geometries for the stable structures of **1-7** were fully optimised at the *ab initio* MP2/6-311++g(d,p) level,[41,42] since this is a robust method for structure prediction of organic molecules, both in the gas phase and considering a polar implicit solvent (DMSO) through the polarisable continuum model.[43] For the acids (**3**), the H−O−P=O dihedral angle was scanned in steps of 30° at the same level of theory to identify the hydroxyl orientation, whereas the scans for **PF** and **PP** were carried out in steps of 10°. Frequency calculations were performed at the B3LYP-D3BJ/6-311++g(d,p)[44-46] level of theory for all stable conformers to ensure the absence of imaginary frequencies and to obtain the Gibbs free energies. This level of theory requires less computational cost than traditional *ab initio* MP2, but usually presents similar or even better termochemical results.[47,48] The energy decomposition analysis based on natural bond orbitals (NEDA) was performed considering a rigid rotation around the C−C bond of **PF** and **PP**; the C−C distance between the $\cdot CH_2PH_3$ and $\cdot CH_2X$ (X = F for **PF** and PH_3 for **PP**) open-shell fragments was fixed at the corresponding equilibrium distance of the *gauche* (for **PF**) and *anti* (for **PP**) conformers. The same procedure was done considering minus and plus 0.5 Å to the C−C distance to confirm that the rotational profiles were independent of the C−C distance. These calculations were performed using the Gaussian program and the software

NBO 7.0.[49,50] The quantum theory of atoms in molecules (QTAIM) analysis[51] was performed using the wavefunctions obtained from the optimised geometries using the AIMAII software package.[52]

(Ethane-1,2-diyl)bis(triphenylphosphonium) iodide (9). A mixture of 1.474 g (8.0 mmol) of 1-fluoro-2-iodoethane and 0.528 g (2.0 mmol) of triphenylphosphine in acetonitrile (3 mL) was stirred under reflux for one hour. The mixture was cooled, and the solvent was distilled off on a rotatory evaporator. The solid was washed with diethyl ether and air-dried to give compound **9** (0.430 g). The solid was solubilised in hot acetonitrile for further purification. The solution was cooled, no solid was observed. The crystals precipitated after three days (0.215 g, 30.0 %). Compound **9** was subsequently analysed through X-ray crystallography.

Supporting Information. Standard coordinates of the optimised geometries, DFT and NBO results, and X-ray diffraction data. The X-ray crystallographic data for this paper has been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1971685.

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SECOND PART

Biological and Environmental Impact of Fluorine Atom

Theoretical study of fluorinated bioisosteres of organochlorine compounds as effective and eco-friendly pesticides

Francisco A. Martins, Joyce K. Daré and Matheus P. Freitas

ABSTRACT

Chlordane is a worldwide banned organochlorine insecticide because of its hazard to animal and human health. It is also a persistent organic pollutant, which can affect either the soil or the aquatic life. The same applies to other chlorinated cyclodiene insecticides, such as dieldrin and aldrin. In turn, organofluorine compounds have a widespread use in agriculture. Therefore, density functional calculations and docking studies showed that the bioisosteric replacement of chlorines in the above-mentioned compounds by fluorines improves some physicochemical parameters used to estimate the toxicity and environmental risk of these compounds, as well as the ligand-enzyme ($GABA_A$ receptor-chloride channel complex) interactions related to their insecticidal activity. This work is an effort to provide an improved new class of organofluorine pesticides.

Keywords: Organofluorines; Chlorinated Cyclodienes; Insecticides; Environment; Molecular Modeling

INTRODUCTION

Chlordane is a chemical that can be prepared through a Diels-Alder reaction followed by a double bond chlorination, which yields a mixture of *cis* and *trans* isomers, also named α- and β-chlordane, respectively (Figure 1). Both isomers are organochlorine compounds effective against insects that threaten the agriculture. Their mode of action involves the opening of ion channels in the nerve cells of the insects, whilst the $GABA_A$ receptor works as a major ligand-activated ionic channel responsible for mediating the effects of the γ-aminobutyric acid (GABA) neurotransmitter (Fishman and Gianutsus, 1985; Anand et al., 1998). However, all uses of chlordane were banned by the United States Environmental Protection Agency (EPA) because of its harm to human health and environment, although it is still used in many developing countries (ATSDR, 2018). Just as chlordane, aldrin and dieldrin are also classified as cyclodienes and interact by the same mechanism of action with $GABA_A$ (Bloomquist and Soderlund, 1985; Pomes et al., 1994). It is worth mentioning that these compounds are structurally similar to the picrotoxin, a known noncompetitive antagonist at $GABA_A$ receptors that has been used as potency indicator (Abalis et al., 1986). This class of compounds has been

reported as one of the causes of diseases, such as Parkinson's disease and some types of cancer (Mathur et al., 2002; Uversky et al., 2001; Sharma et al., 2010; Davis and Fitzhugh, 1962).

The presence of chlorine in organic compounds does not ensure toxicity, but this halogen has a lipophilic character, which enhances the persistence of the organochloride both in soil and aquatic living systems. Accordingly, organochlorines can move from soil to plants and then be transferred to the food chain, while in water they can accumulate in the fatty tissue of aquatic living systems (Piu et al., 2019; Egeler et al., 1997). Risks to animal and human health have also been reported, which can be related to the relative ease for C–Cl bond cleavage (Liang et al., 2017). In turn, organofluorine agrochemicals have been widely used as pesticides (herbicides, fungicides and insecticides) (Fujiwara and O´Hagan, 2014; Theodoridis, 2006), with several advantages over organochlorine compounds. These include lower lipophilicity, reduced steric effects, enhanced electronic effects (which result in modified physical properties and chemical reactivity), and higher stability of the C–F bond (Theodoridis, 2006). Nevertheless, a more detailed comprehension of organofluorine pesticides is necessary, once the high stability of the C–F bond hampers their degradation; therefore, it has been found that they can persist in the environment (Murphy et al., 2011). However, these compounds are usually inert agents and more polar (less hydrophobic) than organochlorine compounds, thus suggesting a lower toxicity.
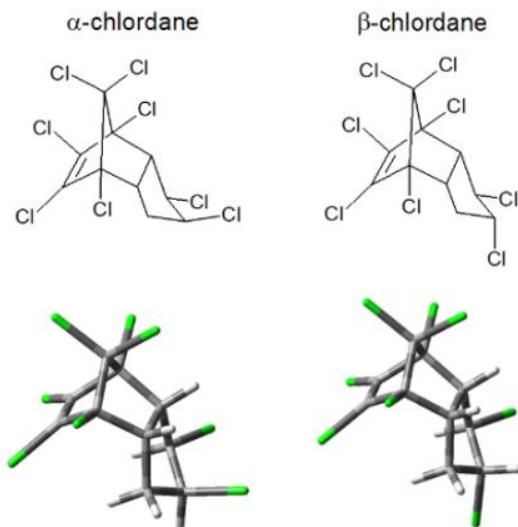
Figure 1. Isomers *cis* (α) and *trans* (β) of chlordane. Computationally optimized structures are also shown.

Since the C–F bond brings desirable properties to an agrochemical, the bioisosteric replacement of the chlorines by fluorines in chlordane may lead to a novel, improved class of

pesticides for use in agriculture – exemplified as "fluordane" herein. The same approach can be applied to other chlorinated cyclodiene insecticides, such as aldrin and dieldrin. In this sense, a computational exploitation can be performed before time and cost-demanding experimental procedures by calculating physicochemical data for health and environment risk assessment. Inhibition of the cytochrome P450 enzymes is also worth to predict, since they also function to metabolize toxic compounds, principally in the liver. In addition, the insecticide-likeness of the proposed compounds may be searched taking into consideration their interaction with the GABA$_A$ receptor-chloride channel through docking studies. Accordingly, this computer simulation study may be helpful to generate baseline data for experimental work, thus alerting the community to a possible strategy for next-generation agrochemicals.

MATERIALS AND METHODS

The geometry optimization of both isomers of chlordane, as well as of their fluorinated bioisosteres, was carried out at the density functional theory (DFT) B3LYP/6-311++g(d,p) level (Becke, 1988; Lee et al., 1988; Krishnan et al., 1980), in order to obtain the molecular dipole moments of the compounds. The same procedure was carried out for aldrin, dieldrin and pentachlorophenol, as well as for their fluorinated derivatives, which do not have stereoisomers. These calculations were performed using the Gaussian 09 program (Frisch et al., 2016). Physicochemical properties and toxicity endpoints were predicted using the Percepta platform of the ACD/Labs program, which provides all required data (ACD/Labs Percepta, 2012); these estimations are obtained either by additive atomic contributions (*e.g.* for the calculation of lipophilicity – log *P*) or by interpolation of the chemical structure descriptors in an empirical or calculated model.

The ligand-enzyme fitting was obtained by docking studies, using Glide module with standard precision (Friesner et al., 2004; Halgren et al., 2004). The crystal structure of α1β3γ2-GABA$_A$ in complex with picrotoxin, GABA and megabody Mb38 was obtained from the Protein Data Bank (PDB code: 6HUG) with resolution of 3.1 Å (Masiulis et al., 2019). The receptor crystal structure was prepared using the Protein Preparation Wizard (from Schrödinger Suite 2011) with OPLS2005 force field; the co-crystallized ligand and megabody Mb38 were excluded, and missing atoms/connections were added.

The ligands were prepared apart from the receptor. The structures of chlordane, aldrin and dieldrin, as well as of their corresponding fluorinated analogs, were optimized at the density functional theory (DFT) B3LYP/6-311++g(d,p) level (Becke, 1988; Lee et al., 1988; Krishnan et al., 1980). The charges were calculated according to the electrostatic potential scheme of

CHELPG (Breneman and Wiberg, 1990) at the B3LYP/6-311++g(d,p) level using the Gaussian 09 program (Frisch et al., 2016).

Finally, the prepared ligands were docked at the picrotoxin binding site of the Cys-loop receptor, since earlier studies demonstrated that cyclodienes act by the same mechanism of picrotoxin (Abalis et al., 1986). A rigid docking was performed, in which the ligands are allowed to move, but the residues remain rigid in the active site. Forty poses were generated for each cyclodiene. The best poses were chosen by superposition similarity with picrotoxin and energy criteria, *i.e.* the lowest energy pose which shows an acceptable superposition with picrotoxin was used for each ligand. Moreover, the superposition of the chlorinated compounds with the corresponding fluorinated bioisosteres was taken as reference. Docking results were also analyzed according to the docking scores of intermolecular interaction energies

RESULTS AND DISCUSSION

Lipophilicity is ubiquitous in the estimation of bioactivity and toxicity of drug-like and agrochemical-like molecules (Waring, 2010). It is usually described in terms of the octanol-water partition coefficient (log P), which can be calculated from additive contributions of atoms and/or group fragments. Such approach does not account for stereochemistry though, despite a recent study describing that accurate lipophilicity measurements inform on subtle stereoelectronic effects (O´Hagan and Young, 2016); consequently, the stereochemistry that controls the molecular polarity can also modulate the log P of a substance. Accordingly, the molecular geometries of chlordane (Figure 1) and of the corresponding fluorinated derivatives were optimized in gas phase, and the molecular dipole moments were then obtained. Because of the orientation and high polarity of the C–F bonds, both fluordane isomers are more polar than the respective chlordane isomers (2.99 against 2.57 Db for the α isomers, and 2.48 against 1.81 Db for the β isomers – Figure 2). This suggests that fluordane is more water soluble than chlordane and also less absorbed either by soil particles or fatty tissues of living organisms. Indeed, this finding is confirmed by direct log P calculations using the Percepta program: 5.96 for chlordane (in good agreement with the experimental log P = 6.16) (Simpson et al., 1995) and 2.96 for fluordane. The calculated solubility is also consistent with the lipophilicity data, since chlordane is calculated to be rather insoluble (experimental aqueous solubility at 25ºC = 1.37×10^{-7} mol L^{-1}) (Sanborn et al., 1976), while fluordane is calculated to be about a thousand-fold more soluble than chlordane (1.44×10^{-4} mol L^{-1}). Because soil can be rich in organic matter, the soil sorption of an agrochemical is usually dependent on its lipophilicity (Sabljić et

al., 1995). Therefore, fluorinated derivatives of organochlorides should have limited persistence in soil. In turn, these organofluorines should be more soluble in water, thus affecting the aquatic life through bioconcentration or bioaccumulation – also directly related to log P (Devillers et al., 1996) – in a smaller extent.
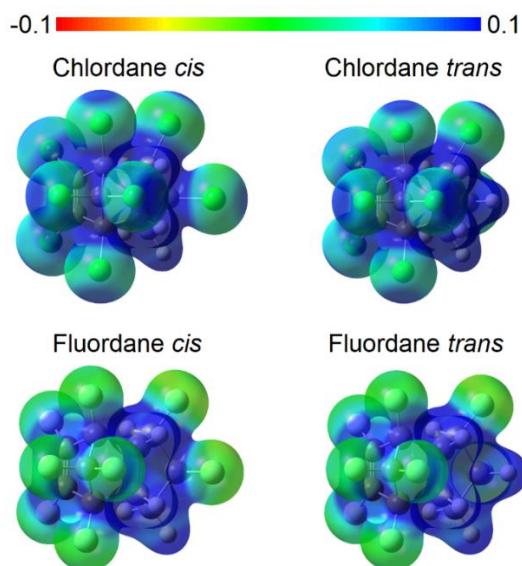
Figure 2. Electrostatic potential surfaces (at 0.02 a.u.) from -0.1 (red) to 0.1 (blue) a.u. for chlordane and fluordane obtained at the B3LYP/6-311++g(d,p) level; colors are more contrasting in the latter, indicating more polar bonds.

Despite both fluordane and chlordane not being prone to cause mutagenicity according to the calculations for simulation of the Ames test through the ACD/Labs Percepta program, the latter compound was calculated to be a probable CYP3A4 enzyme inhibitor. The cytochrome P450 3A4 (CYP3A4) is a key oxidizing enzyme involved in molecule metabolism, *e.g.* by the hydroxylation of $C(sp^3)$–H bonds (Meunier et al., 2004). While inhibition of the CYP3A4 enzyme is undesirable, the insecticidal activity of chlordane is related to targets at the central nervous system, particularly by blocking specific GABA receptors, contributing to its neurotoxic effects (Narahashi et al., 1998). Since fluordane appears to be advantageous in many aspects compared to chlordane, the binding affinity of both ligands towards the known picrotoxin binding site at the GABA$_A$ receptor of the Cys-loop ligand-gated ion channel superfamily can be searched and compared to each other with the aim at estimating the pesticide-likeness of fluordane.

Docking studies were performed in order to gain insight into the insecticidal potency of fluordane compared to chlordane. Because of the lack of a suitable GABA$_A$ receptor from an insect, the human $\alpha 1\beta 3\gamma 2$-GABA$_A$ in complex with picrotoxin, GABA and megabody Mb38 was considered (Masiulis et al., 2019). Since the effect caused by a small amount of active

fluordane/chlordane bound to the human receptor is possibly negligible compared to the effect in the insect, its human toxicity should be proportionally lower than in the insect. In addition, the bioaccumulation problem is attenuated in the case of fluorinated compounds, since they have lower lipophilicity. It is worth mentioning that although the GABA receptors exhibit considerable pharmacological variety between invertebrates and vertebrates, they have remarkable structural similarities – the GABA receptor subunits of invertebrates are between 30% and 47% of identity to vertebrates (Hosie et al., 1997). Moreover, alanine (which interacts with most of compounds studied herein, see the Supplementary Material) is an important residue involved in pesticide activity; in many cases, insecticide resistance is observed when alanine is replaced (Ffrench-Constant et al., 2016). The receptor selection step also took into account the structural similarity among the crystallized ligand (picrotoxin) and the chlordane derivatives. In addition, the picrotoxin is similar to the biological ligand TBPS (*t*-butyl bicyclophosphorothionate), which is employed for indication of activity potency in sample preparations from mammalian brains (Coats, 1990; Casida and Lawrence, 1985).

The fluorinated analogs of chlordane showed lower protein-ligand energies, suggesting higher complex ligand-protein stabilities (Table 1). While the complex protein/α-chlordane showed a docking score (the free energy of protein-ligand binding) of –5.61 kcal mol^{-1}, the corresponding value for the complex with α-fluordane is –6.56 kcal mol^{-1}. The same pattern was observed for β-compounds: –5.73 against –6.61 kcal mol^{-1}. It is worth mentioning that β-chlordane is known to be more active than α-chlordane (Metcalf, 2000), which is in agreement with the docking scores. Moreover, the satisfactory superposition of the cyclodienes with picrotoxin also validates our approach.

Table 1. Calculated physicochemical data (molecular dipole moments in Db – μ, octanol-water partition coefficient – log P, and water solubility – S_{water} – in mol L^{-1}), cytochrome P450 target (CYP), and docking score ($E_{docking\ score}$) data for the studied compounds (in kcal mol^{-1}). Available experimental data are given in parenthesis (second entries).

| | Dieldrin | F-Dieldrin | Aldrin | F-Aldrin | PCP | PFP |

Compound	μ	log P	S_{water}	CYP	$E_{docking\ score}$
α-Chlordane	2.57	5.96	Insoluble	CYP3A4	−5.61
		$(6.16)^a$	$(1.37 \times 10^{-7})^b$		
β-Chlordane	1.81	5.96	Insoluble	CYP3A4	−5.73
		$(6.16)^a$	$(1.37 \times 10^{-7})^b$		
α-Fluordane	2.99	2.96	1.44×10^{-4}	-	−6.56
β- Fluordane	2.48	2.96	1.44×10^{-4}	-	−6.61
Aldrin	3.03	6.07	Insoluble	CYP3A4	−6.19
		$(6.50)^c$	$(4.66 \times 10^{-8})^d$		
F-aldrin	3.71	3.54	Insoluble	-	−6.83
Dieldrin	1.47	4.81	Insoluble	-	−4.99
		$(5.40)^c$	$(5.80 \times 10^{-7})^e$		
F-dieldrin	2.31	2.22	Insoluble	-	−6.21
Pentachloropheno	1.76	5.12	4.8×10^{-3}	CYP1A2	-
(PCP)		$(5.12)^f$	$(5.26 \times 10^{-5})^g$	CYP2C9	
Pentafluorophenol	2.15	2.91	0.39		-
(PFP)					

[a] Simpson et al. (1995); [b] Sanborn et al. (1976); [c] De Bruijn et al. (1989); [d] Dannenfelser and Yalkowsky (1991); [e] Biggar and Riggs (1974); [f] Hansch et al. (1995); [g] Yalkowsky and He (2003).

It is also possible to observe specific interactions, such as hydrogen bond and hydrophobic interactions, between picrotoxin and some amino acid residues in GABA$_A$ (Supplementary Material). Since the action mechanisms of picrotoxin and cyclodienes are similar, it is worth paying attention to these interactions in the picrotoxin-protein complex.

THR256 and SER267 residues are involved in hydrogen bonds with picrotoxin; at least one of these residues also interacts with all fluorinated bioisosteres (and also with dieldrin). These interactions determine the higher affinity of fluorinated compounds with the protein. Furthermore, the fluorinated derivatives presented a reasonable superposition with their chlorinated analogs, thus allowing for a direct comparison of the fluorinated bioisosteres with the corresponding chlorinated compounds. As an example, it is possible to observe more effective interactions (hydrogen bonds) in the protein/fluordane complex than in the protein/chlordane complex (Figure 3).
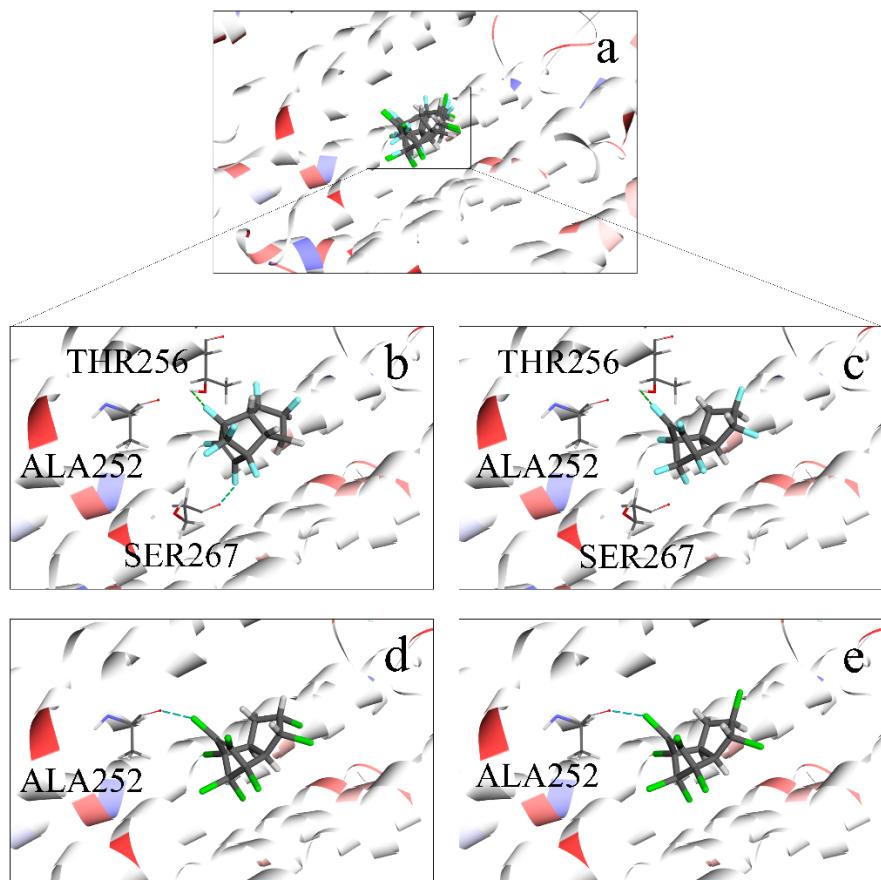
Figure 3. a) Superposition of chlordane and fluordane inside the binding site of GABA$_A$; b) and c) specific interactions of α- and β-fluordane, respectively, in the binding site of GABA$_A$; d) and e) specific interactions of α- and β-chlordane, respectively, in the binding site of GABA$_A$. ALA = alanine, SER = serine, and THR = threonine.

These outcomes are supported by other aromatic and alicyclic organochlorines, whose fluorinated analogs resemble the same advantages of fluordane over chlordane. Accordingly, dieldrin and its synthetic precursor, aldrin, as well as their respective fluorinated derivatives (F-dieldrin and F-aldrin), were further analyzed on the basis of their potential toxicity, environmental risk and insecticidal potency (Table 1). Pentachlorophenol (PCP) and its fluorinated analog pentafluorophenol (PFP) were also evaluated, except for their insecticidal

potential, because the mode of action of phenol insecticides is rather dictated by an oxidation mechanism (Michałowicz and Duda, 2007). The hydrophobicity of the fluorinated analogs is lower than that of the corresponding chlorinated compounds, while the water solubility is higher. Cytochrome inhibition appeared only for the chlorinated compounds; similar to cytochrome P450 3A4, the CYP1A2 and CYP2C9 enzymes (efficiently inhibited by PCP, according to Percepta predictions) are monooxygenases involved in the metabolism of compounds.

Persistence and toxicity are major topics to be accounted for when designing performance pesticides. Some studies have established a critical role for lipophilicity on the bioconcentration (BCF), bioaccumulation (BAF) and biomagnification (BMF) factors of organochlorines in fish species (Thomann, 1989; Moses et al., 2015; Arnot and Gobas, 2003), whilst others included additional descriptors to encode persistence-related parameters, such as molecular weight and topological polar surface area (Fatemi and Baher, 2009; Miller et al., 2019). According to Thomann (1989), food chain effects are not significant up to log P of *ca.* 5, while for log P of 5-7, calculated and observed BCF´s in top predators indicate significant elevations above calculated field BCF values; above log P of 7, food chain effects are sensitive to the chemical assimilation efficiency and phytoplankton BCF. Therefore, according to the experimental and calculated log P values in Table 1, the fluorinated pesticides would be advantageous over their chlorinated analogs, as the organofluorines exhibit log P values below 5, while the corresponding organochlorines all have log P between 5 and 7.

Pierre et al. (2019) developed a predictive QSAR model for the estimation of toxicity data (log LC_{50}, LC_{50} = lethal concentration required to kill 50% of a population of *Poecilia reticulata*, the rainbow fish) of a series of organochlorine compounds using quite a few molecular descriptors. This model applies log P, index of refraction (IR), surface tension (ST), density (d), and polarizability (pol) as molecular descriptors in the following multilinear regression equation (1):

$$\log LC_{50} = 9.95 - 0.11 \times \log P - 3.31 \times IR + 0.03 \times ST - 0.73 \times d - 0.22 \times pol \quad (1)$$

$N = 50$; $R^2 = 0.90$; $MSE = 0.12$; $R^2_{adj} = 0.89$; $R^2_{CV} = 0.89$

The calculated molecular descriptors obtained through the ACD/Labs program for the studied compounds were used in the equation above, thus yielding the predicted log LC_{50} values of Table 2. According to this model, the most toxic compound is assumed to display the smallest log LC_{50} value, that is chlordane. Actually, the chlorinated compounds were all calculated to be

more toxic than the fluorinated analogs, therefore confirming organofluorines as promising alternatives for chlordane, Aldrin and Dieldrin.

Table 2. Molecular descriptors and predicted toxicity (log LC_{50}) for the organochlorine pesticides and their respective fluorinated analogs.

Compound	log P	IR	ST (dyne cm^{-1})	d (g cm^{-3})	Pol ($\times 10^{-24}$ cm^3)	log LC_{50}
Chlordane	5.96	1.63	54.0	1.80	31.82	-2.8
Fluordane	2.96	1.40	20.9	1.58	16.87	0.8
Aldrin	6.07	1.66	55.3	1.73	30.81	-2.6
F-aldrin	3.54	1.48	27.6	1.54	19.60	0.1
Dieldrin	4.81	1.68	60.2	1.84	30.71	-2.4
F-dieldrin	2.22	1.50	30.6	1.68	19.50	0.1
PCP	5.12	1.63	54.7	1.80	20.85	-0.3
PFP	2.91	1.43	31.4	1.69	11.14	2.2

Overall, prospective next-generation organofluorine agrochemicals have been explored and they are expected to display a better performance than their chlorinated analogs. Future challenges include the synthesis of fluorinated derivatives of known chlorinated pesticides and further comparison of their potency and physicochemical parameters related to toxicity and environmental persistence with the chlorinated compounds. This seems to be feasible, since *e.g.* a route to obtain the all-*cis*-hexafluorocyclohexane, a fluorinated stereoisomer of the insecticide lindane (γ-hexachlorocyclohexane), has already been developed (Keddie et al., 2015) and its preparation is currently quite straightforward (Wiesenfeldt et al., 2017). Indeed, preparation of perfluorocyclopentadiene has long been known (Banks et al., 1965; 1967).

CONCLUSIONS

Although the proposal of fluordane as a new pesticide was not the pivotal goal in this study, the bioisosteric switch of chlorine with fluorine atoms may be beneficial in all cases, either by accounting for the predicted bioactivity (once the stability of the compounds inside the biding site of GABA$_A$ is enhanced) or environmental impact (a lower bioaccumulative capability is expected). Facing these results, fluordane can indeed be considered an example of

compound that opens the possibility of studying other organofluorines as a novel benchmark class of pesticides.

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Theoretical exploitation of 1,2,3,4,5,6-hexachloro- and 1,2,3,4,5,6-hexafluorocyclohexane isomers as biologically active compounds

(Submitted)

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Abstract: Hexachlorocyclohexanes (HCHs) have been widely explored as biological compounds during the last century. However, most of them were banned due to their potential toxicity in humans, animals, and the environment. Revisiting HCHs to explore their biological activity while improving key features is valuable and may lead to a new class of pesticides that utilizes the biological response of HCHs without their toxic characteristics. In this sense, the fluorine atom can be a possible alternative since a large number of therapeutics and agrochemicals have been developed with this halogen in their structure. We have evaluated herein the conformational behavior of HCHs and their bioisosteric fluorinated compounds, namely, hexafluorocyclohexanes (HFHs), through quantum-chemical calculations. We also explored the potential of the HCH and HFH isomers as biological compounds by docking them inside three possible targets. It was demonstrated that HCH and HFH have similar ligand–protein interactions with three pockets: the picrotoxin and barbiturate sites of the $GABA_A$ receptor and the ryanodine receptor. The results support HFHs as possible alternatives for HCHs since the replacement of Cl with F does not forfeit the main ligand–protein interactions. Finally, we demonstrated that HFHs have a lower log P than HCHs by almost two logarithmic units. This result highlights the role of fluorine in distribution and bioaccumulation.

Introduction

Over the past decades, the increasing number of agrochemicals in use indicates the critical role of these compounds in the development of society. While new molecules have been proposed or improved, the use of a variety of chemicals *such as* organochlorines has been restricted due to health and environmental issues, .[1] Organochlorines used to be widely employed in pest control during the mid-20th century.[2] However, the indiscriminate use of these compounds leads to severe ecological problems. Organochlorines have shown high mobility since trace amounts are present in places where they have never been used before around the globe.[3] Likewise, the toxicity of organochlorines extends to mammals, and the effects can be pronounced in humans due to bioaccumulation and biomagnification through the food chain.[4] In addition, risks are related to the relative ease of C–Cl bond cleavage, which leads to distinct metabolites that can be even more toxic than the original molecule.[5] Despite the serious issues related to organochlorine compounds, they have performed well against crop plagues.[6] In this sense, taking advantage of the biological activity of these compounds while mitigating the

toxicity can lead to new molecules with high potential in agrochemistry. Therefore, revisiting molecules and optimizing parameters to improve biological properties is necessary since pest control is challenging and food demand is high.

Organochlorine pesticides are classified into three main classes, namely, dichlorodiphenylethanes, cyclodienes, and hexachlorocyclohexanes (HCHs);[7] the latter is the focus of this work. The HCH class is represented by eight diastereomers (Figure 1). These molecules are six-membered rings in which each carbon has one chlorine attached, that is, the isomers differentiate from each other only by their spatial orientation, not by their positions.[8] This fact makes the study of these compounds through ligand-based approaches challenging since only subtle structural changes explain the variance in the biological response in different targets.[9] However, structure-based modeling studies are valuable for gaining insight into the binding modes of these compounds. As mentioned, the stereochemistry of these compounds plays a pivotal role in bioactivity. For example, delta- and beta-isomers have a depressant response, while the gamma-isomer (lindane) is a widely known pesticide with stimulant properties.[10] Additionally, some HCH isomers have unknown biological properties and have never been synthesized (*e.g.,* ζ-HCH), so they can be further explored.
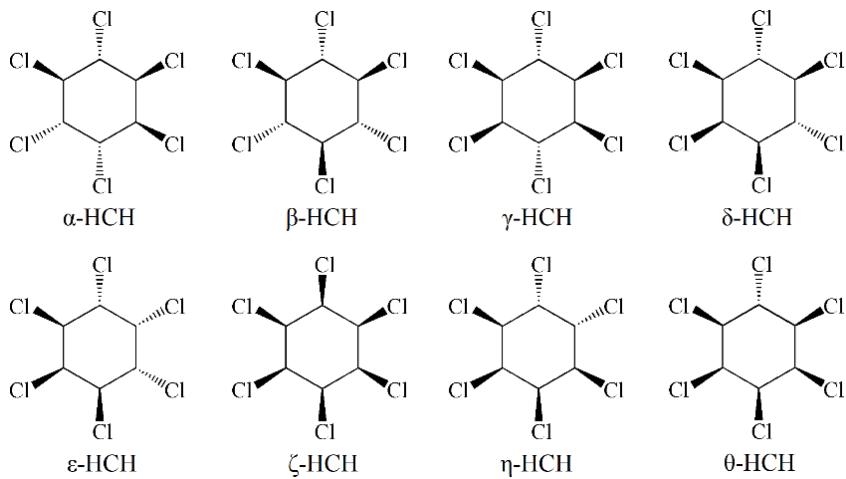
Figure 1. Diastereomers of 1,2,3,4,5,6-hexachlorocyclohexanes (HCHs).

HCH molecules may act on many targets and produce different biological responses, but their mechanisms of action remain poorly understood. For instance, lindane (γ-HCH) has been used as an agricultural insecticide and pharmaceutical treatment for lice and scabies, and it has stimulant properties.[11] Unlike cyclodienes, lindane is a poor inhibitor *via* GABA receptors, and its biological properties are related to releasing calcium rather than avoiding chloride influx by targeting the picrotoxin site.[12] δ-HCH is a non-insecticide isomer with depressant effects, but it can act as a stimulant at higher doses. In addition, the effects of both

lindane and δ-HCH are dose-dependent in GABA receptors.[10] On the other hand, α- and β-HCH are more toxic than lindane and lack insecticidal activity.[13]

Studies suggest that some HCHs act in the picrotoxin site as organochlorine cyclodienes and are responsible for the excitatory response due to disruption in chlorine influx to the cell; on the other hand, depressant effects are due to the interaction of HCHs with the barbiturate site of the GABA receptor.[14] Although the interaction with GABA receptors is well known, alternative targets and mechanisms of action are expected to produce the same HCH response since lindane is one of the least active pesticides inhibiting GABA-dependent chlorine uptake.[15] HCHs have a lipophilic character; consequently, they interact with intracellular components. In this sense, intracellular calcium storage is an important component responsible for muscle contraction. Signaling occurs by releasing Ca^{2+} from the intracellular storage.[16] Several studies report HCH molecules acting in intracellular calcium channels and producing an excitatory response, making intracellular calcium storage signaling one of the possible alternative mechanisms of action of HCH compounds.[17]

There are two major intracellular calcium channels: the ryanodine receptor (RyR) and the inositol (1,4,5)-triphosphate receptor (InsP$_3$R). These receptors are responsible for intracellular calcium modulation.[18] Some observations support the HCH action over the Ca^{2+} channel. For example, dantrolene is a RyR inhibitor that inhibits intracellular calcium release in the cell. When dantrolene is applied with lindane, no convulsant effect is observed, indicating that the action of the lindane is related to this specific receptor.[19] Furthermore, InsP$_3$R has an endogenous ligand [inositol (1,4,5)-triphosphate], and its ring shares a similar stereochemistry as δ-HCH, which makes InsP$_3$R a natural receptor for HCH. In addition, it has been shown that δ-HCH is capable of releasing Ca^{2+} cations from both receptors. [12b,20]

While chorine may be hazardous for biological and environmental systems,[21] organofluorine compounds have been widely employed as bioactive chemicals.[22] It has been estimated that almost 30% of agrochemicals and therapeutics in use worldwide contain at least one fluorine atom.[23] This element provides interesting features for biological compounds in terms of pharmacokinetics and pharmacodynamics.[24] It is worth mentioning that the C–F bond is highly polarized; consequently, it has a minor potential for bioaccumulation and biomagnification compared to the C–Cl bond since having fewer lipophilic molecules makes the compound less prone to interactions with the cell's phospholipid bilayer.[25] For these reasons, replacing chlorine atoms with fluorine is an intuitive way to explore organochlorine optimization.

Therefore, the arguments presented give us intriguing topics to observe for future applications of HCHs and their fluorinated bioisosteres—hexafluorocyclohexanes (HFHs). In this sense, we report herein the evaluation of HCHs and their fluorinated bioisosteres to gain insight into the protein–ligand interactions and the possible effects of chlorine replacement. Furthermore, HCHs have different stereochemistries that can be employed to explore the role of the chemical space in biological activity. The last topic we investigated was the characteristics of all HCH diastereomers since not all HCHs have well-understood biological properties.

Results and Discussion

Conformational Analysis

The replacement of one hydrogen in each carbon of cyclohexane produces 1,2,3,4,5,6-hexasubstituted rings. The highly substituted pattern creates a significant number of isomers with distinct configurational and conformational isomerism, where the conformers can interconvert through ring flip inversion (Figure 2). In this study, we evaluate the conformational preferences of eight diastereomers of 1,2,3,4,5,6-hexachloro- (HCH) and 1,2,3,4,5,6-hexafluorocyclohexane (HFH), namely, α-, β-, γ-, δ-, ε-, ζ-, η-, and θ-isomers, through *ab initio* calculations. It is known that substituents in cyclohexane rings adopt axial or equatorial positions, and their preference is ruled by steric, dipolar, and hyperconjugative interactions. Additionally, it is generally accepted that substituents in equatorial positions attenuate the 1,3-dipolar and steric repulsion, while hyperconjugative interactions can favor axial or equatorial groups.[26] Therefore, the conformational behavior is dictated by these competing factors.
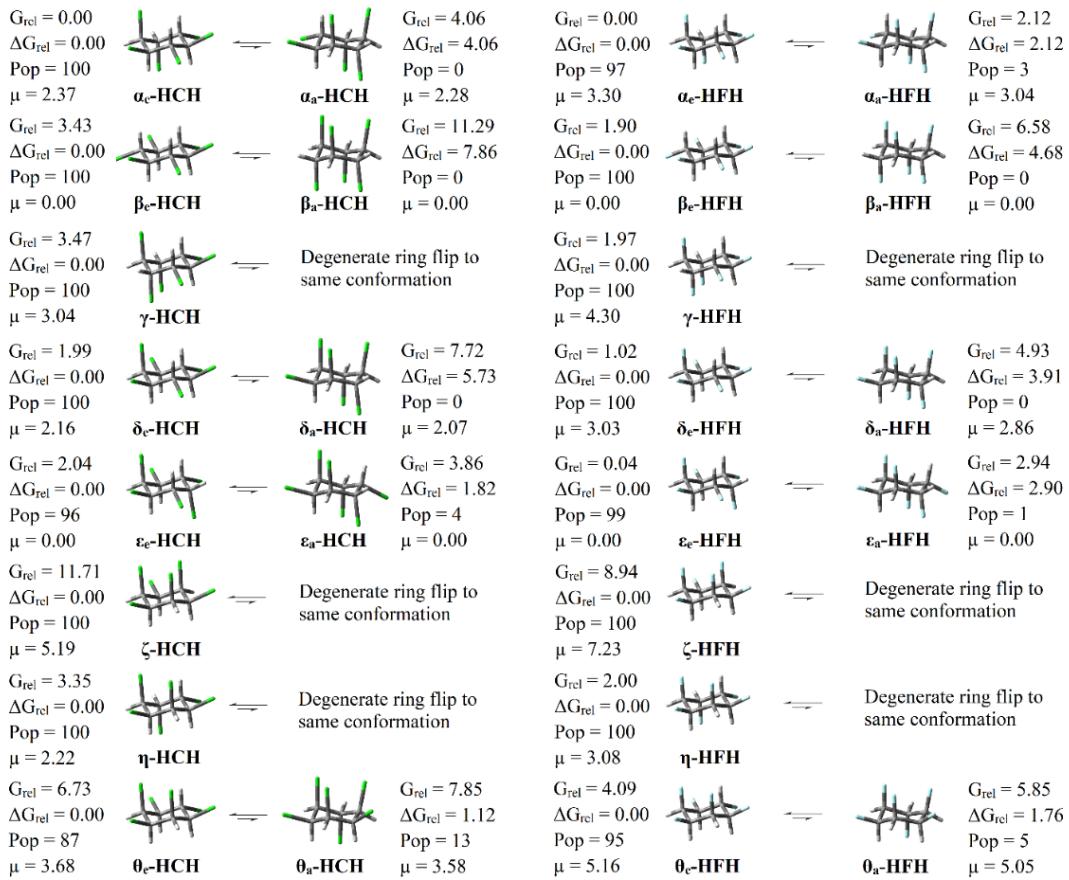
Figure 2. All eight isomers, α, β, γ, δ, ε, ζ, η, and θ, of HCH and HFH in the chair form and their conformational flip. The relative conformational Gibbs free energies (ΔG_{rel}), and relative configurational Gibbs free energies (G_{rel}) are given in kcal mol^{-1}, conformational population in %, and dipole moment in debye (Db). Data obtained through calculations at the MP2/6-311++g(d,p) level. Labels: H = white, C = gray, F = cyan, Cl = green.

The results are straightforward about the chair flip isomerism of HCH and HFH diastereomers since the equilibrium is shifted to conformers with more substituents in equatorial positions. For example, the α-diastereomer is found to be in equilibrium between two chairs, named **α$_e$** and **α$_a$**. The subscripts **e** and **a** denote a chair with predominant equatorial and axial substituents, respectively. The equilibrium is completely shifted toward conformer **α$_e$**, which has two axial and four equatorial halogens (Figure 2). This observation extends to all compounds in the gas phase, since the least stable equatorial conformer shows a population of 87% (**θ$_e$-HCH**). These findings suggest a high cost to conformers bearing more axial groups in the ring flip inversion.

Despite the clear conformational behavior of HCHs and HFHs, by inspecting the whole set of isomers, it is possible to observe that **βe**, the most equatorially substituted ring, is not the lowest energy isomer. This observation demonstrates that all groups in equatorial regions do

not ensure a higher stability to the molecule; however, a balance between axial and equatorial groups seems to dictate the molecular stability. The conformer δ_e-HCH (G_{rel} = 2.0 kcal mol^{-1}) has one axial halogen; and is less stable than α_e-HCH (G_{rel} = 0.0 kcal mol^{-1}) and more stable than β_e-HCH (G_{rel} = 3.4 kcal mol^{-1}), which have two and zero halogens in the axial position, respectively. This fact indicates that two axial halogens are the ideal number to produce stability in the chairs in 1,2,3,4,5,6-hexachloro- and 1,2,3,4,5,6-hexafluorocyclohexanes.

A closer inspection of α_e, ε_e, and θ_e is insightful since they differ in relative configurational energy but share the feature of two axial and four equatorial halogens. The conformers α_e and ε_e have their axial substituents in an antiparallel orientation, while in θ_e, these groups are parallel. This fact explains why θ_e lies in a higher energy level, since both C–X bonds are on the same side of the ring, and it provides more steric/electrostatic repulsion than conformers with both bonds on opposite sides. According to natural bond orbital (NBO) analysis, steric/electrostatic effects are the primary factor governing the energy differences among diastereomers since the total energy (E_{Full}) is dictated by the Lewis energy component (E_{Lewis}); see Supporting Information. The E_{Full} is divided into two terms: one relative to classical factors, E_{Lewis}, and a second relative to delocalization effects, $E_{non\text{-}Lewis}$. By inspecting the energy components, it is possible to observe that the most stabilizing $E_{non\text{-}Lewis}$ term is unable to generate a minimum E_{Full} due to the higher E_{Lewis} value. However, hyperconjugative effects may play a critical role in determining the preference of α_e over ε_e. For example, both α_e-HCH and ε_e-HCH have the same substitution pattern, but the vicinal axial groups are preferred since α_e is 2.0 kcal mol^{-1} more stable than ε_e. This preference can be attributed to the interactions of the σ_{CCl} and σ^*_{CCl} orbitals of axial chlorine with vicinal bonds. In the α_e isomer, each axial chlorine experiences one $\sigma_{CH} \rightarrow \sigma^*_{CCl}$ (6.35 kcal mol^{-1}), one $\sigma_{CCl} \rightarrow \sigma^*_{CH}$ (1.74 kcal mol^{-1}), and two $\sigma_{CCl} \rightarrow \sigma^*_{CCl}$ (3.79 kcal mol^{-1}) interactions, while the ε_e isomer exhibits two $\sigma_{CH} \rightarrow \sigma^*_{CCl}$ (1.78 kcal mol^{-1}) and two $\sigma_{CCl} \rightarrow \sigma^*_{CH}$ (5.78 kcal mol^{-1}) interactions. In this sense, α_e comprises 15.47 kcal mol^{-1} of stabilization, while ε_e comprises 15.12 kcal mol^{-1} of stabilization.

The results are in good agreement with previous reports on the conformational analysis of HCH and HFH.[27] In addition, several studies indicate that steric and dipolar factors rule the conformational isomerism of dihalocyclohexanes, while hyperconjugative interactions play a secondary role.[28] In this sense, a comparison between HCH and HFH can be useful to decide whether steric or electrostatic effects are the primary source for the energetic profile of the 1,2,3,4,5,6-hexa-halogenocyclohexane isomers. Fluorine is smaller than chlorine and provides more polar bonds since it is a more electronegative atom. Therefore, the replacement of chlorine

with fluorine works as a tool to evaluate the competing steric/electrostatic factors responsible for the 1,2,3,4,5,6-hexa-halogenocyclohexane isomers. If steric factors are the primary contributor to the molecular stability, the replacement will increase the ring stability; on the other hand, if dipolar repulsion is the source of the energetic behavior, the fluorine atoms will cause a decrease in stability.

Accordingly, all fluorinated compounds have lower G_{rel} values than their HCH analogs and show higher dipole moments, except for those with zero dipole moments (Figure 2). For example, G_{rel} ranges from 0.00 to 11.71 kcal mol^{-1} in the HCH series, while the corresponding range in HFH decreases by almost 3 kcal mol^{-1} (0.00 to 8.94 kcal mol^{-1}). Therefore, steric repulsion among halogens dictates the molecular preferences. Previous reports evaluating 1,2-difluoro-, 1,2-dichloro-, and 1,2-bromocyclohexane demonstrated the role of steric repulsion in the axial–axial (aa) preference. It was shown that the 1,2-dihalocyclohexane preference for the aa conformer increases from fluorine to bromine substituents; therefore, by increasing the halogen size, the aa population increases due to steric hindrance in the ee conformer.[28a] In our case, the high substitution pattern provides a more complex conformational behavior, in which all axial or all equatorial substituents are not the most stable forms.

Finally, an analysis was carried out considering the HCH and HFH isomers in an implicit water environment through the polarizable continuum model (PCM). This analysis aids the evaluation of the compounds in polar media and gives more insight into the steric/electrostatic effects. Because steric repulsion has been found to be the main source of molecular stability, polar solvents are expected to favor conformers with higher dipole moments without drastically changing the stability profile, since steric effects, not electrostatic effects, contribute the most to the molecular preferences. The observation is still the same for HCH in water compared to HCH in the gas phase, with small changes (e.g., $\mathbf{\eta}$ and $\mathbf{\beta_e}$ have almost the same G_{rel}; however, $\mathbf{\eta}$ is more stable in the gas phase, while $\mathbf{\beta_e}$ is more stable in water). It is possible to observe an increase in ΔG_{rel} for HCH and HFH molecules in water. This increase is a consequence of the polar medium acting in favor of the conformer with a higher dipole moment (Supporting Information). For the fluorinated compounds, the solvent effect is more pronounced since fluorine ensures more polar bonds and produces a higher dipole moment and, in general, the conformational energy range decreases in conformers with more equatorial substituents. In other words, electrostatic effects from the solvent affect fluorinated compounds more than chlorinated compounds. However, molecular stability is governed by steric factors, so the configurational energy profile does not change significantly in water.

Docking Study

The biological activity of HCHs varies with the diastereoisomers and doses; for example, δ-HCH exhibits depressant effects at lower doses, but it is a stimulant at higher doses. Furthermore, γ-HCH (lindane) is related to GABA receptor inhibition, while α-HCH and β-HCH seem to act poorly in this regard. The picrotoxin and barbiturate sites are mentioned in the literature as possible targets for HCH in chloride flux modulation in the GABA receptor.[14] On the other hand, some studies suggest intracellular calcium storage as the source of the HCH biological response.[17] Since our goal is to evaluate the impact of chlorine replacement, and due to the unclear target for HCHs, we explore the interaction of HCHs and their fluorinated bioisosteres (HFHs) with a few different proteins to determine their potential to cause a biological response. The proteins studied in this work are the human $GABA_A$ receptor, human-type 3 1,4,5-inositol triphosphate ($InsP_3R$), and human ryanodine receptor 3 (RyR). PDB ID codes of 6X40 and 6X3W for $GABA_A$, 6DQN for $InsP_3R$, and 4ERV for RyR were used for docking purposes. We chose human proteins because the three targets are available simultaneously, which allows us to compare the ligand interactions in the same species.

All HCH and HFH isomers were docked into the picrotoxin and barbiturate sites of $GABA_A$, $InsP_3$, and ryanodine receptors. The results show that $InsP_3R$ provides a poor ligand–protein interaction with hexahalocyclohexanes, and among all receptors, it has the lowest docking score values (best D_{score} = -1.30 kcal mol^{-1}) (Supporting Information). Moreover, the superposition of HCH and HFH with the cocrystallized ligand is not efficient, even with the same ring core. This finding indicates that other targets may be responsible for the HCH mechanism of action. The interactions of halogenated cyclohexanes with RyR and $GABA_A$ yield almost the same level of energy. The docking scores in the picrotoxin site range from -3.0 to -4.2 kcal mol^{-1}, -3.4 to -4.7 kcal mol^{-1} in the barbiturate site, and -2.6 to -3.7 kcal mol^{-1} in the RyR site (Figure 3). The docking results do not allow us to properly conclude which target is responsible for the HCH activity, since the interactions in all of them are close in energy, and other factors beyond ligand–protein interaction may be critical to bioactivity. However, these findings indicate that the three binding sites are prone to bind in almost the same manner. Since our primary goal is to explore the bioisosteric replacement of chlorine by fluorine atoms, we will further discuss the differences between HCH and HFH in each target.

In the picrotoxin site of the $GABA_A$ receptor, HCH and HFH isomers do not differ significantly in interaction energy, since no clear preference has been observed for fluorinated or chlorinated molecules in the pocket. In addition, the maximum energy difference is 0.5 kcal

mol^{-1}; for example, **α$_e$-HCH** interacts with an energy of -3.72 kcal mol^{-1}, while the corresponding value for **α$_e$-HFH** is -3.80 kcal mol^{-1}. The only exception is the ζ-isomer, in which the fluorinated molecule binds more effectively than the chlorinated molecule by 1.0 kcal mol^{-1} (Figure 3). The observation does not change appreciably in the barbiturate site of the GABA$_A$ receptor and RyR. However, there is a slight preference for HFH isomers in these two pockets (Figure 3). The docking results are insightful about chlorine replacement with fluorine in 1,2,3,4,5,6-hexahalocyclohexanes. Since the interaction energies do not change drastically, the bioisosteric replacement of chlorine with fluorine does not forfeit the ligand–protein interaction and can be further explored.
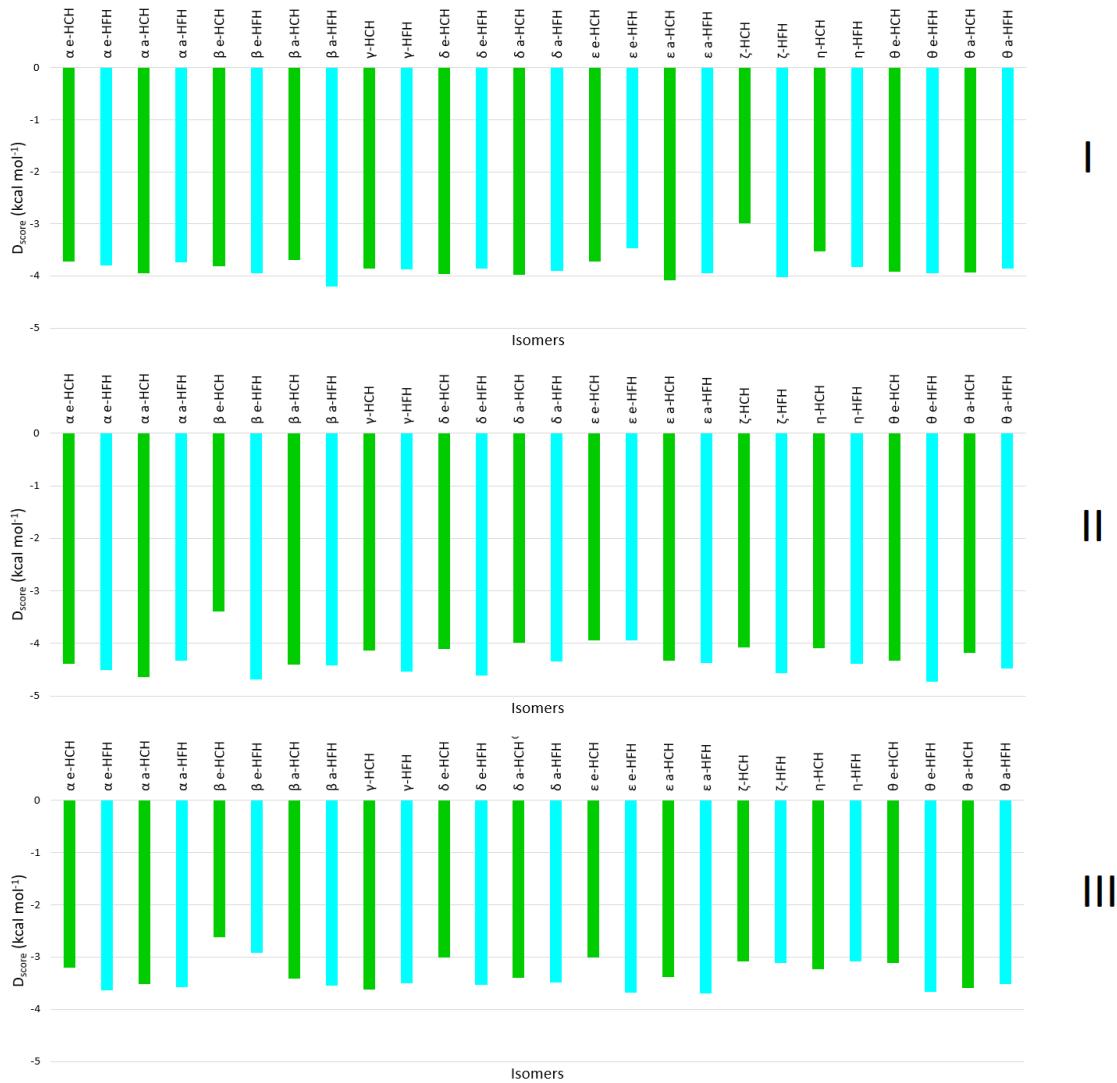
Figure 3. HCH (green) and HFH (cyan) docking scores computed for all isomers in the picrotoxin binding site of GABA$_A$ receptor (I), barbiturate binding site of GABA$_A$ receptor (II), and RyR (III).

The evaluation of specific ligand–protein interactions supports the idea that HFHs are suitable alternatives for HCH since these molecules share similar types of interactions in the

protein pockets. In the picrotoxin site, not all chlorinated and fluorinated molecules display interactions with residues, but if present, most of the interactions are halogen interactions with carbonyl or CH groups. However, in the barbiturate and RyR pockets, all molecules show at least one ligand–protein interaction. In this case, beyond halogen-carbonyl and halogen-HC interactions, it is possible to observe classical hydrogen bonds (X•••HO) and R•••R interactions (Figure 4).
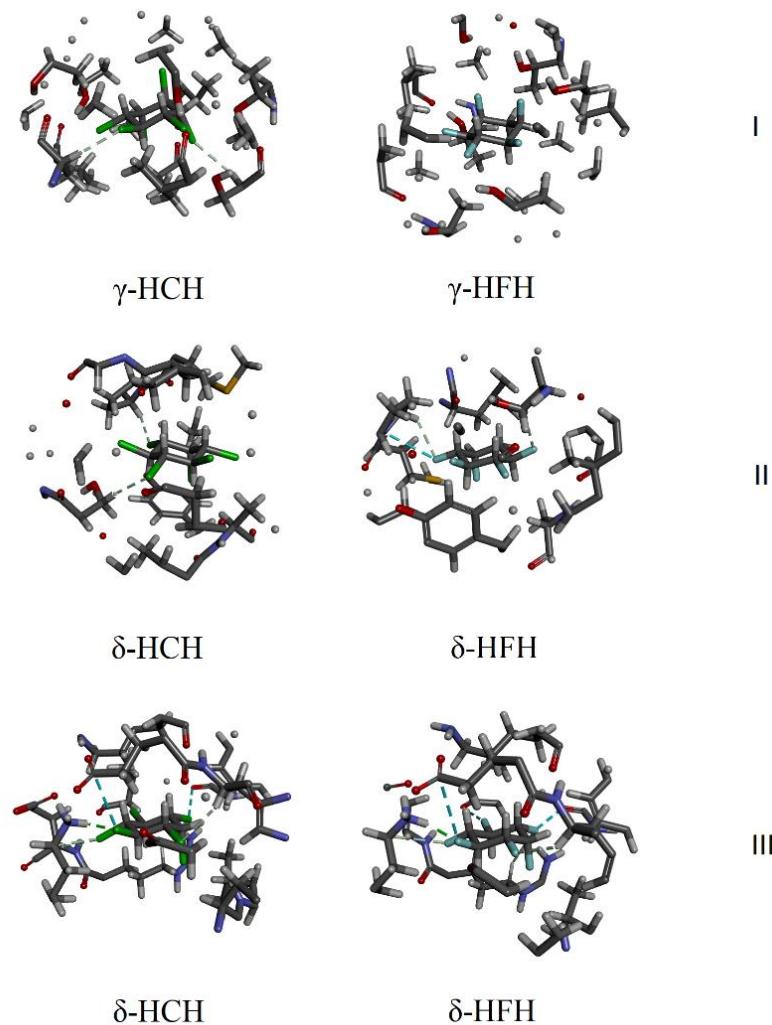
Figure 4. Receptor pockets of GABA$_A$ receptor and RyR. Specific ligand-protein interactions for γ-HCH and γ-HFH in the picrotoxin pocket of GABA$_A$ receptor (I). Specific ligand-protein interactions for δ-HCH and δ-HFH in the barbiturates pocket of GABA$_A$ receptor (II). Specific ligand-protein interactions for δ-HCH and δ-HFH in the pocket of RyR (III). H = white, C = gray, N = blue, F = cyan, Cl = green, O = red, S = yellow, X···HO/N interaction = green dashed line, X–HC interaction = gray dashed line, X–π$_{C=O}$ interaction = cyan dashed line. Note that the γ isomer interacts in the picrotoxin site to cause an excitatory response, while its δ isomer acts in the barbiturate site to cause depressant effects. On the other hand, it is known that δ binds to the RyR site. This explains the choice for the exemplification in this Figure.

Since all isomers show similar affinity to the protein amino acid residues, parameters other than the ligand–protein interaction may be responsible for the difference in the biological activity of the HCH compounds. Pharmacokinetics plays an essential role in drug response because it is related to the movement of a drug through the organism. Therefore, evaluation of pharmacokinetic features for these compounds may be valuable. It has been found that the solubility of HCHs in phospholipids and the degree of inhibition of phosphatidylinositol synthase and other membrane-associated enzymes follow the same order ($\delta > \gamma > \alpha > \beta$).[29] This fact reinforces the crucial role of pharmacodynamics over HCH biological activity. The octanol-water partition coefficient described in terms of log P is an important parameter that gives information about the drug distribution through the body. Despite its experimental nature, it is possible to estimate log P using computational tools. However, most of the computational methods are based on additive contributions from molecular fragments; therefore, it is difficult to predict the log P values for isomers. For this reason, we indirectly evaluate the log P values of the HCH and HFH isomers through quantum-chemical calculations.

The octanol-water partition coefficient (K_{OW} or P) provides a way to measure the molecular affinity for the organic phase since it is defined as the substance's concentration ratio in two phases (octanol and water) when the system achieves equilibrium.[30] It is a ubiquitous parameter in medicinal chemistry and agrochemistry since it is related to drug distribution and chemical fate. Moreover, log P provides a way to estimate the potential of bioaccumulation of chemical compounds, e.g., molecules with log $P > 5$ are known to have a high potential for bioaccumulation, while this feature is less pronounced in compounds with log $P < 2$.[31] The log P for the HCH isomers in the literature is slightly divergent, and generally, this value falls within the range of 3.50 and 4.50, depending on the measurement procedure. For example, the log P for lindane has been reported to be 3.30–3.61 experimentally and 3.83–4.26 theoretically. The same is observed for other isomers, such as α-, β-, and δ-HCH,[32] which is in agreement with our findings (Table 1).

Although the predicted log P values show a small range for the chlorinated isomers, it is valuable for comparison with the HFHs. The fluorinated compounds show a clear decrease in the lipophilicity, since the log P lies in the range of 1.0–2.3, while the corresponding values for the HCHs are higher than 3. This feature provides HFHs with a lower bioaccumulation potential than HCHs. It is worth noting that the all-*cis* isomer (ζ) possesses the smallest log P, but to the best of our knowledge, the corresponding HCH is the only 1,2,3,4,5,6-hexachlorocyclohexane not yet prepared, perhaps due to its low stability (it is the least stable

HCH isomer, Figure 1). However, ζ-**HFH** has been formerly synthesized through a multistep reaction,[33] and can be obtained by a straightforward procedure.[34] In addition to its potential application as a cation and anion carrier,[35] ζ-**HFH** has been found to be one of the most promising barbiturate and RyR inhibitors among HFHs (Figure 3). Therefore, ζ-**HCH** is both synthetically challenging and biologically interesting to study.

Table 1. Theoretical prediction of log P for each diastereomer (weighted by the conformational populations) performed at the ωB97XD/6-311++g(2d,p) level of theory for the hexachloro- and hexafluorocyclohexanes.

Diastereomer	HCH log P	HFH log P
α	4.54 (3.94)[a]	2.26
β	3.89 (3.92)[a]	1.74
γ	4.43 (3.83)[a]	2.20
δ	3.93 (3.19)[a]	1.93
ε	4.26	2.04
ζ	3.25	1.03
η	4.31	2.08
θ	3.74	1.58

[a] Computationally predicted log P by Hale *et al.*[32a]

Methodology

The HCH and HFH diastereomers and their possible chair-flip conformers were fully optimized with vibrational frequencies accounted for using the *ab initio* MP2/6-311++g(d,p) level of theory,[36] both in the gas phase and when considering an implicit polar solvent (water) through the polarizable continuum model (PCM).[37] This step was carried out to gain insight into the ring stabilities and the conformational flip on molecules capable of establishing conformational isomerism. In this step, we also computed the molecular dipole moments. We performed a second set of calculations in the ωB97XD/6-311++g(2d,p) level of theory[38] to determine the octanol-water partition coefficient. In this step, we also considered the implicit solvent model. However, we employed the solvation model based on density (SMD) using the SMD keyword. SMD has been attributed to performing better in the prediction of solvation free energy (ΔGw and ΔGo),[39] which was used to estimate the log P according to Equation 1.[40] Since each conformer had one ΔGw and ΔGo and, consequently, a given log P, the log P for each diastereoisomer could be calculated by conformationally weighing the log P. These values are presented in Table 1. It is worth mentioning that the choice for the DFT method was based

on a reduced computational cost compared to the MP2 method. All described calculations were carried out using the Gaussian 09 package.[41]

$$\log P = \frac{\Delta G w - \Delta G o}{2.303 RT} \qquad (1)$$

The docking studies were performed using the Schrödinger suite 2011 with the OPLS2005 force field.[42] The first step was ligand preparation, in which MP2-optimized HCH and HFH structures were employed. We determined the molecular charges through the B3LYP/6-311++g(d,p) level of theory[43] using the electrostatic potential scheme of CHELPG with the Gaussian 09 program.[41,44] The second step was protein preparation; in this step, we obtained crystal structures of the human $GABA_A$ receptor in a complex with picrotoxin, the $GABA_A$ receptor in a complex with GABA and phenobarbital, the type-3 1,4,5-inositol triphosphate receptor (InsP3) in a complex with D-myo-inositol-1,4,5-triphosphate, and ryanodine receptor 3.[45] The PDB IDs (and protein resolution) are 6X40 (2.86 Å), 6X3W (3.30 Å), 6DQN (3.33 Å), and 4ERV (1.75 Å), respectively. After the protein acquisition and using the protein preparation wizard,[46] all missing hydrogens, side chains, and loops were included, and bond orders were assigned. All water molecules and hetero groups were deleted.

With all proteins properly prepared, we used the Receptor Grid Generation module of the Schrödinger suite to build the receptor grid. Here, two slightly different procedures were employed for grid generation. Since $GABA_A$ and InsP3 receptors include cocrystallized ligands, the receptor grid was generated based on cocrystallized ligands. Picotoxin, phenobarbital, and D-myo-inositol-1,4,5-triphosphate were used for this purpose. In addition, due to the presence of the cocrystallized ligand, it was possible to redock the model to validate the methodology. The redocking results show a respective RMSD and docking score of 0.62 Å and -5.81 kcal mol^{-1} for picrotoxin, 0.12 Å and -7.38 kcal mol^{-1} for phenobarbital, and 0.71 Å and -6.43 kcal mol^{-1} for D-myo-inositol-1,4,5-triphosphate. However, RyR did not include a cocrystallized ligand. For this reason, we employed the SiteMap tool[47] to determine the protein cavities that most likely act as receptors. For RyR, three pockets were generated with SiteScores of 1.01, 0.89, and 0.85. Because drug insertion sites should have a SiteScore higher than 1.00, we chose the first pocket for the docking studies. The results show that the first pocket is the largest at 213 Å² and has the highest volume of 394 Å³

Finally, all HCH and HFH isomers were docked in each receptor pocket using the Glide module with extra precision.[48] Here, we accounted for no ring inversion, since we manually built the possible conformers to evaluate each ring conformation.

Conclusion

The quantum-chemical calculations have shown a clear conformational behavior for HCH and HFH isomers. As expected from steric considerations, isomers that establish a conformational ring flip are preferred in rings with more halogens in the equatorial position. However, when comparing the diastereomers, neither **β$_e$-HCH** nor **β$_e$-HFH** are the most stable structures, which indicates that an overall energy minimum cannot be achieved if all substituents adopt the equatorial position. Therefore, a balance between the equatorial and axial substituents is needed, with the former in majority. According to experiments, **ζ-HFH** is by far the least stable isomer of HFH, while the unknown **ζ-HCH** is still higher in energy than its diastereoisomers, which makes it a challenging synthetic target.

The docking results showed that, except in the InsP$_3$ receptor, all isomers of HCH and HFH have a close docking score range in three pockets: the picrotoxin and barbiturate sites of the GABA$_A$ receptor and RyR. Although the literature is unclear about the primary target of HCH, our results demonstrated that the bioisosteric replacement of chlorine with fluorine atoms does not attenuate the ligand–protein interactions in these three possible targets. Moreover, such replacement can be beneficial to parameters related to bioaccumulation and distribution, such as log P, since HFHs have lower log P values than HCHs by almost two logarithmic units.

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An examination of the relationship between molecular dipole moment and blood-gas partition for common anaesthetic gases

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Abstract: The solubility of inhalational anaesthetics in the bloodstream is related to the minimum alveolar concentration (MAC), which is an indicator of anaesthetic gas potency. The blood-gas partition coefficient (K_{bg}) is a measure of how much anaesthetics bind to plasma proteins in the blood compared to air. Just like the octanol-water partition coefficient, the K_{bg} may be related to the molecular dipole moment (μ), which can be modulated by the molecular conformation. Our quantum-chemical calculations demonstrated that subtle stereoelectronic interactions, namely those responsible for the anomeric and *gauche* effects, control the conformational equilibrium of some widely used volatile fluorinated anaesthetics and, consequently, of their molecular dipole moments. Since a remarkable correlation between empirical K_{bg} and calculated μ was found for these anaesthetics, the average molecular dipole moments may be used to predict the anaesthetic gas potency and other properties, such as lipid solubility, of inhalational anaesthetic analogs.

Introduction

The anaesthetic potency of inhalational anaesthetics appears to be dictated by the affinity of these compounds to plasma proteins in the blood, although their mechanism of action is not completely known and it may be a physical rather than a chemical bonding process.[1] To access these plasma proteins, the volatile anaesthetics should be reasonably soluble in the bloodstream and, therefore, the Ostwald coefficient for blood-gas, or simply the blood-gas partition coefficient (K_{bg}), can be a valuable descriptor for the prediction of the anaesthetic potency. The anaesthetic gas potency may be described by the minimum alveolar concentration (MAC), which is correlated to K_{bg} according to Figure 1 for six last-generation fluorinated inhalational drugs.[2,3] However, the experimental measurement of K_{bg} may not be an easy task and, therefore, a straightforward method to obtain a parameter related to K_{bg} would be valuable for drug-likeness prediction purposes.

Linclau et al.[4] and then O'Hagan & Young[5] have recently found an interesting relationship between stereoelectronic effects and the lipophilicity of various fluorine-containing molecules, described as the octanol-water partition coefficient (log *P*). These studies

demonstrated that the lipophilicity of a molecule is related to its polarity, which is in turn governed by the molecular dipole moment (μ) balanced by the molecule's conformational populations. Since the conformational preferences of polar fluorocarbons are consistently driven by stereoelectronic effects, such as the fluorine *gauche* effect,[6] the authors concluded that lipophilicity informs on subtle stereoelectronic effects in fluorine chemistry. Indeed, the calculated average molecular dipole moments of a series of organofluorine herbicides have been properly correlated with the corresponding experimental log *P*; such correlation was even better than that obtained from calculated log *P* values instead of μ.[7] Therefore, a similar approach may be used to analyze the relationship between polarity and the K_{bg} of key fluorinated inhalational anaesthetics.
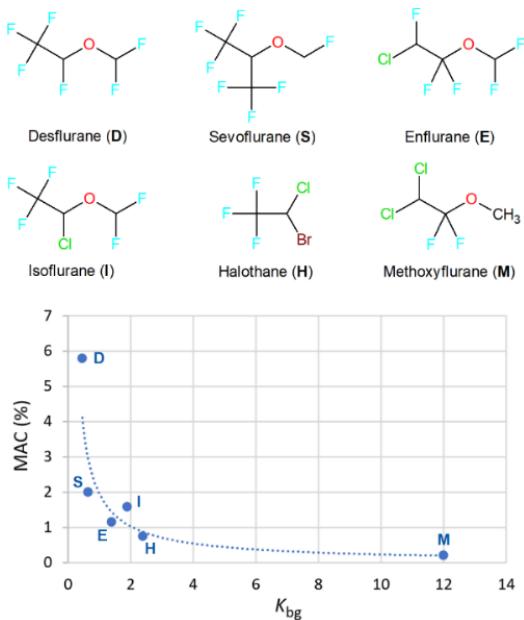
Fig. 1 Correlation between MAC (%) and blood-gas partition coefficients (K_{bg}) for six fluorinated inhalational anaesthetics (MAC = $1.958 \times K_{bg}^{-0.931}$, $R^2 = 0.923$).

The conformational behavior and experimental K_{bg} values for the six last-generation volatile anaesthetics of Figure 1 are well-known.[2,3,8-12] Since most of them possesses oxygen electron lone pairs (n_O), electron-donating bonds (for example, C–H and C–C), and low-lying energy antibonding orbitals (for C–X, X = O, F, and Cl), some stereoelectronic interactions may appear to stabilize the conformations with geometric requirements for orbital overlapping, such as the *gauche* effect (*e.g.* due to $\sigma_{C-H/C-C} \rightarrow \sigma^*_{C-F}$ hyperconjugation) and the anomeric effect (*e.g.* due to $n_O \rightarrow \sigma^*_{C-F/C-Cl}$ electron delocalization).[13] Organofluorine compounds are remarkable in stereochemistry for exhibiting the fluorine *gauche* effect, whose benchmark is the 1,2-difluoroethane

moiety. The surprising stability of its *gauche* conformer over the *anti* conformer is due especially to the antiperiplanar interactions between good electron-donating orbitals (σ_{C-H}) and low-lying energy electron-accepting orbitals (σ^*_{C-F}).[14] In turn, the generalized anomeric effect that takes place in the O–C–X fragment-containing molecules (X = electronegative atom or group) is also importantly stabilizing if a $n_O \rightarrow \sigma^*_{C-X}$ electron delocalization is allowed.[15] These non-Lewis-type interactions counterbalance the Lewis-type contributions stemming from steric and electrostatic interactions, thus yielding the conformational energy differences.[16]

Therefore, the average molecular dipole moments for each fluorinated inhalational anaesthetic of Figure 1 were obtained using *ab initio* calculations, rationalized in terms of the stereoelectronic interactions governing the conformational equilibria, and then correlated with K_{bg}. The outcomes may be useful for the modeling and prediction of new organofluorine compounds with anaesthetic properties.

Results and discussion

Whereas halothane (**H**) does not exhibit conformational isomerism, the remaining five fluorinated anaesthetics of Figure 1 (**D**, **S**, **E**, **I**, and **M**) undergo rotation around the dihedral angles ϕ_1 (H—C$_1$—O—C$_2$), ϕ_2 (C$_1$—O—C$_2$—C$_3$), and ϕ_3 (O—C$_2$—C$_3$—H, for **E** and **M**). The conformational Gibbs free energies for the main conformers of each compound are given in Table 1, and the optimized geometries for the whole series of compounds and respective conformers are shown in the ESI. The overall molecular dipole moment of a molecule is the summation of the individual dipole moment vectors originated from the polar bonds. If this molecule experiences conformational isomerism, the resulting molecular dipole moment corresponds to an average value of the conformations. Considering that stereoelectronic effects rule the conformational preferences of compounds in the gas phase, thus the observed molecular dipole moments are also influenced by the stereoelectronic interactions operating in the system. It is worth mentioning that solvent effects on the conformational preferences are in general small for at least most of the studied compounds,[8-10] and, considering that implicit solvation calculations do not account properly for specific solute-solvent interactions (*e.g.* hydrogen bonding), only the molecular dipole moments obtained for the gas phase conformers will be considered.

Table 1 Conformational Gibbs free energies (in kcal mol^{-1}) and population (%, in parenthesis), molecular dipole moments (μ, in Db), bond lengths (in Å), and dihedral angles (degrees) obtained for the main conformers of the studied fluorinated anaesthetic compounds (**C**).[a]

$C_{\phi1\phi2\phi3}$	G^0_{rel} (%)	μ	O–C$_1$	C$_2$–O	C$_1$–F$_a$	C$_2$–R^2	Φ_1	Φ_2	Φ_3
H	- (100)	1.49	-	-	-	-	-	-	58.29
Esag	0.0 (21)	1.26	1.39	1.36	1.34	1.36	17.26	176.77	56.14
Es'a'g	0.1 (19)	0.45	1.39	1.37	1.34	1.35	340.46	185.33	57.62
Esag'	0.2 (14)	1.06	1.39	1.37	1.34	1.35	20.12	176.57	300.55
Es'a'g'	0.2 (14)	1.81	1.39	1.37	1.34	1.35	342.37	184.84	301.67
Es'a'a'	0.3 (13)	2.37	1.39	1.36	1.34	1.36	340.40	182.66	180.03
Esaa	0.3 (13)	2.51	1.39	1.36	1.34	1.36	19.33	174.25	178.90
Es'g'g'	1.6 (2)	1.48	1.39	1.38	1.34	1.35	353.25	282.10	302.91
Eg'gg	1.6 (1)	1.78	1.39	1.38	1.35	1.35	327.29	107.34	55.14
Esga	1.8 (1)	2.52	1.39	1.37	1.34	1.36	17.39	69.43	175.99
Eg'g'g	2.0 (1)	2.06	1.38	1.38	1.36	1.36	306.15	276.46	62.44
Egg'a	2.0 (1)	2.97	1.39	1.37	1.35	1.35	31.72	255.70	180.00
Iag	0.0 (61)	1.72	1.37	1.40	1.35	1.77	177.22	136.85	58.40
Iga	0.4 (31)	2.11	1.38	1.39	1.36	1.78	60.05	169.45	59.41
Ig'a	1.3 (7)	2.91	1.38	1.39	1.35	1.77	322.35	154.39	59.46
Is'g'	2.5 (1)	1.84	1.39	1.39	1.35	1.78	335.79	295.71	68.55
Dag	0.0 (76)	1.89	1.37	1.39	1.35	1.36	174.93	143.71	56.48
Dga	0.9 (18)	2.02	1.38	1.38	1.36	1.37	57.98	170.26	57.35
Dg'a	1.5 (5)	3.13	1.38	1.38	1.35	1.36	318.43	157.60	57.24
Ds'g'	2.9 (1)	1.59	1.39	1.38	1.35	1.37	336.92	296.68	67.23
Sgg	0.0 (100)	2.56	1.39	1.41	1.38	1.53	51.09	133.73	54.89
Mgaa	0.0 (58)	1.62	1.44	1.34	-	1.37	61.22	180.00	180.00
Mgag	0.2 (42)	2.62	1.44	1.35	-	1.36	59.25	179.07	57.60

[a] Conformers for compounds **C** are named according to the dihedral angles ϕ_1, ϕ_2, and ϕ_3, which can be either *anti* (*a* and *a'*, from 150° to 210°), *syn* (*s* and *s'*, from 330° to 30°), or *gauche* (*g* and *g'*). The C$_1$—F$_a$ stands for the bond length involving the fluorine at anomeric orientation. The C—F, C—Cl, and C—Br bond lengths for halothane are 1.34, 1.76, and 1.91 Å, respectively.

Table 2 Lewis (L) and non-Lewis (NL) contributions to the full conformational electronic energies, and anomeric interactions for the rotationally flexible fluorinated anaesthetic compounds (**C**) studied herein (kcal mol^{-1}).[a]

C$\phi_1\phi_2\phi_3$	E_{full}	E_{NL}	E_L	$n_O \to \sigma^*_{C1\text{-}Fa}$	$n_O \to \sigma^*_{C2\text{-}CF3}$	$n_O \to \sigma^*_{C2\text{-}Fa}$	$n_O \to \sigma^*_{C2\text{-}Cl}$
E*sag*	0.03	-2.27	2.30	13.31	-	32.44	-
E*s'a'g*	0.00	-1.96	1.96	13.67	-	32.38	-
E*sag'*	0.17	-2.05	2.22	13.73	-	31.78	-
E*s'a'g'*	0.22	-2.48	2.70	13.52	-	31.83	-
E*s'a'a'*	0.18	-3.58	3.76	13.62	-	33.56	-
E*saa*	0.19	-3.79	3.98	13.73	-	33.52	-
E*s'g'g'*	1.18	-0.86	2.04	11.83	-	20.36	-
E*g'gg*	1.33	-2.05	3.38	15.92	-	20.12	-
E*sga*	1.24	-2.78	4.02	13.86	-	22.03	-
E*g'g'g*	1.65	0.00	1.65	15.48	-	18.92	-
E*gg'a*	1.67	-3.44	5.11	15.94	-	20.71	-
I*ag*	0.00	0.00	0.00	13.07	-	-	13.09
I*ga*	0.21	-0.75	0.96	12.55	-	-	16.28
I*g'a*	1.93	-6.10	8.03	16.17	-	-	16.15
I*s'g'*	1.92	-6.04	7.96	15.38	-	-	15.66
D*ag*	0.00	-1.79	1.79	13.70	-	16.20	-
D*ga*	0.90	0.00	0.90	13.48	-	17.21	-
D*g'a*	1.90	-8.97	10.8	16.57	-	18.41	-
D*s'g'*	2.34	-6.75	9.09	15.34	-	15.67	-
S*gg*	0.00	0.00	0.00	15.78	8.84	-	-
M*gaa*	0.00	-1.91	1.91	-	-	39.18	-
M*gag*	0.29	0.00	0.29	-	-	37.15	-

[a] *The $n_O \to \sigma^*_{C1\text{-}Fa}$ interaction corresponds to the contribution involving the fluorine at anomeric orientation; $n_O \to \sigma^*_{C2\text{-}CF3}$ corresponds only to the antiperiplanar interaction; $n_O \to \sigma^*_{C2\text{-}CF}$ corresponds to the sum of these interaction energies for the two C–F bonds when possible (for **E** and **M**).*

Whereas compounds **E** and **M** have the requirements to experience the fluorine *gauche* effect, the compounds **D**, **S**, **I**, **E**, and **M** may present the anomeric effect. To gain insight into how these non-Lewis-type interactions contribute to the conformational electronic energies (E_{full}) of the studied compounds, the wavefunctions were localized with all natural bond orbitals (NBO) doubly occupied, and the resulting energy (E_L) was subtracted from E_{full} to give the electron delocalization energy E_{NL}, according to Equation 1 (Table 2).

$$E_{NL} = E_{full} - E_L \qquad\qquad (1)$$

E and **M** are capable of turning on the fluorine *gauche* effect through the $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation along the ϕ_3 dihedral angle. However, since σ_{C-Cl} is a good electron-donating orbital but worse than σ_{C-H}, and σ^*_{C-O} is a good electron-accepting orbital but worse than σ^*_{C-F}, some competing interactions contribute to the rotation around the $O—C_2—C_3—H$ dihedral angle in **E** and **M**. Considering that electron delocalizations from σ_{C-H} and to σ^*_{C-F} are only slightly more favoring than that from σ_{C-Cl} and to σ^*_{C-O} (see ESI), the small differences in the rotational preferences for ϕ_3 are well explained by these stereoelectronic interactions. On the other hand, the anomeric effect appears in most of the studied systems (Table 2). The $n_O \rightarrow \sigma^*_{C-X}$ anomeric interactions are expected to shorten the C–O distance and lengthen the C–X bond. For instance, more stabilizing $n_O \rightarrow \sigma^*_{C-F}$ interactions in some conformers of **E** cause an increase in the respective C–F bonds of *ca.* 0.01 to 0.02 Å in a comparison with the conformers that experience weaker interactions. The effect of these interactions on the dihedral angles is also remarkable, once the bonds rotate to maximize the overlap between the orbitals involved in the anomeric interactions. Therefore, the stereoelectronic effects operating in these systems strongly affect the molecular geometries, conformer stabilities, and, consequently, the overall molecular dipole moment.

Compound **M** experiences both *gauche* and anomeric effects, but the overall contribution from the latter is weaker than in **E** because C-1 is not attached to any fluorine. On the other hand, the two fluorine atoms at C-2 allow for an effective *gauche* effect. These two factors lead **M** to a preferential conformational behaviour in which all bonds are staggered. For the remaining molecules **D**, **S**, and **I**, there is a competition between the $n_O \rightarrow \sigma^*_{C1-R1}$ (leading to a *syn* ϕ_1) and $n_O \rightarrow \sigma^*_{C2-R2}$ interactions (leading to a *gauche* ϕ_2). Compound **S** bears a worse R^2-containing electron-accepting orbital (σ^*_{C-CF3}) compared to **D** and **I**, leading to less stabilizing $n_O \rightarrow \sigma^*_{C2-R2}$ interactions in **S** than in **D** and **I**. Even though, compound **S** presents a single stable conformer in the gas phase, whereas the conformers with a *gauche* ϕ_2 dominate the conformational equilibrium in **D** (**D***ag*) and **I** (**I***ag*). According to the energy decomposition analysis of Table 2, this behaviour is due to a balance of Lewis and non-Lewis-type interactions; whereas the single stable conformer of **S** is substantially more favoured than its metastable conformers due to a large E_{NL} - E_L energy difference, both **D***ag* and **I***ag* are little destabilized by steric effects but also only slightly stabilized by electron delocalization, leading to a non-monotonic conformational equilibrium. The six geometries corresponding to the most stable

conformer in the gas phase for each compound, which are consistent with the literature,[8-12] are shown in Figure 2.
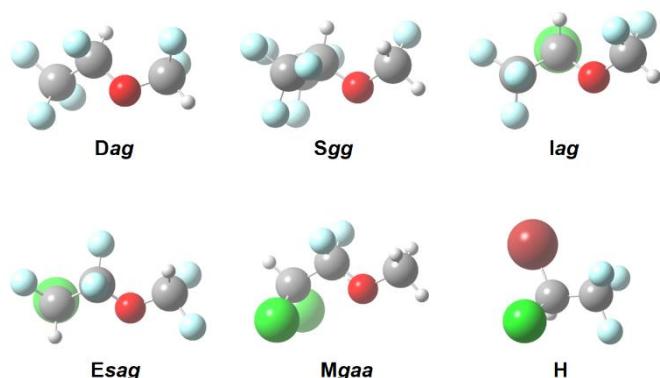
Fig. 2 Most stable conformer for each halogenated anaesthetic.

Considering that the molecular polarity of organofluorine compounds is related to their octanol-water partition coefficient,[4,5,7,17] as well as that blood is mostly constituted by water,[18] the solubility of fluorinated anaesthetics in the bloodstream, described in terms of the blood-gas partition coefficient, may be correlated to the average molecular dipole moment. At first glance, compound **M** demonstrates an outlier behaviour due to its exceedingly high K_{bg} of 12 for an average μ of 2.04 Db (see discussion on vapour pressure further in this discussion). Nevertheless, it is worth mentioning that other factors than binding to plasma proteins may appear to set anaesthetic molecules in the blood, such as the affinity to red blood cells.[19] Accordingly, the average dipole moments for the remaining five fluorinated anaesthetics were plotted against the respective K_{bg} values (Figure 3), yielding a determination coefficient R^2 of 0.65, which is acceptable for quantitative structure-activity relationship purposes.[20] Yet, considering that **D** appears to abnormally influence the regression line, the resulting plot obtained after exclusion of this compound gives an impressive correlation with $R^2 = 0.93$. Although the origin of this outlier behaviour is not clear, it is worth considering an effect of the vapour pressure, which is considerably higher for **D** (667.6 mmHg)[21] in a comparison with **S** (157.5 mmHg),[22] **I** (240.0 mmHg),[23] **E** (174.5 mmHg),[24] **M** (22.5 mmHg),[25] and **H** (243.0 mmHg)[26] at 20ºC.
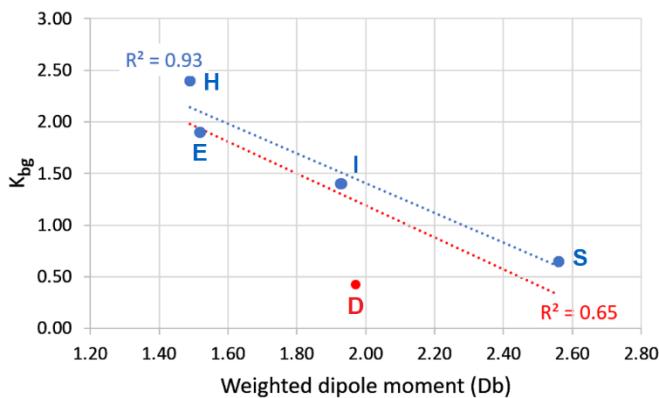
Fig. 3 Linear correlation plots of average dipole moments (μ) *versus* blood-gas partition coefficients (K_{bg}) for **H**, **E**, **S**, and **I** (blue line) and also including **D** (red line). $K_{bg} = -1.4417\mu + 4.2907$ (blue line); $K_{bg} = -1.5463\mu + 4.2811$ (red line).

Computational methods

The geometries corresponding to all possible staggered conformations depicted in Figure 4 were fully optimized and the absence of imaginary frequencies was checked to guarantee that the located conformers were real energy minima. These procedures were performed at the *ab initio* MP2/aug-cc-pVTZ level of theory[27-30] using the Gaussian 09 program.[31] The calculations were carried out using the default integration grid of G09: FineGrid, with 75 radial shells and 302 angular points per shell. The geometries for the main conformers (*i.e.* those with Gibbs population of at least 1% in the gas phase) were consistent with the structures available in the literature[8-12] and, therefore, the molecular dipole moments considered to build a correlation with the experimental blood-gas partition coefficients[2,3] were weighted by these populations. The MP2-derived dipole moments have been demonstrated to be reliable and accurate.[32] The electron delocalization and Lewis-type contributions to the conformational energies were obtained through second-order perturbation analysis of donor-acceptor interactions in the natural bond orbitals (NBO).[16] The Lewis-type energy (E_L) results from the perfectly localized NBO´s and nearly represents the steric energy between doubly occupied orbitals, which is higher than the original energy (E_{full}). The non-Lewis type energy (E_{NL}) corresponds to the stabilizing effect of delocalizing contributions. The NBO calculations were performed using density functional theory at the B3LYP/aug-cc-pVTZ level of theory,[33,34] including the empirical dispersion corrections proposed by Grimme and co-workers.[35,36]
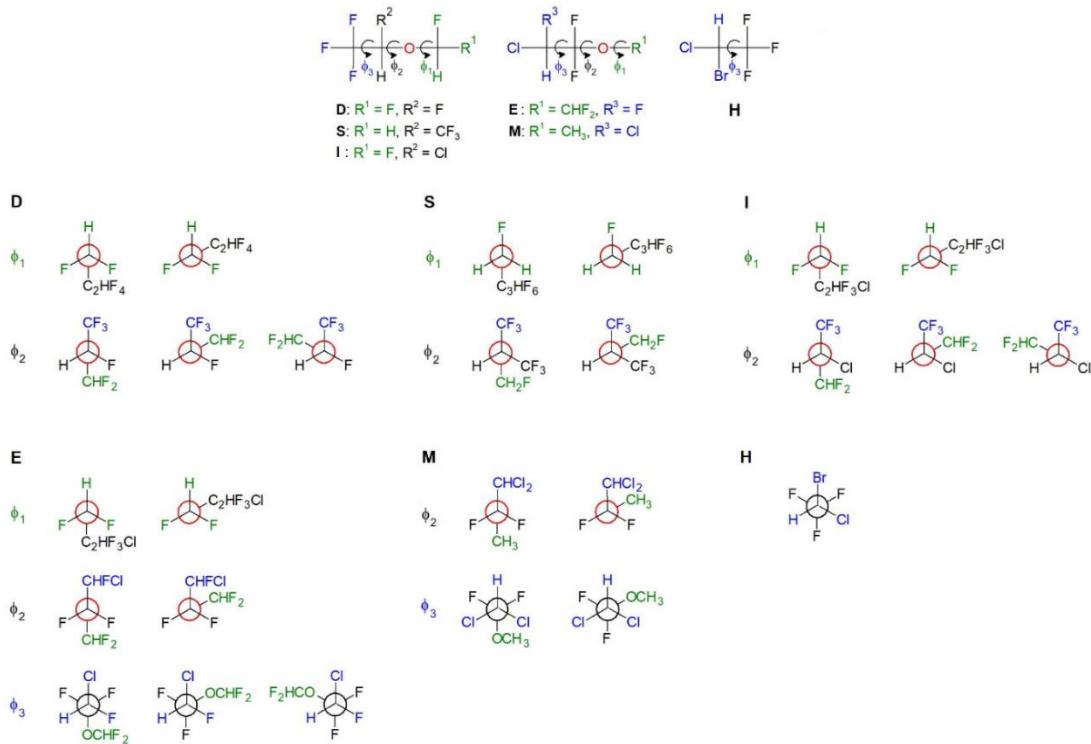
Fig. 4 Staggered conformations for each dihedral angle of the six fluorinated anaesthetics studied herein.

Conclusions

The conformational equilibrium of five fluorinated anaesthetics was discussed in terms of electron delocalization and Lewis-type interactions. Although the classical steric and electrostatic interactions contribute to the conformational balance, the stereoelectronic interactions that rule the anomeric and *gauche* effects appeared to stabilize some conformers with specific geometries more than others. Because each conformer has a given dipole moment, the overall molecular dipole moment μ is a combination of the individual dipole moments balanced by the respective conformer populations. We found a linear dependence of K_{bg} with these average dipole moments for **H**, **E**, **I**, **S**, and **D**, which greatly improves if **D** is removed from the regression. This demonstrates the importance of this parameter for rational drug design. Although the K_{bg} of **M** and **D** may be affected by other physical or chemical mechanisms than the solubility of the anaesthetic in the bloodstream and their interaction with the blood plasma proteins, our findings open the possibility to describe crucial pharmacokinetic data by an easily accessible quantum-chemical parameter.

Acknowledgements

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APPENDICES

APPENDIX A

Supporting Information for:

The fluorine g*auche* effect and a comparison with other halogens in 2-halofluoroethanes and 2-haloethanols

INDEX

STANDARD COORDINATES IN THE GAS PHASE

FF*g*: MP2 energy=-277.7203574(Hartrees), Zero Point Energy =0.0621737(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
----------------------------------------------------------------
1          6          0        0.264808    0.704165    0.516253
2          1          0        1.352922    0.706354    0.418774
3          1          0       -0.030113    1.206800    1.442707
4          6          0       -0.264808   -0.704165    0.516253
5          1          0        0.030113   -1.206800    1.442707
6          1          0       -1.352922   -0.706354    0.418774
7          9          0       -0.264808    1.417097   -0.551000
8          9          0        0.264808   -1.417097   -0.551000
----------------------------------------------------------------
```

FF*a*: MP2 energy=-277.7191662(Hartrees), Zero Point Energy=0.0623141(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
----------------------------------------------------------------
1          6          0        0.426862    0.626197    0.000012
2          1          0        1.051248    0.672343   -0.894026
3          1          0        1.051272    0.672385    0.894035
4          6          0       -0.426862   -0.626197    0.000012
5          1          0       -1.051272   -0.672385    0.894035
6          1          0       -1.051248   -0.672343   -0.894026
7          9          0       -0.426862    1.726003   -0.000009
8          9          0        0.426862   -1.726003   -0.000009
----------------------------------------------------------------
```

FC*g*: MP2 energy=-637.7014765(Hartrees), Zero Point Energy=0.0608512(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
----------------------------------------------------------------
1          6          0        1.192953    0.418316    0.362832
2          1          0        1.053238    0.246826    1.432390
3          1          0        1.956327    1.186404    0.202309
4          6          0       -0.095631    0.844974   -0.296544
5          1          0       -0.381247    1.831583    0.073684
6          1          0        0.032140    0.881802   -1.378793
7          9          0        1.652205   -0.761828   -0.203751
8          17         0       -1.418484   -0.286465    0.065085
----------------------------------------------------------------
```

FC*a*: MP2 energy=-637.7023653(Hartrees), Zero Point Energy=0.0609604(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
----------------------------------------------------------------
1          6          0        0.998726   -0.489121   -0.000080
2          1          0        0.907253   -1.109951   -0.893503
3          1          0        0.907382   -1.110102    0.893252
4          6          0       -0.032714    0.620763    0.000067
5          1          0        0.067681    1.238696    0.891692
6          1          0        0.067623    1.238849   -0.891460
7          9          0        2.265499    0.089731   -0.000118
8          17         0       -1.655030   -0.109113    0.000068
----------------------------------------------------------------
```

FB*g*: MP2 energy =-2750.745897(Hartrees), Zero Point Energy=0.0599783(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X              Y              Z
---------------------------------------------------------------------
1          6          0        1.734435       0.366581       0.375429
2          1          0        1.560878       0.193306       1.439977
3          1          0        2.577501       1.053017       0.240227
4          6          0        0.511309       0.947348      -0.293260
5          1          0        0.302635       1.942321       0.104375
6          1          0        0.644976       0.997429      -1.374268
7          9          0        2.074498      -0.842907      -0.211733
8          35         0       -1.063741      -0.128100       0.028636
---------------------------------------------------------------------
```

FB*a*: MP2 energy=-2750.7473668(Hartrees), Zero Point Energy=0.0600582(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X              Y              Z
---------------------------------------------------------------------
1          6          0        1.561362      -0.483894      -0.000248
2          1          0        1.447894      -1.099308      -0.895049
3          1          0        1.448043      -1.099467       0.894465
4          6          0        0.574454       0.666129      -0.000081
5          1          0        0.678317       1.280046       0.894115
6          1          0        0.678071       1.280096      -0.894274
7          9          0        2.848957       0.052142      -0.000297
8          35         0       -1.220224      -0.054973       0.000154
---------------------------------------------------------------------
```

FI*g*: MP2 energy=-475.2094337 (Hartrees), Zero Point Energy=0.0593936(Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X              Y              Z
---------------------------------------------------------------------
1          6          0        2.118707       0.328515       0.377341
2          1          0        1.944201       0.164883       1.443402
3          1          0        3.009976       0.950731       0.237348
4          6          0        0.936791       0.999025      -0.283406
5          1          0        0.779048       1.992306       0.140818
6          1          0        1.078285       1.071082      -1.362182
7          9          0        2.369149      -0.901243      -0.214369
8          53         0       -0.876733      -0.076095       0.017100
---------------------------------------------------------------------
```

FI*a*: MP2 energy=-475.2114557 (Hartrees), Zero Point Energy=0.0594677 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X              Y              Z
---------------------------------------------------------------------
1          6          0        1.958346      -0.480294      -0.000054
2          1          0        1.834430      -1.094324      -0.894693
3          1          0        1.834330      -1.094478       0.894468
4          6          0        1.000213       0.692591      -0.000037
5          1          0        1.114038       1.303684       0.894919
6          1          0        1.114005       1.303700      -0.894995
7          9          0        3.260832       0.023607       0.000059
8          53         0       -0.999918      -0.035940       0.000006
---------------------------------------------------------------------
```

OF*gg*: MP2 energy=-253.7223362 (Hartrees), Zero Point Energy=0.0747795 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
1          6          0          -0.714535    0.559477   -0.285462
2          1          0          -0.688856    0.518774   -1.376506
3          1          0          -1.296463    1.420242    0.054707
4          6          0           0.682196    0.575331    0.287169
5          1          0           1.190445    1.488691   -0.032769
6          1          0           0.624329    0.573641    1.383215
7          9          0          -1.363169   -0.600131    0.158504
8          8          0           1.457041   -0.512047   -0.188734
9          1          0           0.976776   -1.312641    0.044452
---------------------------------------------------------------------
```

OF*gg'*: MP2 energy=-253.7181412 (Hartrees), Zero Point Energy=0.0744489 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
1          6          0           0.714686    0.506578    0.314523
2          1          0           0.662253    0.402488    1.403990
3          1          0           1.268514    1.417498    0.065506
4          6          0          -0.667568    0.556420   -0.295891
5          1          0          -1.134772    1.505929    0.004899
6          1          0          -0.584159    0.543532   -1.384233
7          9          0           1.428480   -0.579419   -0.175316
8          8          0          -1.476277   -0.555801    0.046352
9          1          0          -1.540649   -0.586253    1.005075
---------------------------------------------------------------------
```

OF*ga*: MP2 energy=-253.7189569 (Hartrees), Zero Point Energy=0.0741382 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
1          6          0           0.717982    0.504462    0.309457
2          1          0           0.642115    0.397067    1.394268
3          1          0           1.273750    1.412438    0.057629
4          6          0          -0.656318    0.544089   -0.307577
5          1          0          -1.107353    1.520822   -0.082281
6          1          0          -0.557146    0.444205   -1.394723
7          9          0           1.435242   -0.582918   -0.179435
8          8          0          -1.424917   -0.513356    0.248645
9          1          0          -2.139191   -0.712730   -0.360419
---------------------------------------------------------------------
```

OF*ag*: MP2 energy=-253.7183493 (Hartrees), Zero Point Energy=0.0745651 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
1          6          0          -0.575173    0.499015    0.047278
2          1          0          -0.520631    1.200094   -0.791729
3          1          0          -0.539304    1.052561    0.987938
4          6          0           0.550445   -0.519702   -0.016874
5          1          0           0.479421   -1.200691    0.832257
6          1          0           0.466396   -1.106737   -0.938751
7          9          0          -1.798108   -0.163536   -0.029700
8          8          0           1.812694    0.126261    0.088499
9          1          0           1.943906    0.640626   -0.712835
---------------------------------------------------------------------
```

OF*aa*: MP2 energy=-253.7187593 (Hartrees), Zero Point Energy=0.0738524(Hartrees), imaginary frequency = -71.15

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.582291	-0.503656	-0.000004
2	1	0	-0.544104	-1.129036	0.894114
3	1	0	-0.544151	-1.129078	-0.894095
4	6	0	0.548838	0.504773	-0.000041
5	1	0	0.469554	1.137636	-0.891596
6	1	0	0.469485	1.137760	0.891420
7	9	0	-1.793509	0.186255	0.000003
8	8	0	1.750558	-0.257334	0.000049
9	1	0	2.487055	0.358398	0.000002

OC*gg*: MP2 energy=-613.7039954 (Hartrees), Zero Point Energy=0.0734768(Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.104596	0.891803	-0.291183
2	1	0	-0.000047	0.942591	-1.375147
3	1	0	-0.424577	1.856558	0.105381
4	6	0	1.200156	0.451800	0.344789
5	1	0	1.959032	1.212231	0.140264
6	1	0	1.070245	0.370326	1.431316
7	8	0	1.692030	-0.753789	-0.207957
8	1	0	1.012879	-1.421499	-0.066726
9	17	0	-1.395714	-0.293618	0.065114

OC*gg'*: MP2 energy=-613.6998155(Hartrees), Zero Point Energy=0.0730991(Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	0.123262	0.853990	0.301041
2	1	0	0.014630	0.895853	1.387818
3	1	0	0.435749	1.835950	-0.060366
4	6	0	-1.187092	0.458865	-0.355446
5	1	0	-1.909481	1.267507	-0.169535
6	1	0	-1.048168	0.361237	-1.433510
7	8	0	-1.687506	-0.789573	0.084045
8	1	0	-1.793648	-0.742009	1.038466
9	17	0	1.422585	-0.304652	-0.065223

OC*ga*: MP2 energy=-613.7005207(Hartrees), Zero Point Energy=0.0727521(Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.127794	0.850903	-0.295840
2	1	0	0.005412	0.874946	-1.378171
3	1	0	-0.449424	1.830974	0.059914
4	6	0	1.172689	0.456318	0.365844
5	1	0	1.879851	1.290323	0.251518
6	1	0	1.003816	0.282235	1.434565
7	8	0	1.659626	-0.708378	-0.282369
8	1	0	2.264119	-1.151983	0.316502
9	17	0	-1.426479	-0.311929	0.067918

OC*ag*: MP2 energy=-613.7013974 (Hartrees), Zero Point Energy=0.0732448(Hartrees), imaginary frequency = 0

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type            X           Y           Z
---------------------------------------------------------------------
1          6           0          -0.045076    0.604723    0.043587
2          1           0           0.052461    1.283082   -0.806539
3          1           0           0.055435    1.169050    0.970540
4          6           0           1.000527   -0.498737   -0.015631
5          1           0           0.879667   -1.168047    0.837358
6          1           0           0.872298   -1.085461   -0.932829
7          8           0           2.310432    0.041747    0.086175
8          1           0           2.482576    0.544178   -0.715107
9          17          0          -1.679917   -0.100747   -0.012386
---------------------------------------------------------------------
```

OC*aa*: MP2 energy=-613.7013742(Hartrees), Zero Point Energy=0.0724203(Hartrees), imaginary frequency = -27.40

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type            X           Y           Z
---------------------------------------------------------------------
1          6           0           0.050255    0.612125   -0.000005
2          1           0          -0.047362    1.230991    0.891469
3          1           0          -0.047364    1.230986   -0.891482
4          6           0          -0.996346   -0.484242    0.000001
5          1           0          -0.870508   -1.111180   -0.890509
6          1           0          -0.870486   -1.111192    0.890500
7          8           0          -2.257810    0.175355    0.000022
8          1           0          -2.940258   -0.500682   -0.000027
9          17          0           1.677353   -0.112298   -0.000006
---------------------------------------------------------------------
```

OB*gg*: MP2 energy=-2726.7490106(Hartrees), Zero Point Energy=0.0725105(Hartrees), imaginary frequency = 0

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type            X           Y           Z
---------------------------------------------------------------------
1          6           0           0.507492    0.997147   -0.289326
2          1           0           0.617480    1.057615   -1.372395
3          1           0           0.270901    1.976395    0.130057
4          6           0           1.740417    0.390687    0.356625
5          1           0           2.585180    1.062056    0.173466
6          1           0           1.586481    0.310895    1.440423
7          8           0           2.095511   -0.853360   -0.212947
8          1           0           1.336737   -1.435840   -0.093436
9          35          0          -1.047095   -0.127750    0.029190
---------------------------------------------------------------------
```

OB*gg'*: MP2 energy=-2726.7444269(Hartrees), Zero Point Energy=0.0722478(Hartrees), imaginary frequency = 0

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type            X           Y           Z
---------------------------------------------------------------------
1          6           0          -0.490543    0.960257    0.299031
2          1           0          -0.608802    1.009126    1.384300
3          1           0          -0.259145    1.956541   -0.083109
4          6           0          -1.735066    0.405146   -0.372386
5          1           0          -2.542921    1.137149   -0.219395
6          1           0          -1.564859    0.299110   -1.445352
7          8           0          -2.109807   -0.876789    0.093924
8          1           0          -2.254198   -0.811797    1.042456
9          35          0           1.070344   -0.136235   -0.028290
---------------------------------------------------------------------
```

OB*ga*: MP2 energy=-2726.7450559(Hartrees), Zero Point Energy=0.0718177(Hartrees), imaginary frequency = 0

```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type            X           Y           Z
---------------------------------------------------------------------
1          6          0         0.486080    0.966259   -0.290516
2          1          0         0.621796    1.008298   -1.372045
3          1          0         0.247717    1.957399    0.098159
4          6          0         1.720845    0.404945    0.378873
5          1          0         2.518656    1.157652    0.294093
6          1          0         1.514600    0.228787    1.440788
7          8          0         2.088030   -0.790394   -0.291909
8          1          0         2.608133   -1.322789    0.314240
9          35         0        -1.070191   -0.140955    0.029426
---------------------------------------------------------------------
```

OB*ag*: MP2 energy=-2726.7463862(Hartrees), Zero Point Energy=0.0723293(Hartrees), imaginary frequency = 0

```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type            X           Y           Z
---------------------------------------------------------------------
1          6          0         0.567747    0.647451    0.048251
2          1          0         0.667229    1.317135   -0.808453
3          1          0         0.669238    1.213380    0.974308
4          6          0         1.573727   -0.493733   -0.008283
5          1          0         1.437051   -1.150574    0.852120
6          1          0         1.420242   -1.081212   -0.921152
7          8          0         2.901204    0.008936    0.079099
8          1          0         3.080315    0.497176   -0.729698
9          35         0        -1.238073   -0.051134   -0.006849
---------------------------------------------------------------------
```

OB*aa*: MP2 energy=-2726.7463588(Hartrees), Zero Point Energy=0.0715683(Hartrees), imaginary frequency = -50.03

```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type            X           Y           Z
---------------------------------------------------------------------
1          6          0         0.562857    0.659614    0.000027
2          1          0         0.661599    1.274576   -0.894089
3          1          0         0.661587    1.274522    0.894182
4          6          0         1.566086   -0.477433   -0.000004
5          1          0         1.417405   -1.097574    0.891870
6          1          0         1.417380   -1.097544   -0.891895
7          8          0         2.850831    0.139400   -0.000008
8          1          0         3.508840   -0.561028    0.000008
9          35         0        -1.235632   -0.057178   -0.000004
---------------------------------------------------------------------
```

OI*gg*: MP2 energy=-451.2122769(Hartrees), Zero Point Energy=0.0718522(Hartrees), imaginary frequency = 0

```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type            X           Y           Z
---------------------------------------------------------------------
1          6          0         0.933040    1.039051   -0.284596
2          1          0         1.056158    1.108319   -1.365883
3          1          0         0.749803    2.024413    0.147397
4          6          0         2.120735    0.348782    0.365627
5          1          0         3.005202    0.972163    0.197221
6          1          0         1.956310    0.265072    1.447643
7          8          0         2.415186   -0.905264   -0.216327
8          1          0         1.629520   -1.453462   -0.104643
9          53         0        -0.868701   -0.075498    0.017409
---------------------------------------------------------------------
```

OI*gg'*: MP2 energy=-451.2082845(Hartrees), Zero Point Energy=0.0716881(Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
1           6           0        -0.919519    1.015721    0.289820
2           1           0        -1.046205    1.085018    1.372967
3           1           0        -0.741962    2.013327   -0.116822
4           6           0        -2.121300    0.364873   -0.376166
5           1           0        -2.982509    1.033921   -0.223717
6           1           0        -1.950475    0.265228   -1.449767
7           8           0        -2.399671   -0.938736    0.097887
8           1           0        -2.550402   -0.878384    1.045846
9           53          0         0.881393   -0.080996   -0.016859
---------------------------------------------------------------------
```

OI*ga*: MP2 energy =-451.208745(Hartrees), Zero Point Energy=0.07124 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
1           6           0         0.915765    1.021906   -0.283259
2           1           0         1.058003    1.083693   -1.363066
3           1           0         0.732098    2.014359    0.130589
4           6           0         2.108101    0.367167    0.379420
5           1           0         2.962817    1.053503    0.279774
6           1           0         1.904218    0.213067    1.445736
7           8           0         2.369388   -0.857832   -0.287270
8           1           0         2.945607   -1.382343    0.274200
9           53          0        -0.881152   -0.084039    0.017999
---------------------------------------------------------------------
```

OI*ag*: MP2 energy=-451.2104291 (Hartrees), Zero Point Energy=0.0717605 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
1           6           0         0.996713    0.673248    0.045851
2           1           0         1.103092    1.337963   -0.813943
3           1           0         1.110804    1.239504    0.970402
4           6           0         1.976138   -0.490954   -0.010982
5           1           0         1.827164   -1.147542    0.847774
6           1           0         1.814214   -1.074639   -0.925175
7           8           0         3.315547   -0.019043    0.079734
8           1           0         3.499897    0.482882   -0.719669
9           53          0        -1.013522   -0.033577   -0.003896
---------------------------------------------------------------------
```

OI*aa*: MP2 energy=-451.2101458 (Hartrees), Zero Point Energy=0.0709462 (Hartrees), imaginary frequency = -61.82

```
                        Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
1           6           0         0.991132    0.687087    0.000076
2           1           0         1.099683    1.299619   -0.894673
3           1           0         1.099634    1.299500    0.894912
4           6           0         1.967123   -0.473386    0.000018
5           1           0         1.807356   -1.091693    0.891551
6           1           0         1.807353   -1.091601   -0.891578
7           8           0         3.267559    0.112360    0.000049
8           1           0         3.907989   -0.604714    0.000057
9           53          0        -1.011548   -0.037589   -0.000023
---------------------------------------------------------------------
```

STANDARD COORDINATES IN CHLOROFORM

FF*g*: MP2 energy=-277.7254635(Hartrees), Zero Point Energy=0.0621742 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ----------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type           X           Y           Z
 ----------------------------------------------------------------------
    1          6           0         0.261954    0.704079    0.527243
    2          1           0         1.349746    0.717451    0.439301
    3          1           0        -0.050244    1.213235    1.442406
    4          6           0        -0.261954   -0.704079    0.527243
    5          1           0         0.050244   -1.213235    1.442406
    6          1           0        -1.349746   -0.717451    0.439301
    7          9           0        -0.261954    1.406867   -0.560574
    8          9           0         0.261954   -1.406867   -0.560574
 ----------------------------------------------------------------------
```

FF*a*: MP2 energy=-277.7227706 (Hartrees), Zero Point Energy=0.0622585 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ----------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type           X           Y           Z
 ----------------------------------------------------------------------
    1          6           0         0.429061    0.624479    0.000058
    2          1           0         1.050345    0.674796   -0.894904
    3          1           0         1.050301    0.674926    0.895051
    4          6           0        -0.429061   -0.624479    0.000058
    5          1           0        -1.050301   -0.674926    0.895051
    6          1           0        -1.050345   -0.674796   -0.894904
    7          9           0        -0.429061    1.728121   -0.000055
    8          9           0         0.429061   -1.728121   -0.000055
 ----------------------------------------------------------------------
```

FC*g*: MP2 energy=-637.7059534(Hartrees), Zero Point Energy=0.0608612 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ----------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type           X           Y           Z
 ----------------------------------------------------------------------
    1          6           0         1.195346    0.424972    0.358939
    2          1           0         1.067835    0.262188    1.430334
    3          1           0         1.965457    1.179788    0.179761
    4          6           0        -0.092799    0.855082   -0.294578
    5          1           0        -0.381108    1.835450    0.087177
    6          1           0         0.024820    0.899760   -1.377013
    7          9           0         1.637413   -0.774045   -0.202132
    8         17           0        -1.413470   -0.287712    0.065457
 ----------------------------------------------------------------------
```

FC*a*: MP2 energy=-637.7054666 (Hartrees), Zero Point Energy=0.0609149 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ----------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type           X           Y           Z
 ----------------------------------------------------------------------
    1          6           0         0.995617   -0.491335   -0.000074
    2          1           0         0.909235   -1.110092   -0.894450
    3          1           0         0.909437   -1.110217    0.894235
    4          6           0        -0.031119    0.622275    0.000082
    5          1           0         0.065345    1.238470    0.892801
    6          1           0         0.065295    1.238613   -0.892548
    7          9           0         2.268143    0.090112   -0.000172
    8         17           0        -1.655858   -0.109025    0.000086
 ----------------------------------------------------------------------
```

FB*g*: MP2 energy=-2750.7504574 (Hartrees), Zero Point Energy=0.0599534 (Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	1.736528	0.371301	0.371992
2	1	0	1.575576	0.205608	1.438666
3	1	0	2.584919	1.044730	0.218597
4	6	0	0.515077	0.955790	-0.291838
5	1	0	0.304378	1.945692	0.115139
6	1	0	0.640079	1.012172	-1.372974
7	9	0	2.058693	-0.854829	-0.209985
8	35	0	-1.061223	-0.127923	0.028843

FB*a*: MP2 energy=-2750.750534 (Hartrees), Zero Point Energy=0.0600055 (Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	1.558209	-0.485754	-0.000226
2	1	0	1.449898	-1.099373	-0.895959
3	1	0	1.450053	-1.099491	0.895446
4	6	0	0.576176	0.667768	-0.000084
5	1	0	0.675823	1.280071	0.895269
6	1	0	0.675593	1.280088	-0.895455
7	9	0	2.851752	0.052309	-0.000284
8	35	0	-1.220670	-0.054976	0.000146

FI*g*: MP2 energy =-475.21379 (Hartrees), Zero Point Energy=0.0594145 (Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.119760	0.332627	0.374347
2	1	0	1.955812	0.174435	1.441816
3	1	0	3.014294	0.943620	0.218678
4	6	0	0.939397	1.005572	-0.282469
5	1	0	0.779905	1.994020	0.150997
6	1	0	1.073287	1.084504	-1.361186
7	9	0	2.355883	-0.911377	-0.212574
8	53	0	-0.875117	-0.075913	0.017200

FI*a*: MP2 energy =-475.2145918(Hartrees), Zero Point Energy=0.0594124 (Hartrees), imaginary frequency = 0

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	1.954543	-0.481926	-0.000057
2	1	0	1.836275	-1.094244	-0.895650
3	1	0	1.836181	-1.094405	0.895417
4	6	0	1.001169	0.693807	-0.000039
5	1	0	1.110880	1.303385	0.896162
6	1	0	1.110858	1.303389	-0.896249
7	9	0	3.263676	0.023912	0.000062
8	53	0	-1.000029	-0.035936	0.000006

OF*gg*: MP2 energy=-253.7273907 (Hartrees), Zero Point Energy=0.0745773 (Hartrees), imaginary
frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.714041    0.560303   -0.286476
   2          1          0       -0.689674    0.518665   -1.376828
   3          1          0       -1.293335    1.420990    0.054819
   4          6          0        0.679497    0.574410    0.290563
   5          1          0        1.181761    1.493005   -0.021727
   6          1          0        0.622064    0.561247    1.385432
   7          9          0       -1.371135   -0.601861    0.156781
   8          8          0        1.464956   -0.508590   -0.192285
   9          1          0        1.007016   -1.316722    0.061028
---------------------------------------------------------------------
```

OF*gg'*: MP2 energy=-253.7252632 (Hartrees), Zero Point Energy=0.0743852 (Hartrees), imaginary
frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.712597    0.515163    0.315608
   2          1          0        0.660561    0.414075    1.403325
   3          1          0        1.271249    1.418348    0.056165
   4          6          0       -0.664554    0.556025   -0.302963
   5          1          0       -1.140009    1.501856   -0.011168
   6          1          0       -0.576126    0.534359   -1.390635
   7          9          0        1.427651   -0.584486   -0.170116
   8          8          0       -1.469146   -0.562284    0.049368
   9          1          0       -1.599620   -0.537118    1.002547
---------------------------------------------------------------------
```

OF*ga*: MP2 energy=-253.7256002 (Hartrees), Zero Point Energy=0.0740572 (Hartrees), imaginary
frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.718739    0.514545    0.306251
   2          1          0        0.662471    0.416119    1.392321
   3          1          0        1.276311    1.414035    0.035531
   4          6          0       -0.658965    0.550225   -0.298406
   5          1          0       -1.117199    1.513916   -0.040207
   6          1          0       -0.575743    0.479599   -1.388507
   7          9          0        1.431085   -0.588696   -0.180460
   8          8          0       -1.409773   -0.536051    0.234325
   9          1          0       -2.206061   -0.625627   -0.296664
---------------------------------------------------------------------
```

OF*ag*: MP2 energy=-253.7240898 (Hartrees), Zero Point Energy=0.0744781 (Hartrees), imaginary
frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.571946    0.503286    0.043950
   2          1          0       -0.524367    1.198584   -0.798145
   3          1          0       -0.539874    1.056720    0.984043
   4          6          0        0.549063   -0.519924   -0.019604
   5          1          0        0.472295   -1.203416    0.827110
   6          1          0        0.471470   -1.100176   -0.945279
   7          9          0       -1.800497   -0.165086   -0.026681
   8          8          0        1.813976    0.124514    0.092092
   9          1          0        1.950442    0.637779   -0.710401
---------------------------------------------------------------------
```

OF*aa*: MP2 energy=-253.7239885 (Hartrees), Zero Point Energy=0.0737812 (Hartees), imaginary frequency = -82.84

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       -0.580895    0.506140    0.000007
     2         1          0       -0.550027    1.129981   -0.894799
     3         1          0       -0.550091    1.129981    0.894817
     4         6          0        0.548760   -0.503488    0.000034
     5         1          0        0.473515   -1.135380    0.891640
     6         1          0        0.473470   -1.135462   -0.891510
     7         9          0       -1.796862   -0.188277   -0.000027
     8         8          0        1.753887    0.256855   -0.000022
     9         1          0        2.486609   -0.365371    0.000023
---------------------------------------------------------------------
```

OC*gg*: MP2 energy=-613.7084301 (Hartrees), Zero Point Energy=0.0733459 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       -0.104507    0.893132   -0.290612
     2         1          0       -0.004103    0.946899   -1.374441
     3         1          0       -0.423934    1.855679    0.109873
     4         6          0        1.199290    0.454507    0.345206
     5         1          0        1.954181    1.218040    0.140910
     6         1          0        1.072411    0.367224    1.430521
     7         8          0        1.696254   -0.753907   -0.209929
     8         1          0        1.028479   -1.430005   -0.051566
     9        17          0       -1.397986   -0.294848    0.064504
---------------------------------------------------------------------
```

OC*gg'*: MP2 energy=-613.7062584 (Hartrees), Zero Point Energy=0.0732248 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0        0.120131    0.859318    0.301849
     2         1          0        0.013390    0.899261    1.387567
     3         1          0        0.436839    1.836931   -0.064947
     4         6          0       -1.184630    0.459068   -0.359408
     5         1          0       -1.911009    1.261869   -0.174507
     6         1          0       -1.042990    0.360471   -1.436837
     7         8          0       -1.681164   -0.793928    0.085622
     8         1          0       -1.846307   -0.721194    1.031037
     9        17          0        1.422728   -0.305661   -0.063643
---------------------------------------------------------------------
```

OC*ga*: MP2 energy=-613.7064767 (Hartrees), Zero Point Energy=0.0727296 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       -0.127059    0.857033   -0.297001
     2         1          0       -0.009796    0.889696   -1.380428
     3         1          0       -0.449672    1.831179    0.071119
     4         6          0        1.175435    0.460977    0.355791
     5         1          0        1.887706    1.282748    0.203197
     6         1          0        1.026476    0.317819    1.431661
     7         8          0        1.637403   -0.733474   -0.262368
     8         1          0        2.402558   -1.039192    0.233154
     9        17          0       -1.426279   -0.313089    0.069853
---------------------------------------------------------------------
```

OC*ag*: MP2 energy =-613.7065699 (Hartrees), Zero Point Energy=0.0731315 (Hartrees), imaginary
frequency = 0

```
                     Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        -0.042602    0.607896    0.043057
    2          1           0         0.052038    1.283988   -0.807950
    3          1           0         0.051626    1.170629    0.971245
    4          6           0         0.998766   -0.499340   -0.015655
    5          1           0         0.875683   -1.169283    0.836589
    6          1           0         0.875413   -1.081558   -0.935342
    7          8           0         2.311142    0.040987    0.087291
    8          1           0         2.485323    0.539047   -0.717565
    9         17           0        -1.680365   -0.101298   -0.012336
 ---------------------------------------------------------------------
```

OC*aa*: MP2 energy=-613.706056 (Hartrees), Zero Point Energy =0.0723877 (Hartrees), imaginary
frequency = -56.54

```
                     Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
 ---------------------------------------------------------------------
    1          6           0         0.049679    0.614760   -0.000023
    2          1           0        -0.040924    1.233052    0.892338
    3          1           0        -0.040930    1.232991   -0.892426
    4          6           0        -0.996104   -0.482613    0.000019
    5          1           0        -0.874535   -1.108862   -0.890579
    6          1           0        -0.874516   -1.108814    0.890648
    7          8           0        -2.261189    0.174602    0.000015
    8          1           0        -2.939037   -0.507855   -0.000007
    9         17           0         1.678706   -0.113542   -0.000004
 ---------------------------------------------------------------------
```

OB*gg*: MP2 energy=-2726.7534363 (Hartrees), Zero Point Energy=0.0723701 (Hartrees), imaginary
frequency = 0

```
                     Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
 ---------------------------------------------------------------------
    1          6           0         0.508514    0.999076   -0.288142
    2          1           0         0.613949    1.064003   -1.371049
    3          1           0         0.272347    1.975522    0.136377
    4          6           0         1.741029    0.393711    0.356199
    5          1           0         2.582503    1.067657    0.171088
    6          1           0         1.591342    0.309043    1.439041
    7          8           0         2.098730   -0.854793   -0.215000
    8          1           0         1.350780   -1.447096   -0.074003
    9         35           0        -1.048515   -0.128214    0.028863
 ---------------------------------------------------------------------
```

OB*gg'*: MP2 energy =-2726.7509554 (Hartrees), Zero Point Energy=0.0724859 (Hartrees),
imaginary frequency = 0

```
                     Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        -0.494989    0.963135    0.300572
    2          1           0        -0.612587    1.006097    1.384965
    3          1           0        -0.259433    1.957084   -0.082872
    4          6           0        -1.732790    0.404946   -0.377287
    5          1           0        -2.542234    1.133073   -0.226536
    6          1           0        -1.558861    0.297528   -1.449332
    7          8           0        -2.107202   -0.879130    0.095876
    8          1           0        -2.309766   -0.794672    1.033243
    9         35           0         1.071633   -0.136416   -0.027605
 ---------------------------------------------------------------------
```

OB*ga*: MP2 energy=-2726.7511133 (Hartrees), Zero Point Energy=0.0718975 (Hartrees), imaginary frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0        0.488807    0.973459   -0.291598
    2          1          0        0.608838    1.026850   -1.374039
    3          1          0        0.248504    1.957742    0.110788
    4          6          0        1.725491    0.409599    0.367821
    5          1          0        2.529377    1.147928    0.240005
    6          1          0        1.545059    0.265324    1.438887
    7          8          0        2.057028   -0.815683   -0.272669
    8          1          0        2.760809   -1.226419    0.238220
    9         35          0       -1.069560   -0.141266    0.030576
 ---------------------------------------------------------------------
```

OB*ag*: MP2 energy=-2726.751653 (Hartrees), Zero Point Energy=0.0723398 (Hartrees), imaginary frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0        0.570742    0.650448    0.047444
    2          1          0        0.667467    1.318185   -0.810069
    3          1          0        0.665539    1.214481    0.975034
    4          6          0        1.571857   -0.494590   -0.008986
    5          1          0        1.432576   -1.152688    0.850101
    6          1          0        1.423696   -1.076997   -0.924994
    7          8          0        2.901592    0.007840    0.080550
    8          1          0        3.081369    0.495606   -0.729658
    9         35          0       -1.238256   -0.051327   -0.006730
 ---------------------------------------------------------------------
```

OB*aa*: MP2 energy=-2726.7511176 (Hartrees), Zero Point Energy =0.0715509 (Hartrees), imaginary frequency = -66.19

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0        0.564126    0.661986    0.000040
    2          1          0        0.656031    1.276460   -0.894984
    3          1          0        0.656013    1.276375    0.895124
    4          6          0        1.566389   -0.476251   -0.000005
    5          1          0        1.422162   -1.095898    0.891985
    6          1          0        1.422151   -1.095835   -0.892037
    7          8          0        2.854198    0.138835    0.000010
    8          1          0        3.508130   -0.567078    0.000028
    9         35          0       -1.236605   -0.057689   -0.000012
 ---------------------------------------------------------------------
```

OI*gg*: MP2 energy=-451.2165692 (Hartrees), Zero Point Energy =0.0717348 (Hartrees), imaginary frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0        0.933637    1.039735   -0.283947
    2          1          0        1.052776    1.113219   -1.365127
    3          1          0        0.750531    2.022703    0.152272
    4          6          0        2.121732    0.352368    0.365293
    5          1          0        3.002624    0.979300    0.195362
    6          1          0        1.960826    0.263522    1.446243
    7          8          0        2.420544   -0.906024   -0.217947
    8          1          0        1.644706   -1.464624   -0.087329
    9         53          0       -0.869963   -0.075822    0.017247
 ---------------------------------------------------------------------
```

OI*gg'*: MP2 energy=-451.2145102 (Hartrees), Zero Point Energy=0.0717494 (Hartrees), imaginary frequency = 0

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.922717    1.015997    0.292341
   2          1          0       -1.049037    1.076164    1.375073
   3          1          0       -0.741281    2.013011   -0.112574
   4          6          0       -2.117922    0.365301   -0.382361
   5          1          0       -2.978110    1.034328   -0.236132
   6          1          0       -1.940220    0.261837   -1.454260
   7          8          0       -2.403116   -0.938002    0.100280
   8          1          0       -2.615767   -0.859528    1.036000
   9         53          0        0.882890   -0.081313   -0.016419
---------------------------------------------------------------------
```

OI*ga*: MP2 energy=-451.2145721 (Hartrees), Zero Point Energy=0.0713437 (Hartrees), imaginary frequency = 0

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.917796    1.028053   -0.283934
   2          1          0        1.046367    1.101735   -1.364325
   3          1          0        0.731441    2.013812    0.143051
   4          6          0        2.111740    0.370909    0.369919
   5          1          0        2.970263    1.043249    0.230397
   6          1          0        1.934237    0.245056    1.444131
   7          8          0        2.343194   -0.879354   -0.266526
   8          1          0        3.079310   -1.300826    0.187489
   9         53          0       -0.880837   -0.084188    0.018407
---------------------------------------------------------------------
```

OI*ag*: MP2 energy=-451.2155641 (Hartrees), Zero Point Energy=0.0718114 (Hartrees), imaginary frequency = 0

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.998789    0.675453    0.045737
   2          1          0        1.103396    1.338415   -0.814771
   3          1          0        1.106000    1.239890    0.972006
   4          6          0        1.973652   -0.492003   -0.010973
   5          1          0        1.823219   -1.149522    0.846851
   6          1          0        1.816758   -1.071246   -0.927863
   7          8          0        3.315484   -0.019631    0.080419
   8          1          0        3.499182    0.481881   -0.720669
   9         53          0       -1.013341   -0.033643   -0.003915
---------------------------------------------------------------------
```

OI*aa*: MP2 energy=-451.2148032 (Hartrees), Zero Point Energy=0.070905 (Hartrees), imaginary frequency = -73.30

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.991669    0.689131    0.000077
   2          1          0        1.093662    1.301386   -0.895595
   3          1          0        1.093625    1.301252    0.895845
   4          6          0        1.967058   -0.472144    0.000007
   5          1          0        1.812019   -1.090072    0.891642
   6          1          0        1.812021   -1.089957   -0.891708
   7          8          0        3.270794    0.111901    0.000048
   8          1          0        3.906961   -0.610556    0.000054
   9         53          0       -1.012019   -0.037909   -0.000021
---------------------------------------------------------------------
```

STANDARD COORDINATES IN DMSO

FF *g*: MP2 energy=-277.7275486 (Hartrees), Zero Point Energy=0.0621587 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
     1          6          0        0.260723    0.704026    0.532219
     2          1          0        1.348372    0.721888    0.448252
     3          1          0       -0.058499    1.216130    1.442466
     4          6          0       -0.260723   -0.704026    0.532219
     5          1          0        0.058499   -1.216130    1.442466
     6          1          0       -1.348372   -0.721888    0.448252
     7          9          0       -0.260723    1.401463   -0.564893
     8          9          0        0.260723   -1.401463   -0.564893
 ---------------------------------------------------------------------
```

FF*a*: MP2 energy=-277.7240649 (Hartrees), Zero Point Energy=0.0622302 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
     1          6          0        0.429822    0.623872   -0.000021
     2          1          0        1.049847    0.675746   -0.895402
     3          1          0        1.049934    0.675731    0.895309
     4          6          0       -0.429822   -0.623872   -0.000021
     5          1          0       -1.049934   -0.675731    0.895309
     6          1          0       -1.049847   -0.675746   -0.895402
     7          9          0       -0.429822    1.728935    0.000024
     8          9          0        0.429822   -1.728935    0.000024
 ---------------------------------------------------------------------
```

FC*g*: MP2 energy=-637.70782 (Hartrees), Zero Point Energy=0.0608672 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
     1          6          0       -1.196162   -0.427617    0.357700
     2          1          0       -1.073045   -0.267749    1.429632
     3          1          0       -1.968517   -1.177566    0.171695
     4          6          0        0.091455   -0.858840   -0.294002
     5          1          0        0.380881   -1.836987    0.091482
     6          1          0       -0.022732   -0.905745   -1.376452
     7          9          0       -1.632309    0.778718   -0.201501
     8         17          0        1.411908    0.288137    0.065586
 ---------------------------------------------------------------------
```

FC*a*: MP2 energy=-637.7065981 (Hartrees), Zero Point Energy=0.0608918 (Hartrees), imaginary
frequency = 0

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
     1          6          0        0.994480   -0.492229   -0.000067
     2          1          0        0.909931   -1.110208   -0.894788
     3          1          0        0.910229   -1.110124    0.894743
     4          6          0       -0.030507    0.622701    0.000019
     5          1          0        0.064684    1.238206    0.893153
     6          1          0        0.064538    1.238170   -0.893158
     7          9          0        2.269053    0.090333   -0.000310
     8         17          0       -1.656159   -0.108934    0.000184
 ---------------------------------------------------------------------
```

FB*g*: MP2 energy=-2750.7523741 (Hartrees), Zero Point Energy=0.0599722 (Hartrees), imaginary
frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6          0            1.737412    0.373271    0.369865
    2          1          0            1.581612    0.211831    1.437560
    3          1          0            2.588471    1.040198    0.208097
    4          6          0            0.516370    0.960363   -0.290852
    5          1          0            0.304803    1.947264    0.122124
    6          1          0            0.637353    1.021364   -1.371889
    7          9          0            2.050356   -0.860670   -0.209058
    8         35          0           -1.059661   -0.127898    0.028901
 ---------------------------------------------------------------------
```

FB*a*: MP2 energy=-2750.7516958 (Hartrees), Zero Point Energy=0.0599763 (Hartrees), imaginary
frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6          0            1.556998   -0.486497   -0.000205
    2          1          0            1.450550   -1.099327   -0.896356
    3          1          0            1.450690   -1.099436    0.895889
    4          6          0            0.576816    0.668264   -0.000078
    5          1          0            0.674961    1.279846    0.895770
    6          1          0            0.674753    1.279854   -0.895948
    7          9          0            2.852681    0.052430   -0.000252
    8         35          0           -1.220799   -0.054955    0.000132
 ---------------------------------------------------------------------
```

FI*g*: MP2 energy=-475.2156155 (Hartrees), Zero Point Energy=0.0594152 (Hartrees), imaginary
frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6          0            2.120092    0.334362    0.373552
    2          1          0            1.959994    0.177856    1.441427
    3          1          0            3.015718    0.941074    0.211980
    4          6          0            0.940539    1.007885   -0.282321
    5          1          0            0.780050    1.994667    0.153790
    6          1          0            1.071939    1.088680   -1.361015
    7          9          0            2.350617   -0.915319   -0.211982
    8         53          0           -0.874473   -0.075809    0.017250
 ---------------------------------------------------------------------
```

FI*a*: MP2 energy=-475.2157538 (Hartrees), Zero Point Energy=0.0593826 (Hartrees), imaginary
frequency = 0

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6          0            1.953024   -0.482598   -0.000059
    2          1          0            1.836790   -1.094176   -0.896067
    3          1          0            1.836699   -1.094338    0.895829
    4          6          0            1.001462    0.694149   -0.000040
    5          1          0            1.109640    1.303036    0.896704
    6          1          0            1.109624    1.303035   -0.896798
    7          9          0            3.264587    0.024106    0.000064
    8         53          0           -1.000018   -0.035921    0.000007
 ---------------------------------------------------------------------
```

OF*gg*: MP2 energy=-253.7293577 (Hartrees), Zero Point Energy=0.0744799 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.714201    0.560839   -0.285961
   2          1          0       -0.690875    0.520568   -1.376211
   3          1          0       -1.292479    1.421066    0.056906
   4          6          0        0.678551    0.574456    0.291582
   5          1          0        1.178087    1.494882   -0.018846
   6          1          0        0.622609    0.557208    1.386004
   7          9          0       -1.373640   -0.603065    0.155596
   8          8          0        1.467299   -0.507496   -0.194327
   9          1          0        1.020929   -1.317934    0.072662
---------------------------------------------------------------------
```

OF*gg'*: MP2 energy=-253.7283569 (Hartrees), Zero Point Energy=0.0743786 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.711667    0.519626    0.315758
   2          1          0        0.659777    0.420473    1.402879
   3          1          0        1.272927    1.418859    0.050965
   4          6          0       -0.663379    0.556212   -0.305920
   5          1          0       -1.142916    1.499778   -0.017071
   6          1          0       -0.573106    0.531509   -1.393430
   7          9          0        1.426179   -0.587133   -0.167730
   8          8          0       -1.464585   -0.565760    0.051025
   9          1          0       -1.625346   -0.515372    0.998998
---------------------------------------------------------------------
```

OF*ga*: MP2 energy=-253.7284632 (Hartrees), Zero Point Energy=0.0740977 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.719295    0.520300    0.304717
   2          1          0        0.672251    0.427648    1.391496
   3          1          0        1.278164    1.415131    0.024002
   4          6          0       -0.659990    0.553671   -0.293954
   5          1          0       -1.124097    1.508172   -0.016241
   6          1          0       -0.584603    0.501708   -1.385557
   7          9          0        1.426943   -0.591744   -0.180235
   8          8          0       -1.399642   -0.549969    0.222919
   9          1          0       -2.242892   -0.571037   -0.239519
---------------------------------------------------------------------
```

OF*ag*: MP2 energy=-253.7263834 (Hartrees), Zero Point Energy=0.0744715 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.570420    0.504641    0.043685
   2          1          0       -0.523596    1.198687   -0.798642
   3          1          0       -0.540370    1.056938    0.984275
   4          6          0        0.548526   -0.520495   -0.020221
   5          1          0        0.470580   -1.204861    0.825786
   6          1          0        0.472457   -1.097793   -0.947483
   7          9          0       -1.801241   -0.165358   -0.026275
   8          8          0        1.814411    0.123635    0.092499
   9          1          0        1.948175    0.641291   -0.708241
---------------------------------------------------------------------
```

OF*aa*: MP2 energy=-253.7259839 (Hartrees), Zero Point Energy =0.0737559 (Hartrees), imaginary frequency = -80.87

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0      -0.580508    0.507021    0.000034
   2          1          0      -0.552326    1.130360   -0.895029
   3          1          0      -0.552411    1.130232    0.895189
   4          6          0       0.548646   -0.502991    0.000006
   5          1          0       0.475139   -1.134550    0.891576
   6          1          0       0.475117   -1.134510   -0.891590
   7          9          0      -1.797998   -0.189043   -0.000063
   8          8          0       1.755175    0.256738    0.000014
   9          1          0       2.486237   -0.368234    0.000062
---------------------------------------------------------------------
```

OC*gg*: MP2 energy=-613.7101824 (Hartrees), Zero Point Energy=0.0732725 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0      -0.104739    0.894048   -0.289619
   2          1          0      -0.006163    0.949893   -1.373374
   3          1          0      -0.423753    1.855420    0.113298
   4          6          0       1.198959    0.455580    0.345247
   5          1          0       1.952110    1.220498    0.140735
   6          1          0       1.073900    0.365645    1.430067
   7          8          0       1.697400   -0.753731   -0.211830
   8          1          0       1.038969   -1.435291   -0.037384
   9         17          0      -1.398799   -0.295534    0.063972
---------------------------------------------------------------------
```

OC*gg'*: MP2 energy=-613.7091052 (Hartrees), Zero Point Energy=0.0731918 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.118602    0.860382    0.302773
   2          1          0       0.010427    0.897166    1.387857
   3          1          0       0.437004    1.837056   -0.063935
   4          6          0      -1.182827    0.458463   -0.362539
   5          1          0      -1.910136    1.260050   -0.181272
   6          1          0      -1.037813    0.356962   -1.439261
   7          8          0      -1.680803   -0.794702    0.087029
   8          1          0      -1.878723   -0.706312    1.025223
   9         17          0       1.424177   -0.305904   -0.062720
---------------------------------------------------------------------
```

OC*ga*: MP2 energy=-613.7091025 (Hartrees), Zero Point Energy=0.0727356 (Hartrees), imaginary frequency = 0

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0      -0.126476    0.860390   -0.297594
   2          1          0      -0.016035    0.897302   -1.381394
   3          1          0      -0.449074    1.831957    0.076333
   4          6          0       1.176605    0.462889    0.351626
   5          1          0       1.892842    1.275981    0.178674
   6          1          0       1.037258    0.338071    1.430895
   7          8          0       1.627467   -0.747261   -0.248243
   8          1          0       2.463923   -0.978865    0.166984
   9         17          0      -1.426437   -0.313296    0.070015
---------------------------------------------------------------------
```

OC*ag*: MP2 energy=-613.7086763 (Hartrees), Zero Point Energy=0.0731693 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0       -0.041266    0.608563    0.043898
    2          1          0        0.053905    1.283789   -0.807155
    3          1          0        0.050218    1.170082    0.972976
    4          6          0        0.998027   -0.500237   -0.015202
    5          1          0        0.875171   -1.170495    0.836915
    6          1          0        0.875700   -1.080178   -0.936075
    7          8          0        2.311302    0.040507    0.086603
    8          1          0        2.481190    0.543371   -0.716812
    9         17          0       -1.680421   -0.101211   -0.012638
 ---------------------------------------------------------------------
```

OC*aa*: MP2 energy=-613.7078781 (Hartrees), Zero Point Energy=0.0723751 (Hartrees), imaginary frequency = -54.48

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0       -0.049465    0.615339   -0.000005
    2          1          0        0.038773    1.233346   -0.892755
    3          1          0        0.038793    1.233366    0.892730
    4          6          0        0.996008   -0.482362   -0.000005
    5          1          0        0.876480   -1.108340    0.890625
    6          1          0        0.876453   -1.108365   -0.890614
    7          8          0        2.262270    0.174660   -0.000034
    8          1          0        2.938757   -0.509860   -0.000013
    9         17          0       -1.679216   -0.113841    0.000021
 ---------------------------------------------------------------------
```

OB*gg*: MP2 energy=-2726.7551933 (Hartrees), Zero Point Energy=0.0723052 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0        0.508868    1.000407   -0.286864
    2          1          0        0.611886    1.068535   -1.369669
    3          1          0        0.272908    1.975126    0.141017
    4          6          0        1.741507    0.394870    0.355629
    5          1          0        2.581741    1.069485    0.168758
    6          1          0        1.594517    0.308456    1.438200
    7          8          0        2.099065   -0.855542   -0.216676
    8          1          0        1.358840   -1.453566   -0.059072
    9         35          0       -1.048990   -0.128439    0.028617
 ---------------------------------------------------------------------
```

OB*gg'*: MP2 energy =-2726.7538437 (Hartrees), Zero Point Energy=0.0723743 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic     Atomic          Coordinates (Angstroms)
 Number     Number     Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6          0       -0.496585    0.965383    0.300853
    2          1          0       -0.613164    1.007200    1.384845
    3          1          0       -0.259089    1.957637   -0.084864
    4          6          0       -1.731137    0.404760   -0.379329
    5          1          0       -2.541915    1.130482   -0.230532
    6          1          0       -1.554627    0.296474   -1.450880
    7          8          0       -2.104516   -0.880533    0.097177
    8          1          0       -2.346070   -0.785237    1.024639
    9         35          0        1.071924   -0.136662   -0.027136
 ---------------------------------------------------------------------
```

OB*ga*: MP2 energy=-2726.753784 (Hartrees), Zero Point Energy=0.0719051 (Hartrees), imaginary frequency = 0

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number       Type         X           Y           Z
---------------------------------------------------------------------
   1          6           0        0.490120    0.976992   -0.291706
   2          1           0        0.603374    1.036016   -1.374377
   3          1           0        0.248766    1.957789    0.117632
   4          6           0        1.727516    0.411494    0.363070
   5          1           0        2.534307    1.141791    0.215387
   6          1           0        1.559257    0.283069    1.437920
   7          8           0        2.044839   -0.827640   -0.261384
   8          1           0        2.817022   -1.183556    0.189554
   9         35           0       -1.069350   -0.141283    0.030765
---------------------------------------------------------------------
```

OB*ag*: MP2 energy=-2726.7537992 (Hartrees), Zero Point Energy=0.0723333 (Hartrees), imaginary frequency = 0

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number       Type         X           Y           Z
---------------------------------------------------------------------
   1          6           0        0.571918    0.651320    0.048127
   2          1           0        0.668768    1.317999   -0.809655
   3          1           0        0.663729    1.214464    0.976463
   4          6           0        1.571060   -0.495171   -0.008366
   5          1           0        1.431856   -1.153351    0.850763
   6          1           0        1.424010   -1.075636   -0.925409
   7          8           0        2.901747    0.007441    0.080011
   8          1           0        3.079086    0.497046   -0.730264
   9         35           0       -1.238265   -0.051341   -0.006873
---------------------------------------------------------------------
```

OB*aa*: MP2 energy=-2726.7529681 (Hartrees), Zero Point Energy=0.0715329 (Hartrees), imaginary frequency = -63.12

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number       Type         X           Y           Z
---------------------------------------------------------------------
   1          6           0        0.564472    0.662759    0.000026
   2          1           0        0.653867    1.277013   -0.895390
   3          1           0        0.653859    1.276956    0.895481
   4          6           0        1.566388   -0.475874   -0.000007
   5          1           0        1.424173   -1.095371    0.891999
   6          1           0        1.424157   -1.095332   -0.892039
   7          8           0        2.855418    0.138754   -0.000003
   8          1           0        3.507744   -0.569311    0.000012
   9         35           0       -1.236923   -0.057866   -0.000004
---------------------------------------------------------------------
```

OI*gg*: MP2 energy=-451.2182729 (Hartrees), Zero Point Energy=0.0716559 (Hartrees), imaginary frequency = 0

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number       Type         X           Y           Z
---------------------------------------------------------------------
   1          6           0        0.933754    1.040310   -0.283170
   2          1           0        1.051300    1.116219   -1.364273
   3          1           0        0.750676    2.022074    0.155163
   4          6           0        2.122243    0.353759    0.364992
   5          1           0        3.001694    0.981939    0.193722
   6          1           0        1.963432    0.262854    1.445577
   7          8           0        2.421879   -0.906400   -0.219261
   8          1           0        1.652397   -1.470719   -0.075304
   9         53           0       -0.870387   -0.075954    0.017137
---------------------------------------------------------------------
```

OI*gg'*: MP2 energy=-451.2172645 (Hartrees), Zero Point Energy=0.0717754 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.924007    1.017215    0.292955
   2          1          0       -1.049908    1.075261    1.375407
   3          1          0       -0.740613    2.013168   -0.112913
   4          6          0       -2.116440    0.365544   -0.384164
   5          1          0       -2.977115    1.032789   -0.238354
   6          1          0       -1.937135    0.261963   -1.455763
   7          8          0       -2.401589   -0.938867    0.101121
   8          1          0       -2.640594   -0.854102    1.030363
   9         53          0        0.883033   -0.081409   -0.016235
---------------------------------------------------------------------
```

OI*ga*: MP2 energy=-451.217135 (Hartrees), Zero Point Energy=0.0713789 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.918919    1.029902   -0.284622
   2          1          0        1.042444    1.106879   -1.365189
   3          1          0        0.730477    2.013223    0.146385
   4          6          0        2.113243    0.372661    0.366980
   5          1          0        2.972993    1.038681    0.211963
   6          1          0        1.945940    0.258728    1.443861
   7          8          0        2.335823   -0.888289   -0.255651
   8          1          0        3.130754   -1.262853    0.137450
   9         53          0       -0.881173   -0.084221    0.018426
---------------------------------------------------------------------
```

OI*ag*: MP2energy=-451.2176633 (Hartrees), Zero Point Energy=0.0717922 (Hartrees), imaginary frequency = 0

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.999406    0.676451    0.046322
   2          1          0        1.103938    1.338277   -0.814588
   3          1          0        1.103588    1.240308    0.973235
   4          6          0        1.972472   -0.492283   -0.010033
   5          1          0        1.822081   -1.149501    0.848121
   6          1          0        1.816772   -1.070076   -0.927637
   7          8          0        3.315446   -0.019776    0.079947
   8          1          0        3.498415    0.479577   -0.723282
   9         53          0       -1.013201   -0.033687   -0.004022
---------------------------------------------------------------------
```

OI*aa*: MP2 energy=-451.2166347 (Hartrees), Zero Point Energy=0.0708837 (Hartrees), imaginary frequency = -74.70

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.991657    0.690000    0.000074
   2          1          0        1.091117    1.302111   -0.896018
   3          1          0        1.091080    1.301985    0.896255
   4          6          0        1.966804   -0.471581    0.000010
   5          1          0        1.813820   -1.089404    0.891640
   6          1          0        1.813824   -1.089300   -0.891694
   7          8          0        3.272037    0.111704    0.000048
   8          1          0        3.906264   -0.613089    0.000062
   9         53          0       -1.012135   -0.038046   -0.000021
---------------------------------------------------------------------
```
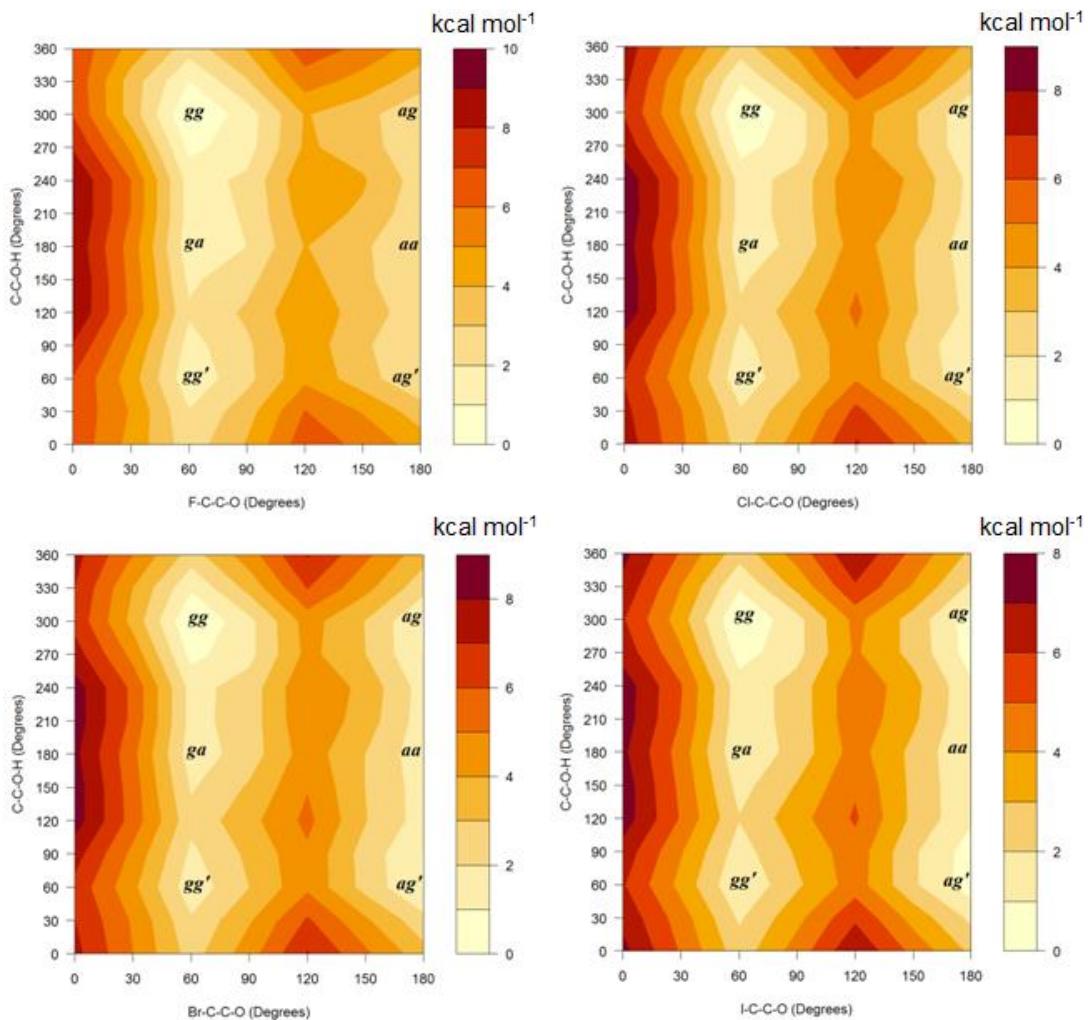
Figure S1. Potential energy surfaces for 2-haloethanols(X–C–C–O and C–C–O–H torsion in the *gauche* and *anti* conformers) in chloroform implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2 TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).
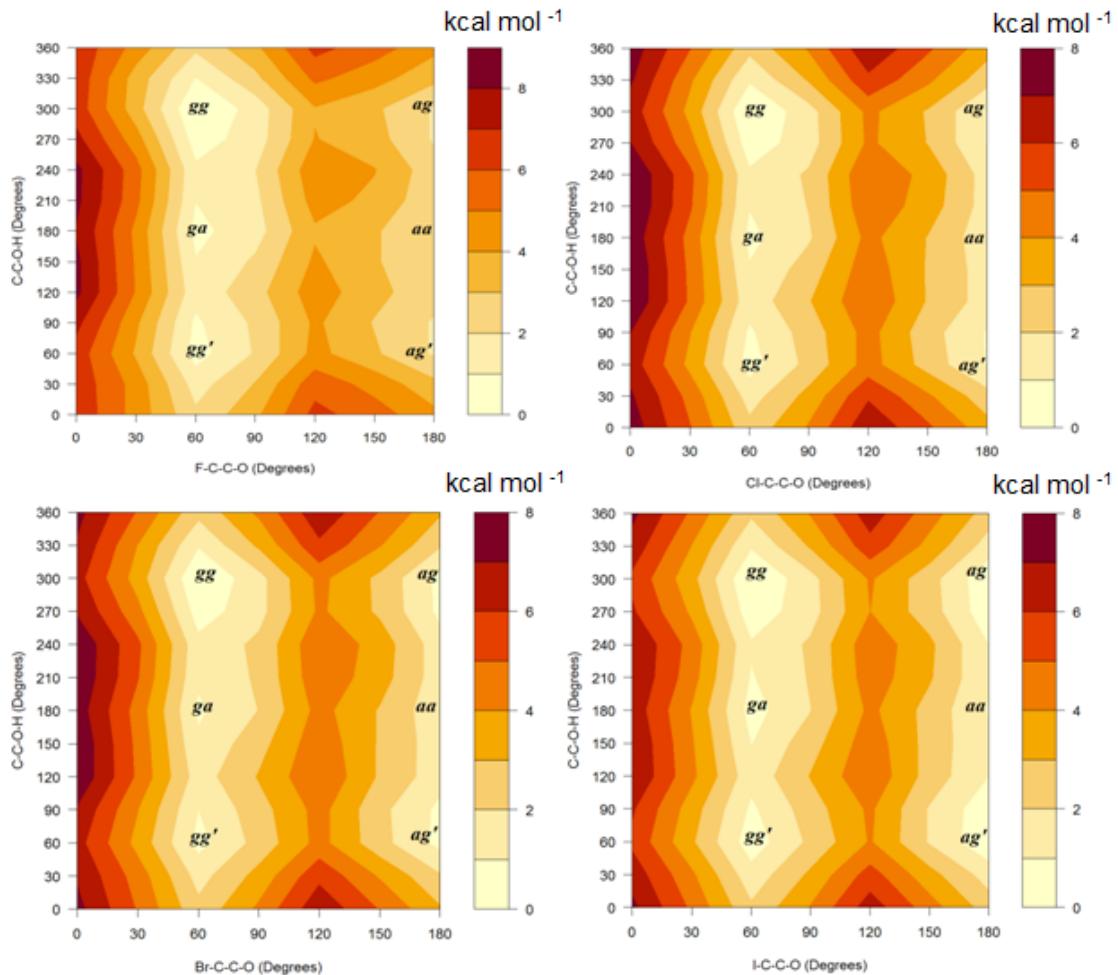
Figure S2. Potential energy surfaces for 2-haloethanols(X–C–C–O and C–C–O–H torsion in the *gauche* and *anti* conformers) in DMSO implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2 TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).

Table S1. Lewis (L) and non-Lewis (NL) contributions to the full electronic conformational energies of 2-halofluoroethanes and 2-haloethanols, and important electron delocalization interactions obtained by NBO analysis (data in kcal mol^{-1}) in chloroform implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2-TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).

Name	Conf.	ΔE_{FULL}	ΔE_L	ΔE_{NL}	$\sigma_{CH}\rightarrow\sigma^*_{CF(OH)}$	$\sigma_{CH}\rightarrow\sigma^*_{CX}$	$\sigma_{CF(OH)}\rightarrow\sigma^*_{CH}$	$\sigma_{CX}\rightarrow\sigma^*_{CH}$	$\sigma_{CH}\rightarrow\sigma^*_{CH}$	$\sigma_{CF(OH)}\rightarrow\sigma^*_{CX}$	$\sigma_{CX}\rightarrow\sigma^*_{CF(OH)}$
FF	*g*	0.00	6.41	-6.41	4.71	4.71	0.68	0.68	4.46	-	-
	a	1.77	1.77	0.00	1.10	1.10	-	-	8.04	1.52	1.52
FC	*g*	0.00	3.00	-3.00	4.59	5.50	0.82	1.38	4.81	-	-
	a	0.39	0.39	0.00	1.24	-	-	-	9.02	1.83	2.96
FB	*g*	0.00	2.73	-2.73	4.50	6.27	0.87	1.71	4.87	-	-
	a	0.01	0.01	0.00	1.22	-	-	-	9.26	2.16	3.84
FI	*g*	0.40	1.97	-1.57	4.53	6.42	0.90	2.16	4.94	-	-
	a	0.00	0.00	0.00	1.22	-	-	-	9.58	2.27	4.99
OF	*gg*	0.00	6.28	-6.28	4.19	4.84	0.78	0.82	4.76	-	-
	gg′	1.27	9.48	-8.21	4.55	4.89	0.71	0.72	4.80	-	-
	ga	1.10	5.92	-4.82	3.86	4.91	0.84	0.72	4.65	-	-
	ag	2.00	4.65	-2.65	-	1.10	-	-	8.66	1.70	1.47
	aa	2.09	2.09	0.00	-	1.14	-	-	8.56	1.96	1.36
OC	*gg*	0.00	5.71	-5.71	4.17	5.66	0.89	1.56	5.02	-	-
	gg′	1.39	7.10	-5.71	4.43	5.79	0.81	1.38	5.11	-	-
	ga	1.24	3.76	-2.52	3.73	5.81	1.02	1.41	5.00	-	-
	ag	1.05	3.75	-2.70	-	-	-	-	9.52	2.06	2.74
	aa	1.39	1.39	0.00	-	-	-	-	9.48	2.40	2.51
OB	*gg*	0.00	6.14	-6.14	4.08	6.45	0.93	1.83	5.07	-	-
	gg′	1.40	7.05	-5.65	4.33	6.62	0.86	1.67	5.17	-	-
	ga	1.34	3.75	-2.41	3.68	6.59	1.08	1.73	5.07	-	-
	ag	0.81	3.55	-2.74	-	-	-	-	9.69	2.42	3.43
	aa	1.33	1.33	0.00	-	-	-	-	9.66	2.80	3.16
OI	*gg*	0.00	6.24	-6.24	4.13	6.75	0.94	2.23	5.10	-	-
	gg′	1.16	6.07	-4.91	4.32	6.82	0.89	2.09	5.22	-	-
	ga	1.14	3.04	-1.90	3.70	6.81	1.12	2.16	5.15	-	-
	ag	0.37	3.23	-2.86	-	-	-	-	9.95	2.54	4.33
	aa	1.02	1.02	0.00	-	-	-	-	9.92	2.93	3.97

Table S2. Lewis (L) and non-Lewis (NL) contributions to the full electronic conformational energies of 2-halofluoroethanes and 2-haloethanols, and important electron delocalization interactions obtained by NBO analysis (data in kcal mol^{-1}) in DMSO implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2-TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).

Name	Conf.	ΔE_{FULL}	ΔE_L	ΔE_{NL}	$\sigma_{CH}\rightarrow\sigma^*_{CF(OH)}$	$\sigma_{CH}\rightarrow\sigma^*_{CX}$	$\sigma_{CF(OH)}\rightarrow\sigma^*_{CH}$	$\sigma_{CX}\rightarrow\sigma^*_{CH}$	$\sigma_{CH}\rightarrow\sigma^*_{CH}$	$\sigma_{CF(OH)}\rightarrow\sigma^*_{CX}$	$\sigma_{CX}\rightarrow\sigma^*_{CF(OH)}$
FF	*g*	0.00	6.06	-6.06	4.76	4.76	0.68	0.68	4.46	-	-
	a	2.28	2.28	0.00	1.10	1.10	-	-	8.00	1.53	1.53
FC	*g*	0.00	3.20	-3.20	4.67	5.55	0.82	1.42	4.82	-	-
	a	0.90	0.90	0.00	1.24	-	-	-	8.98	1.84	2.98
FB	*g*	0.00	2.64	-2.64	4.58	6.34	0.86	1.70	4.87	-	-
	a	0.50	0.50	0.00	1.22	-	-	-	9.22	2.17	3.86
FI	*g*	0.00	1.56	-1.56	4.60	6.51	0.89	2.14	4.92	-	-
	a	0.02	0.02	0.00	1.22	-	-	-	9.56	2.28	5.03
OF	*gg*	0.00	6.29	-6.29	4.26	4.91	0.77	0.81	4.75	-	-
	gg′	0.56	7.87	-7.31	4.56	4.91	0.71	0.73	4.77	-	-
	ga	0.54	5.03	-4.49	3.91	5.04	0.84	0.72	2.70	-	-
	ag	1.81	4.26	-2.45	-	1.11	-	-	8.60	1.71	1.47
	aa	2.08	2.08	0.00	-	1.14	-	-	8.56	1.97	1.36
OC	*gg*	0.00	5.67	-5.67	4.24	5.71	0.87	1.54	5.01	-	-
	gg′	0.66	5.84	-5.18	4.45	5.86	0.81	1.37	5.08	-	-
	ga	0.67	3.04	-2.37	3.82	5.97	1.01	1.39	5.03	-	-
	ag	0.85	3.46	-2.61	-	-	-	-	9.47	2.07	2.74
	aa	1.37	1.37	0.00	-	-	-	-	9.48	2.42	2.51
OB	*gg*	0.00	6.08	-6.08	4.15	6.51	0.91	1.82	5.07	-	-
	gg′	0.71	5.94	-5.23	4.36	6.68	0.85	1.66	5.14	-	-
	ga	0.79	3.24	-2.45	3.76	6.77	1.06	1.71	5.11	-	-
	ag	0.61	3.30	-2.69	-	-	-	-	9.65	2.43	3.43
	aa	1.31	1.31	0.00	-	-	-	-	9.66	2.82	3.16
OI	*gg*	0.00	6.19	-6.19	4.19	6.79	0.92	2.21	5.09	-	-
	gg′	0.52	5.21	-4.69	4.35	6.91	0.88	2.08	5.18	-	-
	ga	0.63	2.58	-1.95	3.76	6.99	1.11	2.13	5.16	-	-
	ag	0.15	3.00	-2.85	-	-	-	-	9.91	2.54	4.35
	aa	0.96	0.96	0.00	-	-	-	-	9.9	2.94	3.97

Table S3. $\varepsilon_i - \varepsilon_j$ and $F(i,j)$ contributions to electron delocalization energies (kcal mol^{-1}) for 2-halofluoroethanes in gas phase.

Name	Structure	Conformer	$\sigma_{CH} \rightarrow \sigma^*_{CX}$		$\sigma_{CX} \rightarrow \sigma^*_{CF}$	
			$\varepsilon_i - \varepsilon_j$	$F(i,j)$	$\varepsilon_i - \varepsilon_j$	$F(i,j)$
FF	F-CH$_2$-CH$_2$-F	g	0.76	0.053	-	-
		a	-	-	1.15	0.037
FC	F-CH$_2$-CH$_2$-Cl	g	0.66	0.053	-	-
		a	-	-	0.90	0.046
FB	F-CH$_2$-CH$_2$-Br	g	0.61	0.054	-	-
		a	-	-	0.83	0.050
FI	F-CH$_2$-CH$_2$-I	g	0.58	0.053	-	-
		a	-	-	0.74	0.054

Table S4. $\varepsilon_i - \varepsilon_j$ and $F(i,j)$ contributions to electron delocalization energies (kcalmol^{-1}) for 2-halofluoroethanes in chloroform implicit solvent.

Name	Structure	Conformer	$\sigma_{CH} \rightarrow \sigma^*_{CX}$		$\sigma_{CX} \rightarrow \sigma^*_{CF}$	
			$\varepsilon_i - \varepsilon_j$	$F(i,j)$	$\varepsilon_i - \varepsilon_j$	$F(i,j)$
FF	F-CH$_2$-CH$_2$-F	g	0.75	0.053	-	-
		a	-	-	1.14	0.037
FC	F-CH$_2$-CH$_2$-Cl	g	0.65	0.054	-	-
		a	-	-	0.89	0.046
FB	F-CH$_2$-CH$_2$-Br	g	0.60	0.055	-	-
		a	-	-	0.82	0.050
FI	F-CH$_2$-CH$_2$-I	g	0.57	0.054	-	-
		a	-	-	0.73	0.054

Table S5. $\varepsilon_i - \varepsilon_j$ and $F(i,j)$ contributions to electron delocalization energies (kcal mol^{-1}) for 2-halofluoroethanes in DMSO implicit solvent.

Name	Structure	Conformer	$\sigma CH \rightarrow \sigma^* CX$		$\sigma CX \rightarrow \sigma^* CF$	
			$\varepsilon_i - \varepsilon_j$	$F(i,j)$	$\varepsilon_i - \varepsilon_j$	$F(i,j)$
FF	F-CH$_2$-CH$_2$-F	g	0.74	0.053	-	-
		a	-	-	1.14	0.037
FC	F-CH$_2$-CH$_2$-Cl	g	0.65	0.053	-	-
		a	-	-	0.89	0.046
FB	F-CH$_2$-CH$_2$-Br	g	0.60	0.055	-	-
		a	-	-	0.81	0.050
FI	F-CH$_2$-CH$_2$-I	g	0.57	0.054	-	-
		a	-	-	0.72	0.054

Table S6. Calculated spin-spin coupling constants (Hz) for the studied 2-halofluoroethanes and 2-haloethanols in gas phase obtained ate the B3LYP/6-311++(d,p) level of theory (def2-TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).
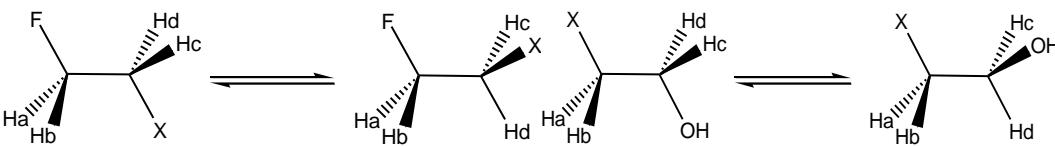
Name	Conf.	$^3J_{HaHc}$	$^3J_{HaHd}$	$^3J_{HbHc}$	$^3J_{HbHd}$	$^3J_{FHc}$	$^3J_{FHd}$	$^2J_{FHa}$	$^2J_{FHb}$
FF	*g*	1.11	1.48	8.61	1.11	17.27	33.75	46.58	51.89
	a	10.01	5.42	5.42	10.01	1.27	1.26	47.13	47.13
FC	*g*	2.40	1.97	9.91	1.45	13.14	31.92	47.37	49.58
	a	10.68	5.47	5.47	10.68	3.68	3.68	47.89	47.89
FB	*g*	2.88	2.28	10.55	1.69	11.46	32.72	48.33	49.06
	a	11.06	5.49	5.50	11.06	4.86	4.86	48.42	48.42
FI	*g*	3.00	1.85	10.73	1.23	8.64	34.06	49.04	47.57
	a	11.07	4.79	4.79	11.07	5.98	5.98	48.63	48.63
OF	*gg*	2.01	1.04	9.22	1.81	15.98	34.40	47.32	52.04
	gg'	2.15	1.25	9.67	1.31	14.85	33.24	46.78	51.73
	ga	1.14	1.93	8.43	0.92	14.43	34.06	47.51	51.19
	ag	9.68	5.48	4.93	10.32	1.83	1.54	47.73	47.63
	aa	9.56	5.34	5.33	9.56	2.85	2.85	47.51	47.51
OC	*gg*	1.92	1.99	9.92	2.63	-	-	-	-
	gg'	2.44	1.76	10.73	2.54	-	-	-	-
	ga	1.69	2.41	9.71	2.07	-	-	-	-
	ag	10.26	5.29	5.06	10.92	-	-	-	-
	aa	10.30	5.35	5.35	10.30	-	-	-	-
OB	*gg*	2.11	2.27	10.49	3.07	-	-	-	-
	gg'	2.55	2.11	11.25	2.92	-	-	-	-
	ga	1.97	2.69	10.35	2.51	-	-	-	-
	ag	10.65	5.35	5.06	11.31	-	-	-	-
	aa	10.69	5.41	5.41	10.69	-	-	-	-
OI	*gg*	1.44	2.07	10.44	2.90	-	-	-	-
	gg'	2.07	1.69	11.30	2.98	-	-	-	-
	ga	1.55	2.23	10.48	2.63	-	-	-	-
	ag	10.60	4.55	4.40	11.25	-	-	-	-
	aa	10.65	4.70	4.70	10.65	-	-	-	-

Table S7. Calculated spin-spin coupling constants (Hz) for the studied 2-halofluoroethanes and 2-haloethanols in chloroform implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2-TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).
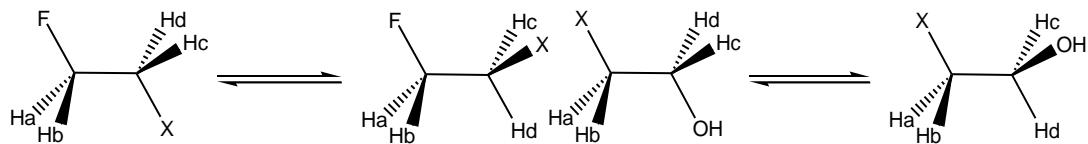
Name	Conf.	$^3J_{HaHc}$	$^3J_{HaHd}$	$^3J_{HbHc}$	$^3J_{HbHd}$	$^3J_{FHc}$	$^3J_{FHd}$	$^2J_{FHa}$	$^2J_{FHb}$
					Chloroform				
FF	g	1.27	1.23	8.68	1.27	17.89	36.73	46.10	52.90
	a	10.03	5.43	5.43	10.03	1.34	1.33	46.88	46.87
FC	g	2.54	1.75	9.94	1.59	13.40	35.03	47.23	50.31
	a	10.71	5.47	5.47	10.71	3.88	3.87	47.78	47.78
FB	g	3.00	2.07	10.56	1.80	11.65	35.91	48.29	49.70
	a	11.09	5.50	5.50	11.09	5.10	5.10	48.38	48.38
FI	g	3.10	1.68	10.71	1.34	8.71	37.44	49.19	48.11
	a	11.10	4.79	4.79	11.10	6.33	6.34	48.71	48.71
OF	gg	1.98	1.09	9.10	1.73	16.86	37.43	47.02	52.75
	gg'	2.16	1.17	9.52	1.29	16.47	36.58	46.87	52.40
	ga	1.66	1.74	8.73	1.11	18.87	38.26	47.14	52.50
	ag	9.71	5.41	5.03	10.30	1.75	2.03	47.70	47.55
	aa	9.72	5.34	5.34	9.72	3.09	3.09	47.43	47.43
OC	gg	1.95	1.97	9.89	2.60	-	-	-	-
	gg'	2.44	1.70	10.58	2.49	-	-	-	-
	ga	1.90	2.28	9.88	2.26	-	-	-	-
	ag	10.29	5.26	5.09	10.90	-	-	-	-
	aa	10.45	5.35	5.35	10.45	-	-	-	-
OB	gg	2.15	2.23	10.47	3.06	-	-	-	-
	gg'	2.50	2.07	11.06	2.82	-	-	-	-
	ga	2.21	2.51	10.54	2.73	-	-	-	-
	ag	10.69	5.31	5.09	11.29	-	-	-	-
	aa	10.83	5.40	5.40	10.83	-	-	-	-
OI	gg	1.47	2.04	10.43	2.88	-	-	-	-
	gg'	1.97	1.71	11.10	2.82	-	-	-	-
	ga	1.76	2.06	10.61	2.85	-	-	-	-
	ag	10.64	4.52	4.42	11.22	-	-	-	-
	aa	10.79	4.69	4.69	10.79	-	-	-	-

Table S8. Calculated spin-spin coupling constants (Hz) for the studied 2-halofluoroethanes and 2-haloethanols in DMSO implicit solvent obtained at the B3LYP/6-311++(d,p) level of theory (def2-TZVP was used for bromine and iodine atoms, and ECP was included for the iodine atom).
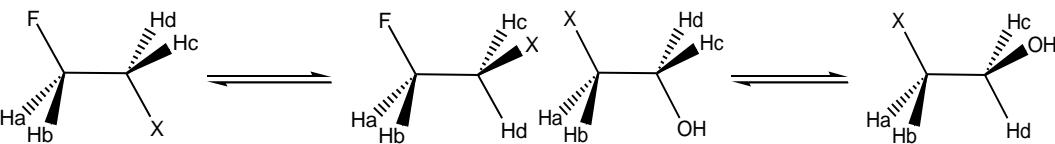
Name	Conf.	$^3J_{HaHc}$	$^3J_{HaHd}$	$^3J_{HbHc}$	$^3J_{HbHd}$	$^3J_{FHc}$	$^3J_{FHd}$	$^2J_{FHa}$	$^2J_{FHb}$
FF	*g*	1.34	1.12	8.68	1.34	18.16	37.93	45.93	53.42
	a	10.03	5.43	5.44	10.03	1.36	1.36	46.78	46.78
FC	*g*	2.58	1.67	9.92	1.63	13.56	36.35	47.24	50.72
	a	10.71	5.47	5.47	10.71	3.95	3.95	47.74	47.74
FB	*g*	3.06	1.97	10.54	1.87	11.58	37.15	48.38	50.07
	a	11.09	5.50	5.50	11.09	5.19	5.19	48.36	48.36
FI	*g*	3.12	1.61	10.68	1.37	8.80	38.89	49.31	40.42
	a	11.10	4.79	4.80	11.10	6.48	6.49	48.75	48.75
OF	*gg*	1.98	1.09	9.06	1.71	17.10	38.51	46.93	53.10
	gg'	2.17	1.13	9.42	1.29	17.19	38.00	46.97	52.81
	ga	1.79	1.62	8.85	1.24	18.85	40.25	46.92	53.21
	ag	9.71	5.39	5.06	10.26	1.76	2.17	47.75	47.50
	aa	9.78	5.34	5.34	9.78	3.18	3.18	47.39	47.39
OC	*gg*	1.96	1.95	9.86	2.60	-	-	-	-
	gg'	2.39	1.70	10.46	2.43	-	-	-	-
	ga	1.99	2.21	9.92	2.37	-	-	-	-
	ag	10.30	5.25	5.10	10.85	-	-	-	-
	aa	10.50	5.35	5.35	10.50	-	-	-	-
OB	*gg*	2.18	2.20	10.46	3.07	-	-	-	-
	gg'	2.48	2.05	10.96	2.78	-	-	-	-
	ga	2.31	2.42	10.59	2.85	-	-	-	-
	ag	10.69	5.31	5.10	11.25	-	-	-	-
	aa	10.89	5.39	5.39	10.89	-	-	-	-
OI	*gg*	1.49	2.01	10.41	2.89	-	-	-	-
	gg'	1.94	1.69	11.00	2.78	-	-	-	-
	ga	1.82	1.99	10.62	2.93	-	-	-	-
	ag	10.64	4.51	4.42	11.19	-	-	-	-
	aa	10.84	4.68	4.68	10.84	-	-	-	-

APPENDIX B

Supporting Information for:

Theoretical and X-ray evidence of electrostatic phosphonium *anti* and *gauche* effects

INDEX

Standard coordinates of the compounds in the gas phase

1-cis-g

```
                    Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic         Coordinates (Angstroms)
Number     Number     Type        X           Y           Z
-----------------------------------------------------------------
   1          6          0       0.003408    1.657035   -0.302449
   2          6          0      -1.364957    1.072191    0.057141
   3          6          0       0.074942   -1.246947    0.714242
   4          6          0       1.308605   -0.427532    0.365679
   5          6          0       1.135341    1.071880    0.545989
   6          1          0      -1.612093    1.306073    1.101423
   7          1          0      -2.149462    1.530705   -0.555767
   8          1          0       0.216927    1.467805   -1.360513
   9          1          0      -0.011822    2.745488   -0.167270
  10          1          0      -0.099753   -1.165632    1.794463
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  12          1          0       0.945074    1.265226    1.610645
  13          1          0       2.083311    1.558262    0.292273
  14         15          0      -1.504089   -0.768884   -0.146332
  15          9          0       1.644031   -0.670489   -0.978060
  16          1          0       2.163919   -0.779168    0.954662
  17          1          0      -0.991549   -0.817705   -1.461571
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1-trans-g

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Number     Number     Type        X           Y           Z
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   1          6          0      -0.001238    1.654011   -0.317193
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   4          6          0       1.302528   -0.431160    0.375325
   5          6          0       1.154431    1.077311    0.507290
   6          1          0      -1.515559    1.236572    1.174358
   7          1          0      -2.166571    1.578458   -0.437911
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   9          1          0      -0.012405    2.742919   -0.195518
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  12          1          0       1.005042    1.309517    1.570370
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  15          1          0      -2.402953   -1.131095    0.595657
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1-trans-a

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   2          6          0       1.645991    0.753173   -0.332630
   3          6          0      -0.350054   -1.224237   -0.281621
   4          6          0      -1.211641   -0.128108    0.309297
   5          6          0      -0.844334    1.262490   -0.174066
   6          1          0       1.646373    0.829430   -1.427774
   7          1          0       2.641255    1.070066   -0.000054
   8          1          0       0.634370    1.652966    1.349922
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  14         15          0       1.464286   -1.045861    0.089109
  15          1          0       1.315081   -0.858864    1.485512
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1-cis-a

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    3          6           0         0.324075   -1.208533    0.315615
    4          6           0         1.212214   -0.147996   -0.307612
    5          6           0         0.864415    1.261346    0.141053
    6          1           0        -1.516079    0.765782    1.477886
    7          1           0        -2.627001    1.116487    0.141368
    8          1           0        -0.665581    1.644488   -1.340245
    9          1           0        -0.736173    2.701087    0.065158
   10          1           0         0.389846   -1.130806    1.406348
   11          1           0         0.680054   -2.198662    0.013934
   12          1           0         0.985746    1.313437    1.230600
   13          1           0         1.586225    1.954739   -0.302967
   14         15           0        -1.425391   -0.968765   -0.287610
   15          9           0         2.543871   -0.408512    0.059453
   16          1           0         1.177241   -0.215875   -1.402284
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2-cis-g

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 Number     Number       Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        -0.640997    1.517095    0.662809
    2          6           0         0.681570    1.594121   -0.105813
    3          6           0        -0.096394   -0.898286   -1.160426
    4          6           0        -1.390857   -0.679411   -0.389463
    5          6           0        -1.726573    0.778718   -0.123658
    6          1           0         0.531240    2.161961   -1.033989
    7          1           0         1.432540    2.146654    0.472259
    8          1           0        -0.496986    1.021211    1.628331
    9          1           0        -0.993655    2.531952    0.883021
   10          1           0        -0.270077   -0.568143   -2.193465
   11          1           0         0.111838   -1.973388   -1.212357
   12          1           0        -1.884835    1.271007   -1.093182
   13          1           0        -2.677883    0.816275    0.418132
   14         15           0         1.444860   -0.031282   -0.579479
   15          6           0         1.704042   -0.786853    1.087388
   16          1           0         1.980008   -1.837698    0.956019
   17          1           0         2.552813   -0.283139    1.560952
   18          1           0         0.836938   -0.739959    1.746832
   19          9           0        -1.306710   -1.341131    0.850961
   20          1           0        -2.219200   -1.159631   -0.924031
 ---------------------------------------------------------------------
```

2-trans-g

                     Standard orientation:

 Center   Atomic   Atomic   Coordinates (Angstroms)
 Number   Number   Type   X   Y   Z
 ----
    1   6   0   0.935838   1.617926   -0.226962
    2   6   0   -0.580572   1.484712   -0.026452
    3   6   0   -0.077307   -1.148073   0.582203
    4   6   0   1.400049   -0.804472   0.439377
    5   6   0   1.720812   0.663295   0.678211
    6   1   0   -0.828154   1.630557   1.035400
    7   1   0   -1.107607   2.254656   -0.601290
    8   1   0   1.192286   1.416370   -1.273509
    9   1   0   1.249979   2.645734   -0.012747
   10   1   0   -0.374187   -0.931011   1.618210
   11   1   0   -0.211446   -2.221377   0.409181
   12   1   0   1.504778   0.887931   1.731487
   13   1   0   2.797089   0.803556   0.530422
   14   15   0   -1.149938   -0.185769   -0.597251
   15   9   0   1.818243   -1.139388   -0.860040
   16   1   0   1.993935   -1.428631   1.116778
   17   6   0   -2.745383   -0.311702   0.326378
   18   1   0   -3.487986   0.345727   -0.135971
   19   1   0   -3.127853   -1.335096   0.262935
   20   1   0   -2.636572   -0.037504   1.381695

2-trans-a

                     Standard orientation:

 Center   Atomic   Atomic   Coordinates (Angstroms)
 Number   Number   Type   X   Y   Z
 ----
    1   6   0   0.033850   1.789868   0.404734
    2   6   0   1.135768   1.288932   -0.534939
    3   6   0   -0.385895   -1.070905   -0.658261
    4   6   0   -1.315411   -0.345795   0.293104
    5   6   0   -1.327543   1.158124   0.094090
    6   1   0   0.907810   1.606120   -1.561204
    7   1   0   2.098854   1.748413   -0.279943
    8   1   0   0.300141   1.586349   1.449105
    9   1   0   -0.050468   2.879698   0.317103
   10   1   0   -0.741477   -0.903428   -1.682703
   11   1   0   -0.434786   -2.150816   -0.477464
   12   1   0   -1.612563   1.369538   -0.945046
   13   1   0   -2.101010   1.586551   0.740307
   14   15   0   1.398131   -0.548199   -0.594609
   15   9   0   -2.623240   -0.827272   0.082254
   16   1   0   -1.076344   -0.585502   1.334979
   17   6   0   1.796520   -0.900879   1.178833
   18   1   0   1.766720   -1.984053   1.333644
   19   1   0   2.821590   -0.572646   1.376608
   20   1   0   1.134992   -0.427852   1.908107

2-cis-a

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        0.511300    1.882355   -0.124161
    2          6           0       -0.892689    1.401467    0.270481
    3          6           0        0.137304   -1.139736    0.085720
    4          6           0        1.445448   -0.471420   -0.293702
    5          6           0        1.608569    0.907494    0.322571
    6          1           0       -0.938717    1.250321    1.358326
    7          1           0       -1.638679    2.158839    0.004370
    8          1           0        0.562477    2.017847   -1.212719
    9          1           0        0.705500    2.862757    0.324485
   10          1           0        0.070372   -1.194502    1.180584
   11          1           0        0.123297   -2.159169   -0.314769
   12          1           0        1.590712    0.798303    1.414527
   13          1           0        2.594520    1.296972    0.048086
   14         15           0       -1.294095   -0.178443   -0.612144
   15          6           0       -2.640798   -0.833007    0.466894
   16          1           0       -3.551712   -0.247739    0.309927
   17          1           0       -2.861705   -1.868382    0.190947
   18          1           0       -2.371545   -0.796493    1.527837
   19          9           0        2.507681   -1.279093    0.152045
   20          1           0        1.542983   -0.413199   -1.384659
 ---------------------------------------------------------------------
```

3axial

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
    1          6           0       -0.098909    1.681077    0.269485
    2          6           0        1.316041    1.153646   -0.049490
    3          6           0       -0.084115   -1.287605   -0.746504
    4          6           0       -1.321734   -0.478791   -0.333454
    5          6           0       -1.200980    1.020527   -0.568768
    6          1           0        1.586673    1.363089   -1.091188
    7          1           0        2.076029    1.604393    0.595625
    8          1           0       -0.315482    1.546751    1.333792
    9          1           0       -0.097037    2.757423    0.079646
   10          1           0        0.106682   -1.181382   -1.819873
   11          1           0       -0.220803   -2.347542   -0.515008
   12          1           0       -1.032686    1.194733   -1.638998
   13          1           0       -2.160872    1.478597   -0.315437
   14         15           0        1.346415   -0.639540    0.150886
   15          9           0       -1.487791   -0.697677    1.038316
   16          1           0       -2.197899   -0.888962   -0.840779
   17          1           0        2.530542   -1.205765   -0.322075
   18          1           0        1.256930   -0.982271    1.498552
 ---------------------------------------------------------------------
```

3equatorial

Standard orientation:

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	0.566789	1.671418	0.266254
2	6	0	1.674921	0.779498	-0.333253
3	6	0	-0.405429	-1.244745	-0.228073
4	6	0	-1.262559	-0.093894	0.323526
5	6	0	-0.841777	1.272747	-0.194425
6	1	0	1.674082	0.841464	-1.427493
7	1	0	2.670139	1.060266	0.024326
8	1	0	0.624712	1.654873	1.362058
9	1	0	0.773336	2.700134	-0.039321
10	1	0	-0.530055	-1.292145	-1.316328
11	1	0	-0.711082	-2.205046	0.197817
12	1	0	-0.903429	1.273621	-1.289640
13	1	0	-1.565831	2.005627	0.171515
14	15	0	1.339796	-0.935635	0.112354
15	9	0	-2.557325	-0.359977	-0.077984
16	1	0	-1.252624	-0.105548	1.420807
17	1	0	2.152991	-1.846519	-0.562989
18	1	0	1.595080	-1.122544	1.471609

4axial

Standard orientation:

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-1.210546	1.468457	0.622384
2	6	0	0.281196	1.614117	0.262916
3	6	0	-0.116055	-0.866073	-1.125553
4	6	0	-1.566801	-0.712779	-0.654501
5	6	0	-2.013876	0.727348	-0.452493
6	1	0	0.396175	2.193688	-0.661798
7	1	0	0.839331	2.132466	1.050276
8	1	0	-1.320561	0.957571	1.584206
9	1	0	-1.623245	2.472468	0.753028
10	1	0	-0.008193	-0.430859	-2.126390
11	1	0	0.153493	-1.925654	-1.183998
12	1	0	-1.943543	1.251553	-1.414291
13	1	0	-3.070426	0.714945	-0.169948
14	15	0	1.035410	-0.002627	-0.022805
15	6	0	1.240768	-0.890878	1.529373
16	1	0	1.651203	-1.884117	1.327652
17	1	0	1.933414	-0.338235	2.170168
18	1	0	0.275944	-1.001787	2.026434
19	6	0	2.640867	0.160327	-0.821718
20	1	0	3.324314	0.703078	-0.162971
21	1	0	3.054260	-0.831329	-1.024991
22	1	0	2.536612	0.707537	-1.761781
23	9	0	-1.671076	-1.384084	0.570425
24	1	0	-2.223565	-1.228277	-1.359784

4equatorial

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type         X           Y           Z
 ---------------------------------------------------------------------
    1          6           0       -0.751657    1.883969    0.110189
    2          6           0        0.614735    1.526505   -0.508809
    3          6           0       -0.352526   -1.164976   -0.280482
    4          6           0       -1.611085   -0.498506    0.288588
    5          6           0       -1.856936    0.891903   -0.274232
    6          1           0        0.550031    1.543282   -1.603813
    7          1           0        1.395013    2.235181   -0.210424
    8          1           0       -0.667216    1.950535    1.201845
    9          1           0       -1.024280    2.883886   -0.237534
   10          1           0       -0.486577   -1.296183   -1.361393
   11          1           0       -0.200615   -2.153979    0.164939
   12          1           0       -1.945895    0.821864   -1.365560
   13          1           0       -2.818526    1.245956    0.107823
   14         15           0        1.114505   -0.140363   -0.024497
   15          9           0       -2.672914   -1.323179   -0.045810
   16          1           0       -1.566807   -0.464037    1.384168
   17          6           0        1.591980   -0.166344    1.713226
   18          1           0        1.830072   -1.190935    2.011750
   19          1           0        2.473610    0.463799    1.859182
   20          1           0        0.778803    0.207423    2.339395
   21          6           0        2.485549   -0.744093   -1.021359
   22          1           0        3.358432   -0.102598   -0.872924
   23          1           0        2.736159   -1.765612   -0.722645
   24          1           0        2.206084   -0.735272   -2.077790
 ---------------------------------------------------------------------
```

```
                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type         X           Y           Z
```

(2-fluoroethyl)triphenylphosphonium *anti*
```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
    1        15          0       0.035407    0.007350    0.411878
    2         6          0      -1.037190   -1.226685   -0.320019
    3         6          0      -1.345333   -2.394985    0.403095
    4         6          0      -1.471138   -1.071733   -1.650313
    5         6          0      -2.107781   -3.397425   -0.204242
    6         1          0      -0.998705   -2.531490    1.424701
    7         6          0      -2.227936   -2.086148   -2.246462
    8         1          0      -1.221378   -0.174379   -2.210992
    9         6          0      -2.548434   -3.243595   -1.525603
   10         1          0      -2.355914   -4.296064    0.353150
   11         1          0      -2.568093   -1.970354   -3.271584
   12         1          0      -3.140595   -4.025503   -1.992476
   13         6          0      -0.269117    1.589386   -0.376400
   14         6          0       0.809416    2.383663   -0.804682
   15         6          0      -1.596527    2.041025   -0.521519
   16         6          0       0.553469    3.637413   -1.371985
   17         1          0       1.831245    2.025820   -0.708659
   18         6          0      -1.835489    3.296389   -1.087414
   19         1          0      -2.433718    1.415115   -0.219710
   20         6          0      -0.762614    4.095332   -1.507009
   21         1          0       1.382385    4.253168   -1.708873
   22         1          0      -2.856558    3.648500   -1.203478
   23         1          0      -0.954455    5.069608   -1.947390
   24         6          0       1.748741   -0.475005    0.201372
   25         6          0       2.750290    0.079994    1.021600
   26         6          0       2.081448   -1.373865   -0.829091
   27         6          0       4.086194   -0.273372    0.806001
   28         1          0       2.503495    0.777843    1.817816
   29         6          0       3.422472   -1.713298   -1.034988
   30         1          0       1.305759   -1.808012   -1.455153
   31         6          0       4.421900   -1.165477   -0.220783
   32         1          0       4.861634    0.146291    1.440360
   33         1          0       3.684437   -2.410159   -1.825902
   34         1          0       5.461164   -1.437050   -0.382269
   35         6          0      -0.301147    0.128804    2.193281
   36         1          0      -0.046324   -0.837099    2.643959
   37         1          0       0.384166    0.877482    2.605110
   38         6          0      -1.739120    0.502165    2.545313
   39         1          0      -1.972809    1.524936    2.240340
   40         1          0      -2.458436   -0.193515    2.103435
   41         9          0      -1.859004    0.426568    3.922061
---------------------------------------------------------------------
```

(2-fluoroethyl)triphenylphosphonium *gauche*
```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number      Type          X            Y           Z
---------------------------------------------------------------------
    1         15          0         0.081464     0.016159    0.532251
    2          6          0        -0.828432    -1.360304   -0.161874
    3          6          0        -0.973430    -2.556412    0.563460
    4          6          0        -1.282674    -1.268100   -1.491224
    5          6          0        -1.595381    -3.653326   -0.039896
    6          1          0        -0.621491    -2.640255    1.587761
    7          6          0        -1.898869    -2.375685   -2.083155
    8          1          0        -1.159549    -0.346424   -2.054512
    9          6          0        -2.055726    -3.564901   -1.360280
   10          1          0        -1.720984    -4.574823    0.521155
   11          1          0        -2.256701    -2.307540   -3.106520
   12          1          0        -2.540164    -4.420117   -1.822771
   13          6          0        -0.481467     1.531214   -0.246612
   14          6          0         0.443273     2.452972   -0.769693
   15          6          0        -1.867846     1.778804   -0.322013
   16          6          0        -0.025402     3.634696   -1.355364
   17          1          0         1.509829     2.248052   -0.734360
   18          6          0        -2.317595     2.966012   -0.906940
   19          1          0        -2.581169     1.053134    0.061361
   20          6          0        -1.399877     3.893020   -1.420512
   21          1          0         0.683813     4.347900   -1.765491
   22          1          0        -3.384249     3.162411   -0.968856
   23          1          0        -1.757007     4.811515   -1.877579
   24          6          0         1.835455    -0.224511    0.231943
   25          6          0         2.788358     0.562445    0.908884
   26          6          0         2.244423    -1.173672   -0.723254
   27          6          0         4.147532     0.392344    0.627975
   28          1          0         2.485778     1.307131    1.641461
   29          6          0         3.607451    -1.331601   -0.995101
   30          1          0         1.510450    -1.785595   -1.241268
   31          6          0         4.556667    -0.552394   -0.322292
   32          1          0         4.884004     0.994781    1.151976
   33          1          0         3.926316    -2.067205   -1.727897
   34          1          0         5.613906    -0.682351   -0.535073
   35          6          0        -0.151332     0.128517    2.340163
   36          1          0         0.038040    -0.863536    2.763187
   37          1          0         0.626322     0.801184    2.719635
   38          6          0        -1.514935     0.657301    2.761875
   39          1          0        -1.666552     1.686409    2.426787
   40          9          0        -2.508227    -0.132235    2.190319
   41          1          0        -1.619667     0.604544    3.847834
---------------------------------------------------------------------
```

7-*cis-g_s*
```
                       Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number      Type          X            Y           Z
---------------------------------------------------------------------
    1          6          0        -1.082092     1.554667    0.455173
    2          6          0         0.401505     1.581065    0.051069
    3          6          0        -0.103080    -1.034645   -0.888153
    4          6          0        -1.558640    -0.751228   -0.523324
    5          6          0        -1.927985     0.725845   -0.517516
    6          1          0         0.518141     1.974858   -0.965789
    7          1          0         0.991859     2.207195    0.727903
    8          1          0        -1.183530     1.143939    1.465414
    9          1          0        -1.467310     2.578831    0.483599
   10          1          0         0.058237    -0.766361   -1.938841
   11          1          0         0.111027    -2.101549   -0.771295
   12          1          0        -2.216297    -1.299820   -1.205894
   13          1          0        -1.816300     1.113298   -1.539168
   14          1          0        -2.987346     0.805865   -0.252277
   15         15          0         1.088166    -0.088832    0.106816
   16          8          0         1.410194    -0.618356    1.460529
   17          9          0        -1.803177    -1.264739    0.756009
   18          8          0         2.384067    -0.014218   -0.891573
   19          1          0         3.165282    -0.334761   -0.425128
---------------------------------------------------------------------
```

7-cis-g_a

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
    1         6          0       -1.054588    1.561709    0.462937
    2         6          0        0.431197    1.576088    0.064535
    3         6          0       -0.097343   -1.025739   -0.901469
    4         6          0       -1.554227   -0.729615   -0.543134
    5         6          0       -1.906487    0.751701   -0.520237
    6         1          0        0.543345    1.988823   -0.947031
    7         1          0        1.023173    2.192581    0.748878
    8         1          0       -1.159945    1.141145    1.468572
    9         1          0       -1.429516    2.589436    0.501744
   10         1          0        0.053231   -0.757306   -1.955049
   11         1          0        0.101183   -2.096687   -0.793466
   12         1          0       -2.211689   -1.259705   -1.240785
   13         1          0       -1.790246    1.150269   -1.537526
   14         1          0       -2.965607    0.839746   -0.256747
   15        15          0        1.096853   -0.108508    0.128531
   16         8          0        1.336219   -0.646825    1.487852
   17         9          0       -1.816930   -1.258831    0.723658
   18         8          0        2.471492   -0.089405   -0.757224
   19         1          0        2.362655    0.253771   -1.650288
---------------------------------------------------------------------
```

7-trans-g_s

Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
    1         6          0       -1.023042    1.551842    0.463765
    2         6          0        0.438520    1.601420   -0.010552
    3         6          0       -0.107480   -1.022793   -0.943025
    4         6          0       -1.547857   -0.737800   -0.521870
    5         6          0       -1.909864    0.740058   -0.486037
    6         1          0        0.503558    2.044248   -1.011935
    7         1          0        1.058889    2.205095    0.659834
    8         1          0       -1.071021    1.116020    1.466866
    9         1          0       -1.412488    2.572586    0.535108
   10         1          0       -0.001909   -0.792053   -2.010320
   11         1          0        0.117777   -2.085605   -0.812045
   12         1          0       -2.230022   -1.275581   -1.189133
   13         1          0       -1.834124    1.138962   -1.506588
   14         1          0       -2.958395    0.821698   -0.181416
   15        15          0        1.171828   -0.046096   -0.100544
   16         9          0       -1.754581   -1.267870    0.757601
   17         8          0        2.530416   -0.154985   -0.703212
   18         8          0        1.091782   -0.544880    1.451073
   19         1          0        1.962304   -0.840544    1.742807
---------------------------------------------------------------------
```

7-trans-g_a

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0      -1.039405    1.555669    0.477830
   2          6          0       0.440366    1.604689    0.066169
   3          6          0      -0.064867   -0.952764   -1.041223
   4          6          0      -1.498904   -0.723937   -0.578375
   5          6          0      -1.902888    0.738864   -0.490959
   6          1          0       0.553867    2.092268   -0.909652
   7          1          0       1.033751    2.175584    0.788146
   8          1          0      -1.131391    1.140287    1.487072
   9          1          0      -1.434030    2.575775    0.525520
  10          1          0       0.032941   -0.613104   -2.078586
  11          1          0       0.177065   -2.020392   -1.019950
  12          1          0      -2.196179   -1.280673   -1.210607
  13          1          0      -1.837509    1.163167   -1.501623
  14          1          0      -2.953354    0.787694   -0.185730
  15         15          0       1.181751   -0.041904   -0.069137
  16          9          0      -1.631236   -1.290185    0.717098
  17          8          0       2.561280   -0.083334   -0.612324
  18          8          0       1.053429   -0.672967    1.424435
  19          1          0       0.186223   -1.065100    1.591040
---------------------------------------------------------------------
```

7-trans-g_s'

```
                        Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0      -1.019081    1.561592    0.430605
   2          6          0       0.444982    1.601012   -0.037936
   3          6          0      -0.101580   -1.041547   -0.925271
   4          6          0      -1.543046   -0.749038   -0.514766
   5          6          0      -1.903616    0.729387   -0.503487
   6          1          0       0.514717    2.021998   -1.048266
   7          1          0       1.063850    2.217072    0.622136
   8          1          0      -1.071745    1.150407    1.443478
   9          1          0      -1.408212    2.584041    0.474630
  10          1          0       0.009616   -0.833455   -1.996577
  11          1          0       0.120431   -2.103599   -0.778349
  12          1          0      -2.223910   -1.294849   -1.176907
  13          1          0      -1.827452    1.108474   -1.531629
  14          1          0      -2.952568    0.817033   -0.201809
  15         15          0       1.176372   -0.046265   -0.094511
  16          9          0      -1.756403   -1.262428    0.771446
  17          8          0       2.526863   -0.201082   -0.703388
  18          8          0       1.090432   -0.436428    1.486248
  19          1          0       1.733002   -1.119659    1.710202
---------------------------------------------------------------------
```

7-trans-a_s

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        -0.619089    1.884966    0.166229
   2          6          0         0.722849    1.469542   -0.462337
   3          6          0        -0.325784   -1.137777   -0.313395
   4          6          0        -1.557141   -0.470797    0.283720
   5          6          0        -1.770356    0.946274   -0.223154
   6          1          0         0.653595    1.463829   -1.556468
   7          1          0         1.527351    2.153088   -0.173278
   8          1          0        -0.516724    1.909376    1.258029
   9          1          0        -0.865608    2.901892   -0.153405
  10          1          0        -0.427568   -1.185617   -1.403408
  11          1          0        -0.212900   -2.154687    0.074340
  12          1          0        -1.878417    0.913264   -1.315003
  13          1          0        -2.712570    1.320442    0.189521
  14         15          0         1.159811   -0.187835    0.104981
  15          8          0         1.590168   -0.286762    1.529591
  16          8          0         2.268650   -0.713097   -0.970126
  17          1          0         3.056919   -1.016390   -0.503760
  18          1          0        -1.498203   -0.477732    1.377812
  19          9          0        -2.677384   -1.240480   -0.061245
---------------------------------------------------------------------
```

7-trans-a_a

```
                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        -0.589037    1.889903    0.144470
   2          6          0         0.749431    1.453079   -0.477716
   3          6          0        -0.326646   -1.142821   -0.307092
   4          6          0        -1.553176   -0.458020    0.281255
   5          6          0        -1.749832    0.958576   -0.234022
   6          1          0         0.671985    1.449550   -1.572823
   7          1          0         1.559296    2.132953   -0.194499
   8          1          0        -0.483442    1.924832    1.235304
   9          1          0        -0.825739    2.905642   -0.186561
  10          1          0        -0.443344   -1.200760   -1.396461
  11          1          0        -0.228677   -2.158090    0.089256
  12          1          0        -1.861971    0.918712   -1.325619
  13          1          0        -2.687417    1.345867    0.176945
  14         15          0         1.167542   -0.202512    0.126982
  15          8          0         1.534222   -0.265598    1.563770
  16          8          0         2.351263   -0.775686   -0.835620
  17          1          0         2.143325   -0.748187   -1.775860
  18          1          0        -1.496714   -0.462509    1.375046
  19          9          0        -2.680973   -1.216040   -0.066225
---------------------------------------------------------------------
```

7-cis-a_s

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
    1         6          0        -0.546903    1.877245    0.176121
    2         6          0         0.766165    1.459485   -0.506833
    3         6          0        -0.339304   -1.141771   -0.392840
    4         6          0        -1.527691   -0.457145    0.267164
    5         6          0        -1.727881    0.973259   -0.203422
    6         1          0         0.673271    1.529304   -1.597378
    7         1          0         1.597502    2.103417   -0.202568
    8         1          0        -0.410064    1.865930    1.263492
    9         1          0        -0.782489    2.907921   -0.106537
   10         1          0        -0.505524   -1.192609   -1.475169
   11         1          0        -0.223066   -2.163000   -0.017367
   12         1          0        -1.867206    0.967839   -1.292255
   13         1          0        -2.650119    1.356503    0.244382
   14        15          0         1.211440   -0.246517   -0.114437
   15         8          0         2.427160   -0.809230   -0.762731
   16         8          0         1.280799   -0.207575    1.523344
   17         1          0         2.123252   -0.565554    1.827550
   18         9          0        -2.679219   -1.195217   -0.045617
   19         1          0        -1.424182   -0.487042    1.356903
---------------------------------------------------------------------
```

8-cis-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
    1         6          0         0.682637    1.558726   -0.540293
    2         6          0        -0.682217    1.564116    0.165370
    3         6          0         0.057400   -1.018498    1.016472
    4         6          0         1.400029   -0.719773    0.353730
    5         6          0         1.731032    0.762042    0.243085
    6         1          0        -0.585329    1.970753    1.181313
    7         1          0        -1.407847    2.178402   -0.377536
    8         1          0         0.579157    1.133887   -1.544452
    9         1          0         1.031407    2.589250   -0.661484
   10         1          0         0.117520   -0.726261    2.073451
   11         1          0        -0.145005   -2.093196    0.972398
   12         1          0         2.195292   -1.240634    0.897962
   13         1          0         1.833513    1.169579    1.258117
   14         1          0         2.708029    0.851222   -0.243047
   15        15          0        -1.352507   -0.123365    0.269424
   16         8          0        -1.925710   -0.684343   -0.992476
   17         9          0         1.388285   -1.258794   -0.937554
   18         1          0        -2.261296   -0.058321    1.349531
---------------------------------------------------------------------
```

8-trans-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
    1         6          0         0.899176    1.597426   -0.276404
    2         6          0        -0.605361    1.523923    0.030851
    3         6          0        -0.057751   -1.174756    0.655831
    4         6          0         1.398672   -0.809815    0.390177
    5         6          0         1.726848    0.659224    0.607922
    6         1          0        -0.801585    1.785491    1.078049
    7         1          0        -1.174871    2.223031   -0.590591
    8         1          0         1.080024    1.350209   -1.328501
    9         1          0         1.245722    2.625822   -0.131654
   10         1          0        -0.276359   -1.048085    1.723254
   11         1          0        -0.232821   -2.226288    0.408266
   12         1          0         2.056204   -1.439313    0.998393
   13         1          0         1.559684    0.894058    1.667432
   14         1          0         2.793534    0.802635    0.406472
   15        15          0        -1.269426   -0.144690   -0.239197
   16         9          0         1.686780   -1.125672   -0.950306
   17         1          0        -0.956054   -0.376695   -1.593370
   18         8          0        -2.700327   -0.383185    0.131587
---------------------------------------------------------------------
```

8-trans-a

                      Standard orientation:

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   0.014798   1.802801   0.358638
    2   6   0   1.145100   1.266004   -0.535691
    3   6   0   -0.355670   -1.104969   -0.571478
    4   6   0   -1.339377   -0.345374   0.306556
    5   6   0   -1.339994   1.151887   0.045354
    6   1   0   0.914692   1.444124   -1.594263
    7   1   0   2.096230   1.756396   -0.304978
    8   1   0   0.271965   1.632561   1.411103
    9   1   0   -0.069280   2.885446   0.223066
   10   1   0   -0.611459   -0.943424   -1.626245
   11   1   0   -0.406687   -2.176787   -0.357515
   12   1   0   -1.606241   1.321157   -1.006193
   13   1   0   -2.123989   1.606615   0.659059
   14   15   0   1.343166   -0.519340   -0.261706
   15   8   0   1.917601   -0.907846   1.066010
   16   1   0   2.061869   -0.976671   -1.386755
   17   9   0   -2.625222   -0.841268   0.043985
   18   1   0   -1.137550   -0.547224   1.364102

8-cis-a

                      Standard orientation:

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -0.386919   1.867951   0.214521
    2   6   0   0.982195   1.394393   -0.299399
    3   6   0   -0.192190   -1.169512   -0.171557
    4   6   0   -1.433921   -0.430534   0.302841
    5   6   0   -1.543237   0.976816   -0.256925
    6   1   0   1.006020   1.397727   -1.395745
    7   1   0   1.787077   2.051015   0.046800
    8   1   0   -0.380455   1.906050   1.312115
    9   1   0   -0.560961   2.892588   -0.127908
   10   1   0   -0.223862   -1.271495   -1.262682
   11   1   0   -0.155154   -2.176037   0.256863
   12   1   0   -1.555930   0.919832   -1.352594
   13   1   0   -2.499635   1.402531   0.062489
   14   15   0   1.354913   -0.298504   0.242305
   15   1   0   1.264477   -0.179166   1.648777
   16   8   0   2.616303   -0.927280   -0.257916
   17   9   0   -2.558183   -1.164870   -0.099456
   18   1   0   -1.467615   -0.398092   1.398860

9-cis-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1          6          0       -1.104203    1.563391    0.424834
    2          6          0        0.386955    1.582060    0.055077
    3          6          0       -0.102125   -1.033790   -0.876927
    4          6          0       -1.568742   -0.741213   -0.567004
    5          6          0       -1.928632    0.738174   -0.568607
    6          1          0        0.520946    1.972731   -0.962484
    7          1          0        0.956352    2.218338    0.741538
    8          1          0       -1.227928    1.150471    1.431750
    9          1          0       -1.488245    2.588532    0.445655
   10          1          0        0.083447   -0.777852   -1.928247
   11          1          0        0.092103   -2.103918   -0.748176
   12          1          0       -2.202961   -1.279141   -1.280546
   13          1          0       -1.788817    1.125644   -1.587249
   14          1          0       -2.994559    0.823020   -0.332281
   15         15          0        1.080666   -0.098579    0.165253
   16          8          0        1.262292   -0.607198    1.563114
   17          9          0       -1.871804   -1.261186    0.695647
   18          6          0        2.613232   -0.075263   -0.809016
   19          1          0        3.348993    0.539106   -0.283110
   20          1          0        3.003480   -1.094384   -0.876917
   21          1          0        2.456181    0.324248   -1.814602
---------------------------------------------------------------------
```

9-trans-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1          6          0       -1.078975    1.496624    0.609919
    2          6          0        0.386566    1.601641    0.160880
    3          6          0       -0.112754   -0.897599   -1.071872
    4          6          0       -1.547041   -0.699115   -0.595198
    5          6          0       -1.950718    0.754951   -0.408133
    6          1          0        0.455032    2.151941   -0.786103
    7          1          0        0.990914    2.150512    0.892076
    8          1          0       -1.146360    0.990934    1.579145
    9          1          0       -1.482336    2.504409    0.756122
   10          1          0       -0.029729   -0.525050   -2.100548
   11          1          0        0.130324   -1.965225   -1.096600
   12          1          0       -2.236071   -1.196106   -1.285981
   13          1          0       -1.892563    1.253165   -1.384980
   14          1          0       -2.999008    0.779724   -0.092075
   15         15          0        1.183125   -0.009273   -0.132263
   16          9          0       -1.703842   -1.355825    0.641216
   17          8          0        2.497018    0.055299   -0.854066
   18          6          0        1.279588   -0.808764    1.490980
   19          1          0        1.676450   -1.818267    1.354727
   20          1          0        1.979625   -0.242368    2.111331
   21          1          0        0.305289   -0.870972    1.978966
---------------------------------------------------------------------
```

9-trans-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
    1         6          0       -0.683241     1.883421     0.091829
    2         6          0        0.676188     1.473008    -0.498448
    3         6          0       -0.309636    -1.145118    -0.290051
    4         6          0       -1.565987    -0.492098     0.265293
    5         6          0       -1.804367     0.904437    -0.285414
    6         1          0        0.618388     1.426254    -1.593631
    7         1          0        1.454660     2.194188    -0.226622
    8         1          0       -0.597979     1.944213     1.183423
    9         1          0       -0.947997     2.883557    -0.265578
   10         1          0       -0.394049    -1.218385    -1.381306
   11         1          0       -0.194898    -2.152511     0.123254
   12         1          0       -1.895007     0.836615    -1.377619
   13         1          0       -2.762521     1.266494     0.100962
   14        15          0        1.155499    -0.153277     0.164070
   15         8          0        1.448618    -0.150072     1.636783
   16         9          0       -2.664240    -1.296689    -0.079603
   17         1          0       -1.526505    -0.468781     1.359506
   18         6          0        2.507712    -0.766836    -0.874205
   19         1          0        3.389183    -0.141747    -0.708693
   20         1          0        2.747602    -1.789637    -0.572002
   21         1          0        2.241848    -0.751221    -1.934602
---------------------------------------------------------------------
```

9-cis-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
    1         6          0       -0.601178     1.880797     0.192376
    2         6          0        0.718723     1.481626    -0.485966
    3         6          0       -0.352183    -1.133176    -0.377168
    4         6          0       -1.548396    -0.464289     0.279763
    5         6          0       -1.768628     0.962349    -0.190925
    6         1          0        0.623270     1.565219    -1.575693
    7         1          0        1.538681     2.143552    -0.185603
    8         1          0       -0.481422     1.884954     1.283172
    9         1          0       -0.850154     2.908276    -0.092027
   10         1          0       -0.525974    -1.191104    -1.458339
   11         1          0       -0.230520    -2.157198    -0.008357
   12         1          0       -1.900162     0.954504    -1.280386
   13         1          0       -2.699318     1.332822     0.250675
   14        15          0        1.224335    -0.236022    -0.154556
   15         8          0        2.351392    -0.749707    -0.998284
   16         9          0       -2.691919    -1.217700    -0.027779
   17         1          0       -1.458223    -0.488649     1.372503
   18         6          0        1.563777    -0.305431     1.628382
   19         1          0        1.755294    -1.345822     1.904505
   20         1          0        2.466547     0.277005     1.831605
   21         1          0        0.740412     0.082470     2.233809
---------------------------------------------------------------------
```

PFgauche

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
    1         6          0        1.352425     0.417425     0.269911
    2         1          0        2.192904     0.977702    -0.139742
    3         1          0        1.403504     0.407783     1.360827
    4         6          0        0.025933     0.988110    -0.233707
    5         1          0        0.059177     1.176410    -1.311116
    6         1          0       -0.229739     1.922029     0.276726
    7         1          0       -1.293577    -0.666895     1.367740
    8         1          0       -2.548459     0.359234    -0.185544
    9         1          0       -1.181499    -1.320509    -0.780394
   10        15          0       -1.301501    -0.213132     0.051085
   11         9          0        1.427783    -0.899109    -0.174666
---------------------------------------------------------------------
```

PF_anti_

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0      -1.136085   -0.512187    0.000003
   2          1          0      -1.077161   -1.137049   -0.895520
   3          1          0      -1.077180   -1.137026    0.895543
   4          6          0      -0.056179    0.579244   -0.000002
   5          1          0      -0.163928    1.212396    0.886764
   6          1          0      -0.163966    1.212369   -0.886773
   7          1          0       1.876100   -0.858350   -1.120466
   8          1          0       2.562513    0.962625   -0.000556
   9          1          0       1.876434   -0.857439    1.121018
  10         15          0       1.627880   -0.069258    0.000000
  11          9          0      -2.344159    0.137667   -0.000002
---------------------------------------------------------------------
```

PP_anti_

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.529551    0.562179    0.000013
   2          1          0       0.441306    1.203928   -0.884349
   3          1          0       0.441502    1.204099    0.884268
   4          6          0      -0.529551   -0.562179    0.000013
   5          1          0      -0.441502   -1.204100    0.884268
   6          1          0      -0.441307   -1.203927   -0.884349
   7          1          0      -2.497332    0.834344   -1.130833
   8          1          0      -3.126954   -1.030161   -0.000869
   9          1          0      -2.497729    0.832807    1.131481
  10          1          0       3.126953    1.030162   -0.000868
  11          1          0       2.497728   -0.832807    1.131481
  12          1          0       2.497334   -0.834344   -1.130833
  13         15          0       2.253136   -0.056414    0.000015
  14         15          0      -2.253136    0.056414    0.000015
---------------------------------------------------------------------
```

Standard coordinates of the compounds in implicit DMSO

1-cis-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic           Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0        -0.031420    1.656950   -0.303993
   2          6           0        -1.389627    1.049218    0.056423
   3          6           0         0.095675   -1.247651    0.712950
   4          6           0         1.313364   -0.403315    0.373416
   5          6           0         1.112002    1.092168    0.542935
   6          1           0        -1.636975    1.274906    1.101836
   7          1           0        -2.181796    1.491607   -0.557777
   8          1           0         0.179815    1.476995   -1.364433
   9          1           0        -0.066817    2.743938   -0.164316
  10          1           0        -0.082649   -1.166247    1.792026
  11          1           0         0.316455   -2.300132    0.506366
  12          1           0         0.918428    1.282064    1.606867
  13          1           0         2.051078    1.595924    0.290194
  14         15           0        -1.485858   -0.790771   -0.147257
  15          9           0         1.667766   -0.649343   -0.976489
  16          1           0         2.171659   -0.737948    0.965042
  17          1           0        -0.991185   -0.839671   -1.468928
---------------------------------------------------------------------
```

1-trans-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic           Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0        -0.023528    1.657029   -0.314881
   2          6           0        -1.375698    1.057347    0.096228
   3          6           0         0.065096   -1.215460    0.751451
   4          6           0         1.305450   -0.415216    0.382285
   5          6           0         1.139614    1.090221    0.506170
   6          1           0        -1.537754    1.213176    1.169241
   7          1           0        -2.188301    1.551500   -0.445818
   8          1           0         0.157352    1.472580   -1.380873
   9          1           0        -0.048994    2.743942   -0.181552
  10          1           0        -0.154713   -1.017267    1.806341
  11          1           0         0.279405   -2.283015    0.643002
  12          1           0         0.987842    1.317614    1.569162
  13          1           0         2.079748    1.564169    0.204708
  14         15           0        -1.388415   -0.752182   -0.320311
  15          1           0        -2.398446   -1.174767    0.570156
  16          9           0         1.647478   -0.710973   -0.962122
  17          1           0         2.157170   -0.749960    0.981872
---------------------------------------------------------------------
```

1-trans-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic           Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0         0.579951    1.664915    0.255287
   2          6           0         1.652691    0.745176   -0.334017
   3          6           0        -0.357477   -1.224960   -0.283564
   4          6           0        -1.205207   -0.121984    0.310590
   5          6           0        -0.836024    1.265616   -0.174985
   6          1           0         1.652313    0.821322   -1.428744
   7          1           0         2.648072    1.054881    0.003598
   8          1           0         0.644224    1.646200    1.350809
   9          1           0         0.767323    2.698491   -0.058391
  10          1           0        -0.476790   -1.227874   -1.373469
  11          1           0        -0.692258   -2.197754    0.090999
  12          1           0        -0.916460    1.288379   -1.269411
  13          1           0        -1.562595    1.978634    0.228545
  14         15           0         1.455362   -1.048030    0.089169
  15          1           0         1.318173   -0.876450    1.486627
  16          1           0        -1.175709   -0.163660    1.404961
  17          9           0        -2.560037   -0.363810   -0.045881
---------------------------------------------------------------------
```

1-cis-a

```
                     Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0      -0.565996    1.664527   -0.246967
   2          6          0      -1.627719    0.751362    0.382063
   3          6          0       0.327272   -1.210476    0.308828
   4          6          0       1.208039   -0.143581   -0.309798
   5          6          0       0.862123    1.262039    0.145941
   6          1          0      -1.525305    0.762838    1.473085
   7          1          0      -2.629815    1.112651    0.129817
   8          1          0      -0.661423    1.648082   -1.340880
   9          1          0      -0.738742    2.698421    0.069468
  10          1          0       0.387947   -1.137268    1.399933
  11          1          0       0.678309   -2.199723   -0.000800
  12          1          0       0.974611    1.309848    1.236385
  13          1          0       1.580703    1.960068   -0.295879
  14         15          0      -1.425028   -0.969388   -0.283241
  15          9          0       2.551498   -0.406877    0.061201
  16          1          0       1.185261   -0.207648   -1.403689
  17          1          0      -2.061932   -1.687779    0.749963
---------------------------------------------------------------------
```

2-cis-g

```
                     Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0      -0.624771    1.522482    0.665715
   2          6          0       0.694070    1.593626   -0.110129
   3          6          0      -0.105614   -0.898237   -1.161842
   4          6          0      -1.396801   -0.667641   -0.391076
   5          6          0      -1.718988    0.789898   -0.114386
   6          1          0       0.538465    2.156206   -1.040033
   7          1          0       1.451468    2.141437    0.463507
   8          1          0      -0.475378    1.031058    1.632970
   9          1          0      -0.970659    2.539769    0.883365
  10          1          0      -0.281736   -0.560688   -2.191490
  11          1          0       0.095232   -1.974243   -1.218719
  12          1          0      -1.879189    1.283181   -1.082388
  13          1          0      -2.667716    0.833366    0.431347
  14         15          0       1.435431   -0.039204   -0.579556
  15          6          0       1.711245   -0.797096    1.081691
  16          1          0       1.962904   -1.853737    0.947794
  17          1          0       2.573917   -0.305771    1.542433
  18          1          0       0.853448   -0.725436    1.751285
  19          9          0      -1.317580   -1.343977    0.853091
  20          1          0      -2.228847   -1.139472   -0.924404
---------------------------------------------------------------------
```

2-trans-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.936243    1.622470   -0.227148
   2          6          0       -0.579960    1.490213   -0.024830
   3          6          0       -0.075331   -1.147283    0.588310
   4          6          0        1.399882   -0.803602    0.442968
   5          6          0        1.725652    0.663220    0.669764
   6          1          0       -0.825767    1.634281    1.036746
   7          1          0       -1.109391    2.257063   -0.600935
   8          1          0        1.189941    1.434856   -1.277441
   9          1          0        1.249998    2.648099   -0.003952
  10          1          0       -0.367225   -0.925020    1.623666
  11          1          0       -0.215147   -2.220516    0.421239
  12          1          0        1.516691    0.886387    1.724063
  13          1          0        2.801343    0.802401    0.517417
  14         15          0       -1.147795   -0.180909   -0.582907
  15          9          0        1.815547   -1.151344   -0.867999
  16          1          0        1.997735   -1.427481    1.114399
  17          6          0       -2.754462   -0.318634    0.310376
  18          1          0       -3.491372    0.336774   -0.163139
  19          1          0       -3.125205   -1.345643    0.240922
  20          1          0       -2.656743   -0.043784    1.365963
---------------------------------------------------------------------
```

2-trans-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.039691    1.787966    0.409370
   2          6          0        1.138933    1.290440   -0.535125
   3          6          0       -0.390463   -1.069588   -0.663462
   4          6          0       -1.309399   -0.342327    0.294054
   5          6          0       -1.324154    1.160310    0.097862
   6          1          0        0.908127    1.609377   -1.559864
   7          1          0        2.103035    1.744831   -0.276431
   8          1          0        0.306662    1.580270    1.452255
   9          1          0       -0.044711    2.877384    0.322912
  10          1          0       -0.742562   -0.892539   -1.687237
  11          1          0       -0.435334   -2.149366   -0.482419
  12          1          0       -1.607278    1.376421   -0.940673
  13          1          0       -2.091364    1.589957    0.750594
  14         15          0        1.391671   -0.544609   -0.592435
  15          9          0       -2.630783   -0.825420    0.083050
  16          1          0       -1.076202   -0.589510    1.334070
  17          6          0        1.802302   -0.913992    1.171078
  18          1          0        1.766390   -1.998013    1.317107
  19          1          0        2.828737   -0.586880    1.362333
  20          1          0        1.145022   -0.440872    1.903763
---------------------------------------------------------------------
```

2-cis-a

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type         X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        0.511902    1.882936   -0.125408
    2          6           0       -0.894086    1.405791    0.265664
    3          6           0        0.139594   -1.141750    0.081199
    4          6           0        1.442333   -0.466121   -0.295823
    5          6           0        1.606926    0.907620    0.327405
    6          1           0       -0.945185    1.257795    1.353127
    7          1           0       -1.638955    2.160867   -0.008512
    8          1           0        0.570773    2.017844   -1.213468
    9          1           0        0.706119    2.861925    0.325244
   10          1           0        0.067967   -1.198637    1.175249
   11          1           0        0.119650   -2.157668   -0.327478
   12          1           0        1.578747    0.797965    1.418940
   13          1           0        2.592280    1.300548    0.055917
   14         15           0       -1.295467   -0.177586   -0.604598
   15          6           0       -2.642941   -0.838903    0.463858
   16          1           0       -3.553116   -0.254190    0.302176
   17          1           0       -2.854645   -1.875318    0.185385
   18          1           0       -2.374132   -0.798977    1.524355
   19          9           0        2.514466   -1.281963    0.151262
   20          1           0        1.549932   -0.408145   -1.384702
 ---------------------------------------------------------------------
```

3axial

```
                      Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic            Coordinates (Angstroms)
 Number     Number       Type         X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        0.045552    1.674447   -0.280697
    2          6           0       -1.354476    1.120550    0.041739
    3          6           0        0.106933   -1.286860    0.710951
    4          6           0        1.330484   -0.441534    0.357283
    5          6           0        1.155410    1.053188    0.575438
    6          1           0       -1.627467    1.326745    1.081795
    7          1           0       -2.122219    1.548184   -0.607540
    8          1           0        0.269141    1.526596   -1.341859
    9          1           0        0.022042    2.753090   -0.106842
   10          1           0       -0.092904   -1.213819    1.784495
   11          1           0        0.272078   -2.335970    0.456168
   12          1           0        0.954774    1.219605    1.640622
   13          1           0        2.106073    1.540988    0.342904
   14         15           0       -1.354687   -0.671237   -0.157327
   15          9           0        1.603738   -0.659179   -1.008264
   16          1           0        2.189972   -0.817824    0.915316
   17          1           0       -2.508105   -1.262391    0.346947
   18          1           0       -1.280139   -1.002771   -1.506008
 ---------------------------------------------------------------------
```

3equatorial
```
                    Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X            Y            Z
-----------------------------------------------------------------------
    1         6          0       0.554428     1.675989     0.264301
    2         6          0       1.666771     0.789361    -0.325156
    3         6          0      -0.396129    -1.242516    -0.226730
    4         6          0      -1.252593    -0.101930     0.322958
    5         6          0      -0.850753     1.266718    -0.198344
    6         1          0       1.676690     0.851054    -1.417903
    7         1          0       2.654753     1.072606     0.046527
    8         1          0       0.606000     1.663002     1.359213
    9         1          0       0.750044     2.703980    -0.049746
   10         1          0      -0.511062    -1.294043    -1.314450
   11         1          0      -0.685733    -2.202555     0.207306
   12         1          0      -0.903791     1.261412    -1.293671
   13         1          0      -1.578220     1.995340     0.169673
   14        15          0       1.352150    -0.931433     0.110896
   15         9          0      -2.569743    -0.370819    -0.075164
   16         1          0      -1.251333    -0.112028     1.417526
   17         1          0       2.148880    -1.824340    -0.597713
   18         1          0       1.608850    -1.131286     1.464099
-----------------------------------------------------------------------
```
4axial
```
                    Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X            Y            Z
-----------------------------------------------------------------------
    1         6          0      -1.181666     1.485410     0.609360
    2         6          0       0.307222     1.616461     0.242809
    3         6          0      -0.121860    -0.888440    -1.092264
    4         6          0      -1.573617    -0.698224    -0.655656
    5         6          0      -1.993913     0.749281    -0.461467
    6         1          0       0.422853     2.179527    -0.690398
    7         1          0       0.873559     2.135580     1.022156
    8         1          0      -1.291522     0.979413     1.573899
    9         1          0      -1.586455     2.493156     0.735270
   10         1          0      -0.001924    -0.484971    -2.103705
   11         1          0       0.134446    -1.951525    -1.120136
   12         1          0      -1.899630     1.260990    -1.427077
   13         1          0      -3.053457     0.759718    -0.189470
   14        15          0       1.046095    -0.009732    -0.020189
   15         6          0       1.235982    -0.868713     1.548931
   16         1          0       1.622171    -1.873202     1.361968
   17         1          0       1.941054    -0.315537     2.173381
   18         1          0       0.269693    -0.940592     2.049424
   19         6          0       2.642906     0.114607    -0.834209
   20         1          0       3.331132     0.667683    -0.191131
   21         1          0       3.035697    -0.889080    -1.011581
   22         1          0       2.526140     0.637919    -1.785333
   23         9          0      -1.742238    -1.375503     0.570846
   24         1          0      -2.225364    -1.195860    -1.377075
-----------------------------------------------------------------------
```

4equatorial

```
                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number       Type         X           Y           Z
---------------------------------------------------------------------
    1         6           0       -0.747280    1.882857    0.109018
    2         6           0        0.617100    1.526088   -0.508151
    3         6           0       -0.351889   -1.162205   -0.278563
    4         6           0       -1.601611   -0.492682    0.287693
    5         6           0       -1.853548    0.892878   -0.278727
    6         1           0        0.556894    1.541074   -1.602384
    7         1           0        1.396136    2.230786   -0.201760
    8         1           0       -0.666618    1.943777    1.200505
    9         1           0       -1.021584    2.881707   -0.239909
   10         1           0       -0.474013   -1.292740   -1.359873
   11         1           0       -0.190613   -2.144336    0.175802
   12         1           0       -1.932818    0.823168   -1.370239
   13         1           0       -2.813025    1.249798    0.106407
   14        15           0        1.119893   -0.138500   -0.022759
   15         9           0       -2.686005   -1.322353   -0.041849
   16         1           0       -1.565232   -0.459079    1.381245
   17         6           0        1.591097   -0.166438    1.713219
   18         1           0        1.828764   -1.193139    2.000572
   19         1           0        2.469858    0.466995    1.854342
   20         1           0        0.773986    0.203832    2.335225
   21         6           0        2.475017   -0.754009   -1.025817
   22         1           0        3.350971   -0.120331   -0.871375
   23         1           0        2.705340   -1.778448   -0.724799
   24         1           0        2.184295   -0.733322   -2.077762
---------------------------------------------------------------------
```

(2-fluoroethyl)triphenylphosphonium *anti*
```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number      Type          X           Y           Z
 ---------------------------------------------------------------------
     1         15          0        0.029468    0.003461    0.425154
     2          6          0       -1.078665   -1.193089   -0.318802
     3          6          0       -1.439656   -2.344456    0.405883
     4          6          0       -1.492865   -1.024664   -1.653207
     5          6          0       -2.235456   -3.317507   -0.206407
     6          1          0       -1.108250   -2.491333    1.430371
     7          6          0       -2.282882   -2.010489   -2.253958
     8          1          0       -1.199561   -0.142898   -2.216635
     9          6          0       -2.657524   -3.151136   -1.532327
    10          1          0       -2.523990   -4.202856    0.352575
    11          1          0       -2.606077   -1.884240   -3.283145
    12          1          0       -3.275439   -3.910756   -2.002640
    13          6          0       -0.210837    1.594104   -0.372163
    14          6          0        0.903903    2.352362   -0.770871
    15          6          0       -1.518498    2.084397   -0.557318
    16          6          0        0.703907    3.610514   -1.350300
    17          1          0        1.911259    1.967274   -0.637496
    18          6          0       -1.701478    3.343957   -1.135302
    19          1          0       -2.384579    1.490313   -0.275790
    20          6          0       -0.593268    4.107158   -1.528435
    21          1          0        1.561929    4.198160   -1.663481
    22          1          0       -2.707946    3.724864   -1.282107
    23          1          0       -0.742178    5.084036   -1.979627
    24          6          0        1.726349   -0.538550    0.212232
    25          6          0        2.735780   -0.086982    1.082730
    26          6          0        2.034359   -1.377289   -0.874670
    27          6          0        4.058518   -0.483170    0.858400
    28          1          0        2.505733    0.564038    1.921332
    29          6          0        3.362475   -1.759430   -1.088308
    30          1          0        1.251748   -1.730214   -1.541426
    31          6          0        4.372200   -1.314361   -0.224898
    32          1          0        4.840685   -0.141498    1.529965
    33          1          0        3.605226   -2.408822   -1.924385
    34          1          0        5.401459   -1.618135   -0.393355
    35          6          0       -0.308563    0.135977    2.205072
    36          1          0       -0.079591   -0.835309    2.656755
    37          1          0        0.393807    0.872653    2.607969
    38          6          0       -1.735438    0.552111    2.538352
    39          1          0       -1.953240    1.564523    2.194355
    40          1          0       -2.471890   -0.149423    2.141132
    41          9          0       -1.857253    0.546773    3.930455
 ---------------------------------------------------------------------
```

(2-fluoroethyl)triphenylphosphonium *gauche*
```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1        15          0        0.080259    0.017058    0.543760
     2         6          0       -0.834461   -1.351885   -0.166657
     3         6          0       -0.955643   -2.559139    0.544632
     4         6          0       -1.316962   -1.243101   -1.484079
     5         6          0       -1.583491   -3.651438   -0.061911
     6         1          0       -0.571815   -2.657188    1.555901
     7         6          0       -1.938999   -2.345941   -2.078962
     8         1          0       -1.205301   -0.316020   -2.039891
     9         6          0       -2.074443   -3.546551   -1.370433
    10         1          0       -1.686719   -4.582780    0.487314
    11         1          0       -2.315741   -2.264871   -3.094491
    12         1          0       -2.561548   -4.398595   -1.836166
    13         6          0       -0.464132    1.535161   -0.245683
    14         6          0        0.474455    2.448962   -0.755640
    15         6          0       -1.846157    1.796920   -0.332684
    16         6          0        0.023091    3.636641   -1.342737
    17         1          0        1.538864    2.238126   -0.702722
    18         6          0       -2.279978    2.989638   -0.918473
    19         1          0       -2.570970    1.079673    0.043881
    20         6          0       -1.348446    3.908461   -1.421763
    21         1          0        0.744149    4.344578   -1.741012
    22         1          0       -3.344061    3.196384   -0.987826
    23         1          0       -1.692039    4.831992   -1.879166
    24         6          0        1.832656   -0.239681    0.241874
    25         6          0        2.794339    0.505836    0.950711
    26         6          0        2.226882   -1.155942   -0.750668
    27         6          0        4.150961    0.327065    0.661030
    28         1          0        2.503815    1.223959    1.712675
    29         6          0        3.587340   -1.321823   -1.030432
    30         1          0        1.485246   -1.733782   -1.295683
    31         6          0        4.547689   -0.583646   -0.327011
    32         1          0        4.894512    0.898887    1.208542
    33         1          0        3.894473   -2.030954   -1.793657
    34         1          0        5.603006   -0.718494   -0.546514
    35         6          0       -0.175472    0.126727    2.344075
    36         1          0        0.009704   -0.863652    2.770575
    37         1          0        0.592887    0.803877    2.733050
    38         6          0       -1.537159    0.661101    2.754239
    39         1          0       -1.693048    1.683892    2.406230
    40         9          0       -2.542421   -0.137055    2.194053
    41         1          0       -1.639935    0.618413    3.839511
---------------------------------------------------------------------
```
7-*cis-g_s*
```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       -1.069803    1.558332    0.470139
     2         6          0        0.419257    1.580101    0.082249
     3         6          0       -0.100687   -1.017315   -0.921119
     4         6          0       -1.553284   -0.734678   -0.545565
     5         6          0       -1.917583    0.740922   -0.510707
     6         1          0        0.545669    1.994836   -0.924158
     7         1          0        1.006918    2.187029    0.778245
     8         1          0       -1.185592    1.154636    1.481734
     9         1          0       -1.443486    2.586008    0.493479
    10         1          0        0.047870   -0.717288   -1.964358
    11         1          0        0.110121   -2.088128   -0.841028
    12         1          0       -2.215432   -1.273819   -1.227941
    13         1          0       -1.804479    1.138728   -1.527008
    14         1          0       -2.976331    0.822953   -0.245226
    15        15          0        1.081915   -0.091957    0.098063
    16         8          0        1.339493   -0.688880    1.449401
    17         9          0       -1.792204   -1.276583    0.737266
    18         8          0        2.420289    0.055111   -0.819894
    19         1          0        3.070193   -0.630358   -0.616107
---------------------------------------------------------------------
```

7-cis-g_a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
    1         6          0       -1.066418    1.564290    0.457442
    2         6          0        0.423337    1.581597    0.069424
    3         6          0       -0.092987   -1.021410   -0.915525
    4         6          0       -1.547454   -0.734946   -0.546100
    5         6          0       -1.913092    0.740426   -0.518669
    6         1          0        0.541470    1.993629   -0.939921
    7         1          0        1.010173    2.196989    0.758815
    8         1          0       -1.181655    1.168029    1.471901
    9         1          0       -1.439122    2.592585    0.472991
   10         1          0        0.050241   -0.735674   -1.964220
   11         1          0        0.115698   -2.091825   -0.826082
   12         1          0       -2.206603   -1.277203   -1.228887
   13         1          0       -1.801176    1.133466   -1.537042
   14         1          0       -2.971981    0.821994   -0.253619
   15        15          0        1.084636   -0.095640    0.108814
   16         8          0        1.318491   -0.652554    1.477325
   17         9          0       -1.790112   -1.272175    0.737227
   18         8          0        2.490140   -0.091374   -0.713224
   19         1          0        2.435049    0.253873   -1.613433
---------------------------------------------------------------------
```

7-cis-g_s'

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
---------------------------------------------------------------------
    1         6          0       -1.084499    1.568201    0.421525
    2         6          0        0.402948    1.589755    0.025625
    3         6          0       -0.089317   -1.043393   -0.888308
    4         6          0       -1.543212   -0.761551   -0.519715
    5         6          0       -1.925561    0.709851   -0.529626
    6         1          0        0.517593    1.966452   -0.996971
    7         1          0        0.986731    2.230404    0.694325
    8         1          0       -1.192483    1.196599    1.446133
    9         1          0       -1.468616    2.592392    0.411384
   10         1          0        0.061453   -0.775676   -1.940053
   11         1          0        0.131509   -2.108760   -0.773420
   12         1          0       -2.201563   -1.329858   -1.181528
   13         1          0       -1.821528    1.076683   -1.558574
   14         1          0       -2.984453    0.786196   -0.262900
   15        15          0        1.080766   -0.080127    0.099701
   16         8          0        1.350800   -0.572462    1.490213
   17         9          0       -1.769600   -1.265343    0.781272
   18         8          0        2.389021   -0.107678   -0.871657
   19         1          0        3.205540    0.019497   -0.370809
---------------------------------------------------------------------
```

7-trans-g_g

```
                    Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X            Y            Z
-----------------------------------------------------------------------
   1          6          0        -0.997829     1.575344     0.455954
   2          6          0         0.477316     1.595298     0.023574
   3          6          0        -0.108478    -1.037710    -0.925370
   4          6          0        -1.548425    -0.711134    -0.534946
   5          6          0        -1.876414     0.772512    -0.508630
   6          1          0         0.577688     2.054495    -0.966916
   7          1          0         1.091663     2.177623     0.719179
   8          1          0        -1.084784     1.159513     1.464786
   9          1          0        -1.365464     2.604961     0.499959
  10          1          0         0.008910    -0.827020    -1.994675
  11          1          0         0.093688    -2.102877    -0.776841
  12          1          0        -2.226816    -1.237151    -1.212056
  13          1          0        -1.765483     1.160505    -1.529195
  14          1          0        -2.930224     0.880493    -0.232916
  15         15          0         1.168676    -0.067099    -0.091165
  16          9          0        -1.797811    -1.240407     0.748806
  17          8          0         2.527512    -0.147537    -0.719625
  18          8          0         1.084670    -0.681946     1.414896
  19          1          0         1.676521    -0.230384     2.031229
-----------------------------------------------------------------------
```

7-trans-g_a

```
                    Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type           X            Y            Z
-----------------------------------------------------------------------
   1          6          0        -1.041578     1.553169     0.484060
   2          6          0         0.437010     1.611435     0.061851
   3          6          0        -0.064372    -0.949500    -1.052219
   4          6          0        -1.496275    -0.726426    -0.575360
   5          6          0        -1.907656     0.731877    -0.477921
   6          1          0         0.535920     2.095532    -0.916798
   7          1          0         1.031650     2.185057     0.780428
   8          1          0        -1.123524     1.143798     1.496613
   9          1          0        -1.434466     2.573118     0.527625
  10          1          0         0.018117    -0.600896    -2.087508
  11          1          0         0.181261    -2.015929    -1.035736
  12          1          0        -2.191372    -1.287797    -1.202716
  13          1          0        -1.855939     1.156609    -1.488180
  14          1          0        -2.954471     0.773054    -0.161368
  15         15          0         1.161267    -0.032658    -0.079719
  16          9          0        -1.606188    -1.301639     0.724677
  17          8          0         2.563026    -0.082603    -0.598224
  18          8          0         1.069323    -0.675131     1.413966
  19          1          0         0.207937    -1.079373     1.592930
-----------------------------------------------------------------------
```

7-trans-g_g′

```
                        Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
-----------------------------------------------------------------------
    1          6          0       -1.011759     1.573141     0.433475
    2          6          0        0.462526     1.601220    -0.004582
    3          6          0       -0.095130    -1.037101    -0.937224
    4          6          0       -1.535162    -0.735450    -0.530909
    5          6          0       -1.888286     0.742569    -0.509449
    6          1          0        0.554232     2.038017    -1.005784
    7          1          0        1.074054     2.200678     0.677639
    8          1          0       -1.087537     1.178177     1.451093
    9          1          0       -1.390121     2.599527     0.456812
   10          1          0        0.014789    -0.813296    -2.004828
   11          1          0        0.118476    -2.102800    -0.805439
   12          1          0       -2.215121    -1.276304    -1.194718
   13          1          0       -1.799928     1.121654    -1.535545
   14          1          0       -2.939785     0.835599    -0.219573
   15         15          0        1.167838    -0.050719    -0.086159
   16          9          0       -1.753675    -1.264892     0.759781
   17          8          0        2.526571    -0.185797    -0.704973
   18          8          0        1.097100    -0.455600     1.488758
   19          1          0        1.353950    -1.371530     1.656547
-----------------------------------------------------------------------
```

7-trans-a_s

```
                        Standard orientation:
-----------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
-----------------------------------------------------------------------
    1          6          0       -0.610282     1.883682     0.184828
    2          6          0        0.740821     1.474026    -0.429222
    3          6          0       -0.330214    -1.138497    -0.316121
    4          6          0       -1.558578    -0.462852     0.276162
    5          6          0       -1.760841     0.954426    -0.229213
    6          1          0        0.685430     1.489898    -1.523294
    7          1          0        1.542397     2.149551    -0.115204
    8          1          0       -0.529377     1.903279     1.278274
    9          1          0       -0.846641     2.902254    -0.134313
   10          1          0       -0.428595    -1.179095    -1.406344
   11          1          0       -0.221669    -2.156494     0.070324
   12          1          0       -1.848645     0.929913    -1.322548
   13          1          0       -2.703415     1.335466     0.175546
   14         15          0        1.159732    -0.192078     0.101493
   15          8          0        1.566626    -0.340579     1.537399
   16          8          0        2.295770    -0.640302    -0.970605
   17          1          0        2.864654    -1.339817    -0.622454
   18          1          0       -1.518439    -0.476804     1.370104
   19          9          0       -2.686253    -1.232737    -0.082828
-----------------------------------------------------------------------
```

7-trans-a_a
```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic           Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1         6           0       -0.605110    1.888742    0.155076
    2         6           0        0.745548    1.466377   -0.452477
    3         6           0       -0.327744   -1.143344   -0.292963
    4         6           0       -1.556412   -0.453877    0.284067
    5         6           0       -1.756624    0.954830   -0.244726
    6         1           0        0.685136    1.476140   -1.546984
    7         1           0        1.547664    2.146074   -0.148514
    8         1           0       -0.523350    1.925448    1.247853
    9         1           0       -0.839277    2.902583   -0.180718
   10         1           0       -0.434105   -1.212002   -1.381731
   11         1           0       -0.221345   -2.152696    0.115918
   12         1           0       -1.844092    0.912847   -1.337574
   13         1           0       -2.699007    1.343227    0.153325
   14        15           0        1.163845   -0.194602    0.111017
   15         8           0        1.570809   -0.285272    1.548027
   16         8           0        2.351635   -0.769874   -0.835948
   17         1           0        2.164232   -0.745378   -1.783337
   18         1           0       -1.517809   -0.450247    1.378062
   19         9           0       -2.683692   -1.229128   -0.063560
---------------------------------------------------------------------
```

7-trans-a_s'
```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic           Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1         6           0       -0.618304    1.890192    0.142841
    2         6           0        0.730883    1.469576   -0.468375
    3         6           0       -0.323853   -1.145078   -0.282123
    4         6           0       -1.554098   -0.457232    0.292826
    5         6           0       -1.764874    0.945902   -0.246920
    6         1           0        0.666504    1.457759   -1.562103
    7         1           0        1.531045    2.157590   -0.178056
    8         1           0       -0.533230    1.934110    1.235206
    9         1           0       -0.860290    2.900228   -0.198929
   10         1           0       -0.422851   -1.219247   -1.370590
   11         1           0       -0.209403   -2.150090    0.134653
   12         1           0       -1.854214    0.894499   -1.339169
   13         1           0       -2.709230    1.330640    0.150201
   14        15           0        1.160458   -0.186444    0.101942
   15         8           0        1.602081   -0.242793    1.534312
   16         8           0        2.227535   -0.806988   -0.956124
   17         1           0        3.138175   -0.707736   -0.648000
   18         1           0       -1.512365   -0.442485    1.386796
   19         9           0       -2.677385   -1.242280   -0.043793
---------------------------------------------------------------------
```

7-*cis*-a_g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1         6           0       -0.524045    1.887160    0.171787
    2         6           0        0.799477    1.456169   -0.481713
    3         6           0       -0.344514   -1.148781   -0.365607
    4         6           0       -1.529940   -0.434127    0.266879
    5         6           0       -1.705193    0.990710   -0.224798
    6         1           0        0.732278    1.535596   -1.572932
    7         1           0        1.629727    2.091911   -0.155689
    8         1           0       -0.415142    1.889019    1.262056
    9         1           0       -0.744656    2.915051   -0.129848
   10         1           0       -0.497439   -1.213336   -1.448642
   11         1           0       -0.240195   -2.162923    0.031690
   12         1           0       -1.816629    0.977087   -1.316291
   13         1           0       -2.629579    1.391743    0.202012
   14        15           0        1.206575   -0.260171   -0.100687
   15         8           0        2.405287   -0.812267   -0.807918
   16         8           0        1.266587   -0.339043    1.526776
   17         1           0        2.012701    0.145008    1.904674
   18         9           0       -2.691457   -1.167174   -0.063854
   19         1           0       -1.456282   -0.458338    1.357807
---------------------------------------------------------------------
```

7-*cis*-a_g'

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
    1         6           0       -0.536834    1.884171    0.160313
    2         6           0        0.792008    1.455755   -0.484605
    3         6           0       -0.342120   -1.153704   -0.357280
    4         6           0       -1.529876   -0.440046    0.271124
    5         6           0       -1.712423    0.979104   -0.233496
    6         1           0        0.727181    1.527624   -1.576309
    7         1           0        1.619210    2.093257   -0.156813
    8         1           0       -0.430593    1.894927    1.250405
    9         1           0       -0.761156    2.908152   -0.151547
   10         1           0       -0.496572   -1.230470   -1.439534
   11         1           0       -0.237290   -2.166397    0.045564
   12         1           0       -1.820954    0.955778   -1.325105
   13         1           0       -2.639746    1.379196    0.187809
   14        15           0        1.209613   -0.251244   -0.100659
   15         8           0        2.385214   -0.846409   -0.811375
   16         8           0        1.367370   -0.136126    1.517575
   17         1           0        1.502657   -0.989720    1.949896
   18         9           0       -2.688636   -1.182725   -0.047004
   19         1           0       -1.454405   -0.450575    1.362613
---------------------------------------------------------------------
```

8-cis-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.679548    1.565467   -0.539846
   2          6          0       -0.692101    1.565453    0.153771
   3          6          0        0.053168   -1.013277    1.028338
   4          6          0        1.392320   -0.715736    0.362386
   5          6          0        1.725216    0.762417    0.240886
   6          1          0       -0.605046    1.973446    1.168686
   7          1          0       -1.418000    2.174535   -0.393948
   8          1          0        0.587139    1.161460   -1.553824
   9          1          0        1.026274    2.598180   -0.640363
  10          1          0        0.114466   -0.705346    2.079719
  11          1          0       -0.149474   -2.088107    1.005178
  12          1          0        2.188177   -1.240397    0.897529
  13          1          0        1.828278    1.167797    1.255404
  14          1          0        2.702348    0.850289   -0.244568
  15         15          0       -1.344991   -0.119543    0.277509
  16          8          0       -1.885646   -0.700302   -1.008535
  17          9          0        1.370371   -1.267732   -0.939125
  18          1          0       -2.296387   -0.072653    1.310747
---------------------------------------------------------------------
```

8-trans-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.883696    1.603388   -0.279526
   2          6          0       -0.620389    1.525441    0.035728
   3          6          0       -0.055997   -1.174818    0.662014
   4          6          0        1.399173   -0.801743    0.395424
   5          6          0        1.721542    0.668851    0.598778
   6          1          0       -0.808541    1.781764    1.085247
   7          1          0       -1.193498    2.219927   -0.586823
   8          1          0        1.056759    1.366430   -1.335256
   9          1          0        1.222311    2.632865   -0.129842
  10          1          0       -0.265408   -1.041740    1.729952
  11          1          0       -0.226293   -2.227603    0.417836
  12          1          0        2.056498   -1.425060    1.007041
  13          1          0        1.561914    0.903801    1.658356
  14          1          0        2.785734    0.816411    0.389313
  15         15          0       -1.253480   -0.145545   -0.238112
  16          9          0        1.688379   -1.133041   -0.949581
  17          1          0       -0.966274   -0.383238   -1.592769
  18          8          0       -2.698072   -0.398717    0.125043
---------------------------------------------------------------------
```

8-trans-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type           X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.001591    1.805367    0.361067
   2          6          0        1.147567    1.272605   -0.515555
   3          6          0       -0.352127   -1.111489   -0.553122
   4          6          0       -1.339692   -0.341702    0.309532
   5          6          0       -1.347243    1.150270    0.030473
   6          1          0        0.935340    1.455387   -1.576275
   7          1          0        2.095453    1.761354   -0.269835
   8          1          0        0.237771    1.646019    1.420123
   9          1          0       -0.083566    2.885820    0.215044
  10          1          0       -0.601591   -0.967220   -1.611272
  11          1          0       -0.390189   -2.180718   -0.324979
  12          1          0       -1.592723    1.309696   -1.026927
  13          1          0       -2.137528    1.610649    0.631391
  14         15          0        1.343017   -0.510833   -0.272145
  15          8          0        1.936056   -0.915694    1.057661
  16          1          0        2.064176   -0.974596   -1.384651
  17          9          0       -2.629416   -0.853117    0.042413
  18          1          0       -1.156673   -0.530598    1.372173
---------------------------------------------------------------------
```

8-cis-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type         X            Y            Z
---------------------------------------------------------------------
   1          6           0       -0.375308     1.867425     0.214249
   2          6           0        0.994117     1.391583    -0.300315
   3          6           0       -0.195032    -1.172150    -0.156416
   4          6           0       -1.433377    -0.420207     0.307393
   5          6           0       -1.534354     0.981953    -0.261792
   6          1           0        1.013393     1.391508    -1.396299
   7          1           0        1.797402     2.046857     0.050464
   8          1           0       -0.370369     1.906237     1.310903
   9          1           0       -0.542201     2.890552    -0.133585
  10          1           0       -0.223726    -1.280299    -1.246966
  11          1           0       -0.159509    -2.170947     0.289422
  12          1           0       -1.539194     0.922446    -1.357028
  13          1           0       -2.486155     1.418220     0.056117
  14         15           0        1.345736    -0.294920     0.249506
  15          1           0        1.305374    -0.193501     1.652296
  16          8           0        2.602616    -0.945185    -0.275953
  17          9           0       -2.561642    -1.160900    -0.108867
  18          1           0       -1.483488    -0.389317     1.400795
---------------------------------------------------------------------
```

9-cis-g

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type         X            Y            Z
---------------------------------------------------------------------
   1          6           0       -1.111642     1.566932     0.422988
   2          6           0        0.383980     1.583862     0.070045
   3          6           0       -0.096878    -1.029182    -0.888300
   4          6           0       -1.561247    -0.741365    -0.574154
   5          6           0       -1.929572     0.733497    -0.569104
   6          1           0        0.527119     1.979259    -0.943138
   7          1           0        0.950527     2.215740     0.762479
   8          1           0       -1.251731     1.174816     1.436164
   9          1           0       -1.491043     2.593320     0.423356
  10          1           0        0.083568    -0.758631    -1.935827
  11          1           0        0.106659    -2.099535    -0.780013
  12          1           0       -2.197137    -1.286723    -1.277023
  13          1           0       -1.787911     1.118015    -1.587354
  14          1           0       -2.996390     0.815096    -0.336933
  15         15           0        1.076873    -0.091490     0.148407
  16          8           0        1.234998    -0.623469     1.558001
  17          9           0       -1.855650    -1.270875     0.703079
  18          6           0        2.627995    -0.070808    -0.779294
  19          1           0        3.352120     0.543821    -0.238068
  20          1           0        3.013231    -1.091267    -0.851754
  21          1           0        2.482942     0.336453    -1.782777
---------------------------------------------------------------------
```

9-trans-g

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number      Type            X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        -1.067902    1.502017    0.610023
    2          6           0         0.394971    1.607336    0.147980
    3          6           0        -0.114792   -0.898068   -1.074795
    4          6           0        -1.547776   -0.695204   -0.593964
    5          6           0        -1.948623    0.756599   -0.397219
    6          1           0         0.448792    2.147233   -0.805566
    7          1           0         1.002908    2.159505    0.873090
    8          1           0        -1.123613    1.007244    1.585505
    9          1           0        -1.465731    2.511977    0.749959
   10          1           0        -0.043235   -0.519873   -2.101744
   11          1           0         0.125845   -1.965909   -1.102325
   12          1           0        -2.236076   -1.189993   -1.284420
   13          1           0        -1.902454    1.252546   -1.375066
   14          1           0        -2.993219    0.780713   -0.070325
   15         15           0         1.166879   -0.009829   -0.129819
   16          9           0        -1.699288   -1.364603    0.644712
   17          8           0         2.495498    0.043432   -0.856147
   18          6           0         1.288898   -0.804735    1.488667
   19          1           0         1.656866   -1.824940    1.351481
   20          1           0         2.005814   -0.246077    2.096255
   21          1           0         0.321862   -0.838694    1.993053
 ---------------------------------------------------------------------
```

9-trans-a

```
                        Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number      Type            X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        -0.694290    1.884118    0.097589
    2          6           0         0.675426    1.482494   -0.474380
    3          6           0        -0.309997   -1.145382   -0.275245
    4          6           0        -1.567167   -0.486349    0.267220
    5          6           0        -1.807296    0.902374   -0.296620
    6          1           0         0.633342    1.446488   -1.569738
    7          1           0         1.449835    2.201995   -0.188004
    8          1           0        -0.633814    1.950655    1.190493
    9          1           0        -0.955801    2.881319   -0.268128
   10          1           0        -0.385737   -1.226829   -1.365911
   11          1           0        -0.187694   -2.148139    0.146578
   12          1           0        -1.875137    0.831825   -1.389566
   13          1           0        -2.769705    1.266415    0.076610
   14         15           0         1.157803   -0.150583    0.151042
   15          8           0         1.468695   -0.164085    1.634048
   16          9           0        -2.667381   -1.305182   -0.078604
   17          1           0        -1.547485   -0.456504    1.361276
   18          6           0         2.504674   -0.763927   -0.881759
   19          1           0         3.384738   -0.135639   -0.722348
   20          1           0         2.740199   -1.788799   -0.583776
   21          1           0         2.228986   -0.744689   -1.938890
 ---------------------------------------------------------------------
```

9-cis-a

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0       -0.592373    1.879768    0.194843
   2          6           0        0.722606    1.480090   -0.494827
   3          6           0       -0.355307   -1.134044   -0.372557
   4          6           0       -1.546069   -0.457672    0.287633
   5          6           0       -1.765927    0.966907   -0.184077
   6          1           0        0.613293    1.557862   -1.583352
   7          1           0        1.542577    2.142421   -0.197331
   8          1           0       -0.464888    1.883353    1.283826
   9          1           0       -0.837798    2.906659   -0.091483
  10          1           0       -0.531242   -1.185968   -1.453642
  11          1           0       -0.231924   -2.154896    0.003429
  12          1           0       -1.901421    0.962170   -1.272826
  13          1           0       -2.688341    1.344554    0.267895
  14         15           0        1.212686   -0.231072   -0.147635
  15          8           0        2.334784   -0.761106   -1.013438
  16          9           0       -2.695846   -1.217365   -0.027815
  17          1           0       -1.462585   -0.489873    1.378849
  18          6           0        1.589410   -0.311058    1.619300
  19          1           0        1.774945   -1.353271    1.891575
  20          1           0        2.492845    0.274121    1.810250
  21          1           0        0.774555    0.080129    2.233285
---------------------------------------------------------------------
```

PF_gauche_

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0        1.318919    0.438778    0.316899
   2          1           0        2.123117    1.111757    0.020769
   3          1           0        1.274488    0.362217    1.404064
   4          6           0        0.003085    0.914152   -0.278670
   5          1           0        0.080437    1.020928   -1.363206
   6          1           0       -0.268661    1.883529    0.148400
   7          1           0       -1.486948   -0.456888    1.417333
   8          1           0       -2.556117    0.304547   -0.411347
   9          1           0       -1.159374   -1.447069   -0.573295
  10         15           0       -1.360862   -0.225843    0.053726
  11          9           0        1.608218   -0.834328   -0.186443
---------------------------------------------------------------------
```

PF_anti_

```
                    Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6           0       -1.123535   -0.507595    0.000013
   2          1           0       -1.073229   -1.129694   -0.894447
   3          1           0       -1.073287   -1.129486    0.894645
   4          6           0       -0.053234    0.577396   -0.000027
   5          1           0       -0.149254    1.207089    0.888209
   6          1           0       -0.149376    1.207163   -0.888170
   7          1           0        1.871094   -0.850333   -1.124108
   8          1           0        2.535809    0.981589   -0.000558
   9          1           0        1.871639   -0.849199    1.124748
  10         15           0        1.631941   -0.071288   -0.000012
  11          9           0       -2.361321    0.134820   -0.000007
---------------------------------------------------------------------
```

PPgauche

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.638059    0.801610    0.431619
   2          1          0        1.099552    1.790197    0.358232
   3          1          0        0.433328    0.628762    1.491193
   4          6          0       -0.638072    0.801624   -0.431621
   5          1          0       -0.433356    0.628757   -1.491194
   6          1          0       -1.099584    1.790197   -0.358211
   7          1          0       -2.301825   -0.139486    1.389455
   8          1          0       -3.062035   -0.128182   -0.733571
   9          1          0       -1.568758   -1.679892   -0.078978
  10          1          0        3.061902   -0.128449    0.733854
  11          1          0        1.568651   -1.679910    0.078562
  12          1          0        2.302129   -0.139168   -1.389333
  13         15          0        1.948332   -0.352071   -0.063792
  14         15          0       -1.948327   -0.352077    0.063792
---------------------------------------------------------------------
```

PPanti

```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.516167   -0.567641    0.000004
   2          1          0        0.424198   -1.202052    0.885752
   3          1          0        0.424177   -1.201972   -0.885782
   4          6          0       -0.516176    0.567752   -0.000007
   5          1          0       -0.424258    1.202179   -0.885765
   6          1          0       -0.424309    1.202173    0.885738
   7          1          0       -2.458477   -0.829729    1.127168
   8          1          0       -3.099813    1.016061    0.000074
   9          1          0       -2.458663   -0.829714   -1.127159
  10          1          0        3.099608   -1.016250   -0.000404
  11          1          0        2.458708    0.829987   -1.126957
  12          1          0        2.458765    0.829325    1.127430
  13         15          0        2.217121    0.055547   -0.000002
  14         15          0       -2.217113   -0.055592   -0.000003
---------------------------------------------------------------------
```

Table S1. Relative Gibbs free energies (kcal mol^{-1}) and conformational populations (%) obtained in the gas phase and implicit DMSO (IEFPCM) at the B3LYP-D3BJ/6-311++g(d,p) theory level.

Compound	Relative energy(gas phase)	Population (gas phase)	Relative energy(Implicit DMSO)	Population (Implicit DMSO)
1-cis-g	1.25	11	1.37	9
1-trans-g	3.72	0	3.46	0
1-trans-a	0.00	88	0.00	90
1-cis-a	2.35	1	2.48	1
2-cis-g	0.98	10	1.48	5
2-trans-g	1.74	3	1.52	5
2-trans-a	0.00	54	0.00	63
2-cis-a	0.28	33	0.49	27
3axial	0.00	100	0.00	72
3equatorial	3.41	0	0.57	28
4axial	0.00	100	0.00	82
4equatorial	3.25	0	0.91	18
5*anti*	1.90	4	0.39	34
5*gauche*	0.00	96	0.00	66
7-cis-g_s	2.82	1	1.12	4
7-cis-g_a	7.74	0	2.65	0
7-cis-g_s'	---	---	1.03	5
7-trans-g_s	1.30	7	---	---
7-trans-g_g	---	---	1.00	5
7-trans-g_a	2.55	1	0.47	12
7-trans-g_g'	---	---	0.65	9
7-trans-g_s'	1.94	3	---	---
7-trans-a_s	0.66	22	0.71	8
7-trans-a_a	4.94	0	2.03	1
7-trans-a_s'	---	---	0.53	11
7-cis-a_s	0.00	66	---	---
7-cis-a_g	---	---	0.00	26
7-cis-a_g'	---	---	0.18	19
8-cis-g	2.72	0	1.48	4
8-trans-g	0.00	37	0.22	33
8-trans-a	0.08	32	0.64	16
8-cis-a	0.10	31	0.00	47
9-cis-g	3.35	0	1.34	4
9-trans-g	0.42	27	0.51	18
9-trans-a	0.00	55	0.11	35
9-cis-a	0.64	18	0.00	43

Table S2. Relative full energies (E_{FULL}), non-Lewis (E_{NL}) and Lewis-type (E_L) contributions, and the main electron delocalization energies obtained for the gas phase compounds at the B3LYP-D3BJ/6-311++g(d,p) theory level (in kcal mol^{-1}).

Conf.	E_{FULL}	E_{NL}	E_L	$\sigma_{C1H}{\to}\sigma^*_{CF}$	$\sigma_{C1H}{\to}\sigma^*_{C2H}$	$\sigma_{C1H}{\to}\sigma^*_{C2C3}$	$\sigma_{CF}{\to}\sigma^*_{CP}$	$\sigma_{C1H}{\to}\sigma^*_{PH/C}$	$\sigma_{CH}{\to}\sigma^*_{PO}$	$\sigma_{CH}{\to}\pi^*_{PO}$	$\sigma_{CP}{\to}\sigma^*_{CF}$
1-cis-g	1.30	-7.04	8.34	5.12	-	3.03	-	0.96	-	-	-
1-trans-g	3.84	0.00	3.84	5.19	-	3.04	-	-	-	-	-
1-trans-a	0.00	-8.16	8.16	0.77	2.81	2.90	1.66	0.98	-	-	4.58
1-cis-a	2.41	-0.23	2.64	0.93	2.79	2.84	1.48	-	-	-	5.20
2-cis-g	0.93	-9.26	10.19	5.29	-	3.06	-	1.27	-	-	-
2-trans-g	1.93	0.00	1.93	5.18	-	3.04	-	-	-	-	-
2-trans-a	0.00	-8.36	8.36	0.89	2.95	2.88	1.51	1.28	-	-	4.31
2-cis-a	0.30	-0.15	0.45	0.93	2.78	2.83	1.33	-	-	-	5.16
3axial	0.00	0.00	0.00	3.83	-	2.45	-	1.85	-	-	-
3equatorial	3.57	-2.95	6.52	1.08	2.18	2.20	1.78	2.08	-	-	2.85
4 axial	0.00	0.00	0.00	4.19	-	2.52	-	2.25	-	-	-
4equatorial	3.60	-0.95	4.55	1.05	2.35	2.28	1.57	2.45	-	-	2.75
5anti	2.39	0.00	2.39	1.15	2.10	-	1.83	2.49	-	-	2.30
5gauche	0.00	-3.68	3.68	4.22	2.03	-	-	2.29	-	-	-
7-cis-g_s	2.72	-23.18	25.90	4.73	-	2.84	-	-	1.62	-	-
7-cis-g_a	7.84	0.00	7.84	4.60	-	2.84	-	-	1.76	-	-
7-trans-g_s	2.09	-34.35	36.44	4.76	-	2.81	-	-	0.74	2.43	-
7-trans-g_a*	1.69	-2.74	4.43	5.18	-	2.92	-	-	0.56	3.02	2.96
7-trans-g_s'	1.99	-34.31	36.30	4.77	-	2.81	-	-	0.91	1.86	-
7-trans-a_s	0.53	-18.58	19.11	0.75	2.53	2.63	1.14	-	1.91	-	4.18
7-trans-a_a	4.89	-0.98	5.87	0.73	2.46	2.64	1.12	-	1.91	-	4.23
7-cis-a_s	0.00	-29.09	29.09	0.85	2.57	2.65	1.14	-	0.73	2.32	4.23
8-cis-g	2.85	-8.08	10.93	4.70	-	2.88	-	-	2.02	-	-
8-trans-g	0.00	0.00	0.00	4.85	-	2.91	-	1.42	-	-	-
8-trans-a	0.18	-1.22	1.40	0.77	2.49	2.66	1.31	-	2.14	-	4.39
8-cis-a	0.14	-5.06	5.20	0.83	2.68	2.70	1.34	1.45	-	-	4.10
9-cis-g	3.39	-6.12	9.51	4.68	-	2.89	-	-	2.02	-	-
9-trans-g	0.00	-0.16	0.16	5.14	-	2.92	-	1.56	-	-	-
9-trans-a	0.13	0.00	0.13	0.78	2.48	2.67	1.21	-	2.17	-	4.48
9-cis-a	0.60	-2.42	3.02	0.89	2.84	2.73	1.26	1.63	-	-	4.02

* The conformer which is prone to establish an intramolecular hydrogen bond possesses an $n_F{\to}\sigma^*_{HO}$ interaction of 2.96 kcal mol^{-1}.

Table S3. Relative full energies (E_{FULL}), non-Lewis (E_{NL}) and Lewis-type (E_L) contributions, and the main electron delocalization energies obtained for compounds in implicit DMSO at the B3LYP-D3BJ/6-311++g(d,p) theory level (in kcal mol^{-1}).

Conf	E_{FULL}	E_{NL}	E_L	$\sigma_{C1H}{\to}\sigma^*_{C2F}$	$\sigma_{C1H}{\to}\sigma^*_{C2H}$	$\sigma_{C1H}{\to}\sigma^*_{C2C3}$	$\sigma_{CF}{\to}\sigma^*_{CP}$	$\sigma_{C1H}{\to}\sigma^*_{PH/C}$	$\sigma_{CH}{\to}\sigma^*_{PO}$	$\sigma_{CH}{\to}\pi^*_{PO}$	$\sigma_{CP}{\to}\sigma^*_{CF}$
1-cis-g	1.44	-7.47	8.91	5.44	-	3.05	-	1.05	-	-	-
1-trans-g	3.58	0.00	3.58	5.54	-	3.05	-	-	-	-	-
1-trans-a	0.00	-7.65	7.65	0.79	2.82	2.93	1.67	0.97	-	-	4.93
1-cis-a	2.58	-0.10	2.68	0.94	2.84	2.86	1.50	-	-	-	5.53
2-cis-g	1.50	-9.61	11.11	5.58	-	3.05	-	1.36	-	-	-
2-trans-g	1.70	-0.03	1.73	5.55	-	3.06	-	-	-	-	-
2-trans-a	0.00	-7.80	7.80	0.90	2.94	2.91	1.52	1.27	-	-	4.64
2-cis-a	0.57	0.00	0.57	0.94	2.84	2.86	1.35	-	-	-	5.53
3axial	0.00	-1.37	1.37	4.56	-	2.64	-	1.83	-	-	-
3equatorial	0.84	0.00	0.84	1.08	2.33	2.41	1.68	1.87	-	-	3.48
4 axial	0.00	-1.88	1.88	4.79	-	2.69	-	2.23	-	-	-
4equatorial	0.88	0.00	0.88	1.05	2.47	2.47	1.50	2.32	-	-	3.36
5*anti*	1.04	0.00	1.04	1.04	2.14	-	1.80	2.50	-	-	2.58
5*gauche*	0.00	-4.77	4.77	4.68	2.08	-	-	2.36	-	-	-
7-cis-g_s	1.74	-2.23	3.97	5.08	-	2.79	-	-	2.03	-	-
7-cis-g_a	2.77	-0.38	3.15	4.99	-	2.79	-	-	2.07	-	-
7-cis-g_s'	1.78	-2.05	3.83	5.02	-	2.81	-	-	2.21	-	-
7-trans-g_g	1.18	-3.79	4.97	4.96	-	2.76	-	-	1.94	-	-
*7-trans-g_a**	0.18	-5.32	5.50	5.20	-	2.83	-	-	2.03	-	-
7-trans-g_g'	0.95	-3.99	4.94	5.00	-	2.78	-	-	2.28	-	-
7-trans-a_s	1.08	-2.10	3.18	0.79	2.60	2.61	1.19	-	2.09	-	4.57
7-trans-a_a	2.06	0.00	2.06	0.80	2.56	2.61	1.19	-	2.13	-	4.53
7-trans-a_g'	1.23	-1.74	2.97	0.81	2.57	2.62	1.18	-	2.27	-	4.50
7-cis-a_g	0.00	-4.88	4.88	0.94	2.56	2.63	1.25	-	1.92	-	4.01
7-cis-a_g'	0.04	-4.97	5.01	0.88	2.58	2.62	1.24	-	2.23	-	4.14
8-cis-g	1.34	-2.15	3.49	5.10	-	2.86	-	-	2.25	-	-
8-trans-g	0.18	0.00	0.18	5.00	-	2.85	-	1.52	-	-	-
8-trans-a	0.62	-0.24	0.86	0.81	2.60	2.65	1.35	-	2.26	-	4.50
8-cis-a	0.00	-0.96	0.96	0.89	2.60	2.65	1.38	1.47	-	-	4.14
9-cis-g	1.28	-1.63	2.91	5.12	-	2.87	-	-	2.28	-	-
9-trans-g	0.12	0.00	0.12	5.24	-	2.86	-	1.67	-	-	-
9-trans-a	0.19	-0.34	0.53	0.79	2.61	2.68	1.25	-	2.32	-	4.62
9-cis-a	0.00	-0.03	0.03	0.95	2.74	2.68	1.30	1.68	-	-	4.08

* The conformer which is prone to establish an intramolecular hydrogen bond possesses an $n_F{\to}\sigma^*_{HO}$ interaction of 3.21kcal mol^{-1}.

Table S4. Electron density and the Laplacian of electron density at the BCP, bond ellipticity, average number of electrons, net charge, intratomic dipole moment contribution, volume obtained at 0.001 isodensity surface, and interacting quantum atoms (IQA) intratomic energy component in the hydrogen atom (in au).[a]

Conformer	ρ	$\nabla^2\rho$	ε	N(H)	Q(H)	|μ(H)|	V(H)	E(H)
2-cis-g	0.011	0.041	0.1615	0.974 (0.984)	0.026 (0.016)	0.133 (0.151)	43.12 (50.41)	-0.453 (-0.460)
4ax	0.011	0.039	0.2300	0.878 (0.921)	0.1221 (0.084)	0.116 (0.134)	40.23 (46.39)	-0.446 (-0.454)
9-trans-g	0.011	0.038	0.1760	0.964 (0.918)	0.0361 (0.083)	0.149 (0.147)	44.51 (47.20)	-0.451 (-0.452)

[a] The values for the hydrogen (CH_3) not involved in hydrogen bond with the fluorine atom are in parenthesis.

Table S5. NEDA energies in kcal mol^{-1} for **PF**: energy of interaction (E_{int}), electrical interaction (E_{EL}), charge transfer (E_{CT}), Core repulsion (E_{CORE}), classical electrostatic interaction (E_{ES}), polarization contribution (E_{POL}), the penalty of polarization (E_{SE}), deformation cost (E_{DEF}), and exchange interaction (E_{XC}). The energies for **PF** in the gas phase are presented for the C–C equilibrium distance in the *gauche* conformer (1.53 Å), as well as with -0.5 Å and +0.5 Å.

C–C Bond distance (Å)	ϕ_{PCCF} (deg.)	E_{int}	E_{EL}	E_{CT}	E_{CORE}	E_{ES}	E_{POL}	E_{SE}	E_{DEF}	E_{XC}
1.53	0	1.79	-11.11	-4.18	17.08	-10.12	-2.98	1.99	19.07	0.00
	30	0.00	-8.38	-4.35	12.73	-7.76	-2.17	1.55	20.24	-5.96
	60	0.26	-4.72	-3.69	8.67	-4.60	-1.25	1.13	21.46	-11.66
	90	4.15	-3.12	-1.16	8.43	-3.36	-0.69	0.93	21.62	-12.26
	120	7.03	-1.93	0.00	8.96	-2.51	0.00	0.58	21.62	-12.08
	150	6.10	-0.54	-2.08	8.72	-0.94	-0.10	0.50	21.94	-12.72
	180	5.15	0.00	-3.62	8.77	0.00	-0.72	0.72	22.07	-12.58
1.03	0	26.17	-37.46	-31.89	95.52	-33.25	-14.62	10.41	105.93	0.00
	30	9.95	-24.55	-35.12	69.62	-21.57	-10.56	7.58	110.69	-33.49
	60	0.00	-9.51	-32.88	42.39	-9.29	-4.36	4.14	116.23	-69.70
	90	13.57	-6.86	-13.70	34.13	-9.35	-0.62	3.11	116.76	-79.52
	120	26.02	-6.89	0.00	32.91	-10.18	0.00	3.29	116.01	-79.81
	150	16.25	-2.64	-18.08	36.97	-4.31	-0.01	1.68	117.59	-78.94
	180	8.16	0.00	-32.48	40.64	0.00	-0.88	0.88	118.61	-77.09
2.03	0	0.00	-5.41	-0.17	5.58	-5.06	-0.62	0.27	5.85	0.00
	30	0.25	-4.50	-0.15	4.90	-4.33	-0.29	0.12	6.08	-1.06
	60	1.21	-3.05	-0.15	4.41	-2.99	-0.12	0.06	6.33	-1.86
	90	2.75	-2.00	0.00	4.75	-1.89	-0.26	0.15	6.39	-1.49
	120	3.92	-1.11	-0.11	5.14	-1.04	-0.18	0.11	6.42	-1.17
	150	4.25	-0.33	-0.34	4.92	-0.33	-0.02	0.02	6.49	-1.55
	180	4.31	0.00	-0.32	4.63	0.00	0.00	0.00	6.53	-1.90

Table S6. NEDA energies in kcal mol^{-1} for **PP**: energy of interaction (E_{int}), electrical interaction (E_{EL}), charge transfer (E_{CT}), Core repulsion (E_{CORE}), classical electrostatic interaction (E_{ES}), polarization contribution (E_{POL}), the penalty of polarization (E_{SE}), deformation cost (E_{DEF}), and exchange interaction (E_{XC}). The energies for **PP** in the gas phase are presented for the C–C equilibrium distance in the *gauche* conformer (1.53 Å), as well as with -0.5 Å and +0.5 Å.

C–C Bond distance (Å)	ϕ_{PCCP} (deg.)	E_{int}	E_{EL}	E_{CT}	E_{CORE}	E_{ES}	E_{POL}	E_{SE}	E_{DEF}	E_{XC}
1.54	0	23.45	0.00	-5.62	29.07	0.00	-5.19	5.19	34.26	0.00
	30	17.57	-0.95	-5.23	23.75	-2.03	-3.29	4.37	35.35	-7.23
	60	10.53	-3.98	-2.77	17.28	-6.13	-1.59	3.74	36.93	-15.91
	90	6.52	-8.02	-0.61	15.15	-10.75	-0.90	3.63	38.12	-19.34
	120	4.82	-10.56	0.00	15.38	-13.89	0.00	3.33	38.66	-19.95
	150	1.85	-11.81	-1.96	15.62	-15.17	-0.03	3.39	38.99	-19.98
	180	0.00	-12.41	-3.24	15.65	-15.43	-0.72	3.74	39.09	-19.70
1.04	0	70.85	0.00	-43.97	114.82	0.00	0.00	0.00	114.82	0.00
	30	43.16	-0.71	-49.59	93.46	-0.34	-2.77	2.40	118.18	-22.32
	60	19.37	-1.55	-31.97	52.89	-0.75	-12.31	11.51	122.17	-57.77
	90	15.40	-7.49	-12.31	35.20	-6.30	-16.60	15.41	124.25	-73.64
	120	20.62	-11.87	0.00	32.49	-10.97	-17.61	16.71	124.44	-75.24
	150	9.40	-12.25	-13.77	35.42	-10.63	-17.98	16.36	125.22	-73.44
	180	0.00	-11.32	-26.83	38.15	-9.19	-18.08	15.95	125.77	-71.67
2.04	0	12.95	0.00	-0.35	13.30	0.00	-3.87	3.87	17.17	0.00
	30	11.00	-0.86	-0.31	12.17	-1.59	-2.46	3.19	17.62	-2.26
	60	7.56	-3.35	0.00	10.91	-5.11	-0.47	2.23	18.40	-5.26
	90	4.45	-6.70	-0.08	11.23	-8.73	0.00	2.03	18.97	-5.71
	120	2.23	-9.42	-0.24	11.89	-11.29	-0.38	2.25	19.22	-5.08
	150	0.65	-10.86	-0.19	11.70	-12.68	-0.51	2.33	19.38	-5.35
	180	0.00	-11.27	-0.15	11.42	-13.12	-0.44	2.29	19.43	-5.72

$q_P = 2.91$
$q_C = 0.61$
$q_C = -0.76$
$q_F = -0.60$

$q_F = -0.62$
$q_P = 2.92$
$q_C = 0.56$
$q_C = -0.69$

$q_P = 2.90$
$q_C = -0.64$

PF *anti*   **PF** *gauche*   **PP** *anti*
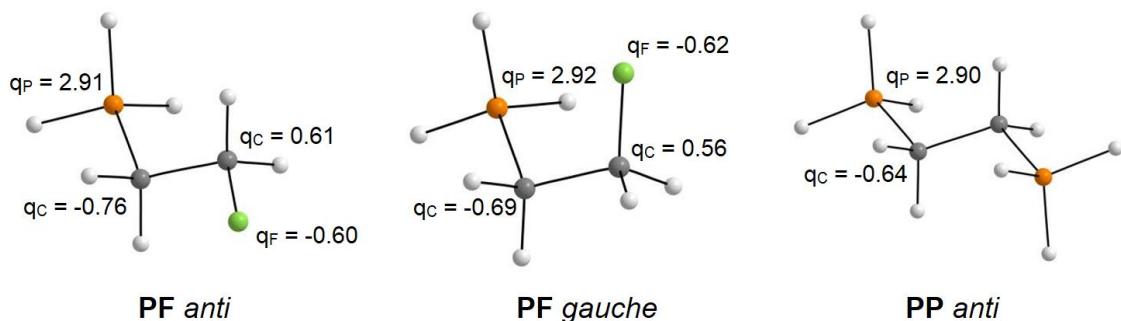
Figure S1. QTAIM plots for **PF** and **PP** in the gas phase (the P and F atomic charges, in a.u., are shown).

qF = -0.521
qH = -0.518
dF...H = 2.684

1-cis-g

qF = -0.522
qH = +0.026
ρ = 0.011
dF...H = 2.400

2-cis-g

qF = -0.500
qH = -0.438
dF...H = 2.800

3ax

qF = -0.505
qH = +0.122
ρ = 0.011
dF...H = 2.461

4ax

qF = -0.517
qH = -0.613
dF...H = 2.821

8-trans-g

qF = -0.517
qH = +0.036
ρ = 0.011
dF...H = 2.462
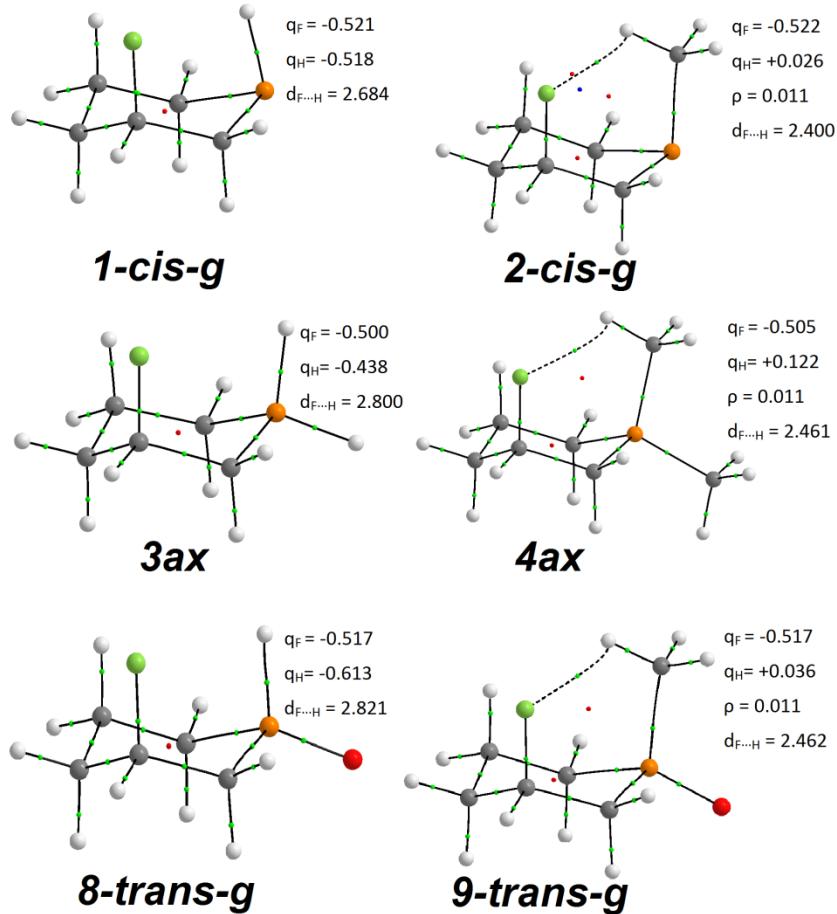
9-trans-g

Figure S2. QTAIM plots indicating bond paths between interacting atoms for *1-cis-g*, *2-cis-g*, *3ax*, *4ax*, *8-trans-g* and *9-trans-g*. The atomic charges (q, in a.u.), electron densities at the bond critical point (ρ), and the distances between interacting atoms (r, in angstroms) are also depicted. (H = white, C = gray, F = green, P = orange, O = red, bond-critical point = green dot, ring-critical point = red dot, cage-critical point = blue dot).

X-ray diffraction

The crystal data were obtained onOxford-Rigaku GEMINI diffractometer with MoKα (λ= 0.71073 Å) radiation at room temperature (298K). The data collection, cell refinements and data reduction were performed using the CRYSALISPRO software.[S1] The structures were solved by direct methods and refined using SHELXL-2018/3.[S2]All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were placed in idealized positions and treated by a rigid model, with Uiso(H) = 1.2Ueq(C).CCDC 1971685 contains the supplementary crystallographic data. The figures were drawn using ORTEP-3 for Windows[S3] and Mercury.[S4]

Crystal structure discussion

The crystal analysis indicates that the compound crystallizes in a non-centrosymmetric tetragonal space group P4$_1$2$_1$2. The compound is a triphenylphosphoniumiodine salt, as can be seen in Figure S1. In the solid state is observed the two-fold axis in the middle of C-C bond of ethane residue reducing the asymmetric unit for this crystal to half of the molecule. Crystal data and selected geometrical parameters are listed in Tables S5 and S6, respectively.
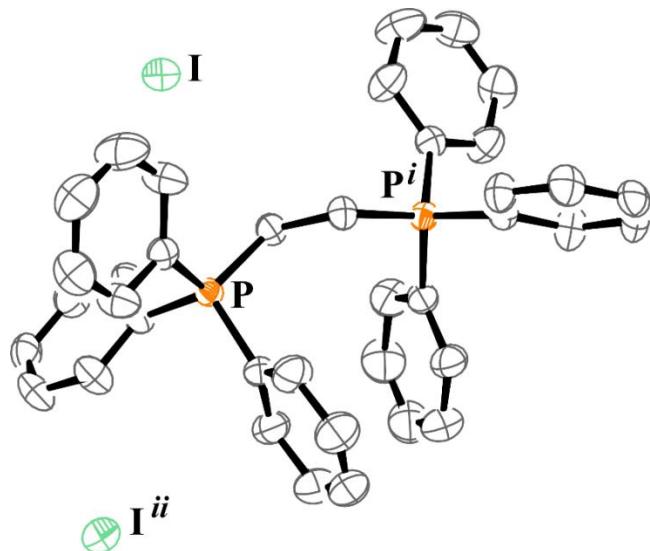
Figure S1. Molecular representation of the crystal with displacement ellipsoids at the 50% probability level. The H atoms were omitted for clarify. Symmetry codes: *i* (*y*, *x*, -*z*) *ii* (*y*, -1 + *y*, -*z*).

Table S5. Crystal data and structure refinement results for the crystal.

Empirical formula	$C_{38}H_{34}I_2P_2$
Formula weight (g.mol^{-1})	806.39
Wavelength (λ)	0.71073
Crystal system	Tetragonal
Space group	$P4_12_12$
Temperature (K)	298(2)
a (Å)	9.9016(2)
b (Å)	9.9016(2)
c (Å)	35.0282(8)
$\alpha = \beta = \gamma$(°)	90.00
V (Å^3)	3434.2(2)
Z	4
Density (calculated) (g cm^{-3})	1.560
Crystal size (mm^3)	0.15 x0.19 x0.32
F(000)	1592
Absorption coefficient (mm^{-1})	1.95
$T_{min}/T_{máx}$	0.773 /1
2θ range for data collection (°)	2.38 to 25.02
Reflections collected	32408
Independent / observed reflections	4508 / 3465
R_{int}	0.0604
Number of parameters	190
Final R indexes [I>2σ(I)]	R_1=0.0389 wR_2= 0.0555
Final R indexes (all data)	R_1=0.0670 wR_2= 0.0628
Goodness-of-fit on F^2	1.055
$\Delta\rho_{max}$. and $\Delta\rho_{min}$.	0.469 and -0.457

The average of P-C bond distance is 1.801(5)Å, which is similar to the periodate (1.797(6)Å)[S5] and tribromide (1.801(4)Å)[S6] salts. The torsion angle P-C-C-P is 134.8(3) ° which is very close to observed in periodate salt (136.1(2) °) but different to tribromide (average of 162.3(3) °). The P(C$_6$H$_5$)$_3$ groups are in eclipsed conformation to each other.The geometry of P atom is tetrahedral slightly distorted with average of C-P-C bond angles of 109.5(2)° (range of 107.7(2) to 113.5(2)°). The torsion angles among aromatic rings are 70.6(5), 72.2(6) and 76.7(5)° and the average deviation of P atom to aromatic ring planes are 0.143, 0.164 and 0.176 Å. The supramolecular arrangement of this crystal is formed by non-classical hydrogen bonds C-H···I interactions that gives rise to a bi-dimensional network in the **ab** crystallographic plane,

as can be seen in Figure S2. The average C···I distance is 3.918(5) Å. All geometrical parameters of non-classical hydrogen bonds are displayed in Table S7.
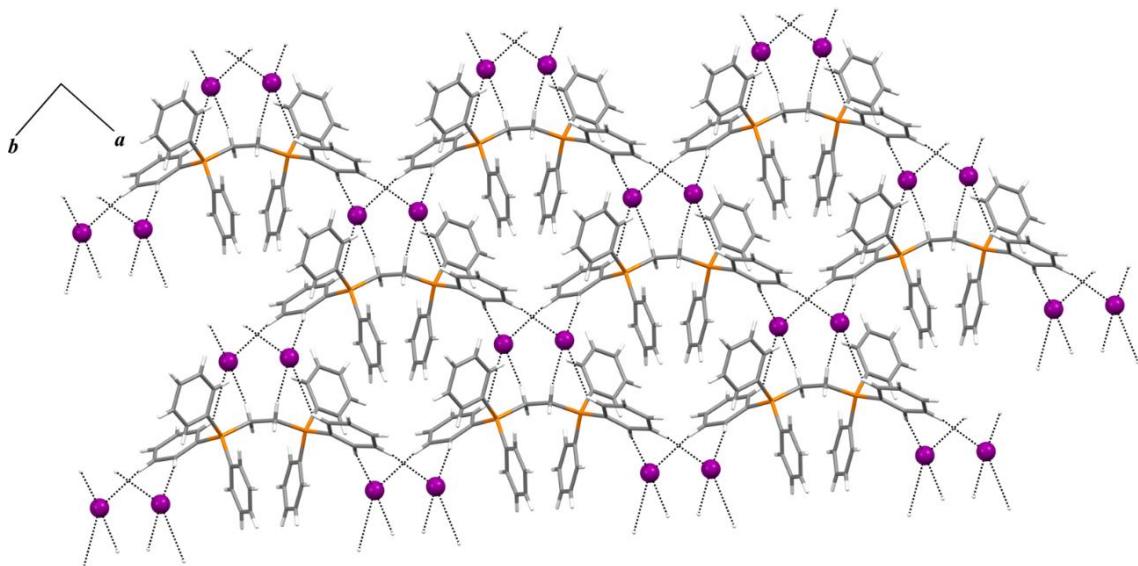
Figure S2. 2-D network of the crystal in **ab** crystallographic plane. The pink sphere represents the iodine anion.

Table S6. Selected geometrical parameters of the crystal.

Bond distance / Å			
P-C1	1.797(5)	P-C19	1.815(5)
P-C7	1.791(5)	C19-C19^i	1.542(9)
P-C13	1.800(5)		

Bond angle / °			
C1-P-C7	109.8(2)	C7-P-C19	108.0(2)
C1-P-C13	107.7(2)	C13-P-C19	113.5(2)
C1-P-C19	109.2(2)	P-C19-C19^i	115.2(4)
C7-P-C13	108.6(2)		

Symmetry code: i (*y*, *x*, -*z*)

Table S7. Geometrical parameters of non-classical hydrogen bonds.

D-H···A	D-H / Å	H···A / Å	D···A / Å	D-H···A / °
C2-H2···I^{ii}	0.93	3.13	3.874(5)	138.0
C19-H19a···I^{ii}	0.94	3.00	3.906(5)	161.0
C6-H6···I	0.93	3.12	4.009(5)	161.0
C5-H5···I^{iii}	0.93	3.16	3.883(5)	136.0

Symmetry code: *ii* (*y*, -1 + *y*, -*z*), *iii* (1 + *y*, -1 + *y*, -*z*)

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APPENDIX C

Supporting Information for:

Theoretical study of fluorinated bioisosteres of organochlorine compounds as effective and eco-friendly pesticides

INDEX

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Aldrin:                 Standard orientation:
---------------------------------------------------------------------
Center    Atomic    Atomic           Coordinates (Angstroms)
Number    Number    Type         X            Y            Z
---------------------------------------------------------------------
   1         6        0      -1.080292     0.785837    -0.889054
   2         6        0       0.296074     1.132168    -0.229112
   3         6        0       0.295995    -1.132306    -0.228498
   4         6        0      -1.080329    -0.786243    -0.888666
   5         6        0       1.201107    -0.000268    -0.845435
   6         6        0       0.318455     0.668680     1.223891
   7         6        0       0.318372    -0.668023     1.224253
   8         6        0      -2.452547     1.132961    -0.213980
   9         6        0      -2.452621    -1.132965    -0.213466
  10         6        0      -2.659000     0.000240     0.823033
  11         1        0      -3.681087     0.000360     1.203796
  12         1        0      -1.977934     0.000407     1.665974
  13         6        0      -3.465529     0.668809    -1.264847
  14         6        0      -3.465558    -0.669217    -1.264558
  15         1        0      -2.549272     2.161604     0.129277
  16         1        0      -2.549424    -2.161445     0.130258
  17        17        0       0.203148     1.715783     2.575178
  18        17        0       0.202941    -1.714376     2.576111
  19        17        0       2.893783    -0.000167    -0.249681
  20        17        0       1.274727    -0.000760    -2.639524
  21        17        0       0.836423     2.804847    -0.509706
  22        17        0       0.836239    -2.805173    -0.508168
  23         1        0      -3.994967    -1.326217    -1.942904
  24         1        0      -3.994904     1.325539    -1.943480
  25         1        0      -1.050319    -1.191881    -1.897635
  26         1        0      -1.050297     1.190976    -1.898224
---------------------------------------------------------------------
Dieldrin:               Standard orientation:
---------------------------------------------------------------------
Center    Atomic    Atomic           Coordinates (Angstroms)
Number    Number    Type         X            Y            Z
---------------------------------------------------------------------
   1         6        0      -0.990460     0.777249     0.733517
   2         6        0       0.455823     0.325035     1.113087
   3         6        0       0.456705     0.160727    -1.148693
   4         6        0      -0.990110     0.665056    -0.839783
   5         6        0       1.276892     0.964905    -0.069757
   6         6        0       0.657505    -1.143942     0.753583
   7         6        0       0.657637    -1.240627    -0.579904
   8         6        0      -2.251760    -0.037242     1.145372
   9         6        0      -2.254034    -0.196253    -1.132642
  10         6        0      -2.359218    -1.148665     0.078463
  11         1        0      -3.327461    -1.643071     0.114401
  12         1        0      -1.588046    -1.905555     0.129732
  13         6        0      -3.373808     0.911490     0.673540
  14         1        0      -3.606670     1.821588     1.216196
  15         6        0      -3.374316     0.809244    -0.795128
  16         1        0      -3.607822     1.634821    -1.459160
  17         1        0      -2.292144    -0.341144     2.190633
  18         1        0      -2.296830    -0.642363    -2.125504
  19        17        0       1.126401     2.750257    -0.198724
  20        17        0       3.027503     0.584066    -0.041272
  21        17        0       0.959785     0.383445    -2.840735
  22        17        0       0.957065     0.791034     2.755478
  23        17        0       0.704335    -2.420325     1.894838
  24        17        0       0.705801    -2.668536    -1.524642
  25         8        0      -4.469284     0.299661    -0.021318
  26         1        0      -1.085390     1.813022     1.059449
  27         1        0      -1.081638     1.644539    -1.309175
---------------------------------------------------------------------
```

α-Chlordane:　　　　　Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	0.783787	0.975884	0.975503
2	6	0	0.278492	1.002519	-0.468335
3	6	0	1.233400	-0.258152	1.227283
4	6	0	-1.016919	0.132895	-0.547101
5	6	0	1.041204	-1.091107	-0.040792
6	6	0	-0.485726	-1.317688	-0.255462
7	6	0	1.331172	0.023615	-1.109245
8	1	0	-1.435173	0.204233	-1.548950
9	17	0	1.845772	-0.867473	2.708131
10	17	0	0.686755	2.298024	2.061876
11	17	0	3.011014	0.639493	-1.090958
12	17	0	0.946762	-0.457294	-2.794607
13	17	0	2.024003	-2.567330	-0.152173
14	17	0	0.155584	2.607501	-1.214562
15	6	0	-2.115229	0.363965	0.502161
16	6	0	-1.324843	-1.854475	0.922736
17	6	0	-2.624497	-1.044140	0.850399
18	1	0	-0.617671	-1.947038	-1.132858
19	17	0	-3.380880	1.543896	0.005084
20	17	0	-3.717534	-1.725770	-0.440234
21	1	0	-3.214038	-1.061174	1.763690
22	1	0	-1.700382	0.774594	1.423161
23	1	0	-1.504301	-2.926697	0.862559
24	1	0	-0.848568	-1.651614	1.886047

β-Chlordane:　　　　　Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.427523	-0.071991	1.364324
2	6	0	-0.460308	-1.091499	0.224613
3	6	0	-0.807998	1.109576	0.866060
4	6	0	0.693436	-0.747807	-0.770795
5	6	0	-1.100922	0.913370	-0.621533
6	6	0	0.249075	0.643983	-1.356824
7	6	0	-1.704531	-0.535084	-0.561295
8	1	0	0.722671	-1.507396	-1.549652
9	17	0	-0.892249	2.612734	1.683396
10	17	0	0.090023	-0.419408	2.959941
11	17	0	-3.248536	-0.652021	0.332941
12	17	0	-1.949998	-1.294534	-2.170502
13	17	0	-2.111131	2.159709	-1.384310
14	17	0	-0.543381	-2.795267	0.711662
15	6	0	2.104822	-0.524225	-0.201508
16	6	0	1.420881	1.612296	-1.107824
17	6	0	2.628525	0.672781	-1.004507
18	1	0	0.040923	0.552952	-2.421720
19	17	0	3.161397	-1.983307	-0.344752
20	1	0	2.093516	-0.276203	0.858060
21	1	0	1.540752	2.346334	-1.904195
22	1	0	1.309773	2.156274	-0.168434
23	17	0	4.067858	1.460178	-0.247784
24	1	0	2.961921	0.342218	-1.988402

```
F-aldrin:               Standard orientation:
-------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
-------------------------------------------------------------------
    1         6         0       -0.768688    0.790426   -0.686573
    2         6         0        0.686011    1.125834   -0.238757
    3         6         0        0.685947   -1.126189   -0.237186
    4         6         0       -0.768717   -0.791337   -0.685536
    5         6         0        1.448720   -0.000726   -0.996377
    6         6         0        0.965505    0.665821    1.178367
    7         6         0        0.965388   -0.664195    1.179309
    8         6         0       -2.019315    1.133671    0.193210
    9         6         0       -2.019405   -1.133387    0.194614
   10         6         0       -2.046591    0.000802    1.249593
   11         1         0       -2.986447    0.001187    1.802809
   12         1         0       -1.228966    0.001196    1.964514
   13         6         0       -3.189603    0.668627   -0.677472
   14         6         0       -3.189634   -0.669331   -0.676663
   15         1         0       -2.061616    2.161431    0.550258
   16         1         0       -2.061790   -2.160694    0.552953
   17         9         0        1.084073   -2.409771   -0.500572
   18         9         0        1.232097   -0.001655   -2.338543
   19         9         0        2.789658   -0.000648   -0.829493
   20         9         0        0.974225   -1.499013    2.212468
   21         9         0        0.974469    1.502103    2.210338
   22         9         0        1.084190    2.409026   -0.503962
   23         1         0       -0.880972   -1.198553   -1.690513
   24         1         0       -0.880991    1.196321   -1.692079
   25         1         0       -3.822704   -1.326793   -1.258817
   26         1         0       -3.822629    1.325414   -1.260434
-------------------------------------------------------------------
F-dieldrin:             Standard orientation:
-------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
-------------------------------------------------------------------
    1         6         0        0.552308    0.652544   -0.793726
    2         6         0       -0.911892    0.240609   -1.127591
    3         6         0       -0.912064    0.240357    1.127554
    4         6         0        0.552240    0.652093    0.793943
    5         6         0       -1.655377    1.016245    0.000035
    6         6         0       -1.221804   -1.169021   -0.665356
    7         6         0       -1.222197   -1.169085    0.665078
    8         6         0        1.767855   -0.252331   -1.142813
    9         6         0        1.767537   -0.253404    1.142586
   10         6         0        1.804923   -1.291742   -0.000556
   11         1         0        2.736149   -1.853562   -0.000668
   12         1         0        0.983644   -1.998920   -0.001092
   13         6         0        2.946310    0.655039   -0.735501
   14         1         0        3.233872    1.508522   -1.340312
   15         6         0        2.946240    0.654310    0.736446
   16         1         0        3.233811    1.507193    1.342088
   17         1         0        1.789885   -0.633092   -2.163330
   18         1         0        1.789231   -0.634950    2.162810
   19         8         0        4.003391    0.024003    0.000190
   20         9         0       -1.405693    2.352989    0.000259
   21         9         0       -2.998162    0.880216   -0.000122
   22         9         0       -1.304842    0.514898    2.409548
   23         9         0       -1.304570    0.515270   -2.409566
   24         9         0       -1.251076   -2.201632   -1.499453
   25         9         0       -1.251915   -2.201762    1.499068
   26         1         0        0.684181    1.659280    1.194783
   27         1         0        0.683947    1.660013   -1.193984
-------------------------------------------------------------------
```

α-Fluordane: Standard orientation:
```
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type         X           Y           Z
---------------------------------------------------------------
    1        6        0       0.937369    0.744248    1.183561
    2        6        0       0.549911    1.135994   -0.233777
    3        6        0       1.221609   -0.555661    1.180425
    4        6        0      -0.815016    0.489955   -0.604551
    5        6        0       1.031283   -1.065195   -0.238101
    6        6        0      -0.476794   -1.052177   -0.611451
    7        6        0       1.511973    0.194099   -1.013846
    8        1        0      -1.122843    0.840078   -1.590280
    9        6        0      -1.982576    0.640791    0.379680
   10        6        0      -1.479735   -1.708640    0.363418
   11        6        0      -2.655778   -0.737249    0.390545
   12        1        0      -0.580140   -1.459320   -1.616870
   13        1        0      -1.641595    0.870350    1.394495
   14        1        0      -1.797965   -2.700965    0.044182
   15        1        0      -1.066561   -1.802972    1.372386
   16        9        0       0.842008    1.584609    2.206362
   17        9        0       1.486763   -1.363897    2.199647
   18        9        0       1.682951   -2.234928   -0.510245
   19        9        0       0.657685    2.469274   -0.500366
   20        9        0       2.823181    0.481909   -0.883883
   21        9        0       1.253489    0.140150   -2.346483
   22        9        0      -2.854230    1.651706    0.007434
   23        9        0      -3.390966   -0.882924   -0.794426
   24        1        0      -3.352303   -0.877265    1.218302
---------------------------------------------------------------
```
β-Fluordane: Standard orientation:
```
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type         X           Y           Z
---------------------------------------------------------------
    1        6        0      -0.675479   -0.265075    1.414916
    2        6        0      -0.637032   -1.135846    0.169141
    3        6        0      -0.938806    0.981309    1.029154
    4        6        0       0.610017   -0.780442   -0.688281
    5        6        0      -1.077733    0.974734   -0.483491
    6        6        0       0.303806    0.701455   -1.144039
    7        6        0      -1.742441   -0.419469   -0.659018
    8        1        0       0.656623   -1.463349   -1.537932
    9        6        0       1.978410   -0.733745   -0.000836
   10        6        0       1.504742    1.547190   -0.680280
   11        6        0       2.639941    0.529221   -0.552588
   12        1        0       0.170196    0.748375   -2.225330
   13        1        0       1.916415   -0.665796    1.088903
   14        1        0       1.746700    2.355660   -1.369420
   15        1        0       1.334324    1.992589    0.304232
   16        1        0       3.106229    0.301401   -1.516154
   17        9        0      -0.357886   -0.728227    2.616096
   18        9        0      -0.954764    2.100145    1.740870
   19        9        0      -1.756661    2.043729   -0.995073
   20        9        0      -0.820360   -2.466585    0.403708
   21        9        0      -2.990110   -0.527788   -0.161004
   22        9        0      -1.800132   -0.831726   -1.953517
   23        9        0       2.726215   -1.872875   -0.292808
   24        9        0       3.651138    0.987231    0.289243
---------------------------------------------------------------
```

```
PCP:                      Standard orientation:
------------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type         X            Y            Z
------------------------------------------------------------------
    1        6         0       1.199227    -0.923776    -0.000088
    2        6         0       1.223282     0.474422    -0.000125
    3        6         0      -0.022445    -1.609811    -0.000096
    4        6         0       0.023952     1.204064    -0.000129
    5        6         0      -1.213014    -0.873445    -0.000105
    6        6         0      -1.200314     0.523349    -0.000106
    7       17         0      -2.711438    -1.774909     0.000005
    8       17         0      -2.698360     1.399248     0.000086
    9       17         0       0.054769     2.940982     0.000030
   10       17         0       2.745841     1.305640     0.000000
   11       17         0       2.659028    -1.860959     0.000094
   12        8         0      -0.000308    -2.956161     0.000025
   13        1         0      -0.908933    -3.289569     0.000059
------------------------------------------------------------------
PFP:                      Standard orientation:
------------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type         X            Y            Z
------------------------------------------------------------------
    1        6         0      -0.246365     1.365538     0.000029
    2        6         0       1.063211     0.900298     0.000004
    3        6         0      -1.321112     0.474973     0.000019
    4        6         0       1.326359    -0.465891     0.000016
    5        6         0      -1.034296    -0.888993     0.000010
    6        6         0       0.268234    -1.366729     0.000045
    7        8         0      -2.584433     0.958092    -0.000019
    8        1         0      -3.211823     0.224038    -0.000035
    9        9         0      -2.072937    -1.751410    -0.000073
   10        9         0       0.502633    -2.681403     0.000050
   11        9         0       2.587326    -0.908633    -0.000023
   12        9         0       2.076264     1.769983    -0.000069
   13        9         0      -0.476496     2.682135     0.000053
------------------------------------------------------------------
```

Table S1. Number of hydrogen bonds, halogen interactions, hydrophobic interactions and destabilizing interactions between ligands and residues (specific residues in parenthesis).

Ligand	H-bond	Halogen interaction	Hydrophobic interaction	destabilizing interactions
Picrotoxin	3 (THR256, THR271, SER267)	-	4	-
Aldrin	-	1 (ALA252)	12	-
Dieldrin	1 (SER267)	-	9	-
α-Chlordane	-	1 (ALA252)	16	-
β-Chlordane	-	1 (ALA252)	14	-
F-Aldrin	2 (SER267, THR256)	1 (ALA252)	1	-
F-Dieldrin	1 (SER267)	1 (THR256)	1	-
α-Fluordane	2 (SER267, THR256)	1 (ALA252)	1	-
β-Fluordane	1 (THR256)	1 (THR256)	1	-

APPENDIX D

Supporting Information for:

Theoretical exploitation of 1,2,3,4,5,6-hexachloro- and 1,2,3,4,5,6-hexafluorocyclohexane isomers as biological compounds

INDEX

Standard Orientation of the optimized structures in the gas phase

αe-HCH   Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0       -0.754103   -1.540602   -0.115583
   2          6          0        0.754574   -1.540682    0.116004
   3          6          0        1.392230   -0.282311   -0.463679
   4          6          0        0.762064    0.993868    0.086186
   5          6          0       -0.762488    0.993861   -0.086101
   6          6          0       -1.392591   -0.282414    0.463695
   7          1          0        1.198409   -2.418389   -0.356876
   8          1          0       -1.197781   -2.418443    0.357184
   9          1          0        1.014806    1.111955    1.143307
  10          1          0       -1.015136    1.111969   -1.143237
  11          1          0       -1.250297   -0.311504    1.546652
  12          1          0        1.249490   -0.311642   -1.546582
  13         17          0       -3.149431   -0.308282    0.196308
  14         17          0       -1.051543   -1.707124   -1.871388
  15         17          0       -1.440424    2.402794    0.767184
  16         17          0        1.440132    2.402636   -0.767107
  17         17          0        3.149138   -0.307588   -0.197028
  18         17          0        1.052270   -1.706805    1.871821
---------------------------------------------------------------------
```

αa-HCH   Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.983839    0.410745   -0.642064
   2          6          0        0.983894   -0.410468    0.641996
   3          6          0       -0.236900   -1.330715    0.675818
   4          6          0       -1.547330   -0.548423    0.537039
   5          6          0       -1.547380    0.548093   -0.537130
   6          6          0       -0.237170    1.330668   -0.675820
   7          1          0       -0.251007   -1.863617    1.627485
   8          1          0       -2.358197   -1.245670    0.325370
   9          1          0       -2.358393    1.245200   -0.325546
  10          1          0       -0.251465    1.863680   -1.627424
  11          1          0        0.923874   -0.259706   -1.503840
  12          1          0        0.923727    0.259994    1.503752
  13         17          0       -0.151357    2.599228    0.582551
  14         17          0        2.464623    1.365234   -0.859835
  15         17          0        2.464866   -1.364658    0.859884
  16         17          0       -0.150640   -2.599437   -0.582356
  17         17          0       -1.931957   -0.165418   -2.138069
  18         17          0       -1.932139    0.165094    2.137893
---------------------------------------------------------------------
```

βe-HCH   Standard orientation:
```
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number      Type          X           Y           Z
---------------------------------------------------------------------
   1          6          0        0.983716    1.078356   -0.222982
   2          6          0       -0.442035    1.391099    0.223075
   3          6          0       -1.425722    0.312745   -0.223046
   4          6          0       -0.983711   -1.078321    0.223038
   5          6          0        0.442038   -1.391136   -0.223045
   6          6          0        1.425783   -0.312781    0.222951
   7          1          0       -0.474730    1.493798    1.312544
   8          1          0        1.056345    1.158077   -1.312445
   9          1          0       -1.056333   -1.157879    1.312518
  10          1          0       -1.530916    0.335821   -1.312530
  11          1          0        1.531130   -0.335935    1.312413
  12          1          0        0.474647   -1.493917   -1.312510
  13         17          0        2.091326    2.292419    0.462586
  14         17          0        3.031016   -0.664853   -0.462644
  15         17          0        0.939833   -2.957327    0.462501
  16         17          0       -2.091471   -2.292321   -0.462344
  17         17          0       -3.031047    0.664750    0.462307
  18         17          0       -0.939691    2.957347   -0.462403
---------------------------------------------------------------------
```

```
βa-HCH                 Standard orientation:
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type        X           Y           Z
---------------------------------------------------------------
   1         6         0       0.160430    0.767796    1.285721
   2         6         0      -0.160234    1.497386   -0.022043
   3         6         0       0.160158    0.729512   -1.307806
   4         6         0      -0.160176   -0.767954   -1.285619
   5         6         0       0.160349   -1.497376    0.022282
   6         6         0      -0.160522   -0.729483    1.307865
   7         1         0      -0.396520   -2.434026    0.036096
   8         1         0       0.396875   -1.248217   -2.089764
   9         1         0       0.396136   -1.185878    2.126056
  10         1         0      -0.396956    1.185761   -2.125773
  11         1         0      -0.396326    1.248196    2.089986
  12         1         0       0.396761    2.433960   -0.035927
  13        17         0       1.887370   -1.984601    0.029880
  14        17         0       1.887525    1.017269    1.704001
  15        17         0      -1.887682   -0.966559    1.733037
  16        17         0       1.886969    0.967301   -1.733918
  17        17         0      -1.887035   -1.018340   -1.704287
  18        17         0      -1.887147    1.984985   -0.028895
---------------------------------------------------------------
γ-HCH                  Standard orientation:
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type        X           Y           Z
---------------------------------------------------------------
   1         6         0      -1.239131    0.474944    0.424798
   2         6         0      -0.001234    1.146833   -0.171355
   3         6         0       1.238046    0.477154    0.424746
   4         6         0       1.293891   -1.022800    0.135580
   5         6         0       0.001626   -1.725996    0.560287
   6         6         0      -1.291895   -1.025018    0.135393
   7         1         0       1.199272    0.599444    1.511970
   8         1         0       0.002535   -2.750942    0.188009
   9         1         0       2.121744   -1.452143    0.702555
  10         1         0      -2.119088   -1.456079    0.702024
  11         1         0      -0.001186    1.080655   -1.262646
  12         1         0      -1.200695    0.597257    1.512027
  13        17         0      -0.002706    2.873861    0.257327
  14        17         0      -2.751883    1.248301   -0.093794
  15        17         0      -1.652902   -1.372456   -1.577600
  16        17         0       0.001574   -1.843286    2.354882
  17        17         0       1.656004   -1.369934   -1.577233
  18        17         0       2.749302    1.253580   -0.093619
---------------------------------------------------------------
δe-HCH                 Standard orientation:
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type        X           Y           Z
---------------------------------------------------------------
   1         6         0       0.000693   -1.586755   -0.249689
   2         6         0      -1.238596   -0.787180   -0.638726
   3         6         0      -1.288242    0.548640    0.093462
   4         6         0      -0.000763    1.347222   -0.137320
   5         6         0       1.287418    0.549148    0.093078
   6         6         0       1.239291   -0.786639   -0.639302
   7         1         0       1.195209   -0.604928   -1.719111
   8         1         0      -1.449855    0.384353    1.160602
   9         1         0       0.000701   -2.539130   -0.784196
  10         1         0      -1.194676   -0.605301   -1.718536
  11         1         0      -0.000958    1.722744   -1.165779
  12         1         0       1.449013    0.384753    1.160211
  13        17         0       0.001065   -1.980548    1.489589
  14        17         0       2.709236   -1.743081   -0.357680
  15        17         0       2.664551    1.510993   -0.499448
  16        17         0      -0.000955    2.775178    0.926843
  17        17         0      -2.666089    1.509058   -0.499643
  18        17         0      -2.707705   -1.745077   -0.357438
---------------------------------------------------------------
```

```
δa-HCH               Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.940890    0.178599   -1.301127
   2          6          0      -0.498130   -0.349899   -1.293450
   3          6          0      -0.786065   -1.101423    0.000131
   4          6          0      -0.497880   -0.349674    1.293575
   5          6          0       0.941136    0.178895    1.300959
   6          6          0       1.411502    0.841865   -0.000207
   7          1          0      -0.094651   -1.951472    0.000128
   8          1          0       1.056141    0.892161    2.117059
   9          1          0      -0.600008   -1.057150    2.117879
  10          1          0       2.501572    0.856631   -0.000317
  11          1          0      -0.600378   -1.057524   -2.117611
  12          1          0       1.055839    0.891657   -2.117420
  13         17          0       0.921239    2.565858   -0.000338
  14         17          0       2.029002   -1.193626   -1.706776
  15         17          0       2.029390   -1.193175    1.706787
  16         17          0      -1.647553    0.962773    1.662524
  17         17          0      -2.412881   -1.808082    0.000334
  18         17          0      -1.647858    0.962459   -1.662472
---------------------------------------------------------------------
εe-HCH               Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0      -1.255837    0.509621    0.566826
   2          6          0      -1.256092   -0.509691   -0.566998
   3          6          0      -0.000130   -1.384193   -0.494981
   4          6          0       1.255456   -0.509346   -0.567232
   5          6          0       1.255717    0.509309    0.567035
   6          6          0       0.000090    1.384341    0.495111
   7          1          0       0.000058   -2.079535   -1.337117
   8          1          0       0.000006    2.079425    1.337452
   9          1          0      -1.248234   -0.014458    1.526491
  10          1          0      -1.248492    0.014339   -1.526703
  11          1          0       1.247752   -0.015161    1.526498
  12          1          0       1.247408    0.015058   -1.526728
  13         17          0       2.714100    1.521799    0.571100
  14         17          0       2.713612   -1.522201   -0.571309
  15         17          0       0.000376   -2.394444    0.979199
  16         17          0      -2.714192   -1.522690   -0.570280
  17         17          0      -2.713801    1.522767    0.570358
  18         17          0       0.000274    2.394773   -0.978976
---------------------------------------------------------------------
εa-HCH               Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type        X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.748158    1.297813    0.169872
   2          6          0      -0.747827    1.297787   -0.169922
   3          6          0      -1.140548    0.000009   -0.868853
   4          6          0      -0.748110   -1.297702   -0.169850
   5          6          0       0.747840   -1.297826    0.169874
   6          6          0       1.140622   -0.000046    0.868869
   7          1          0      -0.955447   -2.125953   -0.849049
   8          1          0       0.955021   -2.126136    0.849052
   9          1          0       0.574340    0.000003    1.807383
  10          1          0      -0.574263   -0.000097   -1.807361
  11          1          0       0.955518    2.126115    0.849023
  12          1          0      -0.955131    2.126048   -0.849116
  13         17          0       2.852212   -0.000162    1.336333
  14         17          0       1.674732    1.655178   -1.315987
  15         17          0       1.674343   -1.655380   -1.315942
  16         17          0      -1.674733   -1.655177    1.315933
  17         17          0      -2.852181    0.000076   -1.336158
  18         17          0      -1.674424    1.655454    1.315828
---------------------------------------------------------------------
```

```
ζ-HCH                   Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic              Coordinates (Angstroms)
Number      Number      Type            X           Y           Z
---------------------------------------------------------------------
    1          6           0        0.778635   -1.199298   -0.924059
    2          6           0       -0.680841   -1.335842   -0.479142
    3          6           0       -1.428030   -0.074793   -0.924180
    4          6           0       -0.816669    1.257429   -0.479258
    5          6           0        0.649135    1.273998   -0.924096
    6          6           0        1.497361    0.078368   -0.479538
    7          1           0       -1.332438    2.051687   -1.025767
    8          1           0        2.442852    0.127867   -1.026467
    9          1           0       -1.364334   -0.071505   -2.020137
   10          1           0        0.743823   -1.146002   -2.020022
   11          1           0       -1.110862   -2.179668   -1.025563
   12          1           0        0.620136    1.217355   -2.020059
   13         17           0        1.723804   -2.654879   -0.561720
   14         17           0        1.948138    0.102010    1.235850
   15         17           0       -0.885515   -1.736843    1.236558
   16         17           0        1.437118    2.820310   -0.561698
   17         17           0       -1.062164    1.635013    1.236400
   18         17           0       -3.161189   -0.165546   -0.561881
---------------------------------------------------------------------
η-HCH                   Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic              Coordinates (Angstroms)
Number      Number      Type            X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.242535   -0.169700    0.515698
    2          6           0       -0.941357    0.803926   -0.618776
    3          6           0        0.563480    1.100228   -0.685497
    4          6           0        1.322090   -0.218633   -0.843635
    5          6           0        1.001192   -1.299107    0.187069
    6          6           0       -0.512528   -1.495739    0.298849
    7          1           0        1.455206   -2.233630   -0.146888
    8          1           0       -0.729277   -2.166434    1.131362
    9          1           0       -1.237357    0.353126   -1.570506
   10          1           0       -0.890240    0.253057    1.460581
   11          1           0        0.993097   -0.630723   -1.803760
   12          1           0        0.756947    1.709751   -1.571697
   13         17           0       -1.079426   -2.340698   -1.177192
   14         17           0        1.655980   -1.001921    1.819334
   15         17           0        3.070261    0.031863   -1.011817
   16         17           0        1.112613    2.078101    0.697368
   17         17           0       -1.865506    2.313701   -0.490845
   18         17           0       -2.981595   -0.469928    0.714838
---------------------------------------------------------------------
θe-HCH                  Standard orientation:
---------------------------------------------------------------------
Center      Atomic      Atomic              Coordinates (Angstroms)
Number      Number      Type            X           Y           Z
---------------------------------------------------------------------
    1          6           0       -0.709373    1.242070   -0.566621
    2          6           0       -1.320357    0.000022    0.086152
    3          6           0       -0.709572   -1.242057   -0.566671
    4          6           0        0.815167   -1.292593   -0.425204
    5          6           0        1.397860   -0.000014   -0.997822
    6          6           0        0.815355    1.292570   -0.425114
    7          1           0        1.186320   -2.126212   -1.026755
    8          1           0        1.186534    2.126181   -1.026661
    9          1           0        1.121483    0.000035   -2.060193
   10          1           0       -0.938099   -1.207322   -1.638732
   11          1           0       -0.937838    1.207309   -1.638695
   12          1           0       -1.149302    0.000006    1.165604
   13         17           0       -1.433890    2.749872    0.028417
   14         17           0        1.323597    1.641645    1.241803
   15         17           0        3.171398   -0.000160   -0.973250
   16         17           0        1.323396   -1.641719    1.241731
   17         17           0       -1.434124   -2.749775    0.028505
   18         17           0       -3.079998    0.000137   -0.179142
---------------------------------------------------------------------
```

```
θa-HCH                 Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X            Y            Z
-----------------------------------------------------------------
   1          6          0      1.234813    -0.142383    -0.888702
   2          6          0      0.000501    -1.046372    -0.885892
   3          6          0     -1.234519    -0.143154    -0.888539
   4          6          0     -1.299823     0.903058     0.222112
   5          6          0     -0.000802     1.716039     0.287653
   6          6          0      1.298900     0.904030     0.221921
   7          1          0     -2.112140     1.590967    -0.019273
   8          1          0      2.110619     1.592652    -0.019452
   9          1          0     -1.174597     0.428311    -1.821794
  10          1          0      1.174542     0.428913    -1.822040
  11          1          0     -0.000980     2.330075     1.188573
  12          1          0      0.000638    -1.604224    -1.826187
  13         17          0      1.705573     0.249631     1.828197
  14         17          0      2.742343    -1.068959    -1.006926
  15         17          0      0.001011    -2.280859     0.390301
  16         17          0     -1.705838     0.248233     1.828380
  17         17          0     -2.741299    -1.070878    -1.007183
  18         17          0     -0.001349     2.869067    -1.096954
-----------------------------------------------------------------
αe-HFH                 Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X            Y            Z
-----------------------------------------------------------------
   1          6          0     -0.746537    -1.439429    -0.152879
   2          6          0      0.746555    -1.439429     0.152840
   3          6          0      1.399571    -0.195189    -0.420509
   4          6          0      0.752600     1.071532     0.110274
   5          6          0     -0.752620     1.071521    -0.110271
   6          6          0     -1.399556    -0.195212     0.420518
   7          1          0      1.233578    -2.337100    -0.234746
   8          1          0     -1.233554    -2.337116     0.234679
   9          1          0      0.977569     1.194858     1.173624
  10          1          0     -0.977594     1.194840    -1.173619
  11          1          0     -1.321219    -0.216206     1.511883
  12          1          0      1.321275    -0.216163    -1.511877
  13          9          0     -0.882314    -1.434506    -1.538192
  14          9          0      0.882328    -1.434555     1.538156
  15          9          0      2.743176    -0.196753    -0.089253
  16          9          0      1.294068     2.157654    -0.559972
  17          9          0     -1.294099     2.157637     0.559974
  18          9          0     -2.743174    -0.196795     0.089312
-----------------------------------------------------------------
αa-HFH                 Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type         X            Y            Z
-----------------------------------------------------------------
   1          6          0     -1.081566    -0.572198    -0.497010
   2          6          0     -1.081539     0.572233     0.497023
   3          6          0      0.143344     1.445880     0.284605
   4          6          0      1.443799     0.655496     0.393451
   5          6          0      1.443768    -0.655546    -0.393466
   6          6          0      0.143282    -1.445884    -0.284599
   7          9          0      0.089557    -1.985602     0.994586
   8          9          0      1.639729    -0.355354    -1.735944
   9          9          0      1.639774     0.355304     1.735932
  10          9          0      0.089628     1.985591    -0.994585
  11          1          0      0.147657     2.270306     1.002363
  12          1          0      2.273306     1.276536     0.044763
  13          1          0      2.273261    -1.276609    -0.044789
  14          1          0      0.147545    -2.270314    -1.002353
  15          1          0     -1.089866    -0.182914    -1.519007
  16          1          0     -1.089855     0.182954     1.519021
  17          9          0     -2.214294    -1.347607    -0.320596
  18          9          0     -2.214235     1.347687     0.320605
-----------------------------------------------------------------
```

```
βe-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0       -1.216513    -0.790191    -0.222974
   2          6          0        0.076064    -1.448639     0.222986
   3          6          0        1.292579    -0.658441    -0.222970
   4          6          0        1.216517     0.790191     0.222970
   5          6          0       -0.076064     1.448640    -0.222984
   6          6          0       -1.292574     0.658439     0.222966
   7          1          0        0.082253    -1.566494     1.312331
   8          1          0       -1.315474    -0.854487    -1.312319
   9          9          0        0.142591    -2.715528    -0.330467
  10          9          0       -2.280435    -1.481229     0.330473
  11          1          0        1.315475     0.854479     1.312318
  12          9          0        2.280432     1.481232    -0.330470
  13          1          0        1.397721    -0.712010    -1.312319
  14          1          0       -1.397725     0.712012     1.312312
  15          1          0       -0.082247     1.566508    -1.312328
  16          9          0       -0.142593     2.715526     0.330482
  17          9          0       -2.423016     1.234263    -0.330478
  18          9          0        2.423015    -1.234265     0.330464
---------------------------------------------------------------------
βa-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0        1.262681    -0.780195     0.175084
   2          6          0       -0.044368    -1.483636    -0.174739
   3          6          0       -1.307029    -0.703355     0.175155
   4          6          0       -1.262679     0.780188    -0.175083
   5          6          0        0.044369     1.483636     0.174736
   6          6          0        1.307033     0.703355    -0.175154
   7          9          0        0.051287     1.713885     1.543101
   8          9          0       -1.458484     0.900898    -1.543504
   9          9          0        1.509619     0.812155    -1.543579
  10          9          0       -1.509605    -0.812150     1.543589
  11          9          0        1.458473    -0.900905     1.543501
  12          9          0       -0.051297    -1.713877    -1.543107
  13          1          0        0.073100     2.444716    -0.346821
  14          1          0       -2.080700     1.285741     0.346250
  15          1          0        2.153828     1.159121     0.346138
  16          1          0       -2.153825    -1.159131    -0.346129
  17          1          0        2.080708    -1.285737    -0.346249
  18          1          0       -0.073093    -2.444721     0.346808
---------------------------------------------------------------------
γ-HFH                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic              Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0       -1.239414     0.540613     0.373813
   2          6          0        0.000072     1.244746    -0.150105
   3          6          0        1.239479     0.540477     0.373814
   4          6          0        1.275921    -0.924961    -0.024518
   5          6          0       -0.000091    -1.651167     0.394196
   6          6          0       -1.276024    -0.924820    -0.024523
   7          1          0        1.259426     0.618054     1.466648
   8          1          0       -0.000146    -2.664553    -0.013619
   9          1          0        2.145455    -1.411692     0.425934
  10          1          0       -2.145606    -1.411452     0.425942
  11          9          0        2.372919     1.164847    -0.112727
  12          9          0        1.392321    -1.020590    -1.401272
  13          9          0       -0.000101    -1.721623     1.786962
  14          9          0       -1.392445    -1.020438    -1.401270
  15          1          0        0.000075     1.288168    -1.241752
  16          1          0       -1.259349     0.618187     1.466647
  17          9          0        0.000143     2.545354     0.331492
  18          9          0       -2.372784     1.165113    -0.112724
---------------------------------------------------------------------
```

δe-HFH   Standard orientation:

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-0.000014	-1.540015	-0.103270
2	6	0	-1.241290	-0.773563	-0.518677
3	6	0	-1.272655	0.588411	0.151037
4	6	0	0.000017	1.371887	-0.131801
5	6	0	1.272669	0.588387	0.151060
6	6	0	1.241264	-0.773571	-0.518685
7	1	0	1.260429	-0.651604	-1.608268
8	1	0	-1.420666	0.475480	1.227968
9	1	0	-0.000016	-2.549138	-0.522191
10	9	0	-0.000017	-1.656213	1.282834
11	9	0	-2.346282	1.308063	-0.350139
12	9	0	2.366626	-1.489892	-0.158088
13	1	0	-1.260480	-0.651628	-1.608263
14	1	0	0.000035	1.699836	-1.177667
15	1	0	1.420652	0.475437	1.227992
16	9	0	-2.366653	-1.489853	-0.158029
17	9	0	0.000017	2.512365	0.653777
18	9	0	2.346320	1.308020	-0.350083

δa-HFH   Standard orientation:

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-0.867958	-1.289586	-0.060768
2	6	0	0.658345	-1.269895	-0.109511
3	6	0	1.150270	0.000000	-0.775939
4	6	0	0.658356	1.269894	-0.109502
5	6	0	-0.867947	1.289597	-0.060771
6	6	0	-1.505709	0.000009	0.454016
7	1	0	0.766771	0.000004	-1.803101
8	1	0	-1.201364	2.121527	0.564802
9	1	0	1.010825	2.137916	-0.674724
10	1	0	-2.562253	0.000009	0.169326
11	1	0	1.010796	-2.137918	-0.674743
12	1	0	-1.201371	-2.121502	0.564827
13	9	0	2.532903	-0.000003	-0.828338
14	9	0	1.136887	-1.373303	1.182303
15	9	0	1.136888	1.373281	1.182315
16	9	0	-1.316846	1.496376	-1.362866
17	9	0	-1.414689	0.000010	1.837044
18	9	0	-1.316871	-1.496378	-1.362851

εe-HFH   Standard orientation:

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-1.255699	0.567017	0.505325
2	6	0	-1.255707	-0.567009	-0.505329
3	6	0	-0.000002	-1.407442	-0.335606
4	6	0	1.255705	-0.567014	-0.505323
5	6	0	1.255702	0.567016	0.505328
6	6	0	0.000001	1.407450	0.335590
7	9	0	0.000005	1.924068	-0.958641
8	9	0	-0.000007	-1.924079	0.958621
9	1	0	0.000001	-2.253627	-1.026506
10	1	0	-0.000003	2.253643	1.026481
11	1	0	-1.309989	0.160707	1.519551
12	1	0	-1.310015	-0.160704	-1.519555
13	9	0	-2.363966	1.369584	0.305304
14	9	0	-2.363966	-1.369579	-0.305287
15	1	0	1.309996	0.160713	1.519556
16	1	0	1.310018	-0.160705	-1.519548
17	9	0	2.363970	1.369578	0.305295
18	9	0	2.363962	-1.369587	-0.305280

```
εa-HFH                    Standard orientation:
-------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
-------------------------------------------------------------------
    1         6          0        0.761959    1.275108    0.058843
    2         6          0       -0.761940    1.275114   -0.058854
    3         6          0       -1.235367    0.000002   -0.735156
    4         6          0       -0.761967   -1.275111   -0.058831
    5         6          0        0.761933   -1.275127    0.058838
    6         6          0        1.235366   -0.000019    0.735152
    7         1          0       -1.093752   -2.141894   -0.636617
    8         1          0        1.093708   -2.141918    0.636615
    9         1          0        0.821551   -0.000020    1.750003
   10         1          0       -0.821540   -0.000011   -1.750005
   11         1          0        1.093704    2.141880    0.636668
   12         1          0       -1.093705    2.141898   -0.636649
   13         9          0        1.283256    1.385408   -1.221319
   14         9          0       -1.283202    1.385394    1.221338
   15         9          0        1.283182   -1.385398   -1.221362
   16         9          0       -1.283222   -1.385361    1.221355
   17         9          0       -2.615800    0.000016   -0.823759
   18         9          0        2.615802   -0.000030    0.823751
-------------------------------------------------------------------
ζ-HFH                     Standard orientation:
-------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
-------------------------------------------------------------------
    1         6          0        1.086141    0.930135   -0.689102
    2         6          0        1.387847   -0.489403   -0.223634
    3         6          0        0.262440   -1.405682   -0.689095
    4         6          0       -1.117765   -0.957211   -0.223596
    5         6          0       -1.348580    0.475549   -0.689094
    6         6          0       -0.270093    1.446609   -0.223603
    7         9          0       -1.219430   -1.044269    1.144502
    8         9          0       -0.294655    1.578180    1.144494
    9         1          0       -1.882835   -1.612390   -0.653555
   10         1          0       -0.454978    2.436767   -0.653554
   11         1          0        0.263392   -1.410897   -1.788099
   12         1          0        1.090176    0.933610   -1.788102
   13         9          0        0.503308   -2.695687   -0.264719
   14         9          0        2.082906    1.783709   -0.264708
   15         9          0        1.514086   -0.533912    1.144478
   16         1          0        2.337780   -0.824398   -0.653584
   17         1          0       -1.353569    0.477302   -1.788094
   18         9          0       -2.586205    0.911981   -0.264742
-------------------------------------------------------------------
η-HFH                     Standard orientation:
-------------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X           Y           Z
-------------------------------------------------------------------
    1         6          0       -1.281247   -0.231503    0.475748
    2         6          0       -0.962836    0.889661   -0.496554
    3         6          0        0.518067    1.238828   -0.425877
    4         6          0        1.355606    0.004667   -0.720036
    5         6          0        1.041215   -1.170390    0.194950
    6         6          0       -0.455335   -1.466941    0.156445
    7         1          0        1.608761   -2.048477   -0.124756
    8         1          0       -0.707942   -2.277533    0.843350
    9         9          0        1.382397   -0.891397    1.506437
   10         9          0       -0.752496   -1.888080   -1.139768
   11         1          0       -1.236271    0.590292   -1.513157
   12         1          0       -1.073446    0.094672    1.498514
   13         9          0       -1.703334    2.010984   -0.171743
   14         9          0       -2.623419   -0.558756    0.385425
   15         1          0        1.140778   -0.314149   -1.746853
   16         1          0        0.757405    2.036268   -1.135104
   17         9          0        2.698696    0.317188   -0.638216
   18         9          0        0.800145    1.713728    0.843415
-------------------------------------------------------------------
```

```
θe-HFH                  Standard orientation:
---------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------
   1          6           0      -0.693803    1.244929   -0.435866
   2          6           0      -1.336717    0.000010    0.154211
   3          6           0      -0.693828   -1.244923   -0.435866
   4          6           0       0.810293   -1.267973   -0.205870
   5          6           0       1.427810   -0.000014   -0.777479
   6          6           0       0.810319    1.267961   -0.205870
   7          9           0       1.053675   -1.353283    1.150461
   8          9           0       1.053714    1.353280    1.150450
   9          1           0       1.253424   -2.150517   -0.676647
  10          1           0       1.253456    2.150491   -0.676666
  11          1           0       1.260131   -0.000012   -1.863201
  12          1           0      -0.905270   -1.281801   -1.512051
  13          1           0      -0.905241    1.281810   -1.512051
  14          1           0      -1.257844    0.000007    1.243813
  15          9           0       2.790267   -0.000028   -0.560120
  16          9           0      -1.254935   -2.370233    0.134444
  17          9           0      -1.254894    2.370250    0.134442
  18          9           0      -2.681506    0.000023   -0.183316
---------------------------------------------------------------
θa-HFH                  Standard orientation:
---------------------------------------------------------------
Center     Atomic      Atomic          Coordinates (Angstroms)
Number     Number      Type        X           Y           Z
---------------------------------------------------------------
   1          6           0       1.232923   -0.430513   -0.711909
   2          6           0       0.000013   -1.290049   -0.478664
   3          6           0      -1.232905   -0.430533   -0.711907
   4          6           0      -1.285973    0.808346    0.168340
   5          6           0      -0.000021    1.624696    0.034924
   6          6           0       1.285950    0.808370    0.168351
   7          9           0      -1.448511    0.465429    1.494160
   8          9           0       1.448487    0.465447    1.494164
   9          1           0      -2.136327    1.429566   -0.130101
  10          1           0       2.136293    1.429611   -0.130075
  11          1           0      -1.216064   -0.091053   -1.755165
  12          1           0       1.216091   -0.091042   -1.755165
  13          9           0      -2.376584   -1.183324   -0.528339
  14          9           0       2.376617   -1.183279   -0.528327
  15          9           0       0.000016   -1.806614    0.797876
  16          9           0      -0.000014    2.185309   -1.245356
  17          1           0      -0.000037    2.428466    0.774466
  18          1           0       0.000012   -2.134159   -1.176377
---------------------------------------------------------------
```

Standard Orientation of the optimized structures in water implicit solvent

```
αe-HCH                  Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
-----------------------------------------------------------------
   1          6          0       -0.755700    -1.545055    -0.112156
   2          6          0        0.754658    -1.545054     0.113553
   3          6          0        1.390177    -0.286563    -0.468820
   4          6          0        0.762363     0.988409     0.086635
   5          6          0       -0.761413     0.989099    -0.087266
   6          6          0       -1.390465    -0.285377     0.468656
   7          1          0        1.193915    -2.424739    -0.358512
   8          1          0       -1.195339    -2.423770     0.361431
   9          1          0        1.016705     1.106143     1.142911
  10          1          0       -1.015582     1.106616    -1.143627
  11          1          0       -1.251788    -0.316085     1.551693
  12          1          0        1.251052    -0.317973    -1.551750
  13         17          0       -3.150865    -0.303531     0.201011
  14         17          0       -1.059780    -1.708029    -1.868363
  15         17          0       -1.440271     2.405592     0.760861
  16         17          0        1.442003     2.404097    -0.762153
  17         17          0        3.150776    -0.305950    -0.201665
  18         17          0        1.058333    -1.705293     1.869970
-----------------------------------------------------------------
αa-HCH                  Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
-----------------------------------------------------------------
   1          6          0        0.979799     0.408271    -0.643676
   2          6          0        0.980171    -0.407629     0.643732
   3          6          0       -0.240620    -1.327212     0.686541
   4          6          0       -1.550431    -0.544667     0.540827
   5          6          0       -1.550717     0.543741    -0.541045
   6          6          0       -0.241528     1.327098    -0.686486
   7          1          0       -0.255565    -1.855536     1.640088
   8          1          0       -2.364545    -1.241210     0.342394
   9          1          0       -2.365342     1.239729    -0.342756
  10          1          0       -0.256724     1.855540    -1.639964
  11          1          0        0.926478    -0.260973    -1.506283
  12          1          0        0.926391     0.261601     1.506326
  13         17          0       -0.153469     2.605384     0.565740
  14         17          0        2.464672     1.364283    -0.859518
  15         17          0        2.465696    -1.362640     0.859547
  16         17          0       -0.151525    -2.605697    -0.565411
  17         17          0       -1.926284    -0.186419    -2.137980
  18         17          0       -1.926780     0.185278     2.137671
-----------------------------------------------------------------
βe-HCH                  Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic            Coordinates (Angstroms)
Number     Number     Type          X            Y            Z
-----------------------------------------------------------------
   1          6          0        0.126751    -1.449949    -0.227877
   2          6          0        1.320184    -0.615505     0.229281
   3          6          0        1.193420     0.834697    -0.228900
   4          6          0       -0.126736     1.449975     0.227813
   5          6          0       -1.320236     0.615525    -0.229212
   6          6          0       -1.193413    -0.834717     0.228865
   7          1          0        1.412565    -0.657190     1.318011
   8          1          0        0.135645    -1.548030    -1.317141
   9          1          0       -0.135582     1.548144     1.317069
  10          1          0        1.277140     0.890947    -1.317717
  11          1          0       -1.277121    -0.891052     1.317678
  12          1          0       -1.412738     0.657251    -1.317929
  13         17          0        0.270320    -3.096289     0.445283
  14         17          0       -2.546536    -1.783095    -0.445426
  15         17          0       -2.817263     1.314604     0.445540
  16         17          0       -0.270335     3.096265    -0.445462
  17         17          0        2.546532     1.783117     0.445345
  18         17          0        2.817297    -1.314615    -0.445268
-----------------------------------------------------------------
```

```
βa-HCH                    Standard orientation:
---------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X          Y          Z
---------------------------------------------------------------
    1         6          0      0.158581   0.705475  -1.321802
    2         6          0     -0.158664  -0.792041  -1.271898
    3         6          0      0.158298  -1.497507   0.049972
    4         6          0     -0.158498  -0.705409   1.321868
    5         6          0      0.158712   0.792111   1.271818
    6         6          0     -0.158487   1.497561  -0.049983
    7         1          0     -0.391745   1.289011   2.069786
    8         1          0      0.392124  -1.148020   2.151069
    9         1          0      0.392461   2.436793  -0.081376
   10         1          0     -0.392832  -2.436633   0.081370
   11         1          0     -0.391910   1.148090  -2.151082
   12         1          0      0.391899  -1.288949  -2.069794
   13        17          0      1.888666   1.049494   1.684518
   14        17          0      1.888510   0.934799  -1.750798
   15        17          0     -1.888148   1.984609  -0.066135
   16        17          0      1.887820  -1.984999   0.066077
   17        17          0     -1.888292  -0.934691   1.751363
   18        17          0     -1.888535  -1.049297  -1.685015
---------------------------------------------------------------
γ-HCH                     Standard orientation:
---------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X          Y          Z
---------------------------------------------------------------
    1         6          0     -1.238588   0.469590   0.433110
    2         6          0     -0.000316   1.140990  -0.162454
    3         6          0      1.238315   0.470521   0.433478
    4         6          0      1.293658  -1.027608   0.136248
    5         6          0      0.000331  -1.732475   0.555452
    6         6          0     -1.293213  -1.028461   0.135497
    7         1          0      1.207266   0.588306   1.520716
    8         1          0      0.000745  -2.756280   0.181323
    9         1          0      2.121685  -1.463743   0.696252
   10         1          0     -2.121308  -1.465162   0.694963
   11         1          0     -0.000143   1.078191  -1.253655
   12         1          0     -1.207839   0.587078   1.520381
   13        17          0     -0.001085   2.873043   0.260840
   14        17          0     -2.749666   1.252526  -0.089503
   15        17          0     -1.652863  -1.361041  -1.584850
   16        17          0     -0.000188  -1.853849   2.348332
   17        17          0      1.654632  -1.360291  -1.583789
   18        17          0      2.749081   1.254099  -0.089145
---------------------------------------------------------------
δe-HCH                    Standard orientation:
---------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type          X          Y          Z
---------------------------------------------------------------
    1         6          0      0.000471  -1.588692  -0.266573
    2         6          0     -1.238376  -0.784596  -0.647548
    3         6          0     -1.283200   0.547678   0.091496
    4         6          0     -0.000541   1.348981  -0.152136
    5         6          0      1.282812   0.548266   0.091025
    6         6          0      1.239244  -0.784527  -0.647472
    7         1          0      1.204896  -0.609704  -1.727208
    8         1          0     -1.432753   0.381732   1.160037
    9         1          0      0.000431  -2.533944  -0.811944
   10         1          0     -1.203685  -0.609252  -1.727187
   11         1          0     -0.000822   1.720986  -1.180751
   12         1          0      1.432764   0.382761   1.159577
   13        17          0      0.000316  -1.999833   1.472846
   14        17          0      2.711598  -1.739481  -0.348553
   15        17          0      2.672720   1.510987  -0.479580
   16        17          0     -0.000563   2.785476   0.907967
   17        17          0     -2.673870   1.509538  -0.478580
   18        17          0     -2.710396  -1.740525  -0.349704
---------------------------------------------------------------
```

```
δa-HCH                    Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X           Y           Z
---------------------------------------------------------------------
    1          6          0        0.944003    0.184116   -1.301325
    2          6          0       -0.490870   -0.356060   -1.294836
    3          6          0       -0.779805   -1.104806   -0.000201
    4          6          0       -0.491177   -0.356451    1.294770
    5          6          0        0.943692    0.183884    1.301453
    6          6          0        1.409475    0.849123    0.000162
    7          1          0       -0.094487   -1.959254   -0.000267
    8          1          0        1.058268    0.892744    2.120978
    9          1          0       -0.590979   -1.061733    2.120344
   10          1          0        2.498619    0.881203    0.000310
   11          1          0       -0.590659   -1.061095   -2.120624
   12          1          0        1.058696    0.893118   -2.120707
   13         17          0        0.900134    2.571030    0.000236
   14         17          0        2.038801   -1.184613   -1.701930
   15         17          0        2.038523   -1.184838    1.702033
   16         17          0       -1.652666    0.951360    1.667571
   17         17          0       -2.410932   -1.809859   -0.000532
   18         17          0       -1.652176    0.951990   -1.667388
---------------------------------------------------------------------
εe-HCH                    Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X           Y           Z
---------------------------------------------------------------------
    1          6          0       -1.253129    0.508285    0.567913
    2          6          0       -1.253088   -0.508406   -0.568120
    3          6          0        0.000020   -1.386088   -0.501274
    4          6          0        1.253317   -0.508578   -0.567981
    5          6          0        1.253227    0.508492    0.567794
    6          6          0        0.000036    1.386052    0.501425
    7          1          0        0.000042   -2.074527   -1.348054
    8          1          0       -0.000004    2.074231    1.348409
    9          1          0       -1.248060   -0.008393    1.531005
   10          1          0       -1.247922    0.008167   -1.531265
   11          1          0        1.248398   -0.007962    1.531008
   12          1          0        1.248334    0.007804   -1.531236
   13         17          0        2.715081    1.522531    0.565157
   14         17          0        2.715172   -1.522541   -0.565293
   15         17          0       -0.000120   -2.403450    0.971217
   16         17          0       -2.715016   -1.522283   -0.565856
   17         17          0       -2.715115    1.522109    0.565695
   18         17          0       -0.000185    2.403760   -0.970827
---------------------------------------------------------------------
εa-HCH                    Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X           Y           Z
---------------------------------------------------------------------
    1          6          0        0.747242    1.298685    0.173967
    2          6          0       -0.746966    1.298778   -0.173414
    3          6          0       -1.139125    0.000015   -0.870803
    4          6          0       -0.747227   -1.298643   -0.173400
    5          6          0        0.746686   -1.298678    0.173638
    6          6          0        1.139637   -0.000171    0.871026
    7          1          0       -0.952329   -2.128187   -0.850651
    8          1          0        0.951785   -2.128408    0.850689
    9          1          0        0.582646   -0.000188    1.814042
   10          1          0       -0.581553   -0.000091   -1.813481
   11          1          0        0.952324    2.128182    0.851300
   12          1          0       -0.951976    2.128321   -0.850705
   13         17          0        2.855867   -0.000602    1.331893
   14         17          0        1.679580    1.657434   -1.310697
   15         17          0        1.678612   -1.657199   -1.311311
   16         17          0       -1.679627   -1.657049    1.311270
   17         17          0       -2.855065    0.000145   -1.332756
   18         17          0       -1.679507    1.657298    1.311173
---------------------------------------------------------------------
```

```
ζ-HCH                    Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0       -1.105121    -0.907813    -0.930760
   2          6          0       -1.403731     0.527935    -0.492425
   3          6          0       -0.233084     1.410990    -0.931415
   4          6          0        1.159274     0.951165    -0.492371
   5          6          0        1.338521    -0.504315    -0.930668
   6          6          0        0.244417    -1.479826    -0.490413
   7          1          0        1.891503     1.551804    -1.036091
   8          1          0        0.398587    -2.414790    -1.033191
   9          1          0       -0.225420     1.362121    -2.026280
  10          1          0       -1.064641    -0.876486    -2.025611
  11          1          0       -2.289960     0.861380    -1.036417
  12          1          0        1.290696    -0.487133    -2.025395
  13         17          0       -2.446567    -2.009183    -0.550109
  14         17          0        0.318316    -1.926574     1.233563
  15         17          0       -1.829989     0.688553     1.231000
  16         17          0        2.963080    -1.115299    -0.549860
  17         17          0        1.510729     1.240138     1.231172
  18         17          0       -0.515711     3.123206    -0.549219
---------------------------------------------------------------------
η-HCH                    Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0       -1.240878    -0.168344     0.515948
   2          6          0       -0.937984     0.803060    -0.619985
   3          6          0        0.566574     1.094705    -0.694845
   4          6          0        1.321268    -0.226767    -0.846001
   5          6          0        0.995887    -1.306433     0.183730
   6          6          0       -0.518227    -1.498373     0.300388
   7          1          0        1.447013    -2.243551    -0.144638
   8          1          0       -0.734055    -2.168454     1.133058
   9          1          0       -1.238329     0.362297    -1.574335
  10          1          0       -0.893063     0.250347     1.463911
  11          1          0        1.001769    -0.635959    -1.809698
  12          1          0        0.759093     1.700255    -1.582736
  13         17          0       -1.092430    -2.338421    -1.175363
  14         17          0        1.652922    -1.005113     1.818567
  15         17          0        3.073546     0.023342    -1.003477
  16         17          0        1.122070     2.080031     0.687792
  17         17          0       -1.856851     2.320197    -0.483265
  18         17          0       -2.985273    -0.459567     0.713336
---------------------------------------------------------------------
θe-HCH                   Standard orientation:
---------------------------------------------------------------------
Center      Atomic     Atomic              Coordinates (Angstroms)
Number      Number     Type          X            Y            Z
---------------------------------------------------------------------
   1          6          0       -0.708321     1.241250    -0.577091
   2          6          0       -1.315861    -0.000008     0.079424
   3          6          0       -0.708367    -1.241216    -0.577153
   4          6          0        0.815493    -1.293536    -0.435866
   5          6          0        1.399502     0.000090    -1.002979
   6          6          0        0.815510     1.293597    -0.435708
   7          1          0        1.187263    -2.126579    -1.035743
   8          1          0        1.187325     2.126712    -1.035461
   9          1          0        1.137027     0.000162    -2.067362
  10          1          0       -0.934304    -1.215081    -1.648302
  11          1          0       -0.934188     1.215155    -1.648253
  12          1          0       -1.143418    -0.000044     1.158546
  13         17          0       -1.435566     2.748287     0.029753
  14         17          0        1.320909     1.644936     1.238867
  15         17          0        3.176050     0.000131    -0.956484
  16         17          0        1.320960    -1.645159     1.238624
  17         17          0       -1.435509    -2.748271     0.029772
  18         17          0       -3.081399    -0.000006    -0.170367
---------------------------------------------------------------------
```

θa-HCH   Standard orientation:

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	1.235262	-0.138215	-0.889721
2	6	0	0.000021	-1.039573	-0.895182
3	6	0	-1.235166	-0.138172	-0.889952
4	6	0	-1.299055	0.909369	0.218591
5	6	0	0.000188	1.721607	0.286605
6	6	0	1.299179	0.909123	0.218896
7	1	0	-2.112394	1.597058	-0.015864
8	1	0	2.112786	1.596592	-0.015278
9	1	0	-1.184288	0.427779	-1.826176
10	1	0	1.184554	0.427830	-1.825897
11	1	0	0.000120	2.337931	1.185484
12	1	0	0.000094	-1.596129	-1.834824
13	17	0	1.705309	0.248930	1.829432
14	17	0	2.742024	-1.074080	-0.998015
15	17	0	-0.000136	-2.285315	0.381169
16	17	0	-1.705860	0.249514	1.829088
17	17	0	-2.742009	-1.073893	-0.998273
18	17	0	0.000468	2.868026	-1.100042

αe-HFH   Standard orientation:

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-0.749660	-1.443912	-0.139860
2	6	0	0.749674	-1.443913	0.139821
3	6	0	1.395018	-0.195242	-0.432679
4	6	0	0.750928	1.065075	0.114239
5	6	0	-0.750942	1.065065	-0.114237
6	6	0	-1.395001	-0.195262	0.432688
7	1	0	1.225960	-2.340646	-0.259420
8	1	0	-1.225939	-2.340660	0.259358
9	1	0	0.974820	1.180744	1.177975
10	1	0	-0.974841	1.180728	-1.177972
11	1	0	-1.319648	-0.212493	1.523189
12	1	0	1.319704	-0.212456	-1.523184
13	9	0	-0.910049	-1.441583	-1.525208
14	9	0	0.910056	-1.441629	1.525175
15	9	0	2.745055	-0.188917	-0.101223
16	9	0	1.296158	2.165764	-0.542874
17	9	0	-1.296182	2.165749	0.542874
18	9	0	-2.745052	-0.188949	0.101280

αa-HFH   Standard orientation:

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-1.075622	-0.566629	-0.502433
2	6	0	-1.075598	0.566664	0.502446
3	6	0	0.149904	1.442981	0.313668
4	6	0	1.447193	0.644878	0.410275
5	6	0	1.447165	-0.644922	-0.410283
6	6	0	0.149847	-1.442984	-0.313667
7	9	0	0.096776	-2.005977	0.960916
8	9	0	1.620316	-0.301281	-1.748644
9	9	0	1.620344	0.301237	1.748642
10	9	0	0.096846	2.005955	-0.960925
11	1	0	0.154256	2.255470	1.042905
12	1	0	2.285080	1.271045	0.096514
13	1	0	2.285037	-1.271111	-0.096524
14	1	0	0.154155	-2.255471	-1.042908
15	1	0	-1.099540	-0.174888	-1.522244
16	1	0	-1.099531	0.174931	1.522259
17	9	0	-2.213657	-1.345477	-0.318285
18	9	0	-2.213602	1.345553	0.318292

```
βe-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number      Type          X            Y            Z
---------------------------------------------------------------------
   1          6           0        0.637692     1.300271    -0.225991
   2          6           0       -0.807257     1.202627     0.226385
   3          6           0       -1.445012    -0.097692    -0.225616
   4          6           0       -0.637692    -1.300272     0.225991
   5          6           0        0.807257    -1.202627    -0.226385
   6          6           0        1.445012     0.097692     0.225616
   7          1           0       -0.874613     1.304260     1.313465
   8          1           0        0.690810     1.409678    -1.313097
   9          9           0       -1.517994     2.261289    -0.329275
  10          9           0        1.199483     2.445192     0.329130
  11          1           0       -0.690810    -1.409678     1.313097
  12          9           0       -1.199483    -2.445192    -0.329130
  13          1           0       -1.566184    -0.105442    -1.312745
  14          1           0        1.566184     0.105442     1.312745
  15          1           0        0.874613    -1.304260    -1.313465
  16          9           0        1.517994    -2.261289     0.329275
  17          9           0        2.717582     0.184053    -0.328996
  18          9           0       -2.717582    -0.184053     0.328996
---------------------------------------------------------------------
βa-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number      Type          X            Y            Z
---------------------------------------------------------------------
   1          6           0       -0.538804    -1.381398     0.181118
   2          6           0       -1.467688    -0.222968    -0.167079
   3          6           0       -0.925142     1.158456     0.183763
   4          6           0        0.538803     1.381401    -0.181118
   5          6           0        1.467686     0.222971     0.167080
   6          6           0        0.925140    -1.158454    -0.183764
   7          9           0        1.682823     0.254295     1.543083
   8          9           0        0.604527     1.574327    -1.559142
   9          9           0        1.044945    -1.320125    -1.562169
  10          9           0       -1.044943     1.320122     1.562171
  11          9           0       -0.604527    -1.574329     1.559140
  12          9           0       -1.682821    -0.254296    -1.543084
  13          1           0        2.424314     0.369084    -0.339964
  14          1           0        0.895888     2.286177     0.316300
  15          1           0        1.535373    -1.917225     0.311807
  16          1           0       -1.535376     1.917230    -0.311800
  17          1           0       -0.895890    -2.286171    -0.316305
  18          1           0       -2.424317    -0.369081     0.339962
---------------------------------------------------------------------
γ-HFH                   Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number      Type          X            Y            Z
---------------------------------------------------------------------
   1          6           0       -1.239510     0.533043     0.385691
   2          6           0       -0.000028     1.235137    -0.136578
   3          6           0        1.239486     0.533096     0.385693
   4          6           0        1.277369    -0.928458    -0.023731
   5          6           0        0.000031    -1.658912     0.385400
   6          6           0       -1.277331    -0.928509    -0.023739
   7          1           0        1.272843     0.607196     1.476689
   8          1           0        0.000052    -2.668947    -0.028050
   9          1           0        2.146971    -1.422053     0.414917
  10          1           0       -2.146921    -1.422139     0.414891
  11          9           0        2.369108     1.170411    -0.113656
  12          9           0        1.390964    -1.002370    -1.408808
  13          9           0        0.000028    -1.736036     1.777380
  14          9           0       -1.390902    -1.002419    -1.408820
  15          1           0       -0.000029     1.281914    -1.227723
  16          1           0       -1.272875     0.607136     1.476686
  17          9           0       -0.000052     2.545050     0.338251
  18          9           0       -2.369162     1.170310    -0.113662
---------------------------------------------------------------------
```

```
δe-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type         X            Y            Z
---------------------------------------------------------------------
   1          6          0       -0.000002    -1.544674    -0.133055
   2          6          0       -1.242433    -0.769759    -0.528621
   3          6          0       -1.263833     0.587602     0.150068
   4          6          0        0.000004     1.375338    -0.150126
   5          6          0        1.263835     0.587597     0.150073
   6          6          0        1.242426    -0.769757    -0.528626
   7          1          0        1.284194    -0.657065    -1.616158
   8          1          0       -1.393058     0.470761     1.228556
   9          1          0       -0.000002    -2.542823    -0.573833
  10          9          0       -0.000004    -1.691408     1.256205
  11          9          0       -2.355102     1.311357    -0.322115
  12          9          0        2.368171    -1.482721    -0.136049
  13          1          0       -1.284204    -0.657075    -1.616155
  14          1          0        0.000007     1.703659    -1.193735
  15          1          0        1.393048     0.470749     1.228562
  16          9          0       -2.368173    -1.482713    -0.136030
  17          9          0        0.000004     2.524549     0.636140
  18          9          0        2.355108     1.311349    -0.322096
---------------------------------------------------------------------
δa-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type         X            Y            Z
---------------------------------------------------------------------
   1          6          0       -0.878729    -1.287441    -0.045739
   2          6          0        0.645452    -1.272162    -0.139462
   3          6          0        1.131737    -0.000010    -0.804722
   4          6          0        0.645472     1.272155    -0.139470
   5          6          0       -0.878708     1.287453    -0.045752
   6          6          0       -1.492354     0.000014     0.500869
   7          1          0        0.761219    -0.000009    -1.835170
   8          1          0       -1.200377     2.129596     0.570518
   9          1          0        0.983880     2.141543    -0.707954
  10          1          0       -2.563623     0.000023     0.285288
  11          1          0        0.983847    -2.141559    -0.707939
  12          1          0       -1.200402    -2.129570     0.570548
  13          9          0        2.521290    -0.000022    -0.843108
  14          9          0        1.160108    -1.376872     1.147953
  15          9          0        1.160131     1.376869     1.147943
  16          9          0       -1.362597     1.468279    -1.341063
  17          9          0       -1.316501     0.000019     1.881579
  18          9          0       -1.362627    -1.468282    -1.341042
---------------------------------------------------------------------
εe-HFH                  Standard orientation:
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number      Type         X            Y            Z
---------------------------------------------------------------------
   1          6          0       -1.253004     0.565533     0.506206
   2          6          0       -1.253012    -0.565527    -0.506211
   3          6          0       -0.000003    -1.410637    -0.349559
   4          6          0        1.253009    -0.565533    -0.506205
   5          6          0        1.253008     0.565530     0.506209
   6          6          0        0.000003     1.410642     0.349549
   7          9          0        0.000007     1.948946    -0.940778
   8          9          0       -0.000009    -1.948949     0.940767
   9          1          0       -0.000002    -2.243791    -1.054136
  10          1          0        0.000001     2.243799     1.054123
  11          1          0       -1.317120     0.168869     1.522501
  12          1          0       -1.317137    -0.168866    -1.522507
  13          9          0       -2.366076     1.369828     0.293165
  14          9          0       -2.366081    -1.369819    -0.293155
  15          1          0        1.317126     0.168873     1.522506
  16          1          0        1.317140    -0.168870    -1.522500
  17          9          0        2.366083     1.369818     0.293158
  18          9          0        2.366074    -1.369830    -0.293149
---------------------------------------------------------------------
```

```
εa-HFH                    Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type        X            Y            Z
-----------------------------------------------------------------
   1          6          0       0.760661     1.276066     0.072458
   2          6          0      -0.760660     1.276067    -0.072458
   3          6          0      -1.232052     0.000001    -0.747362
   4          6          0      -0.760661    -1.276066    -0.072458
   5          6          0       0.760660    -1.276067     0.072458
   6          6          0       1.232052    -0.000000     0.747362
   7          1          0      -1.083472    -2.145347    -0.648899
   8          1          0       1.083470    -2.145347     0.648898
   9          1          0       0.837992    -0.000000     1.768588
  10          1          0      -0.837992     0.000000    -1.768588
  11          1          0       1.083472     2.145347     0.648899
  12          1          0      -1.083470     2.145348    -0.648898
  13          9          0       1.303399     1.382253    -1.205156
  14          9          0      -1.303398     1.382252     1.205156
  15          9          0       1.303398    -1.382253    -1.205156
  16          9          0      -1.303399    -1.382253     1.205155
  17          9          0      -2.619666     0.000001    -0.814355
  18          9          0       2.619666    -0.000001     0.814355
-----------------------------------------------------------------
ζ-HFH                     Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type        X            Y            Z
-----------------------------------------------------------------
   1          6          0      -1.344604    -0.497190    -0.701841
   2          6          0      -1.132326     0.939955    -0.248551
   3          6          0       0.241529     1.412441    -0.701477
   4          6          0       1.380388     0.510443    -0.248408
   5          6          0       1.102861    -0.915517    -0.701713
   6          6          0      -0.248039    -1.450270    -0.248888
   7          9          0       1.506392     0.556789     1.133632
   8          9          0      -0.270535    -1.581419     1.133356
   9          1          0       2.325472     0.860309    -0.670864
  10          1          0      -0.417785    -2.443946    -0.670477
  11          1          0       0.248687     1.452670    -1.796189
  12          1          0      -1.384324    -0.511464    -1.796458
  13          9          0       0.461010     2.697277    -0.226386
  14          9          0      -2.566586    -0.949518    -0.225460
  15          9          0      -1.235395     1.025201     1.133572
  16          1          0      -1.907410     1.584293    -0.670566
  17          1          0       1.135363    -0.941603    -1.796344
  18          9          0       2.105240    -1.748267    -0.225808
-----------------------------------------------------------------
η-HFH                     Standard orientation:
-----------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type        X            Y            Z
-----------------------------------------------------------------
   1          6          0      -1.279464    -0.220674     0.478465
   2          6          0      -0.953690     0.892797    -0.498305
   3          6          0       0.529257     1.227701    -0.448936
   4          6          0       1.355649    -0.016604    -0.728502
   5          6          0       1.027988    -1.185650     0.187935
   6          6          0      -0.471912    -1.468187     0.163453
   7          1          0       1.585807    -2.072205    -0.119569
   8          1          0      -0.725329    -2.272207     0.856068
   9          9          0       1.377253    -0.891875     1.501377
  10          9          0      -0.787374    -1.889697    -1.129747
  11          1          0      -1.242721     0.607397    -1.512956
  12          1          0      -1.075109     0.100282     1.502725
  13          9          0      -1.679605     2.027778    -0.156010
  14          9          0      -2.632819    -0.527794     0.386580
  15          1          0       1.163697    -0.331848    -1.759064
  16          1          0       0.770056     2.015064    -1.166167
  17          9          0       2.703601     0.294103    -0.614794
  18          9          0       0.827459     1.718287     0.820850
-----------------------------------------------------------------
```

```
θe-HFH                    Standard orientation:
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type        X           Y           Z
---------------------------------------------------------------
   1         6         0      -0.695979    1.245813   -0.451547
   2         6         0      -1.328390    0.000000    0.143696
   3         6         0      -0.695980   -1.245813   -0.451547
   4         6         0       0.808139   -1.270029   -0.230175
   5         6         0       1.433165   -0.000000   -0.786821
   6         6         0       0.808140    1.270029   -0.230175
   7         9         0       1.051563   -1.359960    1.136940
   8         9         0       1.051564    1.359960    1.136940
   9         1         0       1.250623   -2.151351   -0.699100
  10         1         0       1.250623    2.151351   -0.699099
  11         1         0       1.310405    0.000000   -1.875308
  12         1         0      -0.917491   -1.303822   -1.521948
  13         1         0      -0.917490    1.303822   -1.521948
  14         1         0      -1.237526    0.000000    1.232238
  15         9         0       2.791755   -0.000001   -0.508459
  16         9         0      -1.255077   -2.365627    0.150819
  17         9         0      -1.255076    2.365627    0.150818
  18         9         0      -2.686254    0.000001   -0.164326
---------------------------------------------------------------
θa-HFH                    Standard orientation:
---------------------------------------------------------------
Center    Atomic    Atomic          Coordinates (Angstroms)
Number    Number    Type        X           Y           Z
---------------------------------------------------------------
   1         6         0       1.236671   -0.415645   -0.720813
   2         6         0       0.000041   -1.274849   -0.518628
   3         6         0      -1.236629   -0.415710   -0.720821
   4         6         0      -1.284388    0.814549    0.169346
   5         6         0      -0.000046    1.633813    0.043085
   6         6         0       1.284332    0.814606    0.169385
   7         9         0      -1.433796    0.444603    1.499729
   8         9         0       1.433709    0.444639    1.499760
   9         1         0      -2.139661    1.437049   -0.104374
  10         1         0       2.139587    1.437151   -0.104288
  11         1         0      -1.251977   -0.077438   -1.762217
  12         1         0       1.252017   -0.077369   -1.762203
  13         9         0      -2.371971   -1.185460   -0.503226
  14         9         0       2.372057   -1.185332   -0.503207
  15         9         0       0.000054   -1.825537    0.757550
  16         9         0      -0.000036    2.197166   -1.234122
  17         1         0      -0.000081    2.434824    0.784340
  18         1         0       0.000060   -2.105502   -1.228929
---------------------------------------------------------------
```

Table S1. Relative Gibbs energy for all isomers, Grel, in kcal mol^{-1}. Relative Gibbs energy from the conformational ring flip isomerism, ΔGrel, in kcal mol^{-1}, and the conformational population, in parenthesis. Nuclear-electronic relative energy, Erel, in kcal mol^{-1}. Dipole moment, μ, Debye. The data were acquired in gas phase and implicit water at the MP2/6-311++g(d,p) level of theory.

Isomer	Gas Phase				Implicit Water			
	G_{rel}	ΔG_{rel}	E_{rel}	μ	G_{rel}	ΔG_{rel}	E_{rel}	μ
α_e-HCH	0.00	0.00 (100%)	0.00	2.37	0.00	0.00 (100%)	0.00	3.31
α_a-HCH	4.06	4.06 (0%)	3.76	2.28	4.36	4.36 (0%)	4.08	3.20
β_e-HCH	3.43	0.00 (100%)	3.95	0.00	2.25	0.00 (100%)	2.38	0.00
β_a-HCH	11.29	7.86 (0%)	10.71	0.00	11.67	9.42 (0%)	11.12	0.00
γ-HCH	3.47	-	3.38	3.04	3.34	-	3.16	4.42
δ_e-HCH	1.99	0.00 (100%)	2.23	2.16	0.66	0.00 (100%)	1.01	3.23
δ_a-HCH	7.72	5.73 (0%)	7.23	2.07	7.76	7.10 (0%)	7.28	3.17
ϵ_e-HCH	2.04	0.00 (96%)	1.96	0.00	1.24	0.00 (99%)	1.13	0.00
ϵ_a-HCH	3.86	1.82 (4%)	3.46	0.00	3.94	2.70 (1%)	3.64	0.00
ζ-HCH	11.71	-	11.48	5.19	7.87	-	7.37	8.07
η-HCH	3.35	-	3.10	2.22	2.74	-	2.48	3.35
θ_e-HCH	6.73	0.00 (87%)	6.84	3.68	4.44	0.00 (97%)	4.40	5.61
θ_a-HCH	7.85	1.12 (13%)	7.42	3.58	6.45	2.01 (3%)	6.05	5.59
α_e-HFH	0.00	0.00 (97%)	0.18	3.30	0.69	0.00 (99%)	0.97	4.17
α_a-HFH	2.12	2.12 (3%)	2.29	3.04	3.27	2.58 (1%)	3.40	3.87
βe-HFH	1.90	0.00 (100%)	2.66	0.00	0.88	0.00 (100%)	1.43	0.00
βa-HFH	6.58	4.68 (0%)	7.03	0.00	7.49	6.61 (0%)	7.79	0.00
γ-HFH	1.97	-	2.20	4.30	2.35	-	2.65	5.59
δ_e-HFH	1.02	0.00 (100%)	1.39	3.03	0.21	0.00 (100%)	0.65	4.10
δ_a-HFH	4.93	3.91 (0%)	5.15	2.86	5.38	5.17 (0%)	5.55	3.82
ϵ_e-HFH	0.04	0.00 (99%)	0.00	0.00	0.00	0.00 (100%)	0.00	0.00
ϵ_a-HFH	2.94	2.90 (1%)	2.92	0.00	3.45	3.45 (0%)	3.46	0.0
ζ-HFH	8.94	-	8.97	7.23	3.89	-	3.82	9.90
η-HFH	2.00	-	1.99	3.08	1.86	-	1.87	4.11
θ_e-HFH	4.09	0.00 (95%)	4.33	5.16	1.68	0.00 (99%)	1.91	7.08
θ_a-HFH	5.85	1.76 (5%)	5.89	5.05	4.31	2.63 (1%)	4.30	6.85

Table S2. Relative full energy (E_{Full}), Lewis energy (E_{Lewis}), and non-Lewis energy ($E_{non\text{-}Lewis}$), in kcal mol^{-1}, obtained through Natural Bond Orbital (NBO) analysis at the B3LYP/6-311++g(d,p) level.

Isomers	HCH			HFH		
	E_{Full}	E_{Lewis}	$E_{non\text{-}Lewis}$	E_{Full}	E_{Lewis}	$E_{non\text{-}Lewis}$
α_e	0.00	15.34	-15.34	0.00	19.91	-19.91
α_a	3.67	21.03	-17.36	2.20	16.22	-14.02
β_e	2.75	2.75	0.00	1.60	27.30	-25.70
β_a	8.83	18.43	-9.60	6.30	6.30	0.00
γ	3.41	20.06	-16.65	2.07	23.14	-21.07
δ_e	2.05	16.63	-14.58	1.05	29.15	-28.10
δ_a	6.65	40.70	-34.05	4.91	21.92	-17.01
ϵ_e	2.23	27.45	-25.22	0.21	30.36	-30.15
ϵ_a	3.90	32.91	-29.01	3.10	35.95	-32.85
ζ	12.53	76.53	-64.00	9.48	72.85	-63.37
η	3.59	30.17	-26.58	2.22	33.15	-30.93
θ_e	7.32	30.28	-22.96	4.38	45.75	-41.37
θ_a	7.72	58.64	-50.92	6.10	44.48	-38.38

Table S3. Docking score (D_{score}), in kcal mol^{-1}, and the ligand efficiency SA (surface area) of HCH and HFH isomers in the picrotoxin and barbiturate sites of GABA$_A$ receptor and InsP$_3$ receptor.

Isomer	Picrotoxin site		Barbiturate site		InsP3 receptor	
	D_{score}	Efficiency SA	D_{score}	Efficiency SA	D_{score}	Efficiency SA
α$_e$-HCH	-3.72	-0.711	-4.39	-0.838	-0.68	-0.129
α$_a$-HCH	-3.94	-0.753	-4.65	-0.887	-0.89	-0.171
β$_e$-HCH	-3.82	-0.728	-3.39	-0.648	-0.56	-0.107
β$_a$-HCH	-3.70	-0.706	-4.41	-0.841	-0.53	-0.101
γ-HCH	-3.86	-0.737	-4.14	-0.790	-1.05	-0.201
δ$_e$-HCH	-3.96	-0.756	-4.10	-0.782	-1.29	-0.247
δ$_a$-HCH	-3.98	-0.760	-3.99	-0.761	-0.60	-0.114
ε$_e$-HCH	-3.73	-0.711	-3.94	-0.751	-0.41	-0.078
ε$_a$-HCH	-4.09	-0.779	-4.33	-0.826	-0.35	-0.066
ζ-HCH	-2.99	-0.570	-4.07	-0.777	-0.57	-0.108
η-HCH	-3.52	-0.672	-4.09	-0.781	-0.92	-0.175
θ$_e$-HCH	-3.91	-0.746	-4.34	-0.827	-0.65	-0.124
θ$_a$-HCH	-3.94	-0.751	-4.18	-0.798	-0.16	-0.031
α$_e$-HFH	-3.80	-0.726	-4.50	-0.859	-0.04	-0.007
α$_a$-HFH	-3.74	-0.714	-4.34	-0.827	-0.46	-0.088
βe-HFH	-3.95	-0.754	-4.69	-0.894	-0.80	-0.153
βa-HFH	-4.20	-0.801	-4.42	-0.844	-1.12	-0.213
γ-HFH	-3.87	-0.738	-4.54	-0.866	-0.46	-0.088
δ$_e$-HFH	-3.86	-0.736	-4.61	-0.879	-0.69	-0.131
δ$_a$-HFH	-3.90	-0.745	-4.34	-0.829	0.01	0.002
ε$_e$-HFH	-3.47	-0.662	-3.95	-0.753	0.16	0.031
ε$_a$-HFH	-3.94	-0.752	-4.38	-0.836	-0.34	-0.064
ζ-HFH	-4.02	-0.768	-4.57	-0.872	-0.60	-0.114
η-HFH	-3.83	-0.731	-4.39	-0.838	-0.24	-0.046
θ$_e$-HFH	-3.95	-0.754	-4.73	-0.903	-0.15	-0.028
θ$_a$-HFH	-3.86	-0.737	-4.48	-0.854	-0.29	-0.056

Table S4. Docking score (D_{score}), in kcal mol^{-1}, and the ligand efficiency SA (surface area) of HCH and HFH isomers in three predicted sites of ryanodine receptor.

Isomer	RyR site 1		RyR site 2		RyR site 3	
	D_{score}	Efficiency SA	D_{score}	Efficiency SA	D_{score}	Efficiency SA
α_e-HCH	-3.21	-0.612	-1.52	-0.289	-1.51	-0.289
α_a-HCH	-3.52	-0.672	-1.77	-0.338	-0.85	-0.162
β_e-HCH	-2.62	-0.500	-1.08	-0.206	-0.23	-0.044
β_a-HCH	-3.42	-0.652	-1.12	-0.214	-1.37	-0.260
γ-HCH	-3.63	-0.692	-2.12	-0.405	-0.49	-0.093
δ_e-HCH	-3.01	-0.573	-1.99	-0.381	-1.78	-0.339
δ_a-HCH	-3.40	-0.648	-1.99	-0.382	-1.60	-0.305
ε_e-HCH	-3.00	-0.573	-2.24	-0.428	-1.48	-0.283
ε_a-HCH	-3.38	-0.646	-1.66	-0.318	-0.26	-0.050
ζ-HCH	-3.08	-0.588	-1.81	-0.346	-1.17	-0.224
η-HCH	-3.23	-0.616	-1.60	-0.306	-1.28	-0.244
θ_e-HCH	-3.11	-0.593	-1.99	-0.381	-1.16	-0.222
θ_a-HCH	-3.59	-0.685	-1.66	-0.317	-0.32	-0.061
α_e-HFH	-3.64	-0.695	-1.31	-0.251	-0.29	-0.055
α_a-HFH	-3.58	-0.684	-1.54	-0.293	-0.19	-0.037
βe-HFH	-2.93	-0.558	-0.49	-0.094	0.22	0.041
βa-HFH	-3.55	-0.677	-0.90	-0.172	-0.66	-0.125
γ-HFH	-3.50	-0.668	-1.34	-0.256	0.36	0.069
δ_e-HFH	-3.54	-0.675	-1.59	-0.304	-0.01	-0.001
δ_a-HFH	-3.48	-0.665	-1.22	-0.232	0.24	0.045
ε_e-HFH	-3.68	-0.702	-1.52	-0.290	0.68	0.130
ε_a-HFH	-3.70	-0.706	-1.24	-0.237	-0.70	-0.133
ζ-HFH	-3.11	-0.595	-1.67	-0.319	-0.66	-0.127
η-HFH	-3.08	-0.588	-1.17	-0.222	0.37	0.070
θ_e-HFH	-3.67	-0.701	-1.86	-0.355	0.29	0.055
θ_a-HFH	-3.52	-0.671	-1.26	-0.240	0.46	0.087

Table S5. Number and types of interactions of HCHs and HFHs in the picrotoxin site of GABA$_A$ receptor.

Isomer	X•••HO	X•••HC	X•••$\pi_{CO/N}$	R•••π_{Ar}	R•••R
α$_e$-HCH	-	-	-	-	-
α$_a$-HCH	-	1	-	-	-
β$_e$-HCH	-	-	-	-	-
β$_a$-HCH	-	-	-	-	-
γ-HCH	-	2	-	-	-
δ$_e$-HCH	-	3	-	-	-
δ$_a$-HCH	-	-	-	-	-
ε$_e$-HCH	-	-	-	-	-
ε$_a$-HCH	-	-	-	-	-
ζ-HCH	-	-	-	-	-
η-HCH	-	-	-	-	-
θ$_e$-HCH	-	1	-	-	-
θ$_a$-HCH	-	2	-	-	-
α$_e$-HFH	1	-	1	-	-
α$_a$-HFH	-	-	-	-	-
βe-HFH	-	-	-	-	-
βa-HFH	-	-	-	-	-
γ-HFH	-	-	-	-	-
δ$_e$-HFH	-	-	-	-	-
δ$_a$-HFH	-	1	-	-	-
ε$_e$-HFH	-	-	-	-	-
ε$_a$-HFH	-	-	-	-	-
ζ-HFH	-	-	-	-	-
η-HFH	1	1	2	-	-
θ$_e$-HFH	-	-	-	-	-
θ$_a$-HFH	-	-	-	-	-

Table S6. Number and types of interactions of HCHs and HFHs in the barbiturate site of GABA$_A$ receptor.

Isomer	X•••HO	X•••HC	X•••$\pi_{CO/N}$	R•••π_{Ar}	R•••R
α_e-HCH	-	4	2	1	-
α_a-HCH	-	4	2	1	-
β_e-HCH	-	-	1	-	-
β_a-HCH	-	1	1	-	-
γ-HCH	-	4	1	1	-
δ_e-HCH	-	2	-	-	-
δ_a-HCH	-	4	2	1	-
ε_e-HCH	-	4	2	1	-
ε_a-HCH	-	1	2	-	-
ζ-HCH	-	3	1	1	-
η-HCH	-	4	2	1	-
θ_e-HCH	-	3	-	-	-
θ_a-HCH	-	4	1	1	-
α_e-HFH	-	3	2	-	-
α_a-HFH	-	5	3	1	-
β_e-HFH	-	2	5	-	-
β_a-HFH	-	3	3	1	-
γ-HFH	-	3	3	1	-
δ_e-HFH	2	-	1	-	-
δ_a-HFH	-	3	3	1	-
ε_e-HFH	-	3	1	1	-
ε_a-HFH	-	4	2	1	-
ζ-HFH	-	2	2	-	-
η-HFH	-	3	1	-	-
θ_e-HFH	-	2	2	-	-
θ_a-HFH	-	3	2	1	-

Table S7. Number and types of interactions of HCHs and HFHs in the site 1 of ryanodine receptor.

Isomer	X•••HO	X•••HC	X•••$\pi_{CO/N}$	R•••π_{Ar}	R•••R
α_e-HCH	-	4	2	-	-
α_a-HCH	1	5	2	-	-
β_e-HCH	1	3	4	-	-
β_a-HCH	-	3	-	-	-
γ-HCH	-	3	1	-	-
δ_e-HCH	1	4	3	-	-
δ_a-HCH	-	2	-	-	-
ε_e-HCH	-	4	2	-	-
ε_a-HCH	-	3	-	-	-
ζ-HCH	-	5	2	-	1
η-HCH	-	2	1	-	-
θ_e-HCH	-	4	2	-	-
θ_a-HCH	-	6	3	-	-
α_e-HFH	2	4	4	-	-
α_a-HFH	2	3	4	-	-
βe-HFH	2	3	5	-	-
βa-HFH	2	3	3	-	-
γ-HFH	2	4	4	-	-
δ_e-HFH	1	3	4	-	-
δ_a-HFH	2	3	5	-	-
ε_e-HFH	1	2	5	-	-
ε_a-HFH	2	3	4	-	-
ζ-HFH	1	4	4	-	1
η-HFH	-	4	2	-	-
θ_e-HFH	2	3	4	-	1
θ_a-HFH	3	4	7	-	-

APPENDIX E

Supporting Information for:

An examination of the relationship between molecular dipole moment and blood-gas partition for common anaesthetic gases

INDEX

STANDARD COORDINATES

H   Standard orientation:
Free Gibbs Energy (Hartree) = -3408.289718
```
-----------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X            Y           Z
-----------------------------------------------------------------------
   1          6          0      -0.102819     0.360968    -0.523301
   2          1          0      -0.135755     0.348512    -1.607686
   3          6          0      -1.204364    -0.558340    -0.000622
   4          9          0      -1.231299    -0.615950     1.327592
   5          9          0      -2.395775    -0.124076    -0.427818
   6          9          0      -1.029610    -1.795946    -0.476669
   7         17          0      -0.382846     2.006750     0.029356
   8         35          0       1.611354    -0.298722     0.012692
-----------------------------------------------------------------------
```

E*sag*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792883
```
-----------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X            Y           Z
-----------------------------------------------------------------------
   1          6          0       1.529131     0.199256    -0.525229
   2          1          0       1.472187     0.321875    -1.603815
   3          6          0       0.186844     0.577409     0.101733
   4          6          0      -2.068720    -0.009704     0.039353
   5          1          0      -2.171127     0.907693     0.612752
   6          8          0      -0.787041    -0.185033    -0.475259
   7          9          0       2.475122     1.031637    -0.018689
   8         17          0       1.932380    -1.468933    -0.163139
   9          9          0       0.207967     0.432362     1.439770
  10          9          0      -0.037839     1.895216    -0.131574
  11          9          0      -2.907932    -0.003759    -1.002672
  12          9          0      -2.374954    -1.064255     0.809983
-----------------------------------------------------------------------
```

E*s'a'g*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792795
```
-----------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X            Y           Z
-----------------------------------------------------------------------
   1          6          0       1.500772     0.224555    -0.534985
   2          1          0       1.372075     0.318041    -1.610257
   3          6          0       0.171973     0.515264     0.163015
   4          6          0      -2.064911    -0.142512     0.136663
   5          1          0      -2.102834     0.449488     1.047081
   6          8          0      -0.765894    -0.352980    -0.316831
   7          9          0       2.407288     1.137851    -0.100970
   8         17          0       2.052357    -1.399617    -0.167157
   9          9          0       0.291927     0.420781     1.502550
  10          9          0      -0.178100     1.798113    -0.094732
  11          9          0      -2.770753     0.466028    -0.830726
  12          9          0      -2.603603    -1.348778     0.340691
-----------------------------------------------------------------------
```

E*sag'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792552

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   1.354135   0.387545 -0.589719
     2   1   0   1.249949   0.201450 -1.655604
     3   6   0   0.153145 -0.205302   0.148901
     4   6   0   -2.177315 -0.066060   0.152969
     5   1   0   -2.067258 -0.586544   1.100474
     6   8   0   -0.966859   0.401381 -0.350305
     7   9   0   1.382051   1.724314 -0.358349
     8   17   0   2.841156 -0.356401 -0.026037
     9   9   0   0.108099 -1.541037 -0.048862
    10   9   0   0.253428 -0.013900   1.479718
    11   9   0   -2.974463   0.997506   0.293831
    12   9   0   -2.738811 -0.885129 -0.752194

E*s'a'g'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792553

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   1.357959   0.366116 -0.612400
     2   1   0   1.319671   0.149492 -1.676971
     3   6   0   0.158389 -0.280363   0.082091
     4   6   0   -2.172736 -0.170985   0.072421
     5   1   0   -2.069364 -1.051478   0.700980
     6   8   0   -0.968929   0.226112 -0.503419
     7   9   0   1.294530   1.706860 -0.414982
     8   17   0   2.856165 -0.272325   0.043647
     9   9   0   0.212315 -1.624086 -0.073881
    10   9   0   0.169348 -0.044720   1.407252
    11   9   0   -2.667216   0.846481   0.793204
    12   9   0   -3.021794 -0.414089 -0.932851

E*s'a'a'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792488

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   -1.633563   0.419341   0.004013
     2   1   0   -2.278489   0.869888   0.754889
     3   6   0   -0.185984   0.503600   0.486337
     4   6   0   1.995659 -0.084504 -0.073623
     5   1   0   2.241589   0.622719   0.714072
     6   8   0   0.650464 -0.050984 -0.429968
     7   9   0   -1.740365   1.108058 -1.160500
     8   17   0   -2.115808 -1.251377 -0.224158
     9   9   0   0.116407   1.811809   0.691107
    10   9   0   -0.077346 -0.094640   1.693907
    11   9   0   2.311105 -1.328840   0.319551
    12   9   0   2.695227   0.187842 -1.179497

E*saa*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.792427

| Center | Atomic | Atomic | Coordinates (Angstroms) | | |
Number	Number	Type	X	Y	Z
1	6	0	-1.599792	0.487120	-0.070567
2	1	0	-2.226272	1.084555	0.587721
3	6	0	-0.176640	0.473714	0.485432
4	6	0	1.982069	-0.271828	0.036645
5	1	0	2.159402	0.062788	1.055377
6	8	0	0.631423	-0.285383	-0.300404
7	9	0	-1.573747	1.046846	-1.306181
8	17	0	-2.253037	-1.139251	-0.147192
9	9	0	0.266720	1.752239	0.558598
10	9	0	-0.200275	0.015960	1.760550
11	9	0	2.433503	-1.519305	-0.128895
12	9	0	2.638610	0.523033	-0.822589

E*s'g'g'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.790414

| Center | Atomic | Atomic | Coordinates (Angstroms) | | |
Number	Number	Type	X	Y	Z
1	6	0	-1.090682	-0.552274	-0.402712
2	1	0	-1.075599	-0.768339	-1.467771
3	6	0	-0.234305	0.688436	-0.123072
4	6	0	1.933326	-0.227435	0.201011
5	1	0	1.513551	-0.534400	1.152738
6	8	0	1.061213	0.534344	-0.565564
7	9	0	-0.542135	-1.600048	0.279657
8	17	0	-2.748731	-0.306494	0.109168
9	9	0	-0.732335	1.721131	-0.806646
10	9	0	-0.260163	0.985255	1.190931
11	9	0	2.293265	-1.306218	-0.515045
12	9	0	3.035894	0.509438	0.399141

E*g'gg*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.790265

| Center | Atomic | Atomic | Coordinates (Angstroms) | | |
Number	Number	Type	X	Y	Z
1	6	0	-1.509275	0.082208	-0.464964
2	1	0	-1.585083	0.170655	-1.545825
3	6	0	-0.300151	-0.788561	-0.110872
4	6	0	1.779093	0.332265	0.133961
5	1	0	1.331502	0.851892	0.974614
6	8	0	0.845259	-0.288128	-0.686295
7	9	0	-2.630528	-0.495790	0.031647
8	17	0	-1.312178	1.696613	0.214547
9	9	0	-0.182846	-0.916141	1.222471
10	9	0	-0.510356	-2.009020	-0.626827
11	9	0	2.657603	-0.580959	0.585163
12	9	0	2.441743	1.189086	-0.649620

E*sga*   Standard orientation:
Free Gibbs Energ (Hartree) = -1148.790018

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   1.318727   0.065154   0.578502
    2   1   0   2.123562   0.677365   0.977331
    3   6   0   0.260439   0.972065 -0.064118
    4   6   0   -1.698013 -0.343579   0.101438
    5   1   0   -1.661335 -0.052924   1.146412
    6   8   0   -0.778906   0.336918 -0.688140
    7   9   0   0.725739 -0.618766   1.600708
    8   17   0   1.976631 -1.051418 -0.597469
    9   9   0   -0.199213   1.795073   0.913172
   10   9   0   0.850780   1.726619 -0.993756
   11   9   0   -2.907525 -0.083600 -0.411361
   12   9   0   -1.483184 -1.664606 -0.015049

E*g'g'g*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789663

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -1.150554 -0.132535   0.572762
    2   1   0   -0.646158 -0.473057   1.471861
    3   6   0   -0.216805   0.761695 -0.254381
    4   6   0   1.987602   0.021076   0.165138
    5   1   0   2.302123   0.980871   0.562761
    6   8   0   0.914961   0.113594 -0.703663
    7   9   0   -2.239553   0.606657   0.914469
    8   17   0   -1.637055 -1.533397 -0.365729
    9   9   0   -0.847282   1.215729 -1.334536
   10   9   0   0.117128   1.827560   0.516340
   11   9   0   1.681196 -0.798562   1.203504
   12   9   0   2.969936 -0.545853 -0.531892

E*gg'a*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789659

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   1.624323 -0.162124 -0.018011
    2   1   0   2.376428 -0.674232   0.577287
    3   6   0   0.274958 -0.878234   0.118078
    4   6   0   -1.673716   0.468511   0.016888
    5   1   0   -1.288567   0.983823   0.890340
    6   8   0   -0.718022 -0.303785 -0.631075
    7   9   0   1.985698 -0.172162 -1.323365
    8   17   0   1.490649   1.497898   0.556607
    9   9   0   0.438836 -2.134156 -0.323591
   10   9   0   -0.048265 -0.939567   1.428334
   11   9   0   -2.114996   1.344982 -0.889561
   12   9   0   -2.709952 -0.311598   0.376732

Eggg'　　　　　Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789422

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -0.993422 -0.642604   0.035019
    2   1   0   -0.564055 -1.325488 -0.691381
    3   6   0   -0.159819   0.644427   0.111096
    4   6   0   2.074894   0.006520 -0.333049
    5   1   0   2.156381   0.666047 -1.191328
    6   8   0   1.119772   0.413347   0.580784
    7   9   0   -0.985869 -1.218667   1.264087
    8   17   0   -2.642053 -0.272921 -0.451654
    9   9   0   -0.122325   1.210728 -1.117686
   10   9   0   -0.711215   1.507738   0.960301
   11   9   0   3.223418 -0.036606   0.339273
   12   9   0   1.799822 -1.247385 -0.775291

Eaaa　　　　　Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789353

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -1.493005   0.397823   0.440318
    2   1   0   -1.948931   0.322606   1.424701
    3   6   0   -0.061811 -0.137775   0.519562
    4   6   0   1.893670 -0.105677 -0.839101
    5   1   0   2.119936 -0.354185 -1.870405
    6   8   0   0.512808 -0.088132 -0.724290
    7   9   0   -1.446293   1.699396   0.058402
    8   17   0   -2.452010 -0.536634 -0.695606
    9   9   0   0.613510   0.601813   1.421176
   10   9   0   -0.096550 -1.399205   0.991981
   11   9   0   2.413499   1.096677 -0.537087
   12   9   0   2.446674 -1.006105 -0.007733

Eaag　　　　　Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789194

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   1.526015   0.299965 -0.428484
    2   1   0   1.652138   0.473679 -1.494080
    3   6   0   0.070698   0.569636 -0.034119
    4   6   0   -2.025450 -0.488236 -0.461405
    5   1   0   -2.542771 -0.857497 -1.340492
    6   8   0   -0.724418 -0.208202 -0.847221
    7   9   0   2.316490   1.153633   0.270892
    8   17   0   1.966248 -1.361627 -0.069068
    9   9   0   -0.132297   0.332972   1.267120
   10   9   0   -0.181467   1.878145 -0.247417
   11   9   0   -2.045523 -1.423826   0.503617
   12   9   0   -2.642516   0.604510   0.020292

E*a'a'g'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.789031
```
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       1.370581    0.409306   -0.549884
     2         1          0       1.494261    0.300283   -1.624328
     3         6          0       0.073655   -0.277548   -0.111564
     4         6          0      -2.247084    0.220506   -0.378759
     5         1          0      -2.890034    0.494894   -1.208328
     6         8          0      -0.941102    0.319875   -0.832199
     7         9          0       1.288168    1.726546   -0.230445
     8        17          0       2.749023   -0.320880    0.255867
     9         9          0       0.146963   -1.588988   -0.408440
    10         9          0      -0.111878   -0.166960    1.209151
    11         9          0      -2.529798   -1.025376    0.040049
    12         9          0      -2.459200    1.053358    0.654325
---------------------------------------------------------------------
```

E*ag'g*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.788386
```
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0      -1.115640   -0.036098    0.605499
     2         1          0      -0.650160   -0.557603    1.435000
     3         6          0      -0.049688    0.664093   -0.251349
     4         6          0       1.884811   -0.748064   -0.241910
     5         1          0       2.253621   -1.570685   -0.844574
     6         8          0       0.801106   -0.216514   -0.902681
     7         9          0      -1.952798    0.921594    1.084735
     8        17          0      -2.015448   -1.196265   -0.360431
     9         9          0      -0.636549    1.377086   -1.212718
    10         9          0       0.629600    1.507432    0.548296
    11         9          0       2.856530    0.162159   -0.066804
    12         9          0       1.540263   -1.199682    0.989260
---------------------------------------------------------------------
```

E*g'ga*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.788315
```
---------------------------------------------------------------------
Center      Atomic      Atomic          Coordinates (Angstroms)
Number      Number      Type          X           Y           Z
---------------------------------------------------------------------
     1         6          0       1.312261    0.142436    0.555269
     2         1          0       2.173705    0.783286    0.723426
     3         6          0       0.300996    0.900453   -0.320771
     4         6          0      -1.517095   -0.598117    0.029000
     5         1          0      -0.925898   -1.307281    0.600051
     6         8          0      -0.756224    0.192780   -0.826186
     7         9          0       0.736834   -0.159911    1.754325
     8        17          0       1.847900   -1.327506   -0.242991
     9         9          0      -0.123425    1.959665    0.399997
    10         9          0       0.962405    1.371799   -1.387043
    11         9          0      -2.227164    0.171689    0.872237
    12         9          0      -2.369681   -1.245385   -0.768864
---------------------------------------------------------------------
```

E*agg'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.787568

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   -0.762122   -0.606644   -0.162151
   2   1   0   -0.218088   -0.994763   -1.018195
   3   6   0   -0.115988   0.687921   0.354707
   4   6   0   2.138044   -0.086302   0.052228
   5   1   0   3.102109   0.126549   0.500270
   6   8   0   1.184229   0.536021   0.822493
   7   9   0   -0.750490   -1.516305   0.845211
   8   17   0   -2.417429   -0.287837   -0.662597
   9   9   0   -0.150949   1.613692   -0.619058
  10   9   0   -0.796526   1.155894   1.401312
  11   9   0   1.941455   -1.424212   0.014932
  12   9   0   2.109715   0.337979   -1.227571

E*gg'a'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.786243

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   1.413121   -0.041834   -0.386637
   2   1   0   2.396715   -0.461975   -0.194331
   3   6   0   0.362971   -0.945965   0.288847
   4   6   0   -1.537614   0.398887   -0.254447
   5   1   0   -0.970055   1.110342   -0.846376
   6   8   0   -0.928133   -0.845620   -0.154567
   7   9   0   1.173661   -0.039936   -1.725945
   8   17   0   1.400943   1.607455   0.230908
   9   9   0   0.722987   -2.213355   0.016750
  10   9   0   0.444028   -0.781180   1.621583
  11   9   0   -2.718268   0.159173   -0.829933
  12   9   0   -1.761131   0.911224   0.969236

E*g'gg'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.786186

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   0.912187   0.629072   -0.147080
   2   1   0   0.504535   1.048764   -1.063506
   3   6   0   0.180232   -0.674073   0.213284
   4   6   0   -1.900627   0.456224   -0.036548
   5   1   0   -1.566215   1.470917   0.167630
   6   8   0   -1.133713   -0.506100   0.597813
   7   9   0   0.739308   1.515289   0.876999
   8   17   0   2.617298   0.323398   -0.402101
   9   9   0   0.250850   -1.491828   -0.855104
  10   9   0   0.775585   -1.281695   1.240844
  11   9   0   -1.905338   0.257724   -1.375214
  12   9   0   -3.139675   0.285400   0.420380

E*gg'g*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.785920

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-1.095954	0.098285	-0.602338
2	1	0	-0.574046	0.247704	-1.544429
3	6	0	-0.255366	-0.762862	0.355387
4	6	0	1.703347	0.491922	-0.145671
5	1	0	1.242034	1.429929	-0.448323
6	8	0	0.939321	-0.216645	0.767040
7	9	0	-2.255951	-0.560700	-0.841555
8	17	0	-1.434292	1.669726	0.117370
9	9	0	-0.945845	-1.012387	1.469037
10	9	0	-0.039667	-1.940783	-0.266692
11	9	0	2.860629	0.733061	0.467364
12	9	0	1.946195	-0.251845	-1.248502

E*aga*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.785292

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	1.057884	0.120169	0.714660
2	1	0	1.741937	0.780576	1.242699
3	6	0	0.119315	1.000989	-0.124449
4	6	0	-1.663212	-0.556450	-0.639396
5	1	0	-2.355638	-0.652806	-1.468858
6	8	0	-0.731755	0.392705	-1.021351
7	9	0	0.337337	-0.591412	1.617816
8	17	0	2.002409	-0.947359	-0.309867
9	9	0	-0.567138	1.782738	0.733617
10	9	0	0.887250	1.803603	-0.875639
11	9	0	-1.077674	-1.744404	-0.401453
12	9	0	-2.319455	-0.200808	0.476748

E*a'g'g'*   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.784915

Center Number	Atomic Number	Atomic Type	X	Y	Z
1	6	0	-0.808617	-0.576516	-0.342399
2	1	0	-0.641868	-0.833264	-1.385100
3	6	0	-0.183056	0.796593	-0.032129
4	6	0	2.130357	0.086160	-0.240012
5	1	0	3.054453	0.578280	-0.523661
6	8	0	1.113173	0.978662	-0.498452
7	9	0	-0.242465	-1.512845	0.459851
8	17	0	-2.541468	-0.527178	-0.044600
9	9	0	-0.883271	1.744420	-0.667137
10	9	0	-0.243873	1.036598	1.284288
11	9	0	2.173508	-0.279443	1.049579
12	9	0	1.979975	-1.038697	-0.977492

Ea'g'a'   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.783418

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -1.294652   0.332954   0.176751
    2   1   0   -2.319363   0.166200   -0.146944
    3   6   0   -0.501676   -0.944576   -0.159332
    4   6   0   1.781070   -0.301710   0.371062
    5   1   0   2.636673   -0.843072   0.760364
    6   8   0   0.702099   -1.156570   0.477496
    7   9   0   -1.272713   0.509610   1.522517
    8   17   0   -0.704029   1.764290   -0.650263
    9   9   0   -1.267023   -1.973248   0.252969
   10   9   0   -0.376506   -1.045483   -1.492671
   11   9   0   2.007637   0.071496   -0.900069
   12   9   0   1.589264   0.817236   1.093942

Eagg   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.782879

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -1.056053   0.358690   -0.536428
    2   1   0   -0.765957   0.437573   -1.580645
    3   6   0   -0.416492   -0.904228   0.088410
    4   6   0   1.926862   -0.346733   -0.261950
    5   1   0   2.818498   -0.922605   -0.485234
    6   8   0   0.864723   -1.216474   -0.346538
    7   9   0   -2.406229   0.214020   -0.451681
    8   17   0   -0.590194   1.829284   0.299415
    9   9   0   -0.467240   -0.855399   1.425179
   10   9   0   -1.145320   -1.955921   -0.310930
   11   9   0   1.803515   0.652667   -1.167541
   12   9   0   2.030504   0.219368   0.950299

Iag   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.799883

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   -0.089969   0.246587   -0.205939
    2   1   0   0.296773   0.039396   -1.201098
    3   6   0   -1.395659   -0.525761   -0.023955
    4   9   0   -1.927166   -0.328923   1.179324
    5   9   0   -2.284156   -0.161691   -0.951043
    6   9   0   -1.154698   -1.833352   -0.170402
    7   17   0   -0.400228   1.982172   -0.085534
    8   8   0   0.781493   -0.187418   0.803218
    9   6   0   2.069384   -0.414319   0.395199
   10   1   0   2.653524   -0.694663   1.264564
   11   9   0   2.114373   -1.399827   -0.532866
   12   9   0   2.595991   0.681421   -0.194676

I*ga*

```
                        Standard orientation:
Free Gibbs Energy (Hartree) = -1148.799253
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X          Y          Z
---------------------------------------------------------------------
    1         6          0      -0.211771   0.223925  -0.334333
    2         1          0      -0.030556   0.178297  -1.406538
    3         6          0      -1.489066  -0.552510  -0.017919
    4         9          0      -1.780343  -0.524619   1.278482
    5         9          0      -2.515165  -0.039391  -0.700763
    6         9          0      -1.335482  -1.825645  -0.392265
    7        17          0      -0.435404   1.939431   0.091586
    8         8          0       0.803153  -0.376018   0.401335
    9         6          0       2.074309   0.048370   0.066875
   10         1          0       2.215309   1.117729   0.211411
   11         9          0       2.910970  -0.645516   0.837106
   12         9          0       2.336804  -0.251154  -1.229255
---------------------------------------------------------------------
```

I*g'a*

```
                        Standard orientation:
Free Gibbs Energy (Hartree) = -1148.797772
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X          Y          Z
---------------------------------------------------------------------
    1         6          0      -0.240217   0.209529  -0.389237
    2         1          0      -0.127651   0.155691  -1.473084
    3         6          0      -1.533831  -0.512235  -0.008890
    4         9          0      -1.750485  -0.489677   1.300903
    5         9          0      -2.573614   0.049443  -0.629152
    6         9          0      -1.455591  -1.787970  -0.405529
    7        17          0      -0.365922   1.924922   0.043329
    8         8          0       0.787593  -0.445278   0.277991
    9         6          0       2.028851  -0.341521  -0.314921
   10         1          0       1.975383  -0.376594  -1.404266
   11         9          0       2.638413   0.802936   0.052656
   12         9          0       2.757207  -1.360863   0.147246
---------------------------------------------------------------------
```

I*s'g'*

```
                        Standard orientation:
Free Gibbs Energy (Hartree) = -1148.795881
---------------------------------------------------------------------
Center     Atomic     Atomic          Coordinates (Angstroms)
Number     Number     Type         X          Y          Z
---------------------------------------------------------------------
    1         6          0      -0.416341   0.491188  -0.702818
    2         1          0      -0.838338   0.657281  -1.689205
    3         6          0      -1.236396  -0.616760  -0.028275
    4         9          0      -0.871968  -0.818285   1.240629
    5         9          0      -2.532239  -0.296230  -0.048882
    6         9          0      -1.075988  -1.758146  -0.698777
    7        17          0      -0.618875   1.998838   0.222258
    8         8          0       0.914937   0.151922  -0.909464
    9         6          0       1.711584  -0.071271   0.201423
   10         1          0       1.349648   0.430436   1.094936
   11         9          0       1.803825  -1.396100   0.431308
   12         9          0       2.936034   0.368507  -0.116542
---------------------------------------------------------------------
```

Ia'g'   Standard orientation:
Free Gibbs Energy (Hartree) = -1148.790664

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   0.419849   0.424075   0.766278
    2   1   0   0.977343   0.452852   1.697672
    3   6   0   1.021570   -0.722856   -0.059763
    4   9   0   0.556498   -0.788131   -1.302210
    5   9   0   2.348142   -0.554363   -0.116371
    6   9   0   0.783080   -1.886725   0.552418
    7   17   0   0.731986   1.963467   -0.059365
    8   8   0   -0.911966   0.259924   1.160899
    9   6   0   -1.923191   -0.022378   0.266342
   10   1   0   -2.857082   0.148974   0.791876
   11   9   0   -1.861842   0.743972   -0.836649
   12   9   0   -1.867842   -1.307331   -0.142152

Dag   Standard orientation:
Free Gibbs Energy (Hartree) = -788.819857

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   0.102359   -0.420753   -0.248139
    2   1   0   -0.267280   -0.151653   -1.236684
    3   6   0   1.478986   0.203166   -0.024264
    4   9   0   1.955575   -0.083075   1.183865
    5   9   0   2.334977   -0.254839   -0.941165
    6   9   0   1.395713   1.530251   -0.151218
    7   8   0   -0.727160   0.035430   0.771809
    8   6   0   -2.027015   0.272171   0.402961
    9   1   0   -2.589881   0.533164   1.291860
   10   9   0   -2.090915   1.279748   -0.499128
   11   9   0   -2.566612   -0.809341   -0.198462
   12   9   0   0.232202   -1.773016   -0.173113

Dga   Standard orientation:
Free Gibbs Energy (Hartree) = -788.818501

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
    1   6   0   0.236492   0.499303   0.241313
    2   1   0   0.053323   0.651926   1.304826
    3   6   0   1.554991   -0.246714   0.042731
    4   9   0   1.812499   -0.450570   -1.244788
    5   9   0   2.550739   0.470692   0.570164
    6   9   0   1.506905   -1.424752   0.667091
    7   8   0   -0.749422   -0.253158   -0.367002
    8   6   0   -2.036009   0.176188   -0.096139
    9   1   0   -2.210081   1.209805   -0.387380
   10   9   0   -2.847954   -0.640769   -0.764591
   11   9   0   -2.296013   0.049348   1.227743
   12   9   0   0.342634   1.728371   -0.356605

Dg'a   Standard orientation:
Free Gibbs Energy (Hartree) = -788.817401

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   -0.253162   0.433741   -0.366110
   2   1   0   -0.140207   0.453485   -1.452993
   3   6   0   -1.588856   -0.218112   -0.006336
   4   9   0   -1.767198   -0.279032   1.307809
   5   9   0   -2.587097   0.487153   -0.544010
   6   9   0   -1.631911   -1.456375   -0.507566
   7   8   0   0.738576   -0.300441   0.251628
   8   6   0   1.990622   -0.182559   -0.318707
   9   1   0   1.953667   -0.192967   -1.408984
  10   9   0   2.588864   0.955354   0.083646
  11   9   0   2.711711   -1.211452   0.130664
  12   9   0   -0.271447   1.720417   0.084553

Ds'g'   Standard orientation:
Free Gibbs Energy (Hartree) = -788.815255

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   0.409973   0.859343   0.533083
   2   1   0   0.819250   1.254582   1.459507
   3   6   0   1.338264   -0.250984   0.020559
   4   9   0   0.963397   -0.697532   -1.181373
   5   9   0   2.581321   0.227366   -0.079786
   6   9   0   1.343954   -1.271959   0.874998
   7   8   0   -0.874056   0.442108   0.823129
   8   6   0   -1.645039   -0.045352   -0.221223
   9   1   0   -1.321519   0.308072   -1.195843
  10   9   0   -1.629736   -1.392308   -0.198976
  11   9   0   -2.901717   0.348337   0.021183
  12   9   0   0.406729   1.844144   -0.418624

Dgg'   Standard orientation:
Free Gibbs Energy (Hartree) = -788.813402

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
   1   6   0   -0.416271   0.546315   -0.805838
   2   1   0   -0.838916   0.581751   -1.807296
   3   6   0   -1.344187   -0.299384   0.080428
   4   9   0   -1.034598   -0.199771   1.376524
   5   9   0   -2.602262   0.110308   -0.081163
   6   9   0   -1.268428   -1.587133   -0.271995
   7   8   0   0.862385   0.043999   -0.955581
   8   6   0   1.592277   -0.310892   0.170605
   9   1   0   1.080047   -1.019842   0.815357
  10   9   0   2.717795   -0.856238   -0.300971
  11   9   0   1.919825   0.779809   0.887350
  12   9   0   -0.413568   1.805232   -0.280254

D*a'g'* Standard orientation:
Free Gibbs Energy (Hartree) = -788.811079
```
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.359030    0.793841    0.682728
   2          1          0       0.901782    1.050415    1.589858
   3          6          0       1.180013   -0.274571   -0.057472
   4          9          0       0.720261   -0.542214   -1.273747
   5          9          0       2.433248    0.183764   -0.176685
   6          9          0       1.217156   -1.400661    0.657503
   7          8          0      -0.905921    0.416100    1.118639
   8          6          0      -1.842050   -0.126938    0.261788
   9          1          0      -2.797065   -0.084507    0.774925
  10          9          0      -1.909441    0.539873   -0.903203
  11          9          0      -1.545916   -1.410556   -0.029297
  12          9          0       0.302547    1.891049   -0.123032
---------------------------------------------------------------------
```

S*gg* Standard orientation:
Free Gibbs Energy (Hartree) = -927.165191
```
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.138325    0.066696   -0.212311
   2          1          0       0.521900    0.150787   -1.231005
   3          6          0      -0.245030   -1.398367   -0.006157
   4          9          0      -0.639684   -1.640512    1.242436
   5          9          0      -1.232524   -1.752566   -0.837083
   6          9          0       0.812346   -2.170512   -0.266331
   7          8          0       1.110128    0.378833    0.754759
   8          6          0       2.208851    1.070400    0.253962
   9          1          0       2.821078    1.329627    1.111169
  10          9          0       2.939831    0.254113   -0.583006
  11          6          0      -1.036331    1.036857   -0.079454
  12          9          0      -0.572861    2.294045   -0.187497
  13          9          0      -1.656740    0.931034    1.092915
  14          9          0      -1.931324    0.850408   -1.053266
  15          1          0       1.909712    1.941301   -0.327974
---------------------------------------------------------------------
```

S*sg* Standard orientation:
Free Gibbs Energy (Hartree) = -927.158997
```
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
   1          6          0       0.187479   -0.004332   -0.701369
   2          1          0       0.471437   -0.361067   -1.691419
   3          6          0       1.508731    0.317814    0.010601
   4          9          0       1.346156    0.640598    1.301716
   5          9          0       2.346371   -0.720124   -0.050667
   6          9          0       2.091162    1.356352   -0.594502
   7          8          0      -0.575072    1.152479   -0.925848
   8          6          0      -1.247852    1.753001    0.143547
   9          1          0      -1.357387    2.798307   -0.127166
  10          9          0      -2.506553    1.215706    0.269894
  11          6          0      -0.592407   -1.157412   -0.058143
  12          9          0       0.150779   -2.271232   -0.065742
  13          9          0      -0.942113   -0.907283    1.207387
  14          9          0      -1.698709   -1.395103   -0.760639
  15          1          0      -0.733020    1.618271    1.090525
---------------------------------------------------------------------
```

Mgaa   Standard orientation:
Free Gibbs Energy (Hartree) = -1310.466432

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   -0.845395 -0.000000   0.472341
     2   1   0   -1.120270   0.000001   1.522287
     3   6   0   0.681512   0.000001   0.382291
     4   8   0   1.094003 -0.000000 -0.891801
     5   6   0   2.522663 -0.000001 -1.062281
     6   1   0   2.956013 -0.893505 -0.619784
     7   1   0   2.679107 -0.000000 -2.134358
     8   1   0   2.956015   0.893500 -0.619782
     9   17   0   -1.500971 -1.458371 -0.267193
    10   17   0   -1.500974   1.458369 -0.267195
    11   9   0   1.147637   1.081245   1.073139
    12   9   0   1.147639 -1.081239   1.073143

Mgag   Standard orientation:
Free Gibbs Energy (Hartree) = -1310.466116

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   -0.736649   0.107999 -0.516555
     2   1   0   -0.708058   0.115244 -1.601124
     3   6   0   0.644222 -0.306917 -0.001786
     4   8   0   1.556590   0.556765 -0.489185
     5   6   0   2.908404   0.299593 -0.067066
     6   1   0   3.219194 -0.695951 -0.374715
     7   1   0   3.508832   1.050158 -0.567206
     8   1   0   2.992984   0.408627   1.011039
     9   17   0   -1.128616   1.734532   0.036717
    10   17   0   -1.954959 -1.056747 -0.001984
    11   9   0   0.663698 -0.360376   1.352093
    12   9   0   0.898439 -1.579468 -0.422375

Mgg'g   Standard orientation:
Free Gibbs Energy (Hartree) = -1310.461402

Center   Atomic   Atomic   Coordinates (Angstroms)
Number   Number   Type   X   Y   Z
----
     1   6   0   -0.498458   0.202629 -0.451891
     2   1   0   -0.218974   0.312053 -1.494563
     3   6   0   0.617033 -0.547061   0.298400
     4   8   0   1.788909   0.126956   0.396134
     5   6   0   2.368793   0.535049 -0.848338
     6   1   0   1.826450   1.383687 -1.265178
     7   1   0   3.381331   0.839789 -0.609398
     8   1   0   2.394168 -0.292812 -1.554831
     9   17   0   -0.700558   1.815918   0.232121
    10   17   0   -1.999517 -0.718047 -0.404620
    11   9   0   0.235398 -0.830902   1.547279
    12   9   0   0.796027 -1.731972 -0.358573

```
Mgga                    Standard orientation:
Free Gibbs Energy (Hartree) = -1310.460963
---------------------------------------------------------------------
Center     Atomic     Atomic           Coordinates (Angstroms)
Number     Number     Type         X           Y           Z
---------------------------------------------------------------------
    1          6          0       0.633429   -0.145761   -0.582698
    2          1          0       0.833704   -0.400568   -1.618280
    3          6          0      -0.894532   -0.243180   -0.369480
    4          8          0      -1.361918   -0.322401    0.891400
    5          6          0      -1.093570    0.791174    1.757176
    6          1          0      -1.317518    1.731255    1.258260
    7          1          0      -1.756329    0.653273    2.604230
    8          1          0      -0.058047    0.775535    2.089052
    9         17          0       1.448642   -1.327156    0.438336
   10         17          0       1.261422    1.485994   -0.319595
   11          9          0      -1.463408    0.790516   -1.051290
   12          9          0      -1.286539   -1.378730   -0.983492
```

Table S1. Weighted dipole moment (Db), blood-gas partition coefficient (K_{bg}), and MAC(%) for the studied fluorinated anaesthetics.

Molecule	Dipole moment	K_{bg}	MAC (%)
Halothane	1.49	2.40	0.74
Enflurane	1.51	1.90	1.58
Isoflurane	1.93	1.40	1.15
Sevoflurane	2.56	0.65	2.00
Desflurane	1.97	0.45	5.80
Methoxyflurane	2.04	12.00	0.20

Table S2. Conformational Gibbs free energies (in kcal mol^{-1}) and population (%, in parenthesis), molecular dipole moments (μ, in Db), bond lengths (in Å), and dihedral angles (degrees) obtained for the main conformers of the studied fluorinated anesthetics.[a]

C$\phi_1\phi_2\phi_3$	G$^0_{rel}$ (%)	μ	O–C$_1$	C$_2$–O	C$_1$–Faxial	C$_2$–R^2	Φ_1	ϕ_2	Φ_3
H	-- (100)	1.49	-	-	-	-	-	-	58.29
E*sag*	0.0(21)	1.26	1.39	1.36	1.34	1.36	17.26	176.77	56.14
E*s'a'g*	0.1(19)	0.45	1.39	1.37	1.34	1.35	340.46	185.33	57.62
E*sag'*	0.2(14)	1.06	1.39	1.37	1.34	1.35	20.12	176.57	300.55
E*s'a'g'*	0.2(14)	1.81	1.39	1.37	1.34	1.35	342.37	184.84	301.67
E*s'a'a'*	0.3(13)	2.37	1.39	1.36	1.34	1.36	340.40	182.66	180.03
E*saa*	0.3(13)	2.51	1.39	1.36	1.34	1.36	19.33	174.25	178.90
E*s'g'g'*	1.6(2)	1.48	1.39	1.38	1.34	1.35	353.25	282.10	302.91
E*g'gg*	1.6(1)	1.78	1.39	1.38	1.35	1.35	327.29	107.34	55.14
E*sga*	1.8(1)	2.52	1.39	1.37	1.34	1.36	17.39	69.43	175.99
E*g'g'g*	2.0(1)	2.06	1.38	1.38	1.36	1.36	306.15	276.46	62.44
E*gg'a*	2.0(1)	2.97	1.39	1.37	1.35	1.35	31.72	255.70	180.00
E*ggg'*	2.2(0)	2.39	1.38	1.39	1.36	1.35	53.48	84.38	295.59
E*aaa*	2.2(0)	1.11	1.39	1.37	1.34	1.35	163.58	159.42	178.13
E*aag*	2.3(0)	3.25	1.39	1.38	1.34	1.35	164.43	160.17	54.65
E*a'a'g'*	2.4(0)	2.95	1.39	1.38	1.34	1.35	195.91	199.90	302.19
E*ag'g*	2.8(0)	2.78	1.38	1.39	1.36	1.35	166.53	277.08	66.14
E*g'ga*	2.9(0)	2.74	1.39	1.37	1.34	1.35	306.06	49.93	169.72
E*agg'*	3.3(0)	2.28	1.37	1.39	1.35	1.34	166.27	51.31	297.27
E*gg'a'*	4.2(0)	2.69	1.39	1.37	1.35	1.35	53.86	309.42	199.45
E*g'gg'*	4.2(0)	2.45	1.38	1.38	1.35	1.35	293.20	37.14	291.53
E*gg'g*	4.4(0)	2.77	1.39	1.38	1.35	1.35	68.27	320.62	64.09
E*aga*	4.8(0)	0.80	1.38	1.38	1.35	1.35	164.80	58.03	171.75
E*a'g'g'*	5.0(0)	2.46	1.38	1.39	1.35	1.34	192.38	308.32	313.10
E*a'g'a'*	5.9(0)	0.57	1.38	1.38	1.35	1.35	193.94	299.14	198.47
E*agg*	6.3(0)	2.84	1.38	1.39	1.35	1.34	168.88	56.53	36.67
I*ag*	0.0(61)	1.72	1.37	1.40	1.35	1.77	177.22	136.85	58.40
I*ga*	0.4(31)	2.11	1.38	1.39	1.36	1.78	60.05	169.45	59.41
I*g'a*	1.3(7)	2.91	1.38	1.39	1.35	1.77	322.35	154.39	59.46
I*s'g'*	2.5(1)	1.84	1.39	1.39	1.35	1.78	335.79	295.71	68.55
I*a'g'*	5.8(0)	2.48	1.38	1.40	1.35	1.77	193.80	306.44	72.24
D*ag*	0.0(76)	1.89	1.37	1.39	1.35	1.36	174.93	143.71	56.48
D*ga*	0.9(18)	2.02	1.38	1.38	1.36	1.37	57.98	170.26	57.35
D*g'a*	1.5(5)	3.13	1.38	1.38	1.35	1.36	318.43	157.60	57.24
D*s'g'*	2.9(1)	1.59	1.39	1.38	1.35	1.37	336.92	296.68	67.23
D*gg'*	4.1(0)	1.86	1.39	1.38	1.35	1.36	54.79	309.10	73.28
D*a'g'*	5.5(0)	2.61	1.38	1.39	1.35	1.36	194.64	306.13	71.52
S*gg*	0.0(100)	2.56	1.39	1.41	1.38	1.53	51.09	133.73	54.89
S*gg'*	3.9(0)	1.71	1.40	1.40	1.37	1.54	30.89	285.23	72.63
M*gaa*	0.00(58)	1.62	1.44	1.34	-	1.37	61.22	180.00	180.00
M*gag*	0.20(42)	2.62	1.44	1.35	-	1.36	59.25	179.07	57.60
M*gg'g*	3.16(0)	3.60	1.43	1.36	-	1.37	74.78	303.19	66.44
M*gga*	3.43(0)	1.73	1.44	1.35	-	1.36	46.81	62.13	162.67

Table S3. Important electron delocalization interactions obtained through NBO analysis (in kcal mol^{-1}) in the gas phase at the B3LYP/aug-cc-pVTZ level.

C$\phi_1\phi_2\phi_3$	$\sigma_{C3H}\rightarrow$ σ^*_{C4F}	$\sigma_{C3F/Cl}\rightarrow$ σ^*_{C4F}	$\sigma_{C3F/Cl}\rightarrow$ σ^*_{C4X}	$\sigma_{C3O}\rightarrow$ σ^*_{C4F}	$\sigma_{C4H}\rightarrow$ σ^*_{C3F}	$\sigma_{C4H}\rightarrow$ σ^*_{C3O}	$\sigma_{C4F}\rightarrow$ $\sigma^*_{C3F/Cl}$	$\sigma_{C4F}\rightarrow$ σ^*_{C3O}	$\sigma_{C4X}\rightarrow$ σ^*_{C3F}	$\sigma_{C4X}\rightarrow$ σ^*_{C3O}
H	-	1.57	1.75	-	3.80	-	2.39	-	3.01	-
Esag	-	-	1.26	0.93	3.79	-	-	1.25	2.59	-
Es'a'g	-	-	1.26	0.93	3.79	-	-	1.26	2.59	-
Esag'	-	0.91	-	-	3.79	-	1.30	-	-	2.37
Es'a'g'	-	0.91	-	-	3.79	-	1.31	-	-	2.38
Es'a'a'	-	0.93	1.28	-	-	3.34	1.30	-	2.59	-
Esaa	-	0.94	1.27	-	-	3.35	1.29	-	2.60	-
Es'g'g'	-	0.99	-	-	3.46	-	1.16	-	-	2.29
Eg'gg	-	-	1.29	0.99	3.55	-	-	1.09	2.41	
Esga	-	1.00	1.35	-	-	3.43	1.14	-	2.33	-
Eg'g'g	-	-	1.30	0.86	3.34	-	-	1.23	2.46	-
Egg'a	-	0.96	1.29	-	-	3.23	1.17	-	2.35	-
Iag	3.29	2.28	-	1.24	-	-	1.42	0.97	-	-
Iga	3.23	2.29	-	1.18	-	-	1.47	0.93	-	-
Ig'a	3.24	2.29	-	1.16	-	-	1.43	0.93	-	-
Is'g'	3.67	2.42	-	0.89	-	-	1.37	1.14	-	-
Dag	2.99	1.03	-	1.12	-	-	0.76	0.71	-	-
Dga	2.94	1.02	-	1.08	-	-	0.79	0.70	-	-
Dg'a	2.95	1.02	-	1.06	-	-	0.77	0.69	-	-
Ds'g'	3.33	1.11	-	0.83	-	-	0.73	0.85	-	-
Sgg	7.66	-	-	2.44	-	-	-	1.74	-	-
Mgaa	-	-	3.40	-	-	3.46	-	-	5.22	-
Mgag	-	-	1.66	-	4.09	-	-	-	2.62	2.26