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Easy chairs: the conformational preferences of polyfluorocyclohexanes†

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Polyfluorocyclohexanes present an interesting challenge to our current understanding of fundamental organic chemistry. In part to improve molecular mechanics methods and facilitate drug design, a systematic survey of cyclohexanes with up to six fluorine substituents has been carried out, using theoretical methods. The preferred conformers are determined by delocalization effects, such as hyperconjugation, and do not necessarily follow the common assumption that substituents prefer the equatorial position. Thus, accurate *ab intio* results, which can capture electronic effects, are required. The lowest energy conformations of fluorocyclohexane, difluorocyclohexanes (six structural isomers), trifluorocyclohexanes (nine structural isomers), tetrafluorocyclohexanes (seventeen structural isomers), pentafluorocyclohexane (ten structural isomers), and hexafluorocyclohexanes (seven structural isomers) have been determined; relative energies, geometries, dipole moments, and population distributions are reported. We present a model for predicting the relative energies of polyfluorocyclohexane conformers based on the number of 1,2; 1,3; and 1,4 interactions present. The model is based on the energies from the difluorocyclohexanes; the correlation coefficient (R^2) between computed relative energies and model relative energies is 0.967.

1 Introduction

Advances in the pharmaceutical and agrochemical industries, as well as the development of new high-performance materials, rely on understanding the role of fluorine in conformational preferences.[1–8] Fundamental studies of polyfluoro hydrocarbons[9–11] are crucial; the conformation of flexible hydrocarbon groups, such as alkyl chains or rings, may determine how a drug interacts with its substrate. Several fluorines can be used in combination to stabilize or destabilize the ''active'' conformation of a molecule.[12–18] Analogously, fluorination can have a drastic effect on the efficacy of agrochemicals.[19] Thus, fundamental studies not only have implications for understanding biological activity, they are valuable tools in the drug design toolbox.

Substitution of a fluorine atom for a hydrogen is a common motif in drug design.[20–22] Fluorine is an attractive choice because the C–F bond is the strongest single bond to carbon in organic chemistry (bond dissociation energy = 105 kcal mol^{-1}). This makes C–F bonds essentially unreactive in pharmaceutical compounds and inhibits metabolic elimination of the drug.[1,5,23,24] The fluorine atom is relatively similar in size to hydrogen, but a fluorine substitution alters the dipole moment of the molecule in question and can significantly alter its conformational preferences.[1,5,23,24]

Due to its electronegativity, a fluorine atom is also a reasonable substitute for a hydroxyl group. Since fluorine cannot act as a hydrogen bond donor, substitution of F for OH gives insight into the influence of hydrogen bonding on structures and biological activity.[5,23] For example, hydrogen bonds involving the 4(*R*)-hydroxyproline OH group do not contribute to the stability of the collagen trimer.[25] In fact, substituting 4(*R*)-fluoroproline for 4(*R*)-hydroxyproline strengthened the collagen trimer.[26] Dipole–dipole interactions, and the attendant conformational preferences, are more important than hydrogen bonding in this instance.[26–29]

The effect of multiple fluorines on small-molecule conformational preferences has been investigated.[30,31] 1,2-difluoroethane has received much attention because the expected *anti* conformation is not the minimum energy structure; it instead adopts a *gauche* configuration of the two C–F bonds.[32–44] The usual steric arguments cannot explain this preference – hyperconjugative effects and electrostatics must be taken into consideration as well.[11] Although the *gauche* effect in difluoroethane is well studied, analogous effects in larger systems, such as cyclohexanes, are not well understood.

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Substituted cyclohexane conformations are covered extensively in organic chemistry courses, and students are taught that substituents always prefer the equatorial position. Fluorocyclohexane does have the fluorine atom in an equatorial position, although experimental and theoretical studies indicate that the preference is weak (E_{axial}–$E_{\mathrm{equatorial}} \approx$ 0.1–0.2 kcal mol^{-1}).[45–51] The preference for equatorial substituents is often explained in terms of steric repulsion, but that force is negligible in fluorocyclohexane.[47] The relative energies should be understood on the basis of electronic effects, such as hyperconjugation. The best computational study on fluorocyclohexane to date used MP2/6-311G-(2df,2pd) and MP2/6-311++G(d) geometry optimizations.[49] Extrapolation to the CBS limit was performed using CCSD(T) energy points. The extrapolated energies are in good agreement with experiment, but the relative energies from the geometry optimizations are qualitatively incorrect. Difluorocyclohexane has several possible substitution patterns, and their conformational preferences are also determined by delocalization effects. There are three experimental conformational studies of *trans*-1,2-difluorocyclohexane,[52–54] and a single study on *trans*-1,4-difluorocyclohexane.[55] However, difluorocyclohexanes have been studied computationally using molecular mechanics,[55,56] *ab initio*,[57–59] and DFT[51,54,57,59,60] methods. Studies of tri-, tetra-, penta-, and hexa- fluorocyclohexanes are limited. Experimental and computational results are available for 1,2,3,4-tetrafluoro,[9] 1,2,4,5-tetrafluoro,[3] and 1,2,3,4,5,6-hexafluoro[2] isomers. In addition, the hexafluoro isomers have been investigated at the MP2/6-31++G level of theory.[61] Given the enormous interest in polyfluoro hydrocarbons, an improved computational treatment of fluorinated cyclohexane geometries is relevant and timely. We present a systematic study of mono-, di-, tri-, tetra-, penta-, and hexa- fluoro cyclohexanes, including their geometries and relative energies using accurate *ab initio* methods.

2 Methods

All geometries were optimized using a second order Møller-Plesset perturbation theory[62,63] (MP2) with a restricted Hartree–Fock (RHF) reference wave function and a double-ξ quality basis set with polarization functions (DZP).[64,65] Finally, we computed single point energies at the density fitted MP2 (DF-MP2) level of theory, using a density-fitted SCF reference with a polarized triple-ξ quality Dunning basis set (cc-pVTZ).[66] In several test cases, reoptimization at the DF-MP2/cc-pVTZ level of theory did not change the relative energies substantially and thus DZP/MP2 geometries were used. All geometry optimizations were carried out in the Gaussian 09 program package.[67] The DF-MP2 single points were computed with the PSI4 program package.[68] For a given number of fluorines, conformations more than 10 kcal mol^{-1} above the minimum energy structural isomer were excluded from our results. We did not consider structures with geminal fluorines.

Zero-point vibrational corrections are expected to be very small,[69] since we are simply altering the conformation of the molecules. We did not search for the ring inversion transition states, since a cyclohexane ring inversion is a multistep process. It bypasses the expected planar transition state and proceeds through a series of lower-energy intermediates (skew and boat conformations).[51,70]

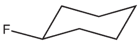
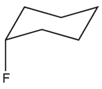
Polyfluorinated cyclohexanes are named according to the IUPAC convention.[71] One subustituent is chosen as the reference point, and its position is preceded by "*r*". The remaining substituent positions are preceded by "*c*" or "*t*" depending on whether they are *cis* or *trans* to the reference group, respectively. For instance, a diaxial chair 1,2-difluorocyclohexane would be *r*-1,*t*-2-difluorocyclohexane according to the IUPAC convention.

3 Results and discussion

3.1 Fluorocyclohexane

The fluorine atom can be either axial or equatorial in chair fluorocyclohexane. A ring flip interconverts these two conformations. The chair equatorial form is the lowest in energy at both levels of theory used in this study, although the preference is weak. Fluorine has the weakest preference for the equatorial position of all the common substituents in organic chemistry, aside from deuterium.[72] This is in agreement with available experiments.[45,47,49,50] Our computational results are displayed in Table 1. There are four possible boat conformations, but these lie at least 5.5 kcal mol^{-1} above both of the

Table 1 Relative energies of fluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lowest energy conformer, and dipole moments (Debye) are based on the SCF/cc-pVTZ density matrix

Species	Figure	Relative Energy	Boltzmann Ratio 298 K	Dipole Moment (Debye)
Fluorocyclohexane		0.000	1.00	2.35
		0.029	0.95	1.98

chair conformers at either level of theory. Thus, the boat conformation is not competitive with the chair conformation.

3.2 Difluorocyclohexane

For chair difluorocyclohexane, there are three substitution patterns (1,2; 1,3; and 1,4), each of which can have *cis* or *trans* stereochemistry. Accounting for the conformations accessible *via* ring flips, there are nine different chair conformations. For *trans*-1,3-difluorocyclohexane and *cis*-1,4-difluorocyclohexane, a ring flip results in an identical configuration. For *cis*-1,2-difluorocyclohexane, a ring flip results in the enantiomer of the original configuration. The remaining six conformations come in pairs which interconvert through ring inversion. The relative energies for each substitution pattern are shown in Table 2. The boat conformations are not competitive, lying at least 4.5 kcal mol^{-1} above the chair conformations for each substitution pattern.

Our results are in agreement with experimental data, which are only available for the *trans*-1,2 isomer. The most recent NMR studies indicate that the diaxial conformation lies 0.10 kcal mol^{-1} below the diequatorial one.[54] This agrees with our computational ordering, although the relative energies differ by 0.2 kcal mol^{-1}. The small difference in relative energies may be due to vibrational effects, which were not considered in this study.

Interestingly, diaxial conformations are preferred for *trans*-1,2 and *trans*-1,4 difluorocyclohexane. The diequatorial conformers of these species are higher in energy, with Δ*E*s much larger than in fluorocyclohexane. However, *cis*-1,3 difluorocyclohexane follows the rules taught in introductory organic chemistry, and the diequatorial conformation is preferred by 1.2 kcal mol^{-1}.

3.3 Trifluorocyclohexane

For chair trifluorocyclohexanes, there are three substitution patterns (1,2,3 [Table 3]; 1,2,4 [Table 4]; and 1,3,5 [Table 5]), with several stereochemical arrangements possible for each. Each of the nine substitution patterns has a pair of conformers linked by a ring flip, resulting in eighteen different chair conformations. Due to symmetry, no ring flips result in identical configurations or enantiomers. With one exception, the boat conformations lie at least 3 kcal mol^{-1} above the relevant chair conformations. The single exception is *r*-1, *c*-3, *c*-5-trifluorocyclohexane; the latter boat conformation is only 1.8 kcal mol^{-1} above the triaxial chair conformation. However, since this boat conformation lies 5.2 kcal mol^{-1} above the

Table 2 Relative energies of difluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lowest energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to diaxial *trans*-1,4-difluorocyclohexane

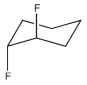
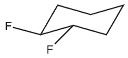
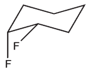
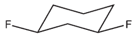
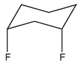
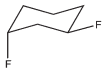
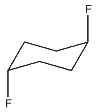
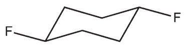
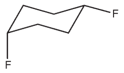
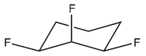
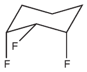
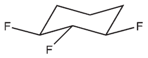
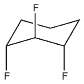
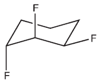
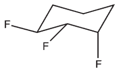
Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
trans-1,2		0.000	1.00	0.80	2.431
		0.326	0.58	3.82	2.757
cis-1,2		A ring flip yields the enantiomer.		3.39	2.861
cis-1,3		0.000	1.00	2.55	1.698
		1.174	0.14	3.85	2.872
trans-1,3		A ring flip yields an identical configuration.		2.50	1.028
trans-1,4		0.000	1.00	0.00	0.000
		1.202	0.13	0.00	1.202
cis-1,4		A ring flip yields an identical configuration.		3.05	0.785

Table 3 Relative energies of 1,2,3-trifluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to 1 eq, 3 eq, 5 ax-trifluorocyclohexane

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *c*-2, *c*-3		0.000	1.00	3.75	3.386
		1.899	0.04	4.94	5.284
r-1, *t*-2, *c*-3		0.000	1.00	4.39	3.305
		0.948	0.20	2.17	4.253
r-1, *t*-2, *t*-3		0.000	1.00	2.41	2.629
		0.212	0.70	4.19	2.841

lowest energy triequatorial conformation, the boat conformations are not competitive.

The lowest energy conformers of the trifluorocyclohexanes are not possible to predict using the simple rules taught in introductory organic chemistry courses. Maximizing the number of equatorial fluorines would fail for five of the nine molecules studied here. The rule does happen to work in the case of 1,3,5-trifluorocyclohexane, although it is certainly not helpful for the 1,2,3 and 1,2,4 substitution patterns. Furthermore, the ΔEs for trifluorocyclohexanes vary widely. All-axial and all-equatorial *r*-1, *t*-2, *t*-4-trifluorocylohexanes are nearly isoenergetic, while all-axial *r*-1, *c*-3, *c*-5-trifluorocyclohexane lies over 3 kcal mol^{-1} above its all-equatorial conformational isomer. If conformational preferences were solely determined by sterics, as is commonly taught, the ΔEs should be fairly similar.

3.4 Tetrafluorocyclohexane

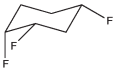
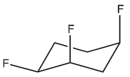
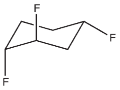
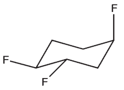
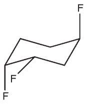
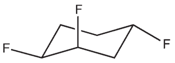
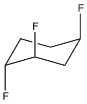
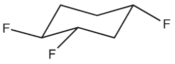
For chair tetrafluorocyclohexanes, there are three different substitution patterns (1,2,3,4 [Table 6]; 1,2,3,5 [Table 7]; and 1,2,4,5 [Table 8]), with numerous stereochemical arrangements for each, yielding a total of seventeen different structural isomers. Ring flips on the *r*-1, *c*-2, *c*-3, *c*-4-tetrafluorocyclohexane and *r*-1, *t*-2, *t*-3, *c*-4-tetrafluorocyclohexane species result in their enantiomers. Because of this, we could not make comparisons with the experimental data or structures for *r*-1, *c*-2, *c*-3, *c*-4-tetrafluorocyclohexane.[9] Likewise, ring flips on *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane, *r*-1, *c*-2, *t*-4, *t*-5-tetrafluorocyclohexane, and *r*-1, *c*-2, *c*-4, *c*-5-tetrafluorocyclohexane result in configurations identical to the originals. Again, this symmetry prevented us from making any useful comparisons with experimental data on the *r*-1, *c*-2, *c*-4, *c*-5 isomer.[3] The remaining twelve molecules have pairs of chair conformations, linked by ring inversions. The boat conformations lie at least 2.5 kcal mol^{-1} above the relevant chair conformations, with one exception. That exception is *r*-1, *t*-2, *c*-3, *c*-5-tetrafluorocyclohexane, since one of the boat conformations lies only 1.2 kcal mol^{-1} above the triaxial chair conformation. However, this boat conformation is over 3 kcal mol^{-1} above the lowest energy chair conformer. Thus, the boat conformers are not competitive with the chair conformations for tetrafluorocyclohexanes.

The all-equatorial conformations, when allowed by stereochemistry, are always preferred for the tetrafluorocyclohexanes in this study (*r*-1, *t*-2, *c*-3, *t*-4; *r*-1, *t*-2, *c*-3, *c*-5; and *r*-1, *t*-2, *t*-4, *t*-5). However, the simple organic rules break down for the other species. This is evident for species such as *r*-1, *c*-2, *c*-3, *t*-5-tetrafluorocyclohexane. Simplistic schemes cannot account for its relatively large (3.2 kcal mol^{-1}) conformational energy difference, since both conformers have two axial and two equatorial substituents.

3.5 Pentafluorocyclohexane

For chair pentafluorocyclohexanes, there is a single substitution pattern (1,2,3,4,5 [Table 9]), with ten possible stereochemical arrangements. Each has a pair of two chair conformers, linked by ring inversion. Due to symmetry, no ring flips result in identical configurations or enantiomers. The boat conformers lie at least 2 kcal mol^{-1} above the related chair conformations, with one exception. The *r*-1, *t*-2, *c*-3, *t*-4, *c*-5-pentafluorocyclohexane all-axial conformation lies only 0.2 kcal mol^{-1} below a boat conformation of the molecule. However, both of these conformers lie at least 2 kcal mol^{-1} above the lowest energy conformer (all-equatorial). Again, the boat conformations are not competitive with the chair conformations.

Table 4 Relative energies of 1,2,4-trifluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to 1 eq, 3 eq, 5 ax-trifluorocyclohexane

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *c*-2, *c*-4		0.000	1.00	3.57	1.562
		1.306	0.11	4.60	2.868
r-1, *t*-2, *c*-4		0.000	1.00	1.71	0.470
		0.289	0.61	3.90	0.758
r-1, *c*-2, *t*-4		0.000	1.00	2.23	0.082
		1.251	0.12	1.79	1.333
r-1, *t*-2, *t*-4		0.000	1.00	1.93	1.574
		0.099	0.85	2.25	1.674

Surprisingly, the textbook rules correctly predict the lowest energy isomer for eight of the ten pentafluorocyclohexanes studied. They only fail for the *r*-1, *t*-2, *t*-3, *t*-4, *t*-5 and *r*-1, *c*-2, *t*-3, *c*-4, *c*-5 pentafluorocyclohexanes, indicating that electrostatic repulsions may play a more significant role in highly fluorinated cyclohexanes.

Table 5 Relative energies of 1,3,5-trifluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to 1 eq, 3 eq, 5 ax-trifluorocyclohexane

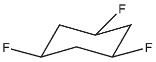
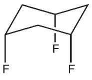
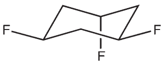
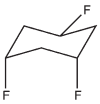
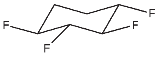
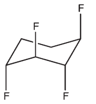
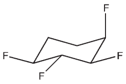
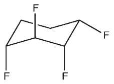
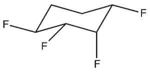
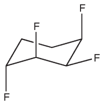
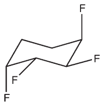
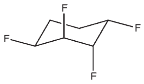
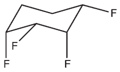
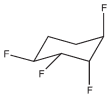
Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *c*-3, *c*-5		0.000	1.00	1.67	1.559
		3.451	0.003	5.70	5.010
r-1, *c*-3, *t*-5		0.000	1.00	1.96	0.000
		1.210	0.13	3.78	1.210

Table 6 Relative energies of 1,2,3,4-tetrafluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *t*-2, *c*-3, *t*-4		0.000	1.00	3.72	3.474
		1.124	0.15	0.96	4.599
r-1, *t*-2, *c*-3, *c*-4		0.000	1.00	4.75	2.919
		1.283	0.11	2.94	4.202
r-1, *t*-2, *t*-3, *t*-4		0.000	1.00	3.15	3.212
		0.636	0.34	3.33	3.848
r-1, *c*-2, *t*-3, *t*-4		0.000	1.00	3.76	1.762
		1.151	0.14	0.70	2.913
r-1, *c*-2, *c*-3, *c*-4		A ring flip yields the enantiomer.		5.13	5.533
r-1, *t*-2, *t*-3, *c*-4		A ring flip yields the enantiomer.		3.47	2.212

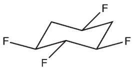
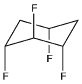
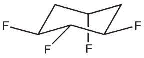
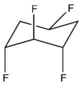
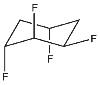
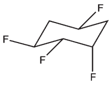
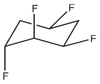
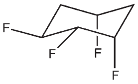
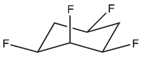
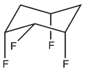
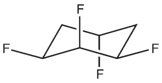
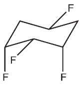
3.6 Hexafluorocyclohexane

For chair hexafluorocyclohexanes, there is a single substitution pattern (1,2,3,4,5,6 [Table 10]), with seven possible stereochemical arrangements. The *r*-1, *t*-2, *c*-3, *c*-4, *t*-5, *c*-6-hexafluorocyclohexane species yields an identical configuration under ring flip. A ring flip on *r*-1, *t*-2, *t*-3, *t*-4, *t*-5, *c*-6-hexafluorocyclohexane yields the enantiomer of the original species; this stereoisomer of hexafluorocyclohexane has recently been synthesized.[2] The boat conformations are not competitive, lying at least 1.5 kcal mol^{-1} above the relevant chair conformations, with one exception. For *r*-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6-hexafluorocyclohexane, one of the boat conformations lies between the lowest energy conformation (all-equatorial chair) and the related chair conformation (all-axial). However, this boat conformation is 2.5 kcal mol^{-1} above the lowest energy conformation, so the boat conformations are not competitive with the lowest energy chair conformations for any of the polyfluorocyclohexane species studied in this work.

With hexafluorocyclohexane, the qualitative organic chemistry rules work for all the stereoisomers studied in this paper. They correctly predict the lower energy chair conformation in all seven molecules, providing further evidence that electrostatic repulsions overwhelm electronic effects for highly fluorinated cyclohexanes.

Our results differ somewhat from previous computations, carried out only on the hexafluorocyclohexanes.[61] At the MP2/6-31++G level of theory, the 1eq, 2ax, 3ax, 4eq, 5eq, 6eq-hexafluorocyclohexane is the lowest energy structure overall. In our work, the lowest energy structure is 1eq, 2ax, 3eq, 4eq,

Table 7 Relative energies of 1,2,3,5-tetrafluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane

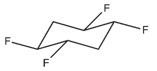
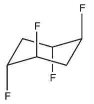
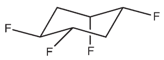
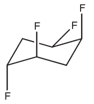
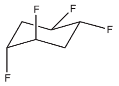
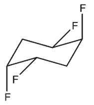
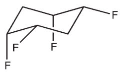
Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *t*-2, *c*-3, *c*-5		0.000	1.00	2.33	2.797
		2.410	0.02	3.80	5.207
r-1, *t*-2, *c*-3, *t*-5		0.000	1.00	4.11	1.159
		1.053	0.17	1.85	2.211
r-1, *t*-2, *t*-3, *c*-5		0.000	1.00	2.54	1.582
		0.057	0.91	2.30	1.639
r-1, *t*-2, *t*-3, *t*-5		0.000	1.00	1.89	1.212
		1.611	0.07	4.95	2.822
r-1, *c*-2, *c*-3, *c*-5		0.000	1.00	3.34	2.845
		4.172	0.001	6.34	7.017
r-1, *c*-2, *c*-3, *t*-5		0.000	1.00	2.17	0.454
		3.182	0.005	3.65	3.636

5ax, 6eq-hexafluorocyclohexane. However, at the cc-pVTZ/DF-MP2 level of theory, these two differ in energy by 0.25 kcal mol^{-1}. At the MP2/6-31++G level, they differ by 2.72 kcal mol^{-1}. For all other structures, their overall energies are 0.9 to 4.5 kcal mol^{-1} higher than our results. The present work should be significantly more accurate, since we used a larger basis set, with extensive polarization functions.

3.7 Accuracy

We computed the DF-MP2/cc-pVTZ single point energies to refine the MP2/DZP energies. In general, the MP2/DZP energies agree with the DF-MP2/cc-pVTZ energies to within 0.7 kcal mol^{-1}, which is within the intrinsic error of the MP2 method. The differences between the DZP and cc-pVTZ results are slightly larger for the *r*-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6-hexafluorocyclohexane species, but still less than 1.2 kcal mol^{-1}. These discrepancies do not alter the identity of the lowest energy conformation for each species, except in the case of *r*-1, *t*-2, *t*-4, *t*-5-tetrafluorocyclohexane (Table 8). The slight energy difference in this case makes it impossible to reliably determine the lower energy conformation without further investigation, even though the DZP and cc-pVTZ results differ by less than 0.2 kcal

Table 8 Relative energies of 1,2,4,5-tetrafluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *t*-2, *t*-4, *c*-5		0.000	1.00	0.00	1.803
		0.558	0.39	0.00	2.361
r-1, *t*-2, *t*-4, *t*-5		0.000	1.00	2.92	1.335
		0.146	0.78	2.84	1.481
r-1, *t*-2, *c*-4, *t*-5		A ring flip yields an identical configuration.		2.98	0.000
r-1, *c*-2, *t*-4, *t*-5		A ring flip yields an identical configuration.		0.00	0.296
r-1, *c*-2, *c*-4, *c*-5		A ring flip yields an identical configuration.		4.90	3.429

mol^{-1}. However, we are confident that these methods are sufficient to correctly identify the lowest energy conformations of the rest of the polyfluorocyclohexane species.

3.8 Dipole moments

The cc-pVTZ/SCF dipole moments of all structures are included in Table 1 through 10. Dipole moments predicted at this level of theory are expected to be qualitatively reasonable. By symmetry, the dipole moments of a number of structures are identically zero: *trans*-1,4-difluorocyclohexane; *r*-1, *t*-2, *t*-4, *c*-5 tetrafluoro; *r*-1, *c*-2, *t*-4, *t*-5 tetrafluoro; *r*-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6 hexafluoro; and the *r*-1, *t*-2, *t*-3, *t*-4, *c*-5, *c*-6-hexafluorocyclohexanes.

Among the polar structures, the smallest predicted dipole moment (μ = 0.70 debye) occurs for the higher-energy (1eq, 2ax, 3ax, 4eq) conformation of *r*-1, *c*-2, *t*-3, *t*-4-tetrafluorocyclohexane, shown in Table 6. This C_2 structure has nearly balancing equatorial C → F dipoles and similarly nearly balancing axial C → F dipoles. However, among the molecules studied, the largest predicted dipole moment (μ = 6.64 Debye) is for the higher-energy (1ax, 2eq, 3ax, 4eq, 5ax) conformation of *r*-1, *c*-2, *c*-3, *c*-4, *c*-5-pentafluorocyclohexane shown in Table 10. In that structure, the three axial C → F bonds are essentially parallel.

This latter observation highlights the correlation between dipole moment and overall relative energy. The *r*-1, *c*-2, *c*-3, *c*-4, *c*-5 isomer with the largest dipole moment has the highest overall energy (7.23 kcal mol^{-1}) of the twenty chair pentafluorocyclohexanes. A similar trend is seen for the tetrafluoro structures. The *r*-1, *c*-2, *c*-3, *c*-5 structure with three parallel axial C → F dipoles has the largest dipole moment (μ = 6.34 Debye) and the highest energy (7.02 kcal mol^{-1}) of all twenty-nine tetrafluoro structures (Table 6 through 8). A nearly analogous relationship is predicted among the eighteen trifluoro structures; the triaxial *r*-1, *c*-3, *c*-5 structure has the largest dipole moment (μ = 5.70 Debye), and the second highest overall energy (5.01 kcal mol^{-1}, Table 5). For the trifluoro structures, the truly highest energy structure (*r*-1, *c*-2, *c*-3 with two parallel C → F dipoles) also has a large overall dipole moment of 4.94 Debye (Table 3). Clearly, the more polar structures lie rather high energetically; in other words, structures with unbalanced axial fluorines tend to be destabilized and have large dipole moments.

3.9 Thermodynamics

We have presented relative energies of pairs of conformers since, under normal circumstances, the various structural isomers cannot interconvert at room temperature. However, some synthetic methods (involving higher temperatures) may result in a mixture of structural isomers of polyfluorocyclohexanes. Thus, in the last column of each table, the overall relative energies for each set of compounds are presented. This gives a

Table 9 Relative energies of 1,2,3,4,5-pentafluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to 1eq, 2ax, 3eq, 4eq, 5ax-pentafluorocyclohexane

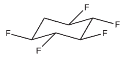
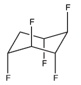
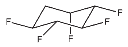
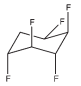
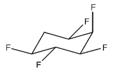
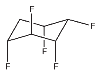
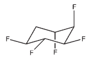
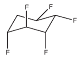
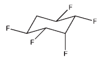
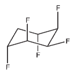
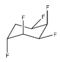
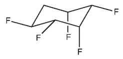
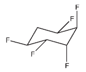
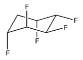
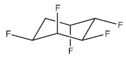
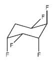
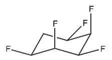
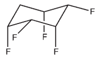
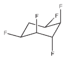
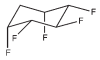
Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *t*-2, *c*-3, *t*-4, *c*-5		0.000	1.00	2.13	2.059
		2.922	0.01	1.97	4.981
r-1, *t*-2, *c*-3, *t*-4, *t*-5		0.000	1.00	3.83	0.859
		1.457	0.09	1.46	2.316
r-1, *t*-2, *c*-3, *c*-4, *c*-5		0.000	1.00	3.32	1.774
		3.277	0.004	4.50	5.052
r-1, *t*-2, *c*-3, *c*-4, *t*-5		0.000	1.00	3.72	0.069
		1.601	0.07	3.38	1.670
r-1, *t*-2, *t*-3, *t*-4, *c*-5		0.000	1.00	1.53	1.138
		1.198	0.13	2.26	2.337
r-1, *t*-2, *t*-3, *t*-4, *t*-5		0.000	1.00	3.24	1.950
		1.266	0.12	4.42	3.216
r-1, *t*-2, *t*-3, *c*-4, *c*-5		0.000	1.00	1.70	0.718
		0.359	0.55	3.90	1.077
r-1, *c*-2, *c*-3, *t*-4, *t*-5		0.000	1.00	2.11	0.000
		1.858	0.04	1.91	1.858
r-1, *c*-2, *c*-3, *c*-4, *c*-5		0.000	1.00	4.97	4.561
		2.669	0.01	6.64	7.229

Table 9 (*Continued*)

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *c*-2, *t*-3, *c*-4, *c*-5		0.000	1.00	2.92	2.676
		0.092	0.86	5.63	2.768

measure of the relative thermodynamic favorability of all of the structural isomers, and indicates which species may most likely be formed in high temperature experiments.

For fluorocyclohexane, the axial and equatorial isomers are nearly isoenergetic (Table 1). However, the difluorocyclohexane structural isomers have a 3 kcal mol^{-1} range of overall relative energies (Table 2). The lowest energy conformation is diaxial *trans*-1,4-difluoro, probably because the opposing C → F dipoles are balanced. The diequatorial conformation of this molecule lies 1.2 kcal mol^{-1} higher, which is much larger than the axial–equatorial difference in fluorocyclohexane, not to mention being in the opposite direction. The highest energy chair difluorocyclohexane is diaxial *cis*-1,3-difluoro, in which the C → F bond dipoles are parallel and in close proximity to one another. The *cis*-1,2-difluoro and diequatorial *trans*-1,2-difluoro species are also quite high in energy.

In the trifluoro family (Tables 3–5), the lowest energy structure is (1ax, 3ax, 5eq) *r*-1, *c*-3, *t*-5-trifluoro. It is not readily apparent why this is the lowest energy arrangement. Based on the results from the difluoro family, one would expect a structure with a diaxial-1,4 motif to be the lowest. Indeed, the lower energy conformation (1ax, 2eq, 4ax) of *r*-1, *c*-2, *t*-4-trifluoro is nearly isoenergetic with *r*-1, *c*-3, *t*-5-trifluoro. In this case, the "additional" fluorine on diaxial *trans*-1,4-difluorocyclohexane is equatorial. Adding an axial fluorine, as in *r*-1, *t*-2, *t*-4-trifluorocyclohexane, does not result in a low energy structure. The highest energy trifluoro structure can be inferred from the difluoro pattern; a diaxial 1,3 substitution pattern characterizes the highest energy difluoro structure, and the addition of a third fluorine in between the first two results in the highest energy chair trifluorocyclohexane (1ax, 2eq, 3ax) *r*-1, *c*-2, *c*-3-trifluoro.

With four fluorines (Tables 6–8), it is again difficult to rationalize the lowest energy structure, *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane. It does not follow any discernable pattern from the trifluoro family. However, structures with a diaxial-1,4 motif, where all of the other fluorines are equatorial, are relatively low energy structures (*r*-1, *c*-2, *t*-3, *t*-4; *r*-1, *c*-2, *c*-3, *t*-5; and *r*-1, *c*-2, *t*-4, *t*-5). The highest energy chair tetrafluoro structure is easily deduced based on trifluoro results. In the three-fluorine family, the highest energy structure was (1ax, 2eq, 3ax) *r*-1, *c*-2, *c*-3-trifluoro, and the highest energy tetrafluoro structure is generated by adding an axial fluorine at the five position. This species has three parallel C → F bond dipoles, and the highest overall relative energy in the chair tetrafluoro family.

There are twenty chair pentafluoro structures, two of which have very low overall energies (Table 9). The lowest energy structure features the *trans*-1,4 motif, along with three equatorial fluorines: (1eq, 2ax, 3eq, 4eq, 5ax) *r*-1, *c*-2, *c*-3, *t*-4, *t*-5-pentafluorocyclohexane. The second lowest structure is (1eq, 2eq, 3eq, 4ax, 5ax) *r*-1, *t*-2, *c*-3, *c*-4, *t*-5-pentafluoro; it is similar to the lowest energy tetrafluoro structure, with the addition of one more equatorial fluorine. As before, the highest energy structure is easier to rationalize than the lower energy structures; (1ax, 2eq, 3ax, 4eq, 5ax) *r*-1, *c*-2, *c*-3, *c*-4, *c*-5 pentafluoro is similar to the highest energy tetrafluoro structure, with the addition of an equatorial fluorine at the fourth carbon. This means there are three parallel C → F bond dipoles, with two equatorial fluorines in between.

Finally, twelve hexafluoro structures were examined in this study. There were two structures with very low overall energies: (1eq, 2eq, 3ax, 4eq, 5eq, 6ax) *r*-1, *t*-2, *t*-3, *t*-4, *c*-5, *c*-6 and (1eq, 2eq, 3eq, 4eq, 5ax, 6ax) *r*-1, *t*-2, *c*-3, *t*-4, *t*-5, *c*-6. The former is the lowest in energy, and has a *trans*-1,4 motif, with equatorial fluorines at the other four positions. The latter is slightly higher, and is similar to *r*-1, *t*-2, *c*-4, *t*-5-tetrafluorocyclohexane with the addition of two additional equatorial fluorines. The highest energy structure considered here is the all-axial *r*-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6, in which the six fluorine atoms are in close proximity to each other. The expected highest-energy isomer, *r*-1, *c*-2, *c*-3, *c*-4, *c*-5, *c*-6 hexafluoro, fell outside the 10.0 kcal mol^{-1} cutoff, and was not considered further in this study.

3.10 Model energetics

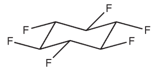
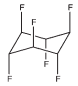
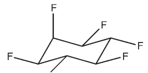
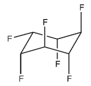
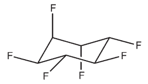
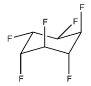
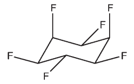
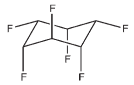
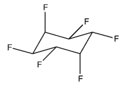
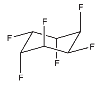
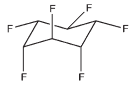
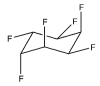
Is it possible to rationalize the thermodynamic stabilities of polyfluorocyclohexanes using a model based on the difluoro isomers? Initially, we based a model based solely on the difluorocyclohexanes. The molecules were grouped according to base stereochemistry (*e.g.* 1,2-difluoro and 1,3-difluoro fall into different groups), and, for each group the all-equatorial conformation was chosen as the reference point. Values were assigned to each type of pairwise fluorine–fluorine interaction: 1,2 diaxial; 1,2 axial, equatorial ; 1,3 diaxial; 1,3 axial, equatorial; 1,4 diaxial; and 1,4 axial, equatorial. The resulting equation (in kcal mol^{-1}) is

$$\Delta E_{\text{intial}} = -0.326 \times a_1a_2 + 0.104 \times a_1e_2 + 1.174 \times a_1a_3 - 0.67 \times a_1e_3 - 1.202 \times a_1a_4 - 0.435 \times a_1e_4 \quad (1)$$

The total energy is given by

$$E_{\text{total}} = E_{\text{all equatorial}} + \Delta E_{\text{initial}} \quad (2)$$

Table 10 Relative energies of 1,2,3,4,5,6-hexafluorocyclohexane conformers in kcal mol^{-1} at the DF-MP2/cc-pVTZ level of theory at MP2/DZP geometries. The leftmost carbon atom is position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios are relative to the lower energy conformer, and dipole moments are based on the SCF/cc-pVTZ density matrix. The overall relative energies are with respect to 1eq, 2eq, 3ax, 4eq, 5eq, 6ax-hexafluorocyclohexane

Species	Figure	Relative Energy Pairs	Boltzmann Ratio 298 K	Dipole Moment (Debye)	Relative Energy Overall
r-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6		0.000	1.00	0.00	2.295
		4.680	0.0004	0.00	6.975
r-1, *t*-2, *c*-3, *t*-4, *c*-5, *c*-6		0.000	1.00	2.77	1.309
		3.770	0.002	2.64	5.079
r-1, *t*-2, *c*-3, *t*-4, *t*-5, *c*-6		0.000	1.00	3.06	0.247
		2.001	0.03	2.83	2.248
r-1, *t*-2, *c*-3, *c*-4, *c*-5, *c*-6		0.000	1.00	4.72	4.024
		1.662	0.06	4.65	5.686
r-1, *t*-2, *t*-3, *t*-4, *c*-5, *c*-6		0.000	1.00	0.00	0.000
		2.839	0.01	0.00	2.839
r-1, *t*-2, *c*-3, *c*-4, *t*-5, *c*-6		A ring flip yields an identical configuration.		3.98	2.095
r-1, *t*-2, *t*-3, *t*-4, *t*-5, *c*-6		A ring flip yields the enantiomer.		2.82	1.906

In this equation, a_1a_2 is the number of 1,2-diaxial pairs in the molecule, a_1e_2 is the number of 1,2 axial, equatorial pairs in the molecule, and so forth. The negative terms indicate stabilizing interactions, while positive terms indicate destabilizing interactions, all relative to the all-equatorial conformation. A chart depicting the relationship between the computed energies and this initial model is shown in Fig. 1. The low correlation coefficient (R^2 = 0.701) and the large RMS error (0.99 kcal mol^{-1}) of this initial model clearly highlight its shortcomings.

We adjusted the parameters slightly, in order to improve the model's accuracy. Each parameter was increased by about 0.2 kcal mol^{-1}; this results in a new model with the equation

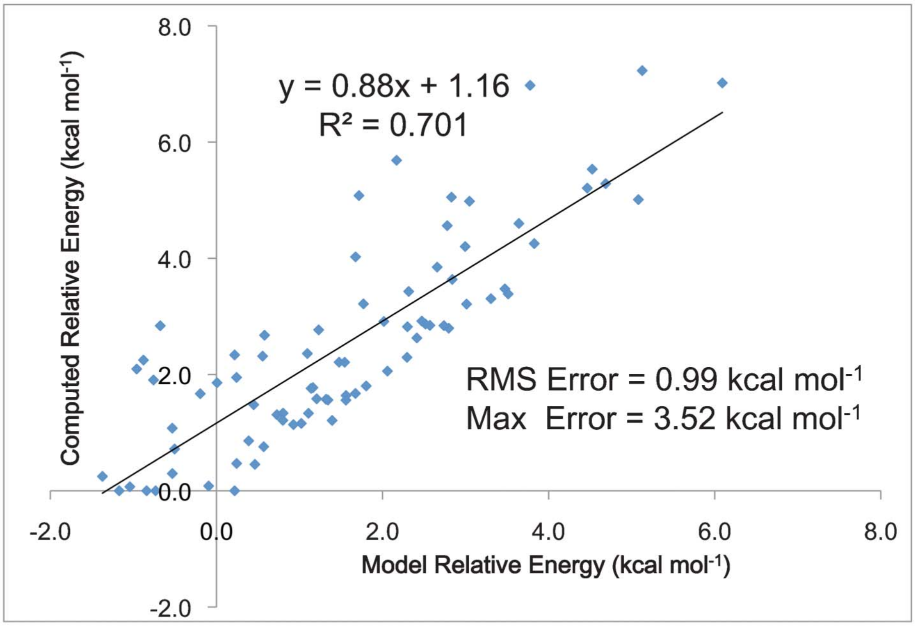


Fig. 1 Initial model of polyfluorocyclohexane relative energies. The parameters were based solely on the relative energies of the difluorocyclohexanes.

$$\Delta E_{\text{adjusted}} = 0.1 \times a_1a_2 + 0.3 \times a_1e_2 + 1.4 \times a_1a_3 - 0.5 \times a_1e_3 - 1.0a_1a_4 - 0.2 \times a_1e_4 \quad (3)$$

Again, the total energy is

$$E_{\text{total}} = E_{\text{all equatorial}} + \Delta E_{\text{adjusted}} \quad (4)$$

This slight adjustment dramatically improves the correlation coefficient ($R^2 = 0.96$), and reduces the RMS error to 0.28 kcal mol^{-1} (Fig. 2). Moreover, the model accurately predicts the relative energies of sets of polyfluorocyclohexane conformers, with the exception of nearly isoenergetic conformers ($\Delta E < 0.3$ kcal mol^{-1}). Since all of the parameters were adjusted upwards, this indicates that the pairwise stabilizing effects (a_1a_2, a_1e_3, a_1a_4, and a_1e_4) are not cooperative. The stabilizing contribution from each of these types of interaction decreases as the overall number of interactions increases. However, the

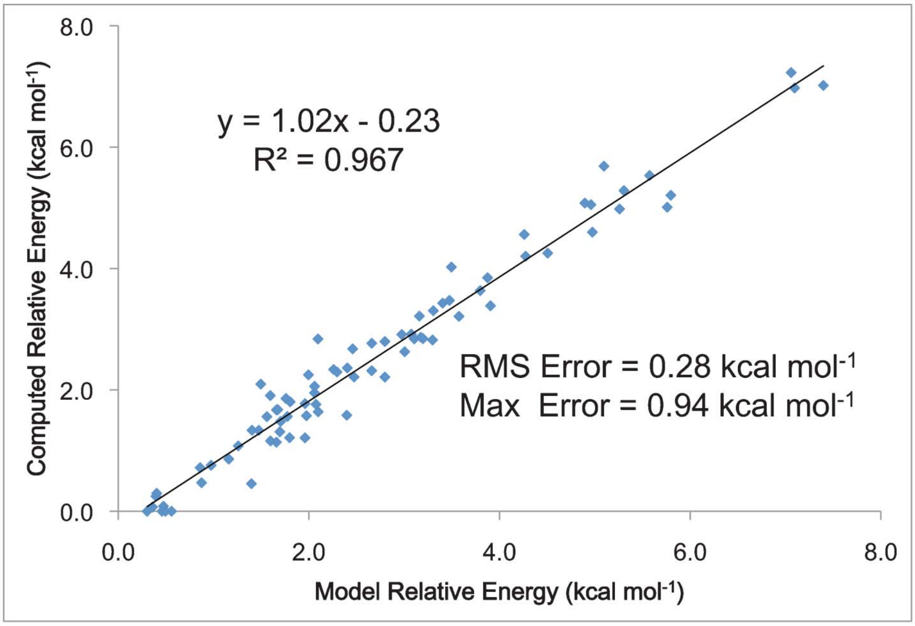


Fig. 2 Improved model of polyfluorocyclohexane relative energies. The parameters from the initial model were adjusted to better fit the whole set of polyfluorocyclohexane relative energies.

destabilizing effects (a_1e_2 and a_1a_3) are cooperative. The destabilizing contribution from each of these types of interaction increases as the overall number of interactions increases. This simple model indicates that the sometimes confusing energetics of polyfluorocyclohexanes can be explained in terms of pairwise interactions between the fluoromethylene (CHF) subunits.

3.11 Relevance and future directions

In order to aid in interpretation of the relative energies, we have provided the Boltzmann ratios for pairs of conformers in each table. For instance, axial fluorocyclohexane lies 0.029 kcal mol^{-1} above the equatorial conformation at the DF-MP2/cc-pVTZ level of theory. According to Boltzmann statistics, at 298 K, there are nineteen molecules in the axial conformation for every twenty in the equatorial conformation (1.00 : 0.95 equatorial–axial ratio). In contrast, diaxial 1,3-difluorocyclohexane is predicted to lie 1.174 kcal mol^{-1} above the diequatorial conformation. Thus, there are approximately three diaxial molecules for every twenty diequatorial molecules (1.00 : 0.14 diequatorial–diaxial ratio).

These relative energies should aid in developing more accurate molecular mechanics force fields. Existing force fields may not accurately capture the complex electronic effects which govern conformational preferences in polyfluorocyclohexanes. However, we have demonstrated that these complex effects can be modelled using a simple equation. In addition, drug design programs often utilize molecular building blocks to create candidates which are tailored to the active sites of enzymes. Understanding which conformations of polyfluorocyclohexanes are energetically favorable, and how large that energetic preference is, should make it easier to find viable drug candidates using computer aided drug design.

4 Conclusions

We have completed a systematic survey of polyfluorocyclohexanes with up to six fluorines. The conformational relative energies have been determined at the DF-MP2/cc-pVTZ level of theory, using MP2/DZP geometries. We have shown that simplistic schemes for determining the preferred conformer, such as those taught in introductory organic chemistry courses, are not generally applicable. The conformational energies are determined by a combination of steric and electronic effects. Our results should be useful in developing more accurate molecular mechanics force fields, and in computer-aided drug design. It is also our goal to inspire further *ab initio* work to unravel the precise role of sterics, electrostatics, and hyperconjugation in this important class of molecules.

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