The Conformational Preferences of Polychlorocyclohexanes

Journal:	*New Journal of Chemistry*
Manuscript ID	NJ-ART-06-2019-002997.R1
Article Type:	Paper
Date Submitted by the Author:	26-Oct-2019
Complete List of Authors:	Gong, Shida; Qingdao University, Chen, Yuan; South China Normal University Luo, Qiong; South China Normal University, School of Chemistry and Environment Schaefer, Henry; University of Georgia, Computational Chemistry

The Conformational Preferences of Polychlorocyclohexanes

Shida Gong,[a,b] Yuan Chen,[a] Qiong Luo,[a]* Henry F. Schaefer[c]*

[a] MOE Key Laboratory of Theoretical Chemistry of Environment, Center for Computational Quantum Chemistry, South China Normal University, Guangzhou 510631, P. R. China

[b] School of Chemistry and Chemical Engineering, Qingdao University, Qingdao 266071, P. R. China

[c] Center for Computational Chemistry, University of Georgia, Athens, GA 30602, USA

Email: Qiong Luo: luoqiong@scnu.edu.cn Henry F. Schaefer: ccq@uga.edu

Abstract

Quantitative conformational analysis (Eliel, Stereochemistry of Organic Compounds, Wiley-Interscience, 1994) has been with us at least as long as Pitzer's landmark 1937 paper (J. Am. Chem. Soc., 1937, 59, 276) on ethane. Cyclohexanes have played a critical role in the quest for understanding. Notably, 1, 2, 3, 4, 5, 6 hexachlorocycloxane ($C_6H_6Cl_6$) was apparently synthesized for the first time by Michael Faraday in 1825 (Philos. T. R. Soc. B, 1825, 115, 440). The γ-1, 2, 3, 4, 5, 6 hexachlorocycloxane molecule subsequently acquired the common name lindane. Although banned or limited by many countries in 2006, nearly one billion tons of lindane have been manufactured and employed, mostly in agriculture, but also for treatment of human diseases such as lice. Although not as well characterized as lindane, other chlorocyclohexanes have been made and to some degree characterized. The pioneering experimental conformational studies by LeFevre and coworkers (J Chem. Soc. B, 1970, 1608) of 1,2 dichlorocyclohexane, 1,1,2 trichlorocyclohexane, and 1,2,3,4,5,6 hexachlorocyclohexane are particularly noteworthy. The chlorocyclohexanes have also played a role in the development of molecular mechanics methods by Allinger and coworkers (J. Am. Chem. Soc., 1983, 105, 1716 and 1723). In the present research, we report the first systematic studies of all the chlorocyclohexanes, excluding those with two chlorines attached to a single carbon atom. We make careful comparisons with previous experimental and computational studies. A simple system is established to estimate the relative energies of the different isomers of a particular molecular species. Predicted dipole moments range from identically zero to 5.7 debye.

1 Introduction

Chlorinated chemicals are discharged into our biosphere by plants, marine organisms, insects, bacteria, fungi, mammals, and other natural processes.[1] Chlorine organic compounds have been found to be important to the higher plants and ferns. For example, chlorinated chlorophyll is a potential important part of photosystem 1, and highly biologically active 4-chloroindoleacetic acid is found from vegetables such as peas and in the cancerostatic maytansinoids.[2] Cyclohexanes are commonly used as organic solvents in chemical technology.[3,4] Cyclohexane is also a saturated six-carbon cyclic hydrocarbon that may be considered as a structural unit of adamantane.

Various mono- and poly-chlorine substituted cyclohexanes have been reported.[5,6,7,8,9,10,11,12,13] Chlorocyclohexanes can be detected as a product in the catalytical oxidation of cyclohexane, suggesting free-radical mechanisms.[14,15] Hexachlorocyclohexane (HCH) is a name used collectively for the eight isomers of 1,2,3,4,5,6-hexachlorocyclohexane. It was reported in 1998 that the most populated isomers are α-(60 to 70 %), β-(5 to 12%), γ-(10 to 12 %), δ-(6 to 10 %), and ε– (3 to 4 %) isomers, respectively.[16] Among them, the γ-isomer is called lindane. HCHs are broadly used and easily detected pesticides, which has led to global environmental problems, even in the sparsely inhabited Arctic.[16] HCHs are involved in many chemical reactions, including elimination, degradation, hydrolysis, reduction, and oxidation processes.[17,18,19,20,21]

Quantitative conformational analysis[22] has been with us at least as long as Pitzer's landmark paper on ethane.[23] For the substituted cyclohexanes, students could find that the favorable conformations prefer to have the maximized equatorial substituent groups in the organic chemistry textbooks.[24] Specifically, chlorocyclohexane with an equatorial chlorine atom has weak preference rather than chlorocyclohexane with an axial chlorine atom ($E_{\text{axial}} - E_{\text{equatorial}}$ = 0.1 – 0.2 kcal/mol) experimentally and theoretically.[25,26,27,28,29,30] For the conformation preferences of polychlorocyclohexanes, the existing investigations have given deep insights. Based on the experimental dipole moments and Kerr constants, Calderbank et. al. suggested the predominant existing conformations of the di-, tri-, and hexachlorocyclohexanes. They found that the chair conformation and the twist boat conformation can coexist for the dichlorohexanes and trichlorocyclohexanes, although the twist boat form for them are predominant. For the α−, β−, γ−, and δ-hexachlorocyclohexanes, the predominant conformations are twist boat-chair mixture/distorted, traditional chair, distorted chair, and twist boat-chair mixture/distorted, respectively.[31] Abraham and Rossetti concluded that the attraction between the 1-halogen and the 3-hydrogen atoms gives the most of the additional stabilization to the diaxial 1,4-dichlorocyclohexane.[32] Allinger's group developed the molecular mechanics method, induced dipole moment and energy (IDME), to confirm and predict the dipole moments and the conformational energies of the mono- and dihalogencyclohexanes as well as many other organic compounds, giving good agreement with the experiment results.[28, 33] Wiberg studied the conformational properties of dihalocyclohexanes by using several DFT and post-HF methods. In that theoretical work, he found the axial-axial, axial-equatorial, and axial-axial conformations are preferable for 1,2-, 1,3-, and 1,4-dichlorocyclohexanes by at most 3.7 kcal/mol at the QCISD/6-311+G(2df,p) level of theory.[34]

The conformational analysis of very complicated molecules can now be conducted in a seamless way by modern experimental (NMR, ECD, and VCD) and theoretical (DFT and post-HF) methods.[35] Thus, it is meaningful to study the conformations of the common molecules in more detail to give deeper insight.

In 2013, we carried out a systematical study on the conformational preferences of polyfluorocyclohexanes, and propose a scheme in which the relative energies of all isomers are based on the of 1,2; 1,3; and 1,4 interactions present.[36] Now we want to use this scheme for the polychloro hydrocarbons to examine the different roles of these dichloro interactions and the differences between the difluoro and dichloro interactions with respect to the cyclohexanes. As far as we know, no systematic investigation of the whole series of polychlorohydrocarbons has been performed until now. Therefore, we perform a theoretical study on the geometries, dipole moments, and relative energies of mono-, di-, tri-, tetra-, penta-, and hexa-chlorocyclohexanes, using reliable ab initio methods.

2 Methods

All stationary points were optimized using second order Møller-Plesset perturbation theory[37,38] (MP2) with a restricted Hartree–Fock (RHF) reference wave function and a double-ζ quality basis set with polarization functions (DZP).[39,40] Frequency analysis were performed to confirm that all optimized stationary points are the local minimum of the potential energy surface. Single point energies were computed at the MP2 level of theory, with a larger polarized triple-ζ quality Dunning basis set (cc-pVTZ).[41] Reoptimization at the MP2/cc-pVTZ level of theory in selected examples did not change the relative energies substantially and thus MP2/DZP geometries were used. We use DZP basis set to be consistent with our previous research concerning polyfluorocyclohenanes[36] in 2013 to do the comparison. We have also done the test calculation on the di- and hexachlorocyclohenanes at MP2/cc-pVTZ//MP2/cc-pVDZ dual levels of theory, namely using the optimized geometries obtained by the consistent cc-pVDZ basis set. The relative energy differences are as small as less than -0.03 kcal/mol, relative to the results at the MP2/cc-pVTZ//MP2/DZP dual levels of theory. Structural optimizations were carried out in the Gaussian 16 program package.[42] We did not consider structures with geminal chlorines, due to the strong repulsion between two electronegative chlorine atoms.

We anticipated zero-point vibrational corrections to be minor,[43] since we are simply altering the conformation of the molecules. We have also tried to add the MP2/DZP zero-point energies to the MP2/cc-pVTZ single point energies of the polychlorocyclohenanes isomers and found that the mean difference is less than -0.1 kcal/mol, which has no qualitative change to the conformational preferences of current results in this work. 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).[44,45] In this research polychlorinated cyclohexanes are named according to the IUPAC convention.[46] One substituent is chosen as the reference point, and its position is preceded by "r". The remaining substituent locations are preceded by "c" or "t" depending on whether they are cis or trans to the reference group, respectively. As an example, a diaxial chair 1,2-dichlorocyclohexane is designated r-1, t-2-dichlorocyclohexane according to the IUPAC convention.

3 Results and discussion

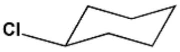
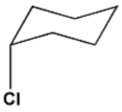
3.1 Chlorocyclohexane

The chair chlorocyclohexane conformations with an axial or equatorial chlorine atom have been optimized. The comformation with an equatorial chlorine atom is lower-lying, similar with the fluorocyclohexane, but the preference for the equatorial position is 0.25 kcal/mol which is nearly ten times larger than that of fluorine.[36] Our calculated conformation energy (0.3 kcal/mol) reported in Table 1 are in agreement with the available experimental observations: 0.26 (Raman),[27] 0.40 (IR), [30] 0.43 (NMR), [47] 0.51 (Microwave),[27] and 0.65 (Electron diffraction)[26] kcal/mol and theoretical predictions (0.38 kcal/mol by MM2 method and 0.43 kcal/mol by MP2 method).[28,30] The theoretical dipole moments for the axial- and equatorial chlorocyclohexane in this work, 2.25 and 2.60 debye (Table S1 in Electronic Supplementary Information), are close to the existing calculated values by MM2 method, 2.17 and 2.41 debye,[28] as well as the experimental values, 2.05 and 2.30 debye.[48] Four boat chlorocyclohexane conformations are also optimized, but lying at least 6.4 kcal/mol above the chair conformers at either level of theory. Thus, the boat conformation is not competitive with the chair conformation. The priority of chair conformations can be explained by the larger repulsive strength of C-C σ bond than that of C-H σ bond for saturated hydrocarbons.[49] Thus we mainly focus on the chair conformations in this work.

3.2 Dichlorocyclohexane

For dichlorocyclohexane, there are a total of nine different chair conformations including three substitution patterns (1,2; 1,3; and 1,4). Although each of substitution pattern has cis or trans stereochemistry, and each stereochemistry includes two conformations via ring flips, the trans-1,3-dichlorocyclohexane and cis-1,4-dichlorocyclohexane have identical configurations after the ring flips. The cis-1,2-dichlorocyclohexane has the enantiomer of the original configuration after a ring flip. The remaining six conformations are shown in pairs in which the two conformers can interconvert after the ring inversion. The relative energies for the pair conformers and for all conformers, are displayed in Table 2. The boat conformations lie at least ~6 kcal/mol above the chair conformations.

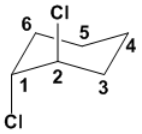
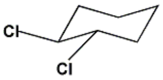
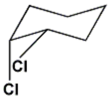
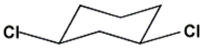
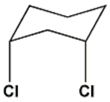
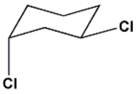
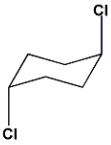
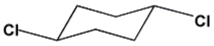
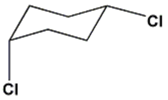
Table 1 Relative energies of chlorocyclohexane conformers in kcal/mol.*

Species	Structure	Relative Energy	Boltzmann Ratio
Chlorocyclohexane		0.0	1.000
		0.3	0.654

*These energies were evaluated at the MP2/cc-pVTZ level of theory using optimized MP2/DZP structures. The leftmost carbon atom is designated position one, with numbering proceeding counterclockwise around the ring. Boltzmann ratios at 298.15K are relative to the lowest energy conformer.

We find that diaxial conformations are preferred for *trans*-1,2 and *trans*-1,4 dichlorocyclohexane. The diequatorial conformers of these species lie higher in energy, with ΔE values much larger than those in monochlorocyclohexane. However, *trans*-1,3 dichlorocyclohexane, which has one axial and one equatorial chlorine atom, is the most stable 1,3 dichlorocyclohexane. For cis-1,3 dichlorocyclohexane, the

Table 2 Relative energies for dichlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_{10}Cl_2$ Isomers
trans-1,2		0.0	1.00	1.4
		1.2	0.14	2.5
cis-1,2		A ring flip yields the enantiomer.		2.7
cis-1,3		0.0	1.00	1.2
		3.6	2×10^{-3}	4.8
trans-1,3		A ring flip yields an identical configuration.		0.8
trans-1,4		0.0	1.00	0.0
		0.8	0.28	0.8
cis-1,4		A ring flip yields an identical configuration.		0.7

*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The diaxial *trans*-1,4 structure is our zero of energy of all $C_6H_{10}Cl_2$ isomers.

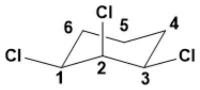
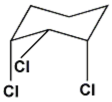
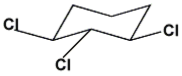
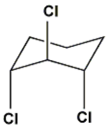
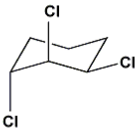
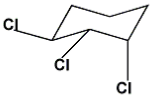
diequatorial conformation is preferred by 3.6 kcal/mol, which follows the rules taught in introductory organic chemistry that favorable conformations prefer to have the maximized equatorial substituent groups.[24] Our theoretical conformation energies agree well with exist experimental values and other calculated results. For the 1,2-dichlorocyclohexane, our theoretical preference for the diaxial conformer, 1.2 kcal/mol, is close to the experimental conformation energy (0.72 kcal/mol)[50] and the calculated MM2 value (0.86 kcal/mol).[28] For the cis-1,3-dichlorocyclohexane, conformation energy obtained in this work (3.6 kcal/mol) is in highly accordance with the calculated MM2 value (3.53 kcal/mol).[28] The NMR study on 1,4-dichlorocyclohexane suggest a 0.8 kcal/mol preference of the diaxial conformation relative to the diequatorial conformation,[32] which is in agreement with the theoretical relative energy (0.8 kcal/mol) in this work. Our result also agrees with the theoretical calculated MM2 comformation energy preference (0.40 kcal/mol).[28] The existing theoretical dipole moment values for the *trans*-1,2-dichlorocyclohexane, 1.26 debye (by the LeFevre's method based on the additive values of C-X bond (X = C1, Br) polarizabilities) and 1.28 debye (by the IDME method), [28, 51] *cis*-1,3-dichlorocyclohexane (3.73 and 2.43 debye, by the IDME method for the aa and ee comformation)[28] are also close to the values, which are 1.07, 4.03, and 2.69 debye for the 1,2-, aa-1,3-, and ee-1,3-dichlorocyclohexane (Table S2). Similar with the corresponding difluorocyclohexane,[36] the lowest-lying isomer of the nine is also the *trans*-1,2 diaxial comformation, and the energetical preference of all ring flip comformation pairs are not changed.

3.3 Trichlorocyclohexane

For the trichlorocyclohexanes, there are totally eighteen possible chair conformations. The conformations of 1,2,3; 1,2,4; and 1,3,5 substitution patterns are shown in Table 3, 4, and 5, respectively. It may be seen that no conformations become the enantiomers or identical configurations after ring inversion. The boat conformations are not discussed due to their lying at least ~7 kcal/mol above the most stable chair conformations.

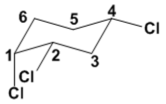
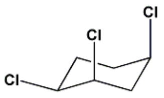
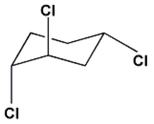
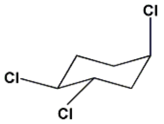
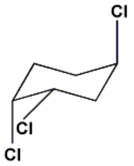
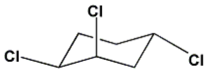
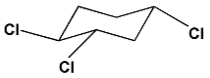
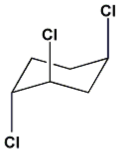
Not all, but six of the nine, lowest-lying trichlorocyclohexane conformers have more equatorial chlorine atoms. Therefore, the rules in many organic chemistry textbooks that favorable conformations prefer to have the maximized equatorial substituent groups[24] do not always work for trichlorocyclohexane conformers. It is certainly helpful for predicting the priority for these three all-equatorial conformers relative to their all-axial conformers after the ring flip. Furthermore, the Δ*E*s for trichlorocyclohexanes vary widely. All-axial and all-equatorial r-1, t-2, c-3- and r-1, t-2, t-4-trichlorocylohexanes are nearly degenerate, while the all-axial r-1, c-3, c-5-trichlorocyclohexane structure is 9.5 kcal/mol higher-lying above its all-equatorial conformer. Due to the large conformational energy differences between the all-axial conformers and their all-equatorial conformers, their conformational preferences are only determined by sterics. Different from the corresponding trifluorocyclohexane,[36] of which the lowest-lying isomer is the (1eq, 3eq, 5ax) r-1, c-3, t-5-trifluoro-comformer, the energetical preference of the r-1, t-2, t-4 pair is also changed.

Table 3 Relative energies for 1, 2, 3-trichlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_9Cl_3$ Isomers
r-1, *c*-2, *c*-3		0.0	1.00	3.7
		3.6	2×10^{-3}	7.2
r-1, *t*-2, *c*-3		0.0	1.00	3.7
		0.9	0.21	4.6
r-1, *t*-2, *t*-3		0.0	1.00	2.0
		1.5	0.08	3.4

*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The 1 ax, 2 ax, 4 eq-structure in Table 4 is our zero of energy of all $C_6H_9Cl_3$ isomers.

Table 4 Relative energies for 1, 2, 4-trichlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_9Cl_3$ Isomers
r-1, *c*-2, *c*-4		0.0	1.00	1.9
		3.8	2×10^{-3}	5.7
r-1, *t*-2, *c*-4		0.0	1.00	0.0
		1.3	0.11	1.3
r-1, *c*-2, *t*-4		0.0	1.00	0.7
		0.9	0.23	1.6
r-1, *t*-2, *t*-4		0.0	1.00	1.8
		1.4	0.10	3.2

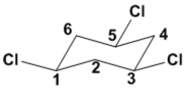
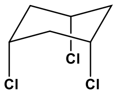
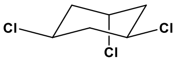
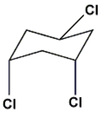
*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The 1 ax, 2 ax, 4 eq-structure is our zero of energy of all $C_6H_9Cl_3$ isomers.

3.4 Tetrachlorocyclohexane

For the tetrachlorocyclohexanes, there are totally seventeen possible chair conformations. The conformations of 1,2,3,4; 1,2,3,5; and 1,2,4,5 substitution patterns are displayed in Table 6, 7, and 8, respectively. The r-1, c-2, c-3, c-4-tetrachlorocyclohexane and r-1, t-2, t-3, c-4-tetrachlorocyclohexane become their enantiomers after the ring inversions. Similarly, ring inversions on r-1, t-2, c-4, t-5-tetrachlorocyclohexane, r-1, c-2, t-4, t-5-tetrachlorocyclohexane, and r-1, c-2, c-4, c-5- tetrachlorocyclohexane lead to the identical configurations. The remaining twelve molecules have pairs of chair conformations, linked by ring inversions.

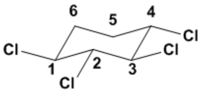
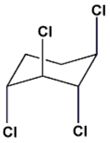
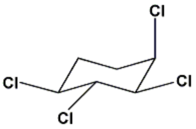
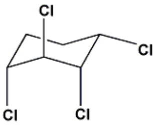
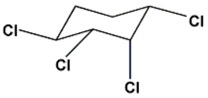
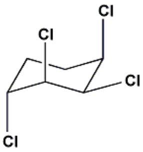
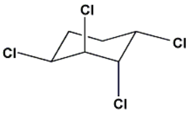
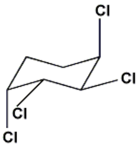
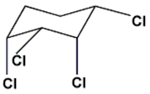
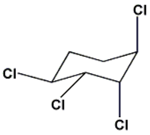
The all-equatorial tetrachlorocyclohexane conformations (r-1, t-2, c-3, t-4; r-1, t-2, c-3, c-5; and r-1, t-2, t-4, c-5), always have lower energies in this work. Furthermore, the rules in organic textbooks that favorable conformations prefer to have the maximized equatorial substituent groups[24] apply to most species. However, they break down for the species having two axial and two equatorial chlorine atoms. Specifically, for the r-1, c-2, c-3, t-5-tetrachlorocyclohexane, these simple organic rules cannot explain its large energy difference (4.4 kcal/mol). Similar with the corresponding tetrafluorocyclohexane,[36] the lowest-lying isomer do not changed, and the energetical preference of most ring flip comformation pairs are not changed, except for the r-1, t-2, t-3, c-5 tetrachloro-pair.

Table 5 Relative energies for 1, 3, 5-trichlorocyclohexane.*

Species	Strucure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_9Cl_3$ Isomers
r-1, *c*-3, *c*-5		0.0	1.00	1.2
		9.5	1×10^{-7}	10.7
r-1, *c*-3, *t*-5		0.0	1.00	0.2
		3.5	3×10^{-3}	3.7

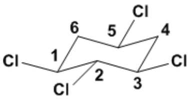
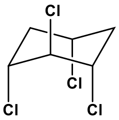
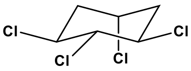
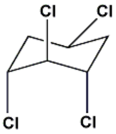
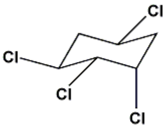
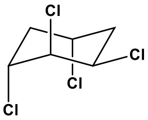
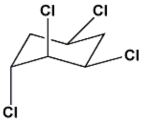
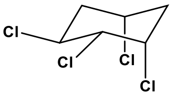
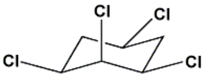
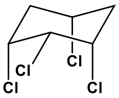
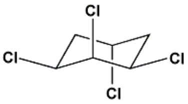
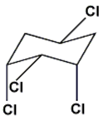
*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The 1 ax, 2 ax, 4 eq-structure in Table 4 is our zero of energy of all $C_6H_9Cl_3$ isomers.

Table 6 Relative energies for 1, 2, 3, 4-tetrachlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_8Cl_4$ Isomers
r-1, *t*-2, *c*-3, *t*-4		0.0	1.00	4.3
		1.8	0.05	6.1
r-1, *t*-2, *c*-3, *c*-4		0.0	1.00	4.0
		1.0	0.17	5.0
r-1, *t*-2, *t*-3, *t*-4		0.0	1.00	3.9
		1.2	0.13	5.1
r-1, *c*-2, *t*-3, *t*-4		0.0	1.00	2.2
		0.9	0.20	3.1
r-1, *c*-2, *c*-3, *c*-4		A ring flip yields the enantiomer.		7.9
r-1, *t*-2, *t*-3, *c*-4		A ring flip yields the enantiomer.		2.1

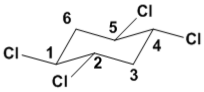
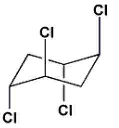
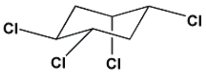
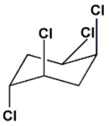
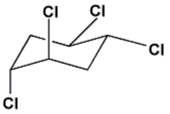
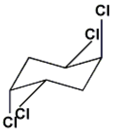
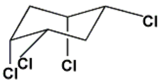
*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The *r*-1, *t*-2, *c*-4, *t*-5-structure in Table 8 is our zero of energy of all $C_6H_8Cl_4$ isomers.

Table 7 Relative energies for 1, 2, 3, 5-tetrachlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_8Cl_4$ Isomers
r-1, *t*-2, *c*-3, *c*-5		0.0	1.00	3.1
		6.1	3×10^{-5}	9.2
r-1, *t*-2, *c*-3, *t*-5		0.0	1.00	2.1
		0.9	0.21	3.0
r-1, *t*-2, *t*-3, *c*-5		0.0	1.00	2.3
		1.1	0.17	3.4
r-1, *t*-2, *t*-3, *t*-5		0.0	1.00	0.7
		5.6	9×10^{-5}	6.3
r-1, *c*-2, *c*-3, *c*-5		0.0	1.00	3.0
		9.6	9×10^{-8}	12.6
r-1, *c*-2, *c*-3, *t*-5		0.0	1.000	1.3
		4.4	1×10^{-3}	5.7

*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The *r*-1, *t*-2, *c*-4, *t*-5-structure in Table 8 is our zero of energy of all $C_6H_8Cl_4$ isomers.

Table 8 Relative energies for 1, 2, 4, 5-tetrachlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_8Cl_4$ Isomers
r-1, *t*-2, *t*-4, *c*-5		0.0	1.00	2.2
		3.9	1×10^{-3}	6.2
r-1, *t*-2, *t*-4, *t*-5		0.0	1.00	1.9
		1.8	0.05	3.7
r-1, *t*-2, *c*-4, *t*-5		A ring flip yields an identical configuration.		0.0
r-1, *c*-2, *t*-4, *t*-5		A ring flip yields an identical configuration.		1.1
r-1, *c*-2, *c*-4, c-5		A ring flip yields an identical configuration.		6.6

*Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The *r*-1, *t*-2, *c*-4, *t*-5-structure is our zero of energy of all $C_6H_8Cl_4$ isomers.

3.5 Pentachlorocyclohexane

For the pentachlorocyclohexanes, there is only one substitution pattern (1,2,3,4,5) and a total of twenty possible chair conformations (Table 9). All ring inversions lead to different conformations.

The simple organic rules that favorable conformations prefer to have the maximized equatorial substituent groups[24] for predicting the lowest-lying conformer work for eight of the ten pentachlorocyclohexanes species. The two failures are predictions for the r-1, t-2, t-3, t-4, t-5 and r-1, c-2, t-3, c-4, c-5 pentachlorocyclohexanes, indicating that electrostatic repulsions may play a more significant role in highly chlorinated cyclohexanes, which is similar with the situation for the pentafluorocyclohexanes. However, the lowest-lying comformation is the (1eq, 2eq, 3eq, 4ax, 5ax) r-1, t-2, c-3, c-4, t-5-isomer, which is different from the pentafluorocyclohexanes.[36] Furthermore, we can conclude that if the parallel axial C-Cl bonds can be partly balanced by the opposite axial C-Cl bond, the pentachlorocyclohexane can lie lower in energy, even though not following the textbook rules that favorable conformations prefer to have the maximized equatorial substituent groups.[24]

3.6 Hexachlorocyclohexane

For the hexachlorocyclohexanes, there are only one substitution pattern (1,2,3,4,5,6) and totally thirteen possible chair conformations (Table 10). These conformers contain all the reported common forms (α–, β–, γ–, δ–, ε–)[52] and other forms. The r-1, t-2, c-3, c-4, t-5, c-6 and r-1, c-2, c-3, c-4, c-5, c-6-hexachlorocyclohexane species yield the identical configurations under ring flips. The boat conformations are not competitive, lying about 7 kcal/mol above the most stable chair hexachlorocyclohexane conformation.

With hexachlorocyclohexane, the qualitative organic chemistry rules that favorable conformations prefer to have the maximized equatorial substituent groups[24] apply to all the possible isomers. These correct predictions for determining the lower-lying chair conformation in all ten molecules indicate that electrostatic repulsions are the most important electronic effect for highly chlorinated structures. The r-1, t-2, c-3, t-4, t-5, c-6 hexachlorocyclohexane is predicted to be the lowest-lying isomer, for having four equatorial chlorine atoms and adjacent trans-diaxial chlorine atoms, keeping faraway from each other, without parallel axial chlorine atoms. This is different from the situation of the hexafluorocyclohexane that the (1eq, 2eq, 3ax, 4eq, 5eq, 6ax) r-1, t-2, t-3, t-4, c-5, c-6-hexafluorocyclohexane is the lowest-lying conformation.[36] However, (1eq, 2eq, 3ax, 4eq, 5eq, 6ax) r-1, t-2, t-3, t-4, c-5, c-6-hexachlorocyclohexane is also low-lying, with the relative energy of 1.5 kcal/mol.

Table 9 Relative energies for 1, 2, 3, 4, 5-pentachlorocyclohexane.*

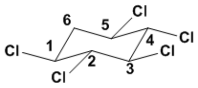
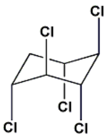
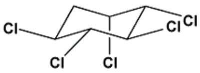
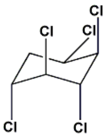
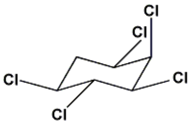
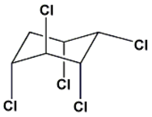
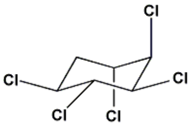
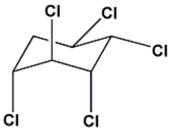
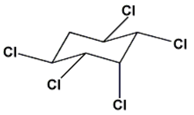
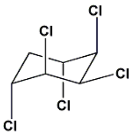
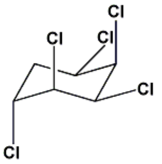
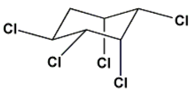
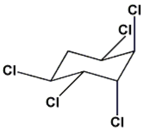
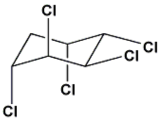
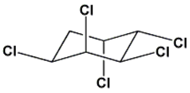
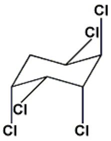
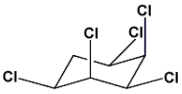
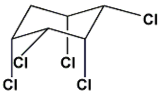
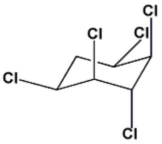
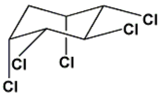
Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_7Cl_5$ Isomers
r-1, *t*-2, *c*-3, *t*-4, *c*-5		0.0	1.00	2.7
		6.4	2×10^{-5}	9.1
r-1, *t*-2, *c*-3, *t*-4, *t*-5		0.0	1.00	1.8
		2.1	0.03	3.9
r-1, *t*-2, *c*-3, *c*-4, *c*-5		0.0	1.00	2.2
		6.3	3×10^{-6}	8.5
r-1, *t*-2, *c*-3, *c*-4, *t*-5		0.0	1.00	0.0
		2.8	0.01	2.8
r-1, *t*-2, *t*-3, *t*-4, *c*-5		0.0	1.00	1.8
		3.5	3×10^{-5}	5.3
r-1, *t*-2, *t*-3, *t*-4, *t*-5		0.0	1.00	3.4
		2.4	0.02	5.8

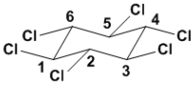
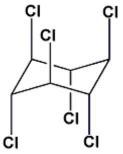
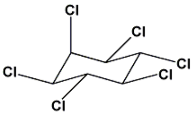
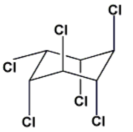
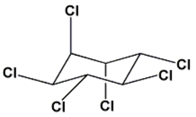
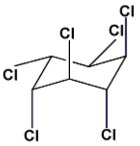
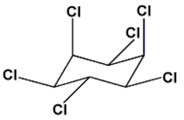
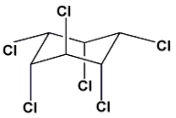
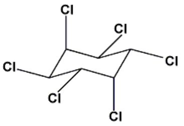
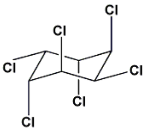
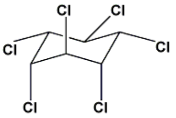
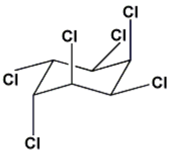
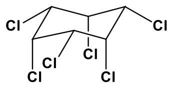
Table 9, continued

r-1, *t*-2, *t*-3, *c*-4, *c*-5		0.0	1.00	0.1
		3.5	3×10^{-3}	3.6
r-1, *c*-2, *c*-3, *t*-4, *t*-5		0.0	1.00	1.2
		1.6	0.07	2.8
r-1, *c*-2, *c*-3, *c*-4, *c*-5		0.0	1.00	6.6
		5.5	9×10^{-5}	12.2
r-1, *c*-2, *t*-3, *c*-4, *c*-5		0.0	1.00	3.4
		3.5	3×10^{-3}	6.9

* Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The 1eq, 2eq, 3eq, 4ax, 5ax-structure is our zero of energy of all $C_6H_7Cl_5$ isomers.

Our results are generally in agreement with existing computations, carried out at the B3LYP/6-31++G and MP2/6-31++G levels of theory for the hexachlorocyclohexanes.[错误!未定义书签。] The previous theoretical work and this research both predict that the (1eq, 2eq, 3eq, 4eq, 5ax, 6ax) r-1, t-2, c-3, t-4, t-5, c-6-hexachlorocyclohexane is the lowest-lying conformation, and the (1ax, 2eq, 3ax, 4eq, 5ax, 6eq) r-1, c-2, c-3, c-4, c-5, c-6-hexachlorocyclohexane is the highest-lying conformation. The energy difference between these two conformations are 14.3

Table 10 Relative energies for 1, 2, 3, 4, 5, 6-hexachlorocyclohexane.*

Species	Structure	Relative Energy of Conformer Pairs	Boltzmann Ratio	Relative Energy of all $C_6H_6Cl_6$ Isomers
r-1, *t*-2, *c*-3, *t*-4, *c*-5, *t*-6		0.0	1.00	3.4
		8.6	5×10^{-8}	11.9
r-1, *t*-2, *c*-3, *t*-4, *c*-5, *c*-6		0.0	1.00	2.1
		6.4	2×10^{-5}	8.5
r-1, *t*-2, *c*-3, *t*-4, *t*-5, *c*-6		0.0	1.00	0.0
		4.4	1×10^{-3}	4.4
r-1, *t*-2, *c*-3, *c*-4, *c*-5, *c*-6		0.0	1.000	7.0
		1.4	0.10	8.4
r-1, *t*-2, *t*-3, *t*-4, *c*-5, *c*-6		0.0	1.00	1.5
		3.3	4×10^{-3}	4.8
r-1, *t*-2, *c*-3, *c*-4, *t*-5, *c*-6		A ring flip yields an identical configuration.		3.7
r-1, *t*-2, *t*-3, *t*-4, *t*-5, *c*-6		A ring flip yields the enantiomer.		3.5
r-1, *c*-2, *c*-3, *c*-4, *c*-5, *c*-6		A ring flip yields an identical configuration.		12.4

* Results are reported in kcal/mol from the MP2/cc-pVTZ method, assuming structures optimized with the MP2/DZP method. In our sketches position one is assigned to the left most C atom. Boltzmann ratios at 298.15K are given with respect to lowest energy conformer. The 1eq, 2eq, 3eq, 4eq, 5ax, 6ax-structure is our zero of energy of all $C_6H_6Cl_6$ isomers.

kcal/mol (MP2/6-31++G) and 15.9 kcal/mol (B3LYP/6-31++G) for the previous work, which are somewhat larger than that (12.4 kcal/mol) predicted here. However, the present results should be significantly more reliable, since we used a larger basis set, with necessary extensive polarization functions (triple zeta versus double zeta). It is similar with the experimental synthesis[53] and theoretical calculation results for the hexafluorocyclohexanes that the r-1, c-2, c-3, c-4, c-5, c-6-isomer has the highest relative energy of all boat isomers.

3.7 Reliability

We performed a dual-level theoretical study, which used the MP2/cc-pVTZ single point energies and the MP2/DZP geometries. The lower level MP2/DZP energies are close to the higher level MP2/cc-pVTZ energies within 0.8 kcal/mol for all polychlorocyclohexane structures, which is within the intrinsic error of the MP2 method. We find only two exceptions, namely the high-lying r-1, c-2, c-3, c-4, c-5-pentachlorocyclohexane, and r-1, c-2, c-3, c-4, c-5, c-6-hexachlorocyclohexane, but the energy differences of them between the MP2/DZP and MP2/cc-pVTZ levels are no more than 1.3 kcal/mol. Generally, these discrepancies would not qualitatively change the lowest-lying conformation for the polychlorocyclohexane species in this work, except for chlorocyclohexane. The axial chair chlorocyclohexane is only 0.008 kcal/mol lower lying than the equatorial chlorocyclohexane for the DZP results. However, for the more reliable cc-pVTZ results, the equatorial chair chlorocyclohexane is lower-lying in accord with the rule that favorable conformations prefer to have the maximized equatorial substituent groups[24] taught in introductory organic chemistry. Therefore, we are confident that the cc-pVTZ relative energies are sufficient to correctly identify the lowest energy polychlorocyclohexane conformations.

3.8 Dipole moments

The theoretical dipole moments of all conformations are given in Tables S1 to S10 in Electronic Supplementary Information. The level of theory we use to compute dipole moments is expected to be qualitatively reasonable and actually close to the existing results (see details in part 3.2). Due to the molecular symmetry, the below conformations have indisputably zero dipole moments: *trans*-1,4-dichlorocyclohexane; r-1, t-2, t-4, c-5 tetrachloro; r-1, c-2, t-4, t-5 tetrachloro; r-1, t-2, c-3, t-4, c-5, t-6 hexachloro; and the r-1, t-2, t-3, t-4, c-5, c-6- hexachlorocyclohexanes.

Among all polar conformations, the (1eq, 2ax, 3ax, 4eq) conformation of r-1, c-2, t-3, t-4-tetrachlorocyclohexane has the smallest theoretical dipole moment (μ = 0.88 debye, Table S6). It has both nearly balancing equatorial and axial C → Cl dipoles. This situation is same as that in polyfluorocyclohexanes (0.70 debye for r-1, c-2, t-3, t-4-tetrachlorocyclohexane).[36]

However, among the molecules studied, the largest predicted dipole moment (μ = 5.71 debye) is the higher-lying (12.6 kcal/mol, highest in the twenty nine chair tetrachlorocyclohexanes) (1ax, 2eq, 3ax, 5ax) conformation of r-1, c-2, c-3, c-5-tetrachlorocyclohexane displayed in Table 7 and Table S7. This structure has three parallel axial C → Cl bonds, which leads to its large dipole moment and suggests the correlation between its large dipole moment and its highest overall relative energy. Similarly, the r-1, c-2, c-3, c-4, c-5 pentachlorocyclohexane conformation with three parallel axial C → Cl bonds has the largest dipole moment (μ = 5.52 debye) and the highest overall relative energy (12.2 kcal/mol, Table 9) in all pentachloro conformations (Table S9). Another similar situation occurs on the r-1, c-3, c-5-trichlorocyclohexane conformation, which has the largest dipole moment (μ = 5.59 debye) and the second highest overall energy (10.7 kcal/mol, Table 5) in all eighteen trichlorocyclohexane structures. The r-1, c-2, c-3, c-4, c-5, c-6 structure with three parallel axial C → Cl dipoles has the largest dipole moment (μ = 5.02 debye) and the highest energy (12.4 kcal/mol) of all thirteen hexachloro structures (Table S10).

It can be concluded that the polychlorocyclohexane structure with more unbalanced parallel axial chlorines has lager molecular polarity and relative energy.

3.9 Thermodynamics

The relative energies of pairs of conformers have been displayed to predict the favorable structural isomers, because of the fact that at room temperature the structural pair isomers can interconvert to each other after ring flip. The pair conformers distribute as Boltzmann distribution after achieving chemical equilibrium, which were reported in 1,2,3,4,5,6-hexafluorocyclohexane.[36,错误!未定义书签。]

To further interpretate the relative energies, the Boltzmann ratios for pairs of conformers are displayed in each table. For example, axial chlorocyclohexane is 0.3 kcal/mol higher-lying above the its equatorial conformer in this work. According to Boltzmann statistics, there are thirteen axial chlorocyclohexane structures for each twenty equatorial structures (1.00 : 0.65 equatorial–axial ratio) at 298 K. Similar relationship between other polychlorocyclohexane conformer pairs can also be obtained.

In the actual synthesis, the obtained polychlorocyclohexanes could contain many different structural isomers. Thus, we also give the overall relative energies for each polychlorocyclohexane species to show the thermodynamic preferences and the most possible synthetic products at high temperature.

Firstly, the axial and equatorial chlorocyclohexane isomers are nearly degenerate, with a narrow conformational energy range (Table 1). While the overall relative energy difference for dichlorocyclohexane isomers is about 5 kcal/mol (Table 2), which is larger than that, 3 kcal/mol, of the difluorocyclohexane.[36] The diaxial *trans*-1,4-dichlorocyclohexane is lowest-lying, with the nearly balanced C → Cl dipoles. The diequatorial strcuture of *trans*-1,4-dichlorocyclohexane is 0.7 kcal/mol higher, much larger than that for chlorocyclohexane. The diaxial *cis*-1,3-dichlorocyclohexane has the highest overall relative energy for containing the parallel and close axial C → Cl bond dipoles. The diequatorial *trans*-1,2-dichloro and *cis*-1,2-dichloro structures are also high-lying.

For the trichlorocyclohexane species (Tables 3–5), the (1ax, 2ax, 4eq) r-1, t-2, c-4-trichloro structure is lowest-lying. In the dichloro family, the structure with a diaxial-1,4 motif has the lowest energy. It can be expected that the related conformation (1ax, 2eq, 4ax) of r-1, c-2, t-4-trichloro is also low-lying, which is 0.71 kcal/mol relative to the with r-1, t-2, c-4-trichloro. In this case, the “additional” chlorine on diaxial trans-1,4-dichlorocyclohexane is equatorial. Additionally, the lower energy conformation (1eq, 3eq, 5ax) of r-1, c-3, t-5-trichloro is also low-lying, with the relative energy of 0.20 kcal/mol to the r-1, t-2, c-4-trichlorohexane. The highest-lying trichloro structural isomer can be inferred as the highest-lying diaxial 1,3 substituted dichloro structure adding a third parallel axial chlorine, which leads to more unbalanced axial chlorines and makes the structure tend to have large dipole moments.

For the tetrachlorocyclohexane isomers (Tables 6–8), the lowest-lying r-1, t-2, c-4, t-5-tetrachlorocyclohexane is not easy to rationalize, although it is same as that for the tetrafluorocyclohexane structures.[36] It does not follow any discernable pattern from the trichloro family. The highest-lying chair tetrachlorocyclohexane conformation can be inferred from the highest-lying trichloro structure, (1ax, 3ax, 5ax) r-1, c-3, c-5-trichloro, by adding an equatorial chlorine at the two position. Thus, the tetrachloro structure continues to have the three parallel axial C → Cl bond dipoles, and the only equatorial chlorine has very limited influence on it.

For the pentachloro structures (Table 9), two lowest-lying by overall energies, (1ax, 2ax, 3eq, 4eq, 5eq) r-1, t-2, t-3, c-4, t-5-pentachloro and (1eq, 2ax, 3ax, 4eq, 5eq) r-1, c-2, t-3, t-4, c-5-pentachlorocyclohexane, both have three equatorial chlorines. These two structures can be seen as addition of one more equatorial chlorine to the two lowest-lying tetrachloro structure. The highest-lying structure, (1ax, 2eq, 3ax, 4eq, 5ax) r-1, c-2, c-3, c-4, c-5 pentachloro, can be rationalized as adding an equatorial chlorine atom to the highest-lying tetrachlorocyclohexane isomer, which result in three parallel axial C → Cl bond dipoles and two equatorial chlorines.

For the hexachloro structures, the lowest-lying structure, (1eq, 2eq, 3eq, 4eq, 5ax, 6ax) r-1, t-2, c-3, t-4, t-5, c-6 hexachloro is similar to r-1, t-2, c-4, t-5-tetrachlorocyclohexane with the addition of two additional equatorial chlorines.

The second lowest-lying structure, (1eq, 2eq, 3ax, 4eq, 5eq, 6ax) r-1, t-2, t-3, t-4, c-5, c-6 hexachloro, is slightly higher (by 1.5 kcal/mol), and has a *trans*-1,4 motif, with equatorial chlorines at the other four positions. The highest-energy isomer, r-1, c-2, c-3, c-4, c-5, c-6 hexachloro, has three parallel axial C → Cl bond dipoles unbalanced by the other three *cis* equatorial chlorines. The second highest-lying structure, r-1, t-2, c-3, t-4, c-5, t-6 hexachloro, has two sets of three, totally six, axial C → Cl bond dipoles. In each set, three chlorine atoms are parallel and in close proximity to each other.

Totally, the relative energetic properties of polychlorocyclohexanes is generally qualitatively same as the corresponding polyfluorocyclohexanes, except for very few cases of tri-, tetra, penta- hexachlorocyclohexanes. The relative energy range of all isomers for polychlorocyclohexanes is obviously larger than that for polyfluorocyclohexanes, which indicates the quantitative different substitution effect of the fluorine and chlorine atoms.

Table 11 Chlorine equilibration energies of polychlorocyclohexanes (kcal/mol).

Reactions	Reaction Energies
$C_6H_{12} + C_6H_{10}Cl_2 \rightarrow 2\ C_6H_{11}Cl$	-0.2
$C_6H_{11}Cl + C_6H_9Cl_3 \rightarrow 2\ C_6H_{10}Cl_2$	-2.6
$C_6H_{10}Cl_2 + C_6H_8Cl_4 \rightarrow 2\ C_6H_9Cl_3$	-1.1
$C_6H_9Cl_3 + C_6H_7Cl_5 \rightarrow 2\ C_6H_8Cl_4$	-3.1
$C_6H_8Cl_4 + C_6H_6Cl_6 \rightarrow 2\ C_6H_7Cl_5$	-0.1
$C_6H_{12} + C_6H_8Cl_4 \rightarrow 2\ C_6H_{10}Cl_2$	-6.4
$C_6H_{11}Cl + C_6H_7Cl_5 \rightarrow 2\ C_6H_9Cl_3$	-7.8
$C_6H_{10}Cl_2 + C_6H_6Cl_6 \rightarrow 2\ C_6H_8Cl_4$	-7.4
$C_6H_{12} + C_6H_6Cl_6 \rightarrow 2\ C_6H_9Cl_3$	-14.9

Based on the most stable polychlorocyclohexane comformations and the optimized cyclohexane (chair comformation) at the same level of theory, we calculate the chlorine equilibration energies (Table 11). It can be found that one chlorine equilibration reactions are generally thermoneutral or slightly exothermic (-0.2 to -3.1 kcal/mol). Two or three chlorine equilibration reactions are exothermic (-6.4 to -14.9 kcal/mol). More chlorine atoms equilibrations are more exothermic. These equilibration reaction energies suggest a trend that coexisting polychlorocyclohexane with different chlorine atoms would be favorable for changing to have same chlorine atoms thermodynamically.

3.10 Model energetics

We tried to rationalize the thermodynamic stabilities of the polychlorocyclohexanes using a model based on all isomers like what we did for the polyfluorocyclohexanes.[36] The molecular overall relative energies were decomposed to the contributions of the different dichloro substitution pairs (e.g. 1,2-dichloro pair , 1,3-dichloro pair, and 1,4-dichloro pair). Values were assigned to six types of pairwise chlorine–chlorine interactions: 1, 2 diaxial; 1, 2 axial, equatorial; 1, 3 diaxial; 1, 3 axial, equatorial; 1, 4 diaxial; and 1, 4 axial, equatorial. For each type of substitution pair, the contribution of the diequatorial conformations (1, 2 equatorial, equatorial; 1, 3 equatorial, equatorial; and 1, 4 equatorial, equatorial) were defined as the zero. Thus the obtained equation for predicting the overall relative energies (ΔE, in kcal/mol) is

$$\Delta E = -1.392a_1a_2 - 0.016a_1e_2 + 3.168a_1a_3 - 0.364a_1e_3 - 0.460a_1a_4 + 0.196a_1e_4 \quad (1)$$

The total energy is given by

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

In equation (1), a_1a_2 and a_1e_4 are the numbers of 1,2-diaxial pairs and 1,4 axial, equatorial pairs in the molecule, respectively, and so forth. The negative and positive terms suggest favorable and disfavored interactions, relative to the all-equatorial conformation. Figure 1 describe the relationship between the relative energies computed at MP2/cc-pVTZ level of theory and by equation (1). The high correlation coefficient ($R^2 = 0.978$) and the small RMS error (0.43 kcal/mol) of this model lead to rather accurate predictions of the relative energies of sets of polychlorocyclohexane conformers. Accurate predictions by this model makes explaining the relative energies of polychlorocyclohexanes in terms of pairwise interactions between the chloromethylene (CHCl) subunits reliable. From the model, we found that both axial-axial and axial-equatorial pairs can give stabilizing or destabilizing effects. Furthermore, the *trans* pairwise interactions (a_1a_2, a_1e_3, and a_1a_4) indicate an obvious favorable effect, and the *cis* pairwise interactions (a_1a_3, and a_1e_4) indicate obvious unfavorable effect. Except for the neglectable a_1e_2 interaction pairwise effect of which the coefficient is close to zero (-0.016). Additionally, the a_1a_3 term has the largest favorable effect, corresponding to the nearly parallel C → Cl bond dipoles, which is similar with that for the polychlorocyclohexanes.

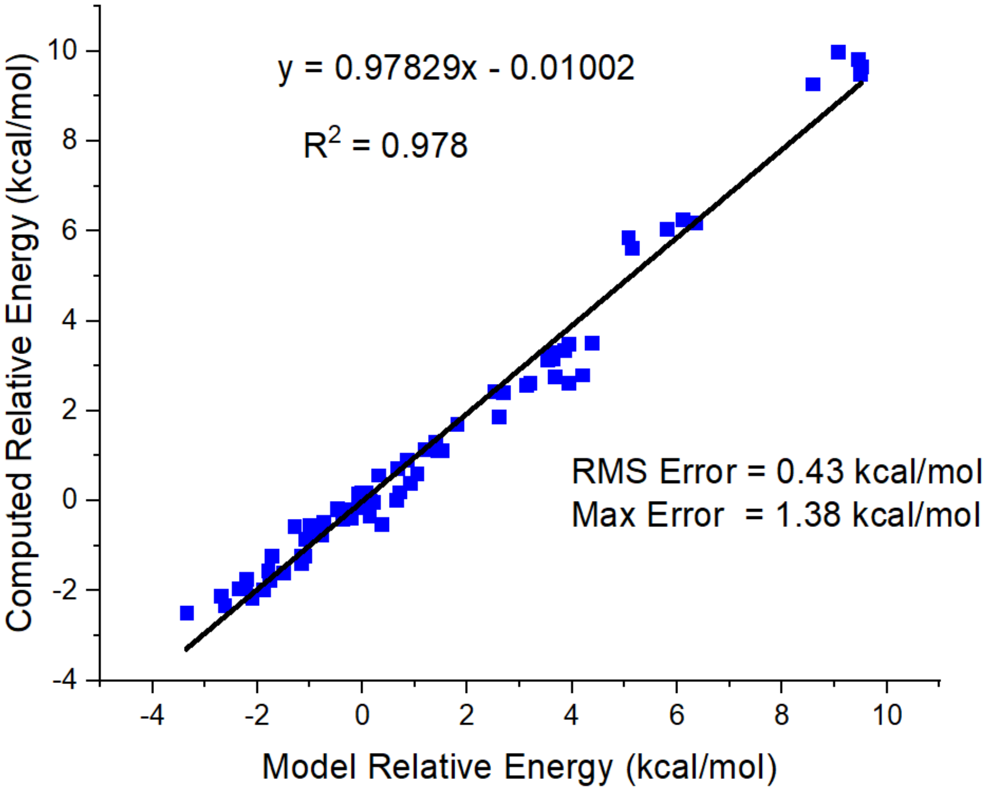


Figure 1 Model of polychlorocyclohexane relative energies. The parameters were adjusted to fit the whole set of polychlorocyclohexane relative energies.

Additionally, Benson and his co-workers used the group additivity scheme[54,55] to estimate the molecular thermodynamic properties, such as C_p, S, and ΔH_f. The terms they use to do the addition are the contributions of different groups to the corresponding property. Each term relates to the contribution of a certain type of group in the molecule. In our scheme, each term in equation (1) corresponds to the contribution, of a certain type of interaction between the two CHCl subunits, to the energy difference relative to the all equatorial comformations.

4 Conclusions

We have systematically carried out a theoretical investigation on the polychlorocyclohexanes containing 1-6 chlorine atoms. The geometries of all polychlorocyclohexane structures are optimized at the MP2/DZP level of theory, and the single point energies of each optimized polychlorocyclohexane structures are refined at the MP2/cc-pVTZ level of theory. The MP2/cc-pVTZ relative energies indicate that the simple rules that favorable conformations prefer to have the maximized equatorial substituent groups[24] in the organic chemistry textbooks do not work for all polychlorocyclohexane conformations. We have proposed a simple but precise model equation to get more accurate conformational energies by the combination of the contributions from the interactions between two CHCl subunits. In addition, the strategy of combination the contributions of the subunits to obtain the total relative energy is similar with that using molecular building blocks to create candidates for active sites of enzymes.

5 Conflicts of interest

There are no conflicts of interest to declare.

6 Electronic Supplementary Information

Table S1-S10. Dipole moments of polychlorocyclohexane conformers in debye at the MP2/cc-pVTZ level of theory, using the geometries optimized at MP2/DZP level of theory. Table S11-S102. Optimized cartesian coordinates and total energies of cyclohexane and polychlorocyclohexane.

7 Acknowledgments

Q.L. was supported by the National Natural Science Foundation of China (21673084) and the Training Plan of Guangdong Province Outstanding Young Teachers in Higher Education Institutions (HS2015003). S.G. was supported by the China Postdoctoral Science Foundation (2016M602093), the Shandong Postdoctoral Innovation Project (201603065), and the Qingdao Postdoctoral Application Research Project (2016006). H.F.S was supported by the U.S. National Science Foundation, Grant CHE-1661604.

References

---

1 Gribble G W. The natural production of chlorinated compounds. *Environ. Sci. Technol.*, 1994, 28, 310A-319A.

2 Engvild K C. Chlorine-containing natural compounds in higher plants. *Phytochemistry*, 1986, 25, 781-791.

3 Lewis, R T. Sax's Dangerous Properties of Industrial Materials, 8th ed.; van Nostrand Reinhold: New York, 1992.

4 Longacre S L. Ethel Browing's Toxicity and Metabolism of Industrial Solvents, 2nd ed.; Snyder, R., Eds.; Elsevier: Amsterdam, 1987; Volume 1.

5 Jensen F R, Bushweller C H. Separation of conformers. II. Axial and equatorial isomers of chlorocyclohexane and trideuteriomethoxycyclohexane. *J. Am. Chem. Soc.*, 1969, 91, 3223-3225.

6 Kozima K, Sakashita K. The Two Stable Isomers of Chlorocyclohexane. *B. Chem. Soc. Jpn.*, 1958, 31, 796-801.

7 Kozima K, Yoshino T. Molecular Structures of trans-1, 4-Dihalogenocyclohexanes. *J. Am. Chem. Soc.*, 1953, 75, 166-171.

8 Abraham R J, Rossetti Z L. Rotational isomerism. Part XV. The solvent dependence of the conformational equilibria in trans-1, 2-and trans-1, 4-dihalogenocyclohexanes. *J. Chem. Soc., Perkin Trans. 2*, 1973, 582-587.

9 Huml K, Hašek J. The crystal and molecular structure of cis-1, 3, 5-trichlorocyclohexane. *Acta Crystallogr. B: Struct. Crystallogr. Cryst. Chem.*, 1972, 28, 2852-2856.

10 Hassel O, Lund E W. The crystal structure of tetrachlorocyclohexane, MP 174° C. *Acta Crystallogr.*, 1949, 2, 309-311.

11 Tanaka K, Kiso M, Yoshida M, Kurihara N. Syntheses and PMR studies of 1, 2, 3, 4, 5-pentachlorocyclohexane isomers, tetrachloromonomethoxycyclohexane isomers and related compounds. *Agric. Biol. Chem.*, 1975, 39, 229-237.

12 Shiro M, Nakai H, Hamada M. A new isomer of pentachlorocyclohexane. *Acta Crystallogr. B: Struct. Crystallogr. Cryst. Chem.*, 1978, 34, 3812-3813.

13 Goss K U, Arp H P H, Bronner G, Niederer C. Partition behavior of hexachlorocyclohexane isomers. *J. Chem. Eng. Data*, 2008, 53, 750-754.

14 Tang S, Wu W, Fu Z, Zou S, Liu Y, Zhao H, Kirk S R, Yin D. Vanadium -

Substituted Tungstophosphoric Acids as Efficient Catalysts for Visible‐Light‐Driven Oxygenation of Cyclohexane by Dioxygen. *ChemCatChem*, 2015, 7, 2637-2645.

15 Nesterova O V, Nesterov D S, Krogul-Sobczak A, da Silva M F C G, Pombeiro A J. Synthesis, crystal structures and catalytic activity of Cu (II) and Mn (III) Schiff base complexes: Influence of additives on the oxidation catalysis of cyclohexane and 1-phenylehanol. *J. Mol. Catal. A: Chem.*, 2017, 426, 506-515.

16 Willett K L, Ulrich E M, Hites R A. Differential toxicity and environmental fates of hexachlorocyclohexane isomers. *Environ. Sci. Technol.*, 1998, 32, 2197-2207.

17 Rossberg M, Lendle W, Pfleiderer G, Tögel A, Dreher E-L, Langer E, Rassaerts H, Kleinschmidt P, Strack H, Cook R, Beck U, Lipper K-A, Torkelson T R, Löser E, Beutel K K, Mann T. *Chlorinated hydrocarbons*. Ullmann's encyclopedia of industrial chemistry, 2006.

18 Brittain D R B, Pandey R, Kumari K, Sharma P, Pandey G, Lal R, Coote M L, Oakeshott J G, Jackson C J. Competing S_N2 and E2 reaction pathways for hexachlorocyclohexane degradation in the gas phase, solution and enzymes. *Chem. Commun.*, 2011, 47, 976-978.

19 Mackenzie K, Battke J, Kopinke F D. Catalytic effects of activated carbon on hydrolysis reactions of chlorinated organic compounds: Part 1. γ-hexachlorocyclohexane. *Catalysis Today*, 2005, 102, 148-153.

20 Nagpal V, Bokare A D, Chikate R C, Rode C V, Paknikara K M. Reductive dechlorination of γ-hexachlorocyclohexane using Fe–Pd bimetallic nanoparticles. *J. Hazard. Mater.*, 2010, 175, 680-687.

21 Usman M, Tascone O, Faure P, Hanna K. Chemical oxidation of hexachlorocyclohexanes (HCHs) in contaminated soils. *Sci. Total Environ.*, 2014, 476: 434-439.

22 Eliel E L, Wilen S H, Mander L M, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994

23 Kemp J D, Pitzer K S. The entropy of ethane and the third law of thermodynamics. Hindered rotation of methyl groups. *J. Am. Chem. Soc.*, 1937, 59, 276-279.

24 Clayden J, Greeves N, Warren S. *Organic Chemistry*. 2nd ed. Oxford University Press Inc. New York 2012.

25 Shen Q, Peloquin J M. The molecular structures and conformations of

chlorocyclohexane and bromocyclohexane as determined by gas-phase electron diffraction. *Acta Chem. Scand.*, 1988, 42, 367.

26 Gardiner D J, Littleton C J, Walker N A. Conformational enthalpy and volume changes in chlorocyclohexane determined by Raman spectroscopy. *J. Raman Spectrosc.*, 1987, 18, 9-11.

27 Caminati W, Scappini F, Damiani D. Microwave spectrum of axial cyclohexyl chloride and conformational equilibrium in cyclohexyl chloride. *J. Mol. Spectrosc.*, 1984, 108, 287-298.

28 Dosen-Micovic L, Jeremic D, Allinger N L. Treatment of electrostatic effects within the molecular-mechanics method. 2. *J. Am. Chem. Soc.*, 1983, 105, 1723-1733.

29 Schneider B, Jakeš J. Determination of the activation energy of chlorocyclohexane conformational transitions by infrared spectra. *J. Mol. Struct.*, 1973, 15, 87-91.

30 Durig J R, El Defrawy A M, Ward R M, Guirgis G A, Gounev T K. Conformational stability of chlorocyclohexane from temperature-dependent FT-IR spectra of xenon solutions, r_0 structural parameters, and vibrational assignment. *Struct. Chem.*, 2008, 19, 579–594

31 Calderbank K E, Le Fèvre R J W, Pierens R K. Molecular polarisability. Some chlorinated cyclohexanes. *J. Chem. Soc. B*, 1970, 1608-1612.

32 Abraham R J, Rossetti Z L. A novel attractive 1–3 interaction in trans-1, 4-dichlorocyclohexane. *Tetrahedron Lett.*, 1972, 13, 4965-4968.

33 Dosen-Micovic L, Jeremic D, Allinger N L. Treatment of electrostatic effects within the molecular-mechanics method. 1. *J. Am. Chem. Soc.*, 1983, 105, 1716-1722.

34 Wiberg K B. Conformational studies in the cyclohexane series. 3. The dihalocyclohexanes. *J. Org. Chem.*, 1999, 64, 6387-6393.

35 Mazzanti A, Casarini D. Recent trends in conformational analysis. *WIRES*: *Comput. Mol. Sci.*, 2012, 2, 613-641.

36 Q. Luo, K. R. Randall, H. F. Schaefer, Easy chairs: the conformational preferences of polyfluorocyclohexanes. *RSC Adv.*, 2013, 3, 6572–6585

37 Møller C, Plesset M S. Note on an approximation treatment for many-electron systems. *Phys. Rev.*, 1934, 46, 618.

38 Pople J A, Binkley J S, Seeger R. Theoretical models incorporating electron

correlation. *Int. J. Quant. Chem.*, 1976, S10, 1-19.

39 Dunning Jr T H. Gaussian basis functions for use in molecular calculations. I. Contraction of (9s5p) atomic basis sets for the first‐row atoms. *J. Chem. Phys.*, 1970, 53, 2823-2833.

40 Dunning T H, Hay P J.in *Methods of Electronic Structure Theory*, ed. H. F. Schaefer, Plenum Press, 1977, vol. 2, pp. 1–27.

41 Dunning Jr T H. Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. *J. Chem. Phys.*, 1989, 90, 1007-1023.

42 Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Petersson G A, Nakatsuji H, Li X, Caricato M, Marenich A V, Bloino J, Janesko B G, Gomperts R, Mennucci B, Hratchian H P, Ortiz J V, Izmaylov A F, Sonnenberg J L, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone A, Henderson T, Ranasinghe D, Zakrzewski V G, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery J A Jr, Peralta J E, Ogliaro F, Bearpark M J, Heyd J J, Brothers E N, Kudin K N, Staroverov V N, Keith T A, Kobayashi R, Normand J, Raghavachari K, Rendell A P, Burant J C, Iyengar S S, Tomasi J, Cossi M, Millam J M, Klene M, Adamo C, Cammi R, Ochterski J W, Martin R L, Morokuma K, Farkas O, Foresman J B, Fox D J. Gaussian 16, Revision B.01, Gaussian, Inc., Wallingford CT, 2016.

43 Bajorek T, Werstiuk N H. UV photoelectron spectroscopic and computational study of 7-substituted cycloheptatrienes. *Can. J. Chem.*, 2008, 86, 444-450.

44 Stortz C A. Conformational pathways of simple six‐membered rings. *J. Phys. Org. Chem.*, 2010, 23, 1173–1186.

45 Dixon D A, Komornicki A. Ab initio conformational analysis of cyclohexane. *J. Phys. Chem.*, 1990, 94, 5630-5636.

46 “IUPAC Commission on Nomenclature of Organic Chemistry”, A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993), 1993.

47 Eliel E L, Martin R J L. Conformational analysis. XIII. Validity of the nuclear magnetic resonance method of establishing conformational equilibriums. *J. Am. Chem. Soc.*, 1968, 90, 682-689.

48 Geise H J, Tieleman A, Havinga E. The conformation of non-aromatic ring compounds—XIX: The dipole moments of trans-2,3- and trans-5, 6-dihalogeno-5α-cholestanes. *Tetrahedron*, 1966, 22, 183-187.

49 Tian S X, Kishimoto N, Ohno K. Intramolecular Hydrogen Bonding in 2-Chloroethanol and 2-Bromoethanol and Anisotropic Interactions with He*(23S) Metastable Atoms: Two-Dimensional Penning Ionization Electron Spectroscopy Combined with Quantum Chemistry Calculations. *J. Phys. Chem. A*, 2003, 107, 53-62.

50 Dosˇen-Mićović L, Allinger N L. Conformational analysis—132: The effects of electrostatic interactions and solvation energies on conformational equilibria in dihalides and haloketones. Tetrahedron 34, 627, 1978. *Tetrahedron*, 1978, 34, 3385-3393.

51 Hageman H J, Havinga E. The conformation of non-aromatic ring-compounds—XXVII: The dipole moments of trans-aa-dihalogeno-4-t-butylcyclohexanes. *Tetrahedron*, 1966, 22, 2271-2274.

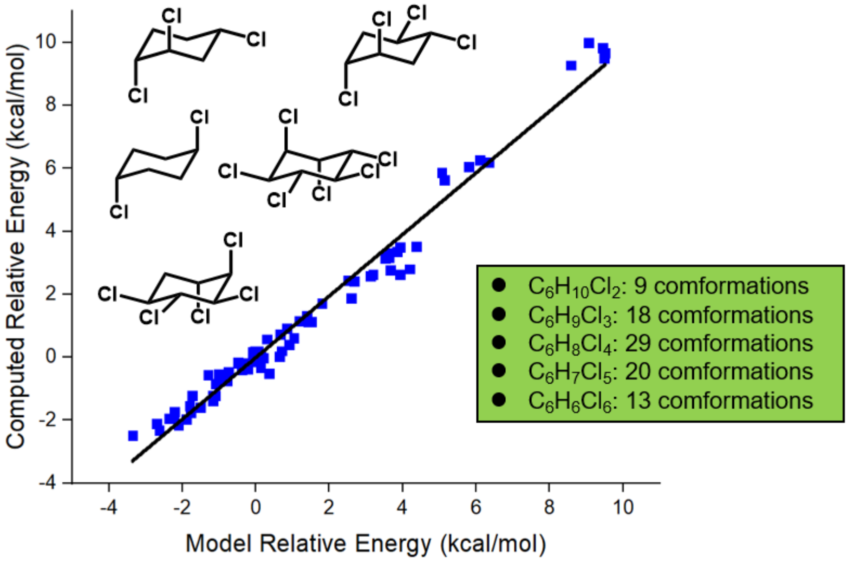
52 Zdravkovski Z. Theoretical study of the stability of hexachloro-and hexafluorocyclohexane isomers. *Bull. Chem. Technol. Macedonia*, 2004, 23, 131-137.

53 Keddie N S, Slawin A M Z, Lebl T, Philp D, O’Hagan D. All-cis 1, 2, 3, 4, 5, 6-hexafluorocyclo- hexane is a facially polarized cyclohexane. *Nat. Chem.*, 2015, 7, 483-488.

54 Benson S W, Buss J H. Additivity rules for the estimation of molecular properties. Thermodynamic properties. *J. Chem. Phys.*, 1958, 29, 546-572.

55 Cohen N, Benson S W. Estimation of heats of formation of organic compounds by additivity methods. *Chem. Rev.*, 1993, 93, 2419-2438.

Table of Contents



A simple but precise model equation to get accurate conformational energies of polychlorocyclohexane conformations.