

## THEORETICAL STUDY OF THE STABILITY OF HEXACHLORO- AND HEXAFLUOROCYCLOHEXANE ISOMERS

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The relative stabilities of hexachloro- and hexafluorocyclohexane isomers due to the various axial or equatorial positions of the substituents were studied by *ab initio* and density functional methods. All isomers were fully optimized at the HF, B3LYP and MP2 levels with the 6–31++G basis set. The energies, relative energies, and some geometric parameters of all possible isomers are given and discussed. In the case of both the chloro and fluoro isomers the most stable structure is the one having two neighboring axial substituents over the all-equatorial isomer which is usually assumed to be more stable. As expected the all-cis isomers with the largest values for the dipole moments are the least stable. Of the possible conformer pairs, the ones with more equatorial substituents are preferred over the ones with more axial substituents. The only exception is the pair of chlorine structures with the highest energies where the structure with more axial substituents (**4**) has negligibly a lower energy than the one with more equatorial substituents (**10**).

**Key words:** 1,2,3,4,5,6-hexachlorocyclohexane; 1,2,3,4,5,6-hexafluorocyclohexane; lindane; *ab initio*; modeling; conformation

### INTRODUCTION

Lindane, an insecticide belonging to the group of persistent organic pollutants, has been produced by chlorination of benzene under UV light. Several stereoisomers of hexachlorocyclohexane are produced under these conditions known as  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ - etc. isomers [1]. The dominant product of this reaction is the  $\alpha$ -isomer which was later determined to have two neighboring chlorine atoms in the axial positions while the other four are equatorial. Lindane, the  $\gamma$ -isomer, has three neighboring axial and three equatorial chlorine atoms attached to the cyclohexane ring [2]. While

there are numerous studies on the axial/equatorial preferences for mono and disubstituted cyclohexanes, the hexasubstituted cyclohexanes and their relative stability has not attracted so much attention. In this study we were interested in the relative stabilities of the possible isomeric structures of 1,2,3,4,5,6-hexachlorocyclohexane which arise from the various possible axial or equatorial positions of the chlorine atoms as well as the fluorine analogues *i.e.* the corresponding isomers of 1,2,3,4,5,6-hexafluorocyclohexane.

### COMPUTATIONAL METHODS

All calculations were performed with the Gaussian 98 and 03 suites of programs [3], while the visualization of the molecules was done with GaussView [4]. Complete optimizations were per-

formed on all possible isomers in the gas phase using the default Gaussian convergence criteria. Three theoretical levels were used: Hartree-Fock, the hybrid density functional B3LYP method and

the correlated second-order perturbation Møller-Plesset (MP2) method with the 6-31++G basis set. All geometry optimizations were performed by

turning off the symmetry constraints imposed by the Gaussian program.

## RESULTS AND DISCUSSION














It is well established that the substituents in the chair conformation of cyclohexane can assume either axial or equatorial positions. When all carbon atoms carry the same substituent other than hydrogen there are many possible conformers and isomers. The structures of the 13 possible isomers are given in Table 1. For simplicity in the structural formulas the axial substituents are not given and only the equatorial substituents are shown: structure **1** has only axial substituents, **2** has one equatorial and five axial substituents, there are three structures with two equatorial and four axial substituents (**3**, **4**, **5**), three with three equatorial and three axial substituents (**6**, **7**, **8**) etc. Lindane, structure **6**, also known as the  $\gamma$ -isomer, has three neighboring axial and three equatorial chlorine atoms. Structure **9**, the  $\alpha$ -isomer, is the only asymmetric structure and exists in two enantiomeric forms.

The results of the calculated energies of all structures at the various levels of theory are given in Table 2. The relative energies are also given in the table and in Fig. 1 for the B3LYP theory level. The density functional model gives lower energies than either of the two models for all isomers. However, all theoretical models predict that the most stable isomer is not the all-equatorial isomer **13** but **9** which has two neighboring axial substituents. As a matter of fact all three model chemistries predict that the all-equatorial isomer is also less stable than isomer **12** with one axial substituent. The correlated MP2 predicts that isomer **11** is more stable than **13**, while the B3LYP energy levels are the same. Only Hartree-Fock predicts that **13** is more stable than **11**.

What is the explanation for this 10 kJ/mol energy difference between the all-equatorial **13** and isomer **9**? A plausible explanation is that when all chlorine substituents are equatorial this "belt" becomes overcrowded and basically the steric hindrance is responsible for this decrease in stability. This might be somewhat of a surprise since it is usually assumed that the most stable isomer is the one where all substituents are in the equatorial positions. However, this is not always true and de-

pends in large part on the nature of the substituents. When they are unpolar alkyls they seem to prefer the equatorial positions. 1,2-Difluorocyclohexane on the other hand is more stable when the two fluorine atoms are axial [5].

Table 1  
*Structures of the possible isomers of hexahalo cyclohexanes*

Structure	Configuration	Formula*
1	aaaaaa	
2	aaaaae	
3	aaaaee	
4	aaaeae	
5	aaeaae	
6	aaae <sub>γ</sub> ee	
7	aaeae <sub>α*</sub> ee	
8	aeaeae	
9	aeae <sub>ε</sub> eee	
10	aeae <sub>δ</sub> eee	
11	aeae <sub>β</sub> eee	
12	aeae <sub>ε</sub> eee	
13	aeae <sub>δ</sub> eee	

\* Only the equatorial substituents are given, the axial are assumed, see text.

Table 2

Calculated energies for the isomers of hexachlorocyclohexane and relative energies compared to the most stable structure 9

Configuration	$E(\text{HF})$	$\Delta E$	$E(\text{B3LYP})$	$\Delta E$	$E(\text{MP2})$	$\Delta E$	
	/ kJ·mol <sup>-1</sup>						
1	aaaaaa	-7843330.9	35.0	-7858839.4	28.5	-7845532.8	34.6
2	aaaaae	-7843335.0	30.9	-7858842.4	25.5	-7845540.1	27.3
3	aaaace	-7843349.6	16.3	-7858855.0	12.9	-7845553.5	13.9
4	aaacee	-7843322.7	43.2	-7858830.6	37.3	-7845532.2	35.2
5	aaceae	-7843342.1	23.8	-7858848.6	19.3	-7845549.8	17.6
6	aaacee	-7843348.7	17.2	-7858853.4	14.5	-7845552.7	14.7
7	aaceee	-7843343.4	22.5	-7858848.9	19.0	-7845550.5	16.9
8	aeaeae	-7843291.2	74.7	-7858801.2	66.6	-7845507.4	60.0
9	aeaeae	-7843365.9	0.0	-7858867.9	0.0	-7845567.4	0.0
10	aeaeae	-7843322.0	43.8	-7858828.4	39.4	-7845531.7	35.7
11	aeaeae	-7843350.7	15.2	-7858854.7	13.2	-7845556.0	11.4
12	aeaeae	-7843354.5	11.3	-7858856.6	11.3	-7845557.6	9.8
13	aeaeae	-7843351.8	14.0	-7858854.6	13.2	-7845554.1	13.3

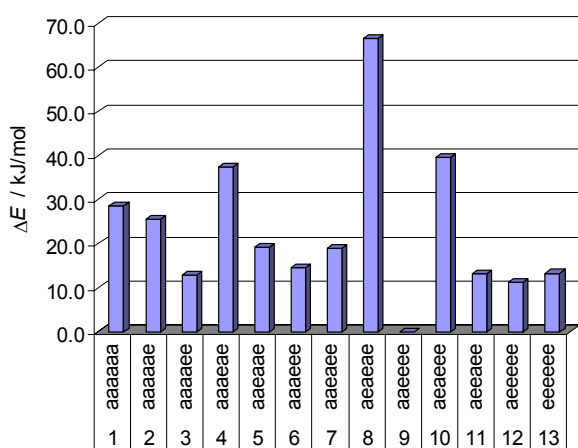


Fig. 1. Relative energies of the hexachlorocyclohexanes at the B3LYP/6-31++G level

The case is more complicated when the number of substituents is even larger. Glucose, although a heterocycle, comes to mind where the  $\beta$ -D-glucopyranose isomer is more stable than the  $\alpha$ -isomer. However, when the anomeric OH group is substituted into glycoside the stability can be shifted to the  $\alpha$ -isomer. This is known as the *anomeric effect* [6]. From Table 1 we see that **12**, the structure with only one axial chlorine atom, has a total energy by 2–3 kJ/mol less when compared to **13**, the all-equatorial isomer. Isomer **9** has two neighboring axial substituents and is significantly

more stable (more than 10 kJ/mol) than the all-equatorial **13**. We can call this a *double anomeric effect* structure. Considering that in the photochemical reaction of chlorine and benzene it is the dominant product, it is safe to assume that the reaction is thermodynamically controlled. At this level of calculations lindane is less stable by almost 15 kJ/mol than the most stable isomer both at the B3LYP and the MP2 levels.<sup>1</sup>

Table 3 gives the total dipole moments for each structure in the gas phase as well as the average C–Cl bond lengths and their standard deviations. It is apparent that the bond lengths are longer when the chlorine atoms assume axial positions. Thus in **1** the bond lengths of all C–Cl bonds are the same 1.91 Å both at the B3LYP and MP2 levels, and the standard deviation is equal to 0.00. The greatest variations in the C–Cl lengths are in **4** where the standard deviation has the largest values. The least stable structure **8** whose energy is higher by more than 60 kJ/mol than the most stable one, has the largest value for the dipole moment. This is easily explained since the layout of the substituents is *aeaeae*, which represents the very unfavorable all-cis arrangement of the chlorine atoms where their interactions are very large.

<sup>1</sup>It should be noted that the calculations were performed for the gas phase and as one of the reviewers commented it would be interesting to consider the solvent effects.

Table 3

Dipole moments, average bond lengths and their standard deviations for the isomers of hexachlorocyclohexane

Configuration	HF			B3LYP			MP2			
	$\mu / \text{D}$	$\bar{l} (\text{C-Cl}) / \text{\AA}$	$\sigma (\text{C-Cl}) / \text{\AA}$	$\mu / \text{D}$	$\bar{l} (\text{C-Cl}) / \text{\AA}$	$\sigma (\text{C-Cl}) / \text{\AA}$	$\mu / \text{D}$	$\bar{l} (\text{C-Cl}) / \text{\AA}$	$\sigma (\text{C-Cl}) / \text{\AA}$	
1	aaaaaa	0.00	1.882	0.000	0.00	1.914	0.000	0.00	1.912	0.000
2	aaaaae	2.40	1.872	0.017	2.21	1.901	0.020	2.52	1.902	0.016
3	aaaeee	2.59	1.869	0.016	2.39	1.898	0.020	2.77	1.899	0.015
4	aaaeae	4.39	1.861	0.020	3.98	1.888	0.024	4.54	1.891	0.018
5	aaeeae	0.00	1.862	0.011	0.00	1.889	0.013	0.00	1.892	0.010
6	aaeeee	3.63	1.865	0.016	3.30	1.892	0.019	3.80	1.892	0.010
7	aaeeae	2.73	1.859	0.013	2.48	1.885	0.016	2.84	1.895	0.015
8	aeaeae	6.65	1.847	0.001	5.99	1.872	0.001	6.85	1.878	0.000
9	aeaeae	2.90	1.863	0.010	2.63	1.889	0.013	3.01	1.893	0.010
10	aeaeae	4.68	1.852	0.004	4.22	1.877	0.004	4.86	1.883	0.003
11	aeaeae	0.00	1.857	0.011	0.00	1.882	0.013	0.00	1.888	0.011
12	aeaeae	2.76	1.858	0.010	2.50	1.883	0.006	2.87	1.888	0.005
13	eeeeee	0.00	1.859	0.000	0.00	1.884	0.000	0.00	1.889	0.000

The calculated energies, dipole moments and bond lengths at the B3LYP and MP2 levels follow similar patterns for the fluoro analogues. Table 4 and Fig. 2 give the relative energies compared to the most stable isomer and Table 5 gives the dipole moments, bond lengths of the C–F bonds and their standard deviations. Again we encounter the double anomeric effect structure **9** as the most stable of all chair isomers. The least stable is **8**, the all-cis structure with the largest value for the dipole mo-

ment. However, there is one difference in the energy levels of the chloro and fluoro isomers. The fluoro isomer **11** at both levels of theory is the next most stable structure after **9** and is more stable than **12** and **13**. This is not the case with the chloro isomer. The effect of the size clearly plays a role here allowing the smaller fluoro substituent to assume positions that the larger chlorine atom would add to the strain of the molecule as a whole.

Table 4

Calculated energies for the isomers of hexafluorocyclohexane and relative energies compared to the most stable structure **9**

Structure	Configuration	$E(\text{B3LYP})$	$\Delta E(\text{B3LYP})$ / (kJ/mol)	$E(\text{MP2})$	$\Delta E(\text{MP2})$
1	aaaaaa	-2182165.9	23.7	-2174935.9	23.8
2	aaaaae	-2182167.2	22.4	-2174937.4	22.3
3	aaaeee	-2182180.5	9.1	-2174952.2	7.5
4	aaaeae	-2182153.0	36.6	-2174922.0	37.7
5	aaeeae	-2182172.1	17.4	-2174942.3	17.4
6	aaeeee	-2182177.9	11.7	-2174948.1	11.6
7	aaeeae	-2182174.4	15.1	-2174945.2	14.5
8	aeaeae	-2182126.3	63.3	-2174892.5	67.2
9	aeaeae	-2182189.6	0.0	-2174959.7	0.0
10	aeaeae	-2182158.1	31.5	-2174925.7	34.0
11	aeaeae	-2182184.7	4.8	-2174956.5	3.3
12	aeaeae	-2182181.2	8.4	-2174949.5	10.3
13	eeeeee	-2182178.1	11.4	-2174943.4	16.3

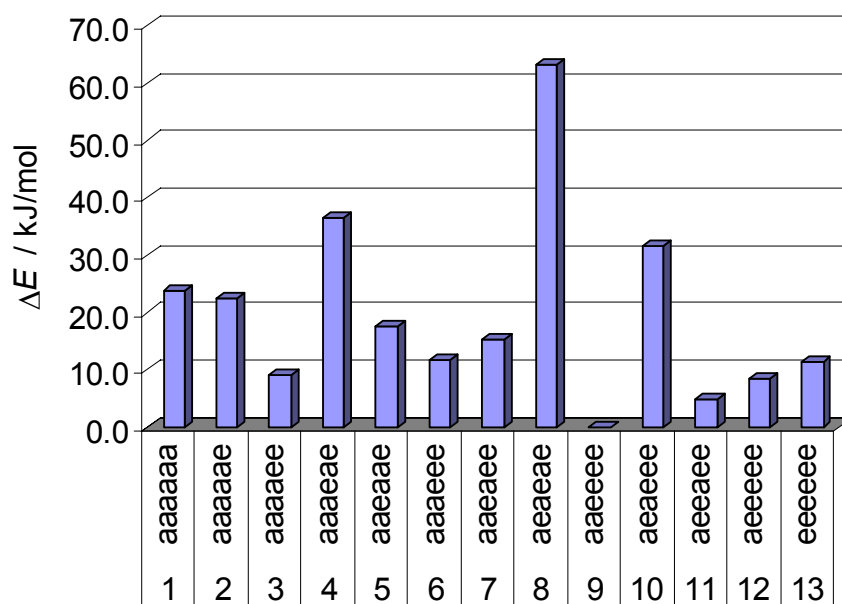


Fig. 2. Relative energies of the hexafluorocyclohexanes at the B3LYP/6-31++G level

Table 5

*Dipole moments, average bond lengths and their standard deviations for the isomers of hexafluorocyclohexane*

Structure	Configuration	B3LYP			MP2		
		$\mu / \text{D}$	$\bar{l} (\text{C-F}) / \text{\AA}$	$\sigma(\text{C-F}) / \text{\AA}$	$\mu / \text{D}$	$\bar{l} (\text{C-F}) / \text{\AA}$	$\sigma(\text{C-F}) / \text{\AA}$
1	aaaaaa	0.00	1.458	0.000	0.00	1.476	0.000
2	aaaaae	3.01	1.453	0.009	3.59	1.471	0.009
3	aaaace	3.14	1.452	0.008	3.73	1.472	0.007
4	aaaeae	5.54	1.446	0.012	6.59	1.464	0.012
5	aaeeae	0.00	1.449	0.005	0.00	1.467	0.005
6	aaeeee	4.61	1.450	0.008	5.51	1.469	0.008
7	aaeeae	3.34	1.448	0.009	4.01	1.467	0.009
8	aeaeae	8.03	1.437	0.002	9.55	1.455	0.002
9	aeaeae	3.55	1.452	0.007	4.30	1.471	0.007
10	aeaeae	5.68	1.443	0.004	6.79	1.461	0.004
11	aeaeae	0.00	1.449	0.010	0.00	1.468	0.010
12	aeaeae	3.30	1.449	0.006	3.97	1.468	0.006
13	eeeeee	0.00	1.448	0.000	0.00	1.467	0.000

It is assumed that there are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane of which two are enantiomers and seven are meso compounds [2]. This is based on the assumption that some of the structures given in Table 1 are equivalent taking into account a possible chair to chair transformation when all substituent that are in axial

positions assume equatorial positions and vice versa. Taking this into account Table 6 gives the possible interconversions and the energy differences of the corresponding structures.<sup>2</sup> It is appar-

<sup>2</sup> These are not the transition state energies which will be calculated and published elsewhere.

ent that the structures with more equatorial positions are preferred over the ones with more axial positions. There is only one exception. In the case of the chloro compounds, **4** has a somewhat lower energy than **10**. It should be noted that these conformers have the largest energy levels of all pairs of structures (tables 2 and 4), which shows that when the compounds have high enough energies the axial positions may be preferred over the equa-

torial. Calculations are under way to determine the activation energies of these transformations which will resolve the questions whether these structures are really conformers or isomers. If the activation energies are high enough, as we expect, these interconversions would be unfavorable and the structures would represent isomers and not simple conformers.

Table 6

Possible chair to chair transformations for the hexasubstituted cyclohexanes

Transition		Cl		F	
		$\Delta E(\text{B3LYP})$	$\Delta E(\text{MP2})$	$\Delta E(\text{B3LYP})$	$\Delta E(\text{MP2})$
1 $\rightleftharpoons$ 13		-15.2	-21.4	-12.3	-7.5
2 $\rightleftharpoons$ 12		-12.2	-17.5	-14.0	-12.1
3 $\rightleftharpoons$ 9		-12.9	-13.9	-9.1	-7.5
4 $\rightleftharpoons$ 10		2.2	0.5	-5.1	-3.7
5 $\rightleftharpoons$ 11		-6.1	-6.2	-12.6	-14.1

## CONCLUSION

There are several points that can be made from this study. The all equatorial positions for chlorine and fluorine as substituents in the chair cyclohexane do not give the most stable structure. The anomeric effect is in play or better the double anomeric effect gives the most stable structure both for chlorine and fluorine as substituents. This is somewhat surprising in view of the fact that they have rather different atomic volumes and electronegativities. The isomer with the highest dipole

moment and the all-cis configuration is the least stable. As for the "conformational" isomers, generally the conformer with more equatorial substituents would be preferred over the one with more axial substituents. The only exception is the pair of chlorine structures with higher energies than the other four pairs, where the structure with more axial substituents (**4**) has a lower energy than the one with more equatorial substituents (**10**).

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## Резиме

### ТЕОРИСКО ИСТРАЖУВАЊЕ НА СТАБИЛНОСТА НА ХЕКСАХЛОРО- И ХЕКСАФЛУОРОЦИКЛОХЕКСАНСКИТЕ ИЗОМЕРИ

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**Клучни зборови:** 1,2,3,4,5,6-хексахлороциклохексан; 1,2,3,4,5,6-хексафлуороциклохексан; линдан; *ab initio*; моделирање; конформација

Релативната стабилност на хексахлоро- и хексафлуороциклохексанските изомери што се должи на нивната различна аксијална или екваторијална положба на супституентите беше истражувана со *ab initio* методи. Сите изомери беа целосно оптимизирани на теориските нивоа HF, B3LYP и MP2 со помош на базисниот сет 6-31++G. Дадени се и дискутирани се соодветните енергии, релативните енергии и некои геометриски параметри на сите изомери. Во случајот и на хлоро- и на флуороизомерите структурата со два соседни аксијални супституенти е постабилна во однос на очекуваните изомери, каде што сите супституенти

се во екваторијална положба. Според очекувањата најмалку стабилни се изомерите каде што сите супституенти се во цис-положба, при што имаат и најголеми диполни моменти. Ако се споредуваат паровите на конформери, конформерот кој има поголем број екваторијални супституенти е постабилен во однос на оној со помалку екваторијални супституенти. Единствен исклучок е парот на хлорни конформери со највисока енергија, каде што изомерот со повеќе аксијални супституенти (**4**) е малку постабилен во однос на оној со повеќе екваторијални супституенти (**10**).