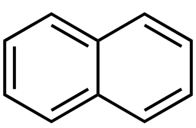
D1CH9116 - MMCO

Molecular Modelling applied to organic chemistry

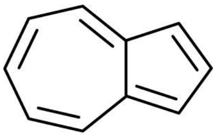
Practical 2: Molecular isomers

A/ Electronic structure of isomers

Determine the optimal geometry and the electronic structure of the naphtalene and azulene isomers at the AM1 level. Check the dipole moment and the HOMO-LUMO gap for the two structures, and comment.



Naphtalene



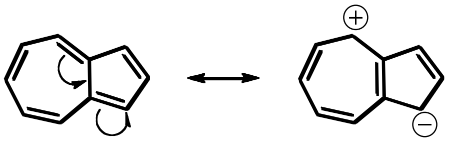
Azulene

Results

Property	**Naphthalene**	**Azulene**
HOMO-LUMO gap (eV)	8.446	7.153
Dipole moment (D)	0.000	1.512

Conclusions

Compared to naphthalene, azulene exhibits a reduced HOMO-LUMO gap. The maximum absorption is shifted from the UV to the visible range; the naphtaleme molecule is colorless, the azulene is blue. The lower maximum absorption energy in naphtalene is due to the larger ground-state charge transfer, as indicates its nonzero dipole moment. This latter is a consequence of the significant contribution of zwitterionic configurations in the ground state wavefunction, as illustrated below.



The zwitterionic forms are stabilized by the fact that both the 5- and 7-membered carbon rings (taken independently) contain 6 electrons, and are thus aromatic regarding the Hückel rule (4n+2).

B/ Relative energies of isomers

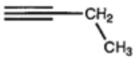
Optimize the structures of isomers **1**-**8** at the AM1 and PM6 levels, and compare their relative energy (heats of formation) to the experimental results.

1

2

3

4



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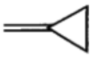

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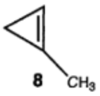


8

Isomer	Energies relative to 1 (kcal/mol)
2	8.6
3	11.2
4	12.4
5	13.2
6	21.7
7	25.6
8	31.9

Results

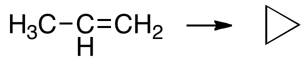
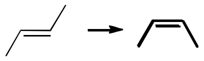
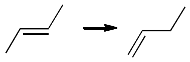
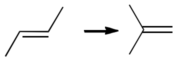
	AM1		PM6	
Isomer	Heat of formation (kcal/mol)	Relative energy (kcal/mol)	Heat of formation (kcal/mol)	Relative energy (kcal/mol)
1	29.91	0.00	28.46	0.00
2	31.98	2,07	35.14	6,68
3	45.76	15,85	33.76	5,30
4	37.11	7,20	30.14	1,68
5	37.49	7,58	41.16	12,70
6	47.66	17,75	35.82	7,36
7	78.10	48,19	59.51	31,05
8	64.66	34,75	50.03	21,57

Conclusions

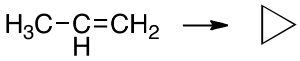
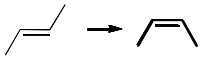
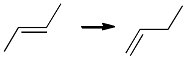
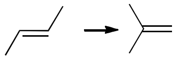
The two parameterizations predict that isomer **1** is the most stable. However, none of them predict the correct ordering. The same conclusion is obtained at the PM3 level.

C/ Isomerization reactions

The Table below reports isomerization reactions together with the experimental heats of isomerization. Optimize in each case the two equilibrium structures at the AM1 and PM6 levels and note their energy (heats of formation). Calculate the heats of isomerization and compare to experimental results.

Isomerization reaction	**Experimental heats of isomerization (kcal/mol)**
	21.8
	7.8
	1.1
	2.8
	-1.3

Calculated heats of isomerization (kcal/mol)

Reaction	AM1	PM3	PM6	Exp.
	31.1	28.0	15.6	21.8
	10.7	9.9	5.6	7.8
	1.1	1.3	1.0	1.1
	3.5	5.2	4.6	2.8
	2.2	0.4	–1.6	–1.3

Conclusions

AM1 and PM3 provide correct heats of isomerization with respect to experiments for the first four reactions. These two parameterizations qualitatively fail for the fifth one, by predicting positive isomerization energies. This discrepancy is corrected when using PM6.

D/ Relative populations of conformers

The population of a conformer *i* at a given temperature T can be evaluated using the Boltzmann distribution:

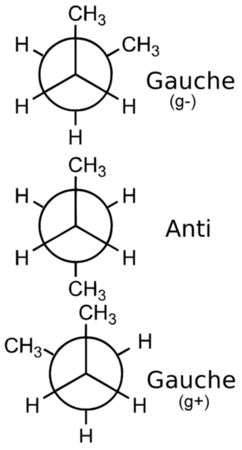
$$\frac{N_i}{N_{total}} = \frac{\exp\left(-E_i/RT\right)}{\sum_{k=1}^{N_{total}} \exp\left(-E_k/RT\right)}$$

where N_{total} is the total number of conformers, E_k is the relative energy of the *k*-th conformer with respect to the minimum energy conformer (J/mol), *R* the molar ideal gas constant equal to 8.31 (J/mol/K) and *T* the temperature in kelvins (K).

1/ Considering a 2-conformation Boltzmann distribution, plot the population of the lowest-energy conformer at room temperature as a function of their energy difference.

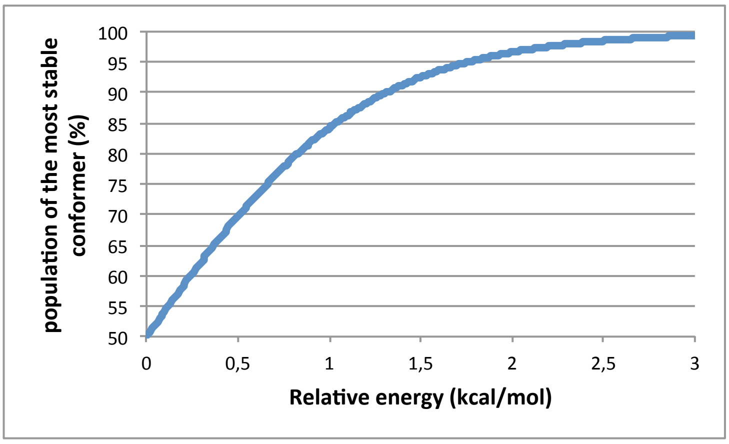
2/ Calculate the energy difference necessary to obtain a population ratio larger than 99% for the most stable form.

3/ Evaluate the relative population of the *gauche* and *anti* rotamers of butane at the AM1 and PM6 levels.



Results

1/ Population of the lowest-energy conformer at room temperature as a function of their energy difference



2/ The population of the less stable conformer is negligible (less than 1%) for an energy difference of about 2.75 kcal/mol.

3/ Relative populations of the *gauche* and *anti* rotamers of butane

	Energy Gauche (kcal/mol)	**Energy Anti (kcal/mol)**	**Difference (kcal/mol)**	**Pop.**
AM1	−30.42	−31.13	0.71	77%
PM6	−25.32	−26.04	0.72	77%

E/ Chiral molecules

The 2-bromo-3-fluorobutane molecule, which contains two chiral centers, has four possible stereoisomers:

- **1.** (2R,3R)
- **2.** (2R,3S)
- **3.** (2S,3R)
- **4.** (2S,3S)

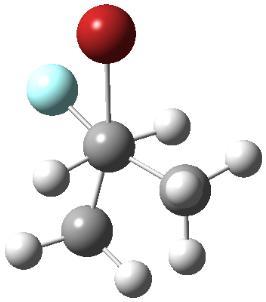
The pairs of compounds (1,4) and (2,3) are enantiomers (mirror images), and are therefore equally stable. The pairs (1,2) and (3,4) are diastereomers (non-mirror images), and have different energies.

1/ Calculate the total energy (heat of formation) of compounds **1** and **2** at the AM1 level and deduce the most stable configuration(s). *Use the tool "switch about an atom" of AGUI to change the configuration of carbon 3.*

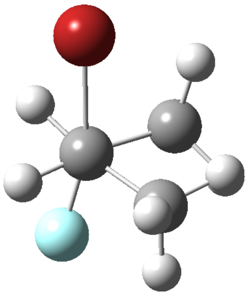
2/ Evaluate the relative populations of **1** and **2** using a Boltzmann distribution at room temperature.

Geometrical structures and associated heats of formation calculated at the AM1 level

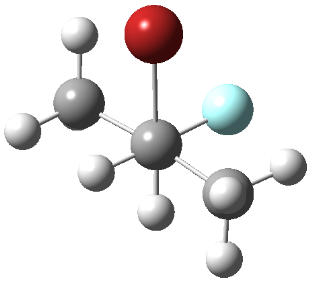
Both diastereoisomer **1** (2R,3R) and **2** (2R,3S) possess 3 rotamers:



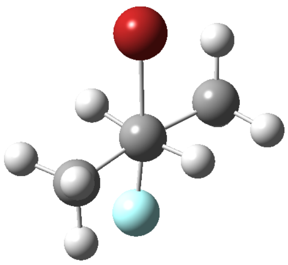
1a
-66.38 kcal/mol
6.9 %



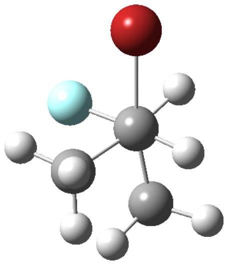
1b
-67.19 kcal/mol
26.9 %



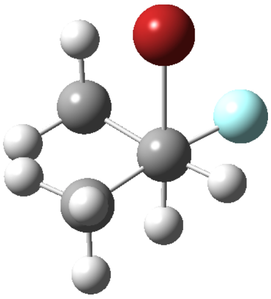
1c
-66.55 kcal/mol
9.2 %



2a
-67.37 kcal/mol
36.3 %



2b
-66.71 kcal/mol
12.0 %

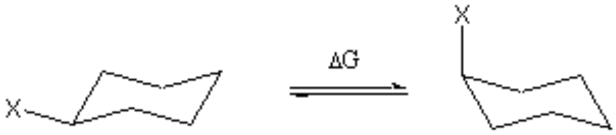


2c
-66.52 kcal/mol
8.7 %

The most stable form is **2a** where the halogen atoms are in *anti* position, as well as the halogen atoms, which minimizes both the steric and electrostatic repulsion. Summing the populations of their different rotamers, the population ratio of diastereoisomers **1** and **2** is 42.9:57.1.

F/ Axial-equatorial conformations in methylcyclohexane

The amount of energy it "costs" to move a substituent group from the equatorial to the axial position is sometimes referred to as the A-value of that substituent group. The A-values of several substituent groups are listed below. Calculate the energy difference between the equatorial and axial conformers at the AM1 and PM6 levels, and compare to the experimental results.



X	ΔG (kcal/mol)
H	0
Me	1.8
Et	1.8
i-Pr	2.1
t-Bu	> 4.5
F	0.25
Cl, Br, I	0.5
OH	0.9