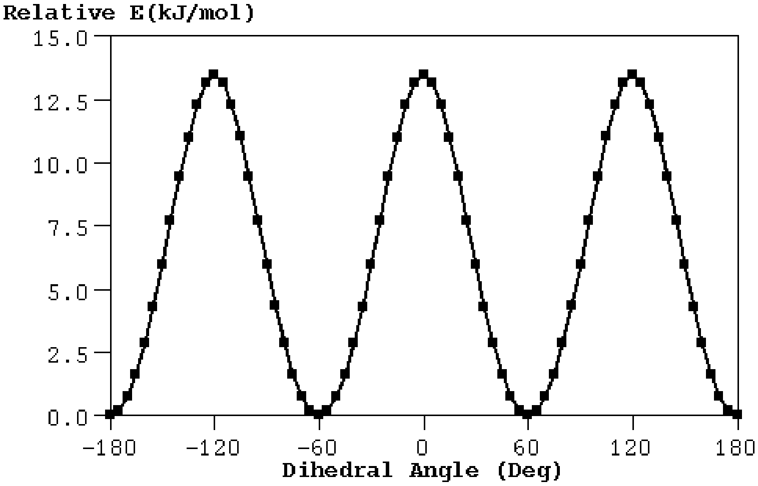
Conformations of Organic Molecules

Conformational Analysis

Organic molecules can assume different spatial arrangements (**conformations**) which are generated by rotation about single bonds. A detailed analysis of the various conformations adopted by individual molecules is termed **Conformational Analysis**. Conformational analysis is an important tool for chemists trying to unravel the complex structure of both organic and bio-organic molecules in an effort to obtain a clearer understanding of the reactivity and interaction with other molecules.

As the simplest example of **Conformational Analysis**, let us look at the rotation of the two methyl groups about the **C-C** bond in **ethane** ($\mathbf{H_3C - CH_3}$) as is shown in the figure below:

Rotational Energy Profile for Ethane (H_3C-CH_3)



Two terms associated with conformational analysis include the following:

- **Conformers** - These are structures that differ by rotation around one or more bonds. Examples of conformers include minima, maxima, and transition states. In the figure above, the **H-C-C-H** torsion angles (or dihedral angles) at ±180° and ±60° are minima and are designated as ***staggered*** conformations. Those at ±120° and 0° are maxima and are ***eclipsed*** conformations.

Conformations of Organic Molecules

What do the terms *staggered* and *eclipsed* mean? How are they derived?

This in not very difficult at all to explain. Imagine picking up the **ethane** molecule with your left hand, grasping it at the center of the **C-C** bond, holding it up to your eye, and looking down the **C-C** axis. The carbon atom closest to your eye has three hydrogen atoms attached to it while the carbon at the other end of the **C-C** bond also has three hydrogens bonded to it. Again, imagine taking your right hand and rotating the carbon atom farthest from you around the **C-C** bond such that those three hydrogen atoms ”hide” behind the three hydrogen atoms closest to your eye. In other words these hydrogen atoms are now ***eclipsed*** similar to the way in which the moon can eclipse the sun. Now, perform this rotation once again but this time stopping when each hydrogen atom on the near carbon atom is situated exactly between (or ***staggered***) the hydrogen atoms on the far carbon atom.

- **Conformations -** These structures correspond to any point on the **Potential Energy Surface**. The **Potential Energy Surface** is really nothing more than the **Rotational Energy Profile** given above. So if I choose a specific value of the dihedral angle (Φ) on the curve above, it will correspond to a **Conformation**. This term usually applies to a molecule which has one or more bonds about which rotation can take place. In the figure above, any value of the **H-C-C-H** torsion angle will produce a **conformation** for ethane.

Quantum Mechanics versus Molecular Mechanics

As we have seen previously, the **Quantum Mechanical** description of a chemical bond is derived from the solution of the Schrödinger Equation and is described by accumulation of electron density between two nuclear centers.

In contrast, **Molecular Mechanics** describes the energies of molecules in terms of ***classical*** potential energy functions. These potential functions are called ***classical*** because they are derived from classical concepts. For example, the bonding between atoms is represented balls connected by springs. The classical potential functions (ball and spring models) and the parameters associated with them (stiffness of the spring, etc) are collectively known as a ***Force Field***. The energy of a molecule obtained from **Molecular Mechanics** is known as the **Strain Energy** and is a simple sum of the energies involved in bond stretching, angle bending, torsional rotation, and non-bonded interactions acting through space.

The following exercises are geared toward deriving an understanding of the conformations of organic molecules using both **Quantum Mechanics** and **Molecular Mechanics** allowing us to determine the manner in which **Conformations** of molecules are intimately intertwined with their reactivity.

Ethane ($H_3C–CH_3$) and Substituted Ethane

The ethane molecule, **C_2H_6**, can exist in both the *staggered* and *eclipsed* conformations where the *staggered* conformation is slightly more stable. The differences in these two conformations for ethane can easily be seen by viewing them both on the screen simultaneously. Look down the **C-C** bond, and you will see that the hydrogen atoms on the two carbon atoms (i.e. **H-C-C-H** dihedral angle) of *staggered* ethane are rotated with respect to each other whereas for *eclipsed* ethane they are not.

View the rotational energy profile (**Energy versus Torsion Angle, Φ**) of the **ethane** molecule as a function of the **H–C–C–H** torsion angle observing the energy changes as the torsion angle varies. Also, try different renderings of the ethane molecule. See how the important conformations appear with the Ball-and-Stick, Polytube, and Space Filling models.

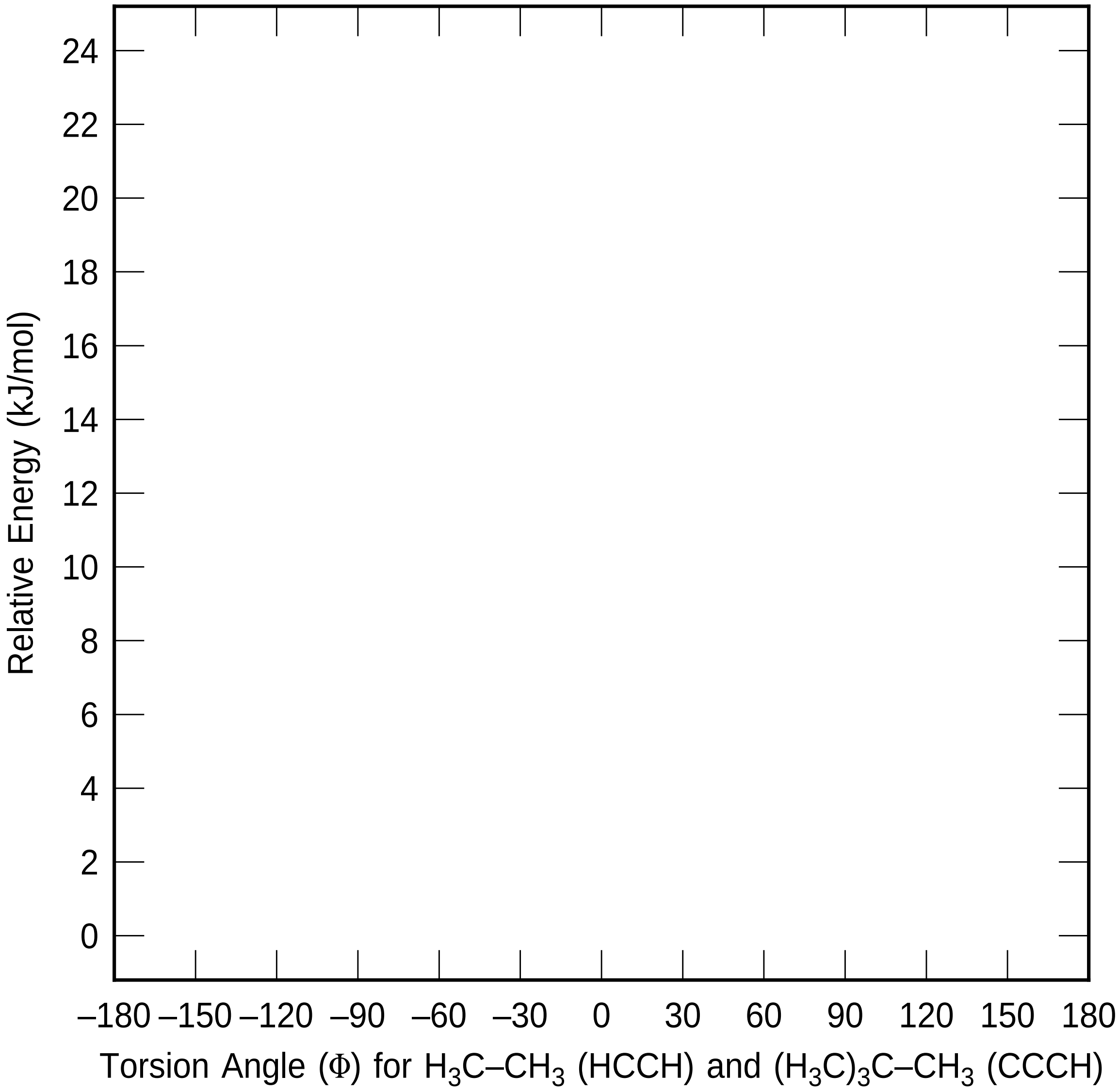
Then, view the electron density distributions for the ***staggered*** and ***eclipsed*** conformations of **ethane**.

These procedures should lead you to a deeper understanding of the interactions involved in the rotation around the **ethane C–C** bond.

Now repeat the above steps for **neopentane, ($(CH_3)_3C – CH_3$)**. In this case, three of the **H** atoms on one **C** atom are replaced by three methyl groups (**CH_3**).

Rotational Energy Profiles for $H_3C–CH_3$ and $(CH_3)_3C$-CH_3

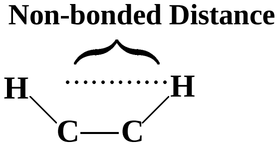
Using the graph provided below, sketch the **Rotational Energy Profile** for **ethane** and **neopentane**. On the graph, also designate the minima (***staggered*** conformations) and maxima (***eclipsed*** conformations).



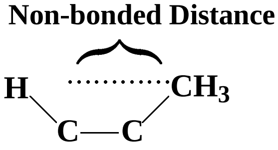
Non-Bonded Interactions for $H_3C–CH_3$ and $(CH_3)_3C$-CH_3

The influence of non-bonded interactions on stable conformations of $\mathbf{H_3C} - \mathbf{CH_3}$ and $(\mathbf{CH_3})_3\mathbf{C} - \mathbf{CH_3}$ can be easily traced. The repulsive non-bonded interaction energy between atoms that are not bonded (*Sometimes this is called the steric interaction energy.*) is related to the non-bonded distances between these atoms. The shorter the non-bonded distance, the larger the repulsive non-bonded interaction. Thus, the ***shortest*** non-bonded distance is the most important one because it is responsible for the largest repulsive energy and destabilizes the molecule the most. Non-bonded interactions sometimes can be a source of confusion for students. Specifically, chemists are interested in those non-bonded interactions between two groups that are bonded to different atoms as shown below:

H ⋯ H Non-Bonded Interaction



H ⋯ CH_3 Non-Bonded Interaction

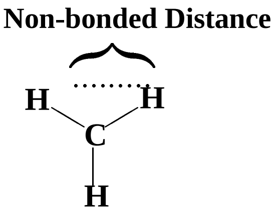


Note that the **H** ⋯ **H** or **H** ⋯ $\mathbf{CH_3}$ nonbonded distances shown in the figures above will vary as rotation around the **C-C** bond takes place. This will also change the non-bonded interaction energy and therefore influence the conformation.

Non-Bonded Interactions for $H_3C–CH_3$ and $(CH_3)_3C$-CH_3

The confusion for students is derived by viewing another type of **H** · · · **H** non-bonded interaction as shown below:

<u>H · · · H Non-Bonded Interaction - H Atoms on Same Center</u>



Both **H** atoms are attached to the same **C** atom. The **H** · · · **H** non-bonded distance in this case is fixed by the **H-C-H** angle. Now, rotation about the **C-C** bond will not change the **H** · · · **H** non-bonded distance. The non-bonded interaction energy will not vary for this type of non-bonded interaction and is usually not of interest to chemists.

Rotational Energy Profiles for $H_3C–CH_3$ and $(CH_3)_3C\text{-}CH_3$

Sketches of Staggered and Eclipsed $\mathbf{H_3C - CH_3}$

Sketches of Staggered and Eclipsed $\mathbf{(CH_3)_3C - CH_3}$

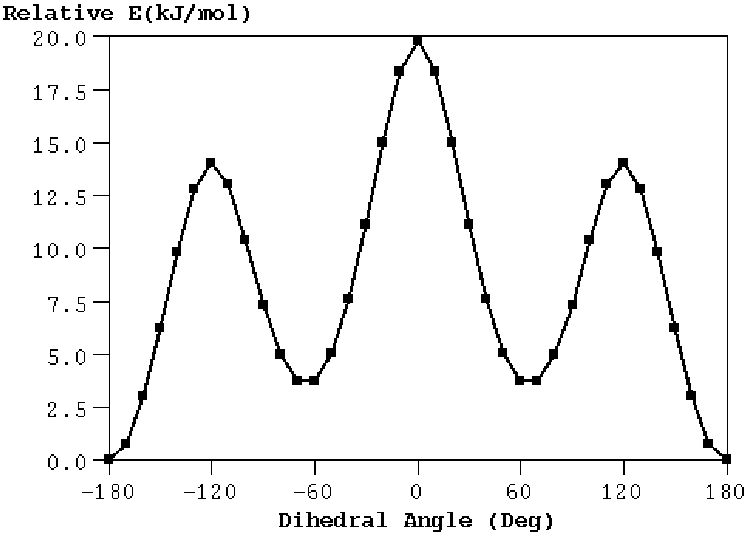
Questions

1. Obtain the $\mathbf{H \cdots H}$ and $\mathbf{H \cdots CH_3}$ non-bonded distances for the eclipsed and staggered forms. Indicate the $\mathbf{H \cdots H}$ and $\mathbf{H \cdots CH_3}$ non-bonded distances on the sketches for $\mathbf{H_3C - CH_3}$ and $\mathbf{(CH_3)_3C - CH_3}$, respectively given above.
2. On the basis of your results, provide an explanation of the influence of non-bonded energies on the relative stabilities of the ***staggered*** and ***eclipsed*** conformations of $\mathbf{(CH_3)_3C - CH_3}$. Explain why the staggered conformation has the lowest energy.
3. Also provide an explanation for the differences (e.g. higher rotational barrier for $\mathbf{(CH_3)_3C - CH_3}$) and similarities (e.g. rotational energy periodicity) for $\mathbf{H_3C - CH_3}$ and $\mathbf{(CH_3)_3C - CH_3}$.

Butane ($H_3C–CH_2–CH_2–CH_3$)

The rotational energy profile for the **butane** molecule is given in the figure below.

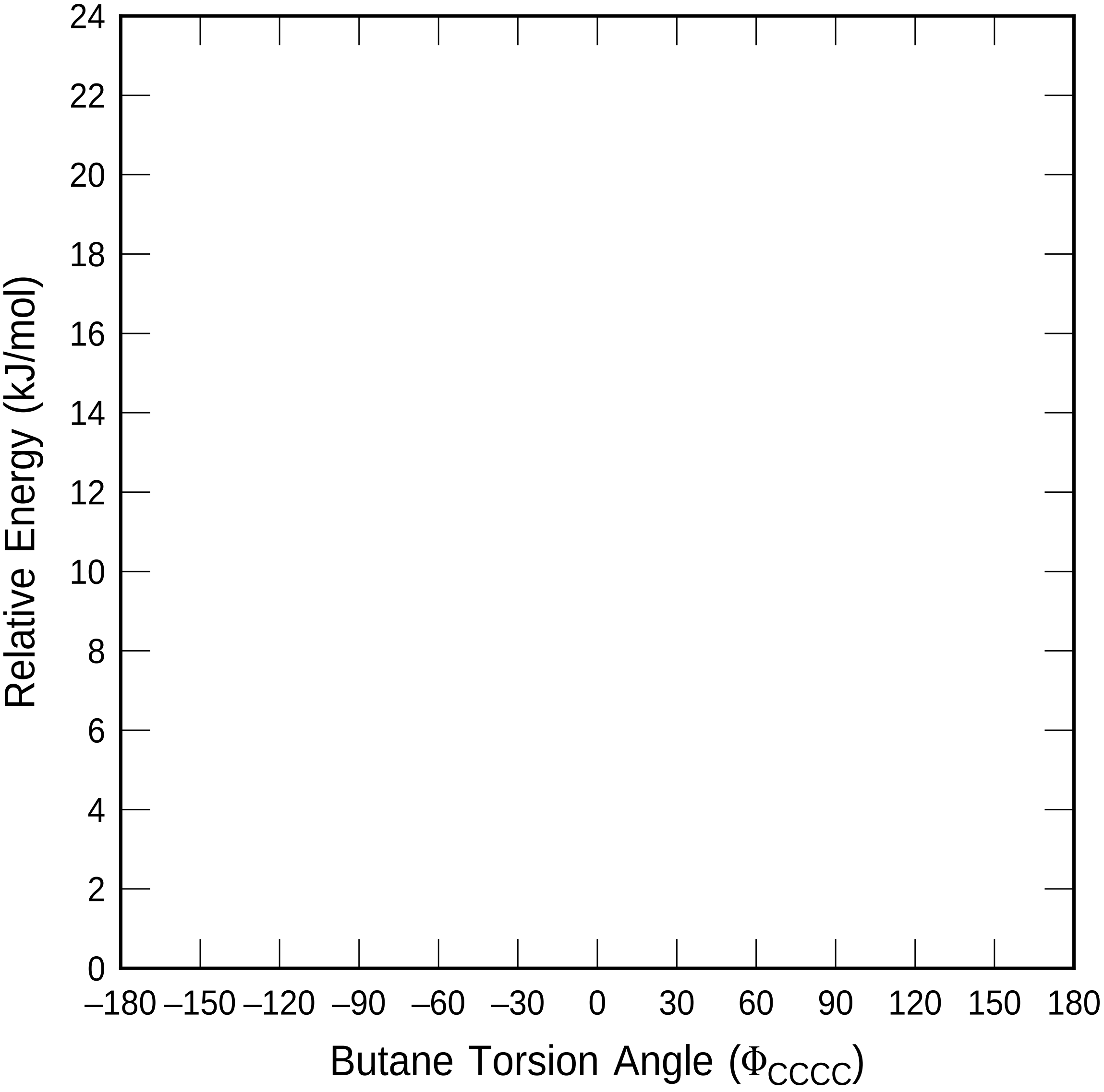
Rotational Energy Profile for Butane (CH_3CH_2 – CH_2CH_3)



Butane has three conformers defined by the **C–C–C–C** torsion angle ($\Phi_{\mathbf{C\text{-}C\text{-}C\text{-}C}}$). These include the ***anti or trans*** **(a)** conformation where $\Phi_{\mathbf{C-C-C-C}} = \pm 180^0$ and the two ***gauche*** (**g^+**, **g^-**) conformations defined by $\Phi_{\mathbf{C-C-C-C}} = \pm 60^0$. There are also three different maxima present: $\Phi_{\mathbf{C-C-C-C}} = \pm 120^0$ and $\Phi_{\mathbf{C-C-C-C}} = 0^0$
View the rotational profile (the energy versus torsion angle) of the butane molecule as a function of the **C–C–C–C** torsion angle from -180^0 to +180^0.

Rotational Energy Profile for $CH_3CH_2–CH_2CH_3$

Using the graph provided below, sketch the rotational energy profile for **butane**.
On the graph, also designate the minima **(a, g^+, g^- conformations)** and maxima (***eclipsed*** conformations).



Rotational Energy Profile for $CH_3CH_2–CH_2CH_3$

Provide sketches for the **(a, g^+, g^- conformations)** and maxima (***eclipsed*** conformations).

The a, g^+, g^- Conformations of Butane

Eclipsed Conformations of Butane

Questions

1. Comment on the relative stability of the minima as well as the relative barrier heights for the maxima. Then provide an explanation of the rotational energy profile for the **butane** molecule.

2. Determine if two conformations (**g^+** and **g^-**) are superimposable, and explain the relationship between these conformations.

The *anti-gauche* Equilibrium for Butane

For the equilibrium between the ***anti*** **(a)** and ***gauche*** **(g)** conformations of **butane**:

$$\textit{anti}\ \mathbf{Butane} \ \leftrightarrows\ \textit{gauche}\ \mathbf{Butane}$$

the equilibrium constant is given by

$$\mathbf{K} = \frac{[\textit{gauche}\ \mathbf{Butane}]}{[\textit{anti}\ \mathbf{Butane}]}$$

The equilibrium constant (**K**) can be related to the **Free Energy** (Δ**G**) between reactants and products by the equation:

$$\Delta\mathbf{G^0} = -\mathbf{R\,T\ln K}$$

where **R** is the gas constant ($\mathbf{8.31451\,J\,mol^{-1}\,K^{-1}}$), and **T** is the temperature in degrees Kelvin. If the change in entropy (Δ**S**) between reactants and products is small, a reasonable approximation involves the neglect of entropy. The **Free Energy** change for the reaction is then given by

$$\Delta\mathbf{G^0} = \mathbf{Strain\,Energy}\,(\textit{gauche}\,\mathbf{Butane})\ -\ \mathbf{Strain\,Energy}\,(\textit{anti}\,\mathbf{Butane})$$

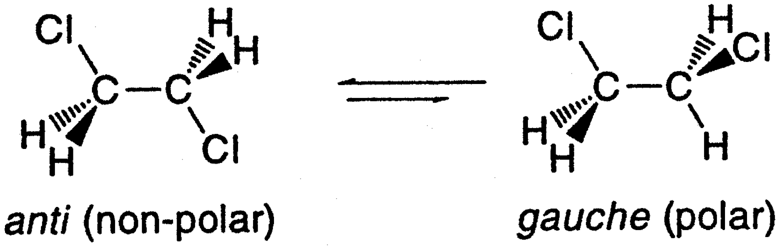
Questions

- Calculate the percentages of **a**, $\mathbf{g}^+$, and $\mathbf{g}^-$ at equilibrium for $\mathbf{T} = \mathbf{25^\circ\,C}$ and $\mathbf{T} = \mathbf{225^\circ\,C}$.

- Discuss what happens to the percentage of the ***anti*** conformation of **butane** as the temperature is **increased** and explain why this happens.

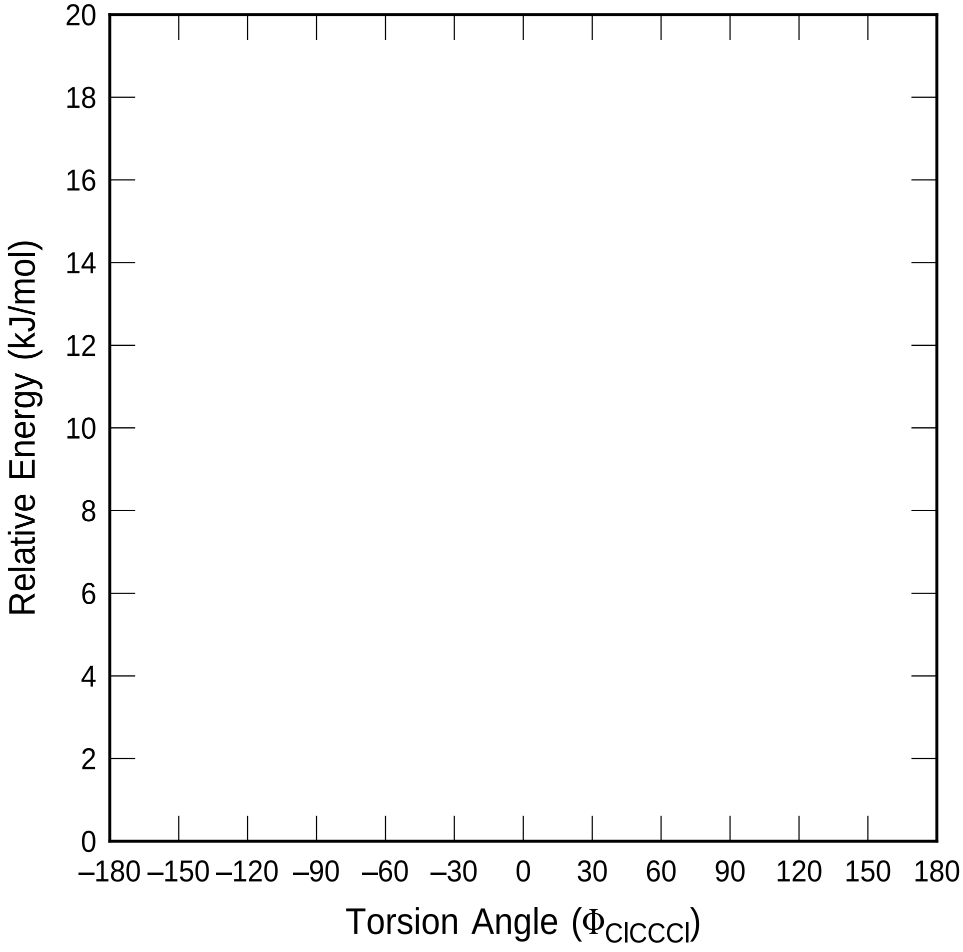
The Role of Solvent on Conformation

Solvent can significantly change the conformation of molecules. In general, **polar** solvents such as **H_2O** will stabilize a **polar** conformation to a greater extent than a **non-polar** conformation. For example the relative populations of ***anti*** and ***gauche*** conformers of **1,2-dichloroethane** (**$ClCH_2CH_2Cl$**) shown in the equilibrium below:



shift with the polarity of the solvent.

Using the graph provided below, sketch the **Rotational Energy Profiles** of **1,2-dichloroethane** in the **gas phase** and in **polar** and **non-polar** solvents.



The Role of Solvent on Conformation

Questions

- Obtain the dipole moments for ***anti*** and ***gauche*** conformations of **$ClCH_2CH_2Cl$**. Place the results in the table provided below.

  Dipole Moments for *anti* and *gauche* $ClCH_2CH_2Cl$

Conformation	**Dipole Moment (μ)**
anti	
gauche	

  Draw a sketch of the ***anti*** and ***gauche*** conformations of **$ClCH_2CH_2Cl$**, and include a vector to show the direction of the dipole moment. Explain the origin of the dipole moment observed for each of these conformations.

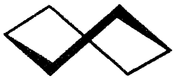
- Explain what happens to the energy difference between ***anti*** and ***gauche*** conformations of **$ClCH_2CH_2Cl$** in **polar** solvent. Calculate the ratio of the ***anti***/***gauche*** conformational equilibrium for **$ClCH_2CH_2Cl$** in going from the **gas phase** to **polar solvent** at room temperature. (Show all calculations on the back of this page.) Comment on the effect of a **non-polar** solvent on the ***anti***/***gauche*** conformational equilibrium.

Cyclohexane

The most stable conformation of cyclohexane is the ***chair*** form. Why is the ***chair*** form of cyclohexane so stable? If one peers down the **C-C** bonds for cyclohexane in the ***chair*** form, the other carbon and hydrogen atoms attached to them have conformations similar to **ethane** in the ***staggered*** conformation. Other conformations of cyclohexane which we will discuss later will not have as many of these stabilizing ***staggered*** **ethane-like** fragments. On the contrary, other higher-energy conformations of cyclohexane will have destabilizing ***eclipsed*** **ethane-like** fragments as well as other repulsive interactions.
Cyclohexane can interconvert from one ***chair*** conformation to another ***chair*** conformation through a series of intermediate structures of higher energy (***boat***, ***twist-boat***, ***half-chair***) shown below:

chair (D_{3d})

boat (C_{2v})

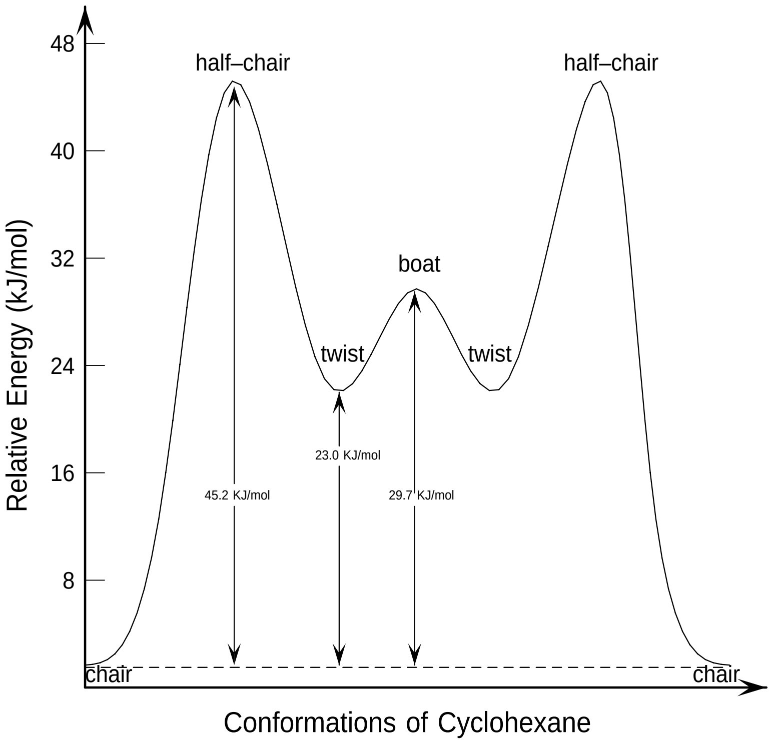


twist-boat (C_2)

half-chair (C_2)

The energy profile for the interconversion of one ***chair*** conformation to another ***chair*** is given below:

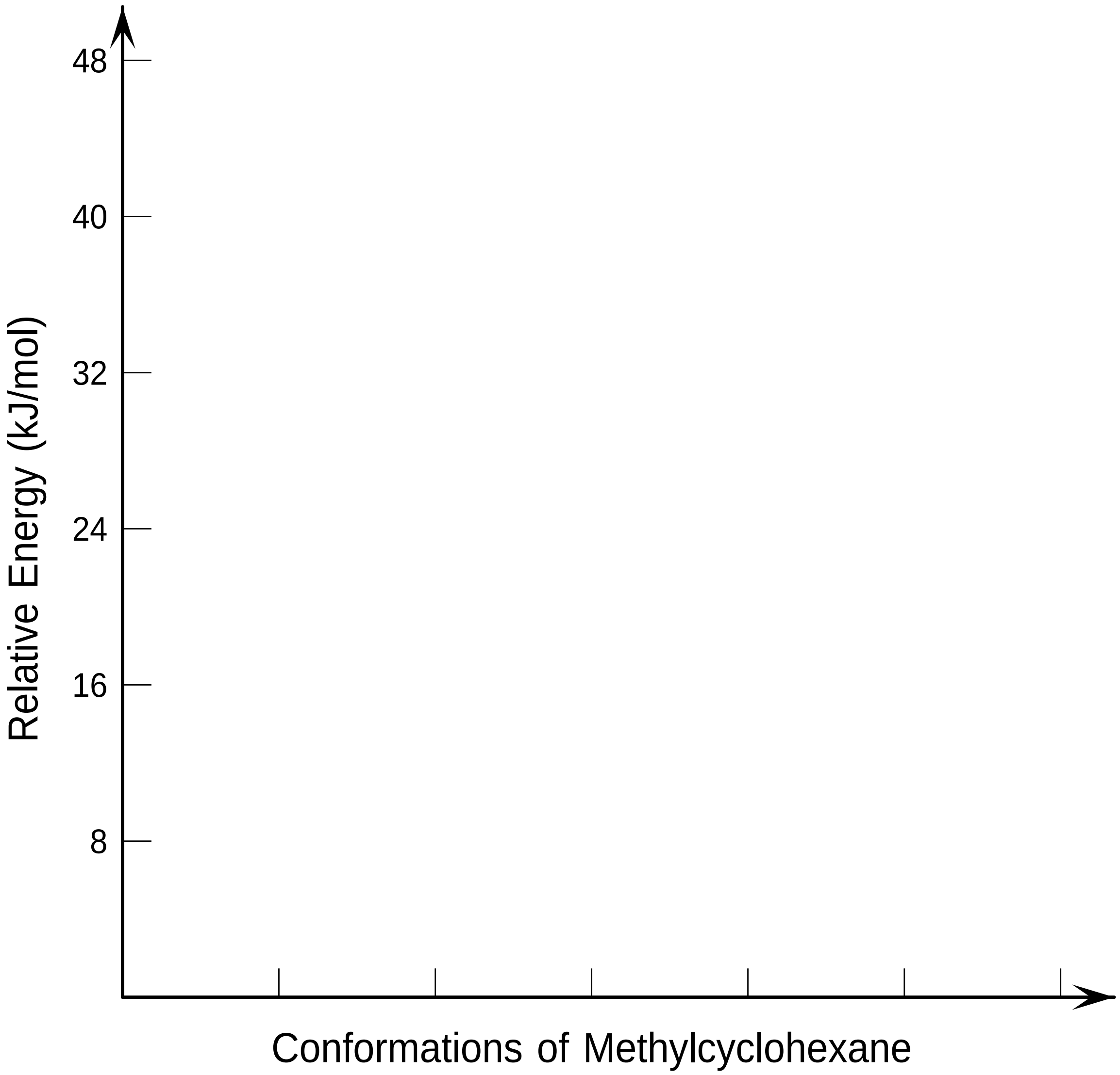
Energy Profile for Cyclohexane



Methylcyclohexane: Axial → Equatorial Interconversion

Using the graph provided below, construct an **Energy Profile** and estimate the barrier for the interconversion of ***axial*** and ***equatorial*** conformers of methylcyclohexane.
The **Energy Profile** should indicate the energy of each intermediate and transition state relative to the ***chair*** conformer of ***equatorial*** methylcyclohexane.

Energy Profile for Methylcyclohexane



Methylcyclohexane: Axial → Equatorial Interconversion

Sketch the various conformations of methylcyclohexane which occur during the interconversion from one ***chair*** conformation in which the substituent is ***axial*** to another ***chair*** conformation in which the substituent is now ***equatorial***.

chair axial

half-chair

twist-boat

boat

chair equatorial

Methylcyclohexane: Axial → Equatorial Interconversion

In answering the questions below, it will help to explain the ***axial*** and ***equatorial*** conformer energy differences by drawing upon the ***anti*** and ***gauche*** conformational energy differences found in **butane**.
Another useful hint is to observe the $\mathbf{H \cdots H}$ and $\mathbf{H \cdots CH_3}$ non-bonded distances for these conformations. Specifically, the ***boat*** conformation has particularly nasty non-bonded interactions that can be very destabilizing because of short $\mathbf{H \cdots H}$ and $\mathbf{H \cdots CH_3}$ distances.
Also, try different renderings for the cyclohexane conformations. See how the important comformations appear with the Ball-and-Stick, Polytube, and Space Filling models.
It will help if you summarize the relative **Strain Energies** for the important conformations of **cyclohexane** and **methylcyclohexane** in the table provided below:

Relative Strain Energies for Conformations of
Cyclohexane and Methylcyclohexanes

Molecule	***chair-equatorial***	***chair-axial***	***boat***	***half-chair***	***twist-boat***
Cyclohexane	**0.0**	**0.0**			
Methycyclohexane	**0.0**				

Questions

- For each conformation you have sketched on the previous page and whose relative energy is tabulated above, provide an explanation of its energy relative to the ***chair*** conformation of ***equatorial*** **methylcyclohexane** in terms of geometrical parameters, non-bonded interactions, and rotational energy about the **C-C** bonds.

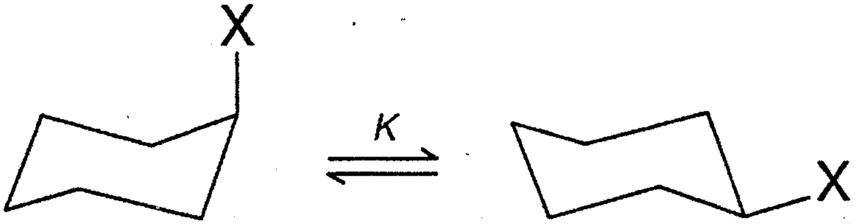
Methylcyclohexane: Axial → Equatorial Interconversion

Questions

- How does the methyl group substituent change the conformational preferences relative to unsubstituted cyclohexane?
- How does the methyl group substituent affect the barrier for interconversion from one ***chair*** conformation to another? Does the methyl substituent *freeze* the ring from interconverting or significantly slow it down?

Substituted Cyclohexanes

Substituted cyclohexanes can exist as a mixture of two conformations where the substituent (**X = -Cl, $-\mathbf{CH_3}$, $-\mathbf{C(CH_3)_3}$, ..., etc.**) resides in either the ***axial*** and ***equatorial*** positions. The **C-C-C-X** torsion angle is 60^0 for the ***axial*** conformation and 180^0 for the ***equatorial*** conformation. Interconversion between the two conformations is slow enough so that each one can be detected experimentally and the energy difference measured experimentally.
For the equilibrium between the ***axial*** and ***equatorial*** conformations of mono-substituted cyclohexane



$$\mathbf{Substituted\,Cyclohexane(X,\ axial)} \ \leftrightarrows\ \mathbf{Substituted\,Cyclohexane(X,\ equatorial)}$$

the equilibrium constant is given by

$$\mathbf{K} = \frac{[\mathbf{Substituted\,Cyclohexane(X,\ equatorial)}]}{[\mathbf{Substituted\,Cyclohexane(X,\ axial)}]}$$

The equilibrium constant (**K**) can be related to the **Free Energy** (**ΔG**) between reactants and products by the equation:

$$\mathbf{\Delta G^0} = -\mathbf{R\,T\,lnK}$$

where **R** is the gas constant ($\mathbf{8.31451\,J\,mol^{-1}\,K^{-1}}$), and **T** is the temperature in degrees Kelvin.
If the change in entropy (**ΔS**) between reactants and products is small as is the case for the **X, axial** ⇆ **X, equatorial** equilibrium, it becomes possible to neglect the entropy. The **Free Energy** change for the reaction is then given by the difference in **Strain Energies** for the **X**-substituted ***axial*** and ***equatorial*** cyclohexanes:

$$\mathbf{\Delta G^0} = \mathbf{Strain\,Energy(X, equatorial)} - \mathbf{Strain\,Energy\,(X, axial)}$$

Substituted Cyclohexanes

Obtain the **Strain Energies** for the ***axial*** and ***equatorial*** conformations of cyclohexane containing the following substituents **$-Cl$, $-CH_3$, $-C(CH_3)_3$.** Place the results in the table provided below.

Strain Energies for Substituted
***Axial* and *Equatorial* Cyclohexanes**

Substituent	***Equatorial***	***Axial***
$-Cl$		
$-CH_3$		
$-C(CH_3)_3$		

Calculate the percent equatorial and axial conformations at **$T = 300°$ K** for the following monosubstituted cyclohexanes: **$-Cl$, $-CH_3$, $-C(CH_3)_3$.** Show all work on back of this page.

Equilibrium Percentages for Substituted
***Axial* and *Equatorial* Cyclohexanes**

Substituent	**% Equatorial**	**% Axial**
$-Cl$		
$-CH_3$		
$-C(CH_3)_3$		

Do the results obtained in the above table agree with what you would expect as the substituent size (bulkiness) increases? Explain your answer.

Last Revised: 02/02/98