

CFQ & PP: Molecular Dynamics

Reading

Brown and Foote: Chapter 2

Lecture Supplement

Molecular Dynamics (page 8 this Thinkbook)

Suggested Text Exercises

Brown and Foote, Chapter 2: 1, 2, 9 – 15, 17 – 19, 21, 27 – 45

Optional Interactive Organic Chemistry CD and Workbook

Supporting Concepts: Conformation (p. 66)

A Note Concerning Organic Nomenclature

Just like you have a name that everyone uses to refer to you, molecules have names as well. The names are based on variety of structural features, the molecule's origin, the person who discovered it, etc. It is very important to be able to name a molecule, or to draw a molecule's structure from its name. The system of rules for this task is called "nomenclature." Nomenclature rules are simple in some parts and complex in others. For the most part, you can easily get by knowing just the simple rules. These simple rules can be learned through study of the text. You are expected to know the names and structures of simple molecules such as 2-butanol for problems sets and exams. On exams you will not be asked to draw a complex structure from a name, nor will you be asked to name a complex molecule.

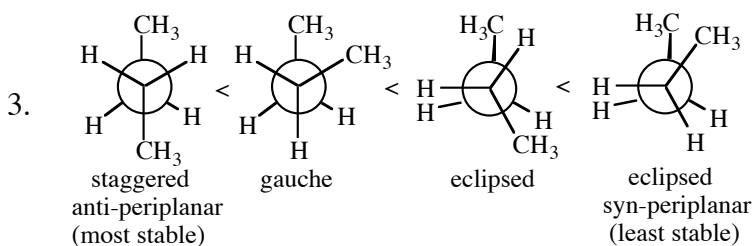
Concept Focus Questions

1. Briefly explain why rotation around a σ bond occurs readily, yet rotation around a π bond is too energetically expensive to occur readily.
2. Using both stick drawings and Newman projections draw and label the most stable and least stable conformations of ethane. Briefly explain the factor(s) that make one conformation more stable than another.
3. Using Newman projections, draw the conformational isomers that result from 60° rotations around the C2-C3 bond of butane. Rank these in order of energy, and briefly explain your reasoning.
4. Define the terms "strain," "torsional strain," "angle strain," and "ring strain." Briefly discuss how they influence the stability and reactivity of cyclopropane.
5. Cyclopentane and cyclohexane are essentially free of strain. Explain.

- Using stick structures, draw the axial and equatorial conformations of methylcyclohexane. Which is more stable? Why?
- The energy difference between axial and equatorial methylcyclohexane is $1.7 \text{ kcal mol}^{-1}$. Calculate the equilibrium constant for this cyclohexane chair-chair conformational change at 298K.
- Cyclohexane and benzene both have six-membered carbon rings. Cyclohexane is not planar, and benzene is planar. Explain the origin of this ring shape difference.

Concept Focus Questions Solutions

- Bond strength is a function of orbital overlap. The greater the volume of space that is shared by the orbitals that overlap to make a bond, the stronger the bond will be. Orbitals that overlap to form σ bonds overlap more (share a greater volume of space) than orbitals that form π bonds. Thus for σ and π bonds between the same atoms (such as a C-O σ bond versus a C-O π bond) σ bonds are stronger than π bonds. We define bond rotation here as rotation of one atom of a bond while the other atom is held still. Bond rotation is allowed so long as it does not significantly decrease orbital overlap. Decreasing orbital overlap would weaken the bond, and make the structure less stable. Rotation around a σ bond does not change the degree of orbital overlap, so this rotation is allowed. Rotation around the σ portion of a π bond, even by only a few degrees, results in a decrease in overlap of adjacent p_z orbitals. This decrease in p_z orbital overlap weakens the π bond. Thus rotation around a π bond is not usually observed. (Bonds can be estimated as overlapping one-atom orbitals, but this is not a truly rigorous treatment of bonds, and it fails to explain certain other features of bonds and molecular orbitals.)
- The single most important factor that influences molecular shape or geometry is electron repulsion. The most stable conformation of ethane will be the one with the least van der Waals repulsions between the various atoms. This is achieved in the staggered conformation, where the hydrogen atoms are as far apart as they can be.



The single most important factor that controls the stability of these butane conformations is electron repulsion. Because the atoms are further apart in a staggered conformation, staggered conformations are generally more stable than eclipsed conformations. Smaller groups have smaller van der Waals repulsions (all else being equal) because the electrons are further apart. Thus, because hydrogen-hydrogen repulsion is smaller than a methyl-methyl repulsion, the anti-periplanar

conformation is more stable than the conformation in which the methyls are gauche. The same logic explains why the conformation with the eclipsed methyl groups is less stable than the other eclipsed conformation shown.

4. Strain: A decrease in molecular stability due to some factor of bonding or geometry.

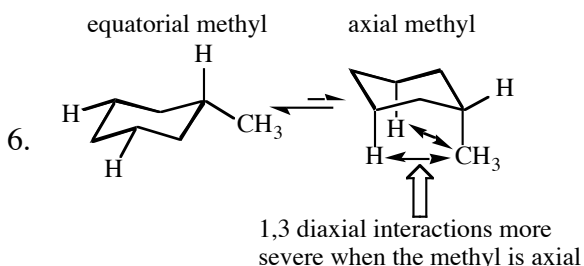
Torsional strain: An increase in energy caused by repulsion of electrons on one atom or group when brought into close proximity of electrons on another atom or group.

Angle strain: Strain that results from bond angles that are not ideal.

Ring strain: Strain that is produced because the molecule has a ring; usually a combination of torsional and angle strain.

Because cyclopropane must be planar, there are six sets of unavoidable hydrogen-hydrogen eclipsing interactions. These provide torsional strain. Each carbon of cyclopropane is attached to four other atoms, so sp^3 hybridization and bond C-C-C bond angles of 109.5° are preferred. Because cyclopropane is planar, and because all the bonds are equivalent, cyclopropane is shaped like an equilateral triangle with actual C-C-C bond angles of 60° . This results in poorer overlap between the sp^3 orbitals than would occur if the bond angles were 109.5° . Poorer orbital overlap means weaker bonds and decreased molecular stability. The sum of torsional and angle strain factors gives cyclopropane ring strain of 27 kcal mol^{-1} . This ring strain means the molecule is less stable and more reactive than a hydrocarbon with less strain. For example, the C-C bonds of cyclopropane are much more easily ruptured than the C-C bonds of propane.

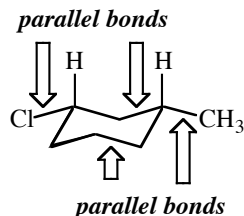
5. Cyclopentane and cyclohexane can both easily adopt conformations that relieve all torsional and angle strain.



As discussed above, interactions between two hydrogen atoms is less severe than interactions between a hydrogen atom and a methyl group. When the methyl group is axial, there are two methyl-hydrogen interactions. These are termed 1,3-diaxial interactions. When the methyl is equatorial, these are relieved. Thus, the more stable conformation is the one in which the methyl group is equatorial.

When drawing any structure, it is critical that you draw neatly. In the case of chair cyclohexanes, it is also critical that the position of the substituent (equatorial versus

axial) is also clear. Note that this clarity is achieved by having the equatorial bonds parallel to bonds in the ring.



7. The equation that relates Gibbs free energy to the equilibrium constant is:

$$\Delta G = -RT \ln K_{\text{eq}}$$

Where: ΔG = Gibbs free energy difference ($1.7 \text{ kcal mol}^{-1}$ in this case)

R = gas constant ($1.987 \text{ cal mol}^{-1} \text{ K}^{-1}$)

T = temperature in K (298K in this case)

K_{eq} = equilibrium constant.

Recall that the equilibrium constant is dependent on what is written on the left and right sides of the equilibrium arrow. If the right side of the equilibrium is favored, $K_{\text{eq}} > 1$. If the left side of the equilibrium is favored $K_{\text{eq}} < 1$. Writing the equilibrium backwards results in a reciprocal equilibrium constant.

Using $\Delta G = -1.7 \text{ kcal mol}^{-1}$ (assuming the equilibrium lies to the right), we find $K_{\text{eq}} = 17.7$. (If $\Delta G = +1.7 \text{ kcal mol}^{-1}$ the equilibrium lies to the left.) This corresponds to a 95:5 ratio of the two conformations.

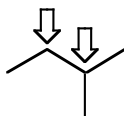
You may not use calculators on an exam. If a question of this nature is asked, you will be required to set up the calculation, but not solve it. It is much more important that you understand the real meaning of the equation, and have a feeling for the magnitude of numbers that it provides.

8. If cyclohexane were planar, it would have a significant amount of ring strain due to hydrogen-hydrogen eclipsing (torsional strain) and bond angles that were not 109.5° (angle strain). To relieve this ring strain, cyclohexane assumes a chair conformation, which has no hydrogen-hydrogen eclipsing, and perfect 109.5° bond angles. Benzene is constrained to be planar to maintain the overlap of the six p_z orbitals. Deviation from planarity reduces p_z orbital overlap, thus decreasing bonding and molecular stability.

Practice Problems

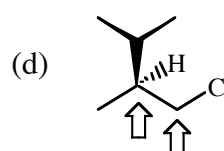
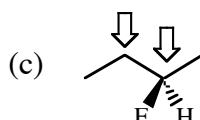
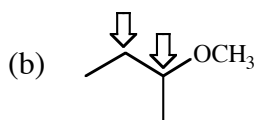
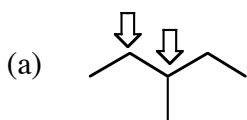
1. Rotation around single bonds generally occurs with little or no barrier, but double bonds make rotation impossible under normal conditions. Briefly explain why rotation around the C-C σ bond of ethane ($\text{H}_3\text{C}-\text{CH}_3$) occurs with relative ease.

- Briefly explain why rotation around the C=C bond of ethylene ($\text{H}_2\text{C}=\text{CH}_2$) does not occur under ordinary conditions.
- Predict which eclipsing interaction causes more torsional strain: one between two methyl groups, or one between a methyl group and a hydroxyl (HO) group? Explain.
- Using Newman projections, draw the most stable and least stable conformation of 2-methylbutane as viewed along the bond connecting the carbon atoms indicated by the arrows. Briefly explain why these conformations are the most and least stable.

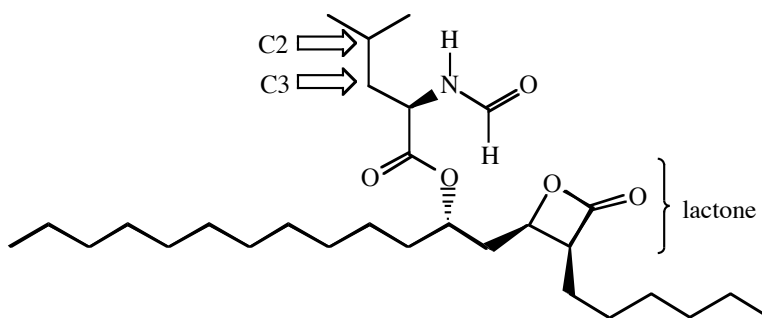


2-Methylbutane

- Using Newman projections, draw the most stable and least stable conformation of the following molecules as viewed along the bond connecting the carbon atoms indicated by the arrows.

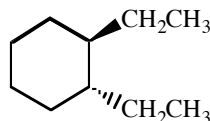


- Xenical (also called orlistat) is a weight loss drug that works by irreversibly blocking stomach and intestinal enzymes that are involved in fat metabolism. Using a Newman projection, clearly draw the single most stable conformational isomer that results from rotation around the C2-C3 bond of the isobutyl alkyl group of Xenical. Use "X" to abbreviate the largest molecule fragment as needed.

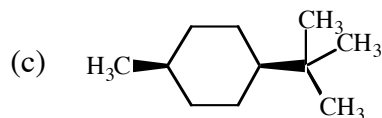
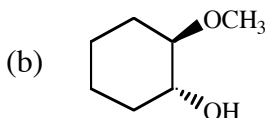
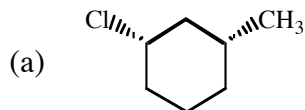


- Briefly explain why the alkyl chains adopt the "W" shape as shown in the Xenical structure above. Use of Newman projections will make your answer clearer.
- Draw a molecule that obviously has more ring strain than cyclopropane.
- Briefly describe two significantly different structural features that contribute to the ring strain of the lactone ring in Xenical (question 6).

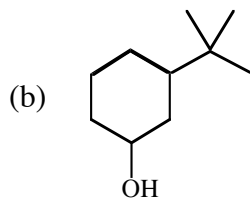
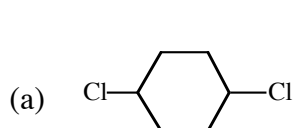
10. Clearly draw and label the most stable and least stable chair conformations of trans-1,2-diethylcyclohexane (shown below). Briefly explain your reasoning.



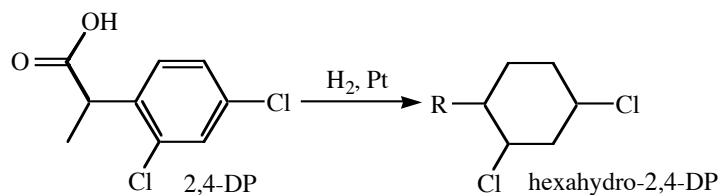
11. Clearly draw the most stable chair conformations of the following molecules.



12. Clearly draw and label the most stable and least stable chair conformations of the following molecules. Use the most stable stereoisomer in each case.

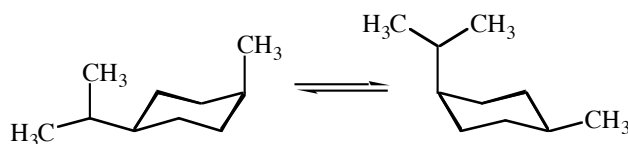


13. Consider the herbicide 2,4-DP shown below. While searching for related compounds that may have similar properties, 2,4-DP was subjected to a reaction called catalytic hydrogenation (shown below). Draw the single most stable conformation of the single most stable stereoisomer of hexahydro-2,4-DP. You may abbreviate the alkyl side chain as R.

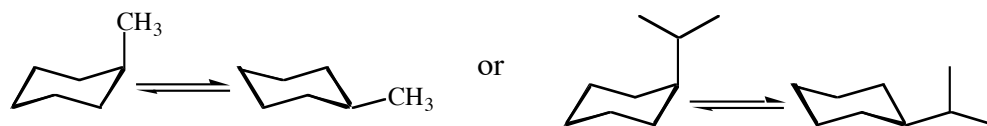


14. Draw the structure of a substituted cyclohexane derivative that would be in a single chair conformation essentially all of the time. (A substituted cyclohexane has one or more of the hydrogen atoms replaced by some other atom or group.) Briefly explain your choice.

15. Circle the side of the equilibrium that is favored, and briefly explain your answer.

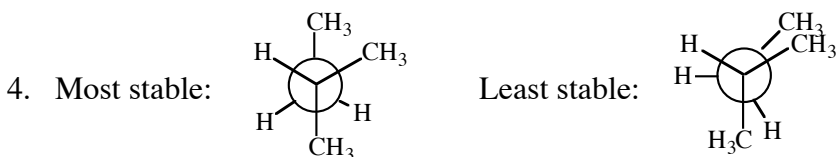


16. Circle the equilibrium that has the largest K_{eq} and briefly explain your answer.



Practice Problems Solutions

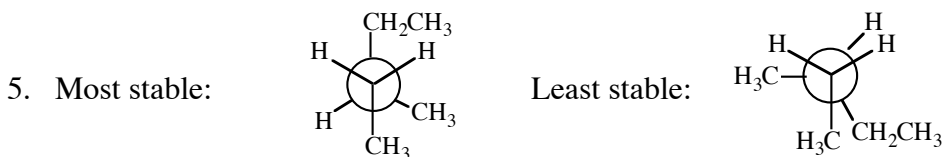
- Bond rotation is allowed as long as orbital overlap is still maintained. The C-C σ bond of ethane is formed by the overlap of two sp^3 orbitals along the bond axis. Rotation does not change the amount of sp^3 orbital overlap, so this rotation is allowed. The actual barrier to rotation around the C-C σ bond of ethane is only about 3 kcal mol⁻¹. (It is insufficient to state that rotation is allowed because there is no π bond, as the lack of this bond does not explain why rotation around a σ bond can occur in the first place.)
- The π bond forms by overlap of two parallel p_z orbitals. Rotation would reduce the overlap of these orbitals. This bond weakening costs a significant amount of energy. Rotation about π bonds generally does not occur. The π portion of a C=C is worth about 63 kcal mol⁻¹.
- Recall that a nonbonding (lone) electron pair repels less strongly (occupies less space) than a single atom unless the lone pair and atom are attached to the same atom. A hydroxyl group consists of two nonbonding electron pairs on the oxygen and one bonding pair in the O-H bond. A methyl group has three bonding pairs in the C-H bonds. The van der Waals repulsion from the HO group will be smaller than for a methyl group. The torsional strain from the methyl-hydroxyl interaction will be smaller than the torsional strain from the methyl-methyl interaction.



Most stable: The most stable conformation is that conformation with the least amount of van der Waals repulsion (electron repulsion). This occurs when the largest groups (the methyls) are as far apart as possible (staggered conformation).

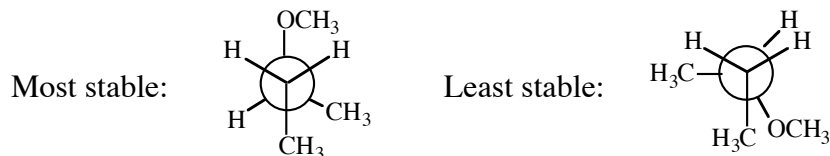
Least stable: The least stable conformation is that conformation with the greatest amount of van der Waals repulsions. This occurs when the methyl groups are as close to each other as possible (eclipsed conformation).

It does not matter which atom is in front in a Newman projection unless specified by the problem.

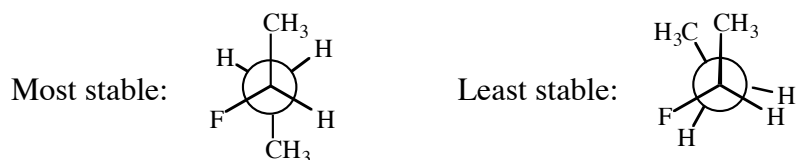


The enantiomers (a term you will encounter in the Stereochemistry lecture topic) of these conformations are also acceptable.

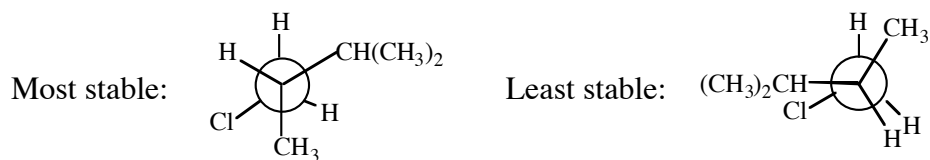
(b) Assume a methoxy group (CH_3O) is larger than a methyl group (CH_3).



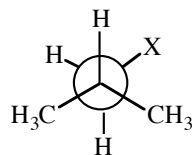
(c) A methyl group (four atoms) is larger than a fluorine atom (one atom), so methyl-methyl repulsion will be more severe than methyl-fluorine repulsion. The absolute stereochemistry at C2 must be the same in the given structure and your Newman projections.



(d) The conformation is more stable when the chlorine is gauche to the smaller methyl group instead of the larger isopropyl group. The absolute stereochemistry at C2 must be present in the Newman projections.

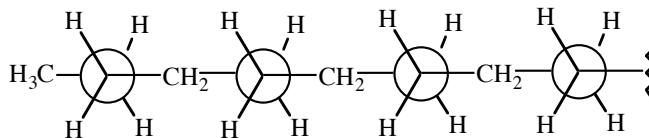


6. The single most stable conformational isomer will be staggered in such a way as to minimize the total repulsions. This is achieved when the X group is gauche to only one (instead of both) of the methyl groups.



7. The carbon-carbon bonds rotate to minimize steric repulsion. The best conformation is the anti-staggered conformation. A long chain of anti-staggered conformations

provides the "W" shape. Make a model of this Newman projection to convince yourself of the "W" shape.



8. There are many possible answers. Cyclopropene has more ring strain than cyclopropane because two of the sp^3 carbons of cyclopropane have been replaced with sp^2 carbons.

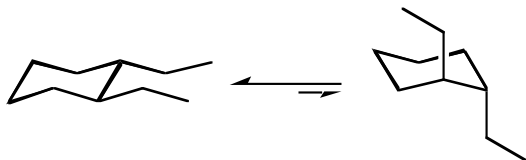


Cyclopropene

9. Torsional strain: A lactone ring has hydrogen eclipsing that cannot be completely eliminated by rotation around a C-C bond.

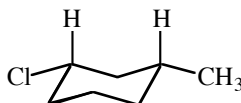
Angle strain: The carbonyl carbon of the lactone ring has three attachments and is therefore sp^2 hybridized with an ideal C-C-C bond angle of 120° . However, the actual bond angle is approximately 90° because of the square shape of the lactone. This results in poor orbital overlap, and a weakened C-C bond. This weakened C-C bond also contributes to ring strain.

10. Diequatorial
More stable

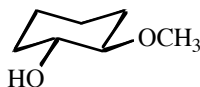


Diaxial
Less stable

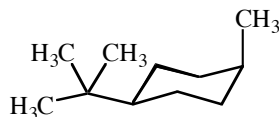
11. (a) The most stable conformation of any cyclohexane derivative is usually the chair. The substituents will prefer to be equatorial. If all the substituents cannot be equatorial, then the conformation that has the best arrangement of substituents is most stable. The most stable stereoisomer of this compound will have a chair cyclohexane with both substituents in the equatorial position. You must have the same constitutional isomer, and the drawing must clearly show the groups as equatorial.



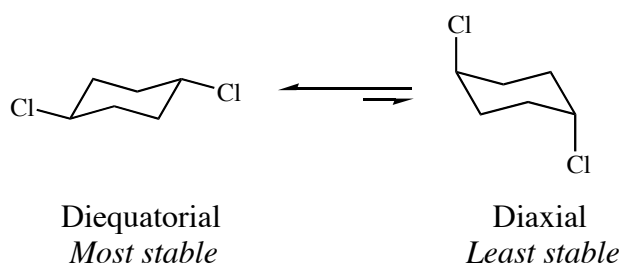
- (b) Be sure that your answer has the same absolute configuration as the structure given in the question.



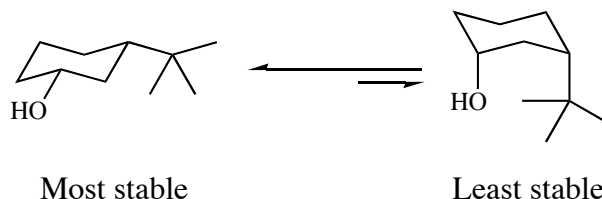
(c) The methyl and *tert*-butyl groups are cis in the given flat structure, so these groups must also be cis in the chair conformation as well. This requires one of the two groups to be axial. The methyl group is smaller than the *tert*-butyl group, and thus has less steric repulsion in an axial position.



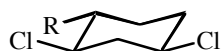
12. (a) Recall that trans means the two substituents are on opposite sides of the ring. In a 1,4-disubstituted cyclohexane, two trans substituents can be diaxial (less stable) or diequatorial (more stable).



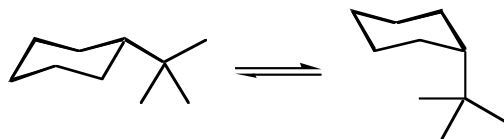
(b) In the most stable chair conformation, both the hydroxyl and *tert*-butyl groups will be in an equatorial position.



13. The single most stable conformation of a cyclohexane derivative is usually the chair conformation. Since we can choose the stereoisomer, the R group and two chlorine atoms should be equatorial. Be careful to keep the three ring substituents in the same 1, 2, 4 relationship.



14. There are several approaches to this problem. Recall that the chair-chair cyclohexane ring flip moves equatorial groups to an axial position, and axial groups to an equatorial position. You could use an example of a cyclohexane with a substituent that is so bulky that it cannot become axial (such as *tert*-butylcyclohexane; shown below). One could also use a case with many substituents arranged so that they are all equatorial (would all become axial in the other chair conformation).



15. Any cyclohexane substituent is gauche to the ring CH_2 groups when axial, causing torsional strain that we call a 1,3-diaxial interaction. This torsional strain is relieved when the group flips into an equatorial position. An isopropyl group is larger than a methyl group, so the isopropyl group has greater torsional strain when axial, and a stronger driving force to be equatorial. Thus, the equilibrium shown above lies to the left, because the larger isopropyl group is in the more favorable equatorial position.
16. An isopropyl group is larger than a methyl group, so the isopropyl group has greater torsional strain when axial, and a stronger driving force to be equatorial. While both equilibria shown above lie to the right, the K_{eq} for isopropylcyclohexane is greater than K_{eq} for methylcyclohexane.