Objectives

After completing this section, you should be able to

1. account for the greater stability of the equatorial conformers of monosubstituted cyclohexanes compared to their axial counterparts, using the concept of 1,3-diaxial interaction.
2. compare the gauche interactions in butane with the 1,3-diaxial interactions in the axial conformer of methylcyclohexane.
3. arrange a given list of substituents in increasing or decreasing order of 1,3-diaxial interactions.

Key Terms

Make certain that you can define, and use in context, the key term below.

• 1,3-diaxial interaction

Study Notes

1,3-Diaxial interactions are steric interactions between an axial substituent located on carbon atom 1 of a cyclohexane ring and the hydrogen atoms (or other substituents) located on carbon atoms 3 and 5.

Be prepared to draw Newman-type projections for cyclohexane derivatives as the one shown for methylcyclohexane. Note that this is similar to the Newman projections from chapter 3 such as n-butane.

Newman projections of methylcyclohexane and n-butane

Because axial bonds are parallel to each other, substituents larger than hydrogen experience greater steric crowding when they are oriented axial rather than equatorial. Consequently, substituted cyclohexanes will preferentially adopt conformations in which the larger substituents are in the equatorial orientation.

When the methyl group in the structure above occupies an axial position it experiences steric crowding by the two axial hydrogens located on the same side of the ring.
The conformation in which the methyl group is equatorial is more stable, and thus the ring flip equilibrium favors the conformation with the equatorial methyl group.

The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane may be determined by the conformational equilibrium of the compound. The corresponding equilibrium constant is related to the energy difference between the conformers, and collecting such data allows us to evaluate the relative tendency of substituents to exist in an equatorial or axial location. Table 4.7.1 summarizes some of these free energy values (sometimes referred to as A values).

Looking at the energy values in this table, it is clear that as the size of the substituent increases, the 1,3-diaxial energy tends to increase, also. Note that it is the size and not the molecular weight of the group that is important.

Table 4.7.1: A Selection of $\Delta G^\circ$ Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$-\Delta G^\circ$ (kcal/mol)</th>
<th>Substituent</th>
<th>$-\Delta G^\circ$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>1.7</td>
<td>$\text{O}_2\text{N}$</td>
<td>1.1</td>
</tr>
<tr>
<td>$\text{CH}_2\text{H}_5$</td>
<td>1.8</td>
<td>$\text{N}#\text{C}$</td>
<td>0.2</td>
</tr>
<tr>
<td>$\text{(CH}_3)_2\text{CH}$</td>
<td>2.2</td>
<td>$\text{CH}_3\text{O}$</td>
<td>0.5</td>
</tr>
<tr>
<td>$\text{(CH}_3)_3\text{C}$</td>
<td>$\geq 5.0$</td>
<td>$\text{HO}_2\text{C}$</td>
<td>0.7</td>
</tr>
<tr>
<td>$\text{F}$</td>
<td>0.3</td>
<td>$\text{H}_2\text{C}=\text{CH}$</td>
<td>1.3</td>
</tr>
<tr>
<td>$\text{Cl}$</td>
<td>0.5</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>3.0</td>
</tr>
<tr>
<td>$\text{Br}$</td>
<td>0.5</td>
<td>$\text{I}$</td>
<td>0.5</td>
</tr>
<tr>
<td>$\text{I}$</td>
<td>0.5</td>
<td>$\text{H}$</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Chlorocyclohexane

This is an example of the next level of complexity, a mono-substituted cycloalkane.

The hexagon structure, Figure 4.7.3A, shows the basic "connectivity" of the atoms. This chemical has one Cl on the ring, and it does not matter where we show it.

The chair structure, Figure 4.7.3B, shows atom connectivity, and also the preferred conformation with the larger chlorine atom in the equatorial position.

Helpful Hints

- Examine a physical model of cyclohexane and chlorocyclohexane, so that you can see the axial and equatorial positions. Common ball and stick models are fine for this. It should be easy to see that the three axial H on one side can get very near each other. If you do not have access to physical models, examining computer models can also be useful. When putting substituents on chair structures, I encourage you to use the four corner positions of the chair as much as possible. It is easier to see the axial and equatorial relationship at the corners.
- Draw both atoms attached to the ring carbons for clarity. In Fig 4.7.3B the H atom that is on the same carbon as the Cl atom is shown. This is not necessary, but showing the H makes it clearer that the chlorine is in the equatorial position.

Exercises

Questions

Q4.7.1

In the molecule, cyclohexyl ethyne there is little steric strain, why?
Solutions

S4.7.1

The ethyne group is linear and therefore does not affect the hydrogens in the 1,3 positions to say to the extent as a bulkier or a bent group (e.g. ethene group) would. This leads to less of a strain on the molecule.

Contributors

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• Prof. Steven Farmer (Sonoma State University)
>Robert Bruner (http://bbruner.org)

Objective

After completing this section, you should be able to use conformational analysis to determine the most stable conformation of a given disubstituted cyclohexane.

Key Terms

Make certain that you can define, and use in context, the key term below.

• conformational analysis

Study Notes

When faced with the problem of trying to decide which of two conformers of a given disubstituted cyclohexane is the more stable, you may find the following generalizations helpful.

1. A conformation in which both substituents are equatorial will always be more stable than a conformation with both groups axial.

2. When one substituent is axial and the other is equatorial, the most stable conformation will be the one with the bulkiest substituent in the equatorial position. Steric bulk decreases in the order
tert-butyl > isopropyl > ethyl > methyl > hydroxyl > halogens
Monosubstituted Cyclohexanes

In the previous section, it was stated that the conformation in which the methyl group is equatorial is more stable because it minimizes steric repulsion, and thus the equilibrium favors the more stable conformer.

Disubstituted Cyclohexanes

In this section, the effect of conformations on the relative stability of disubstituted cyclohexanes is examined using the two principles:

i. Chair conformations are generally more stable than other possibilities, so that's all we'll consider.

ii. Substituents prefer equatorial rather than axial positions in order to minimize the steric hindrance of 1,3-diaxial interactions.

1,1-dimethylcyclohexane does not have cis or trans isomers, because both methyl groups are on the same ring carbon. Both conformers have one methyl group axial and one methyl group equatorial, and they both have the same energy or relative stability. Therefore, the equilibrium between the two conformers does not favor either one. The energy cost of having one methyl group axial (versus equatorial) is 1.7 kcal/mole (from Table 4.7.1), and both conformers will be equal in energy. Note that both methyl groups cannot be equatorial at the same time without breaking bonds and creating a different molecule.
However, if the two groups are different, as in 1-<i>tert</i>-butyl-1-methylcyclohexane, then the equilibrium favors the conformer in which the larger group <i>tert</i>-butyl group is in the more stable equatorial position. The energy cost of having one tert-butyl group axial (versus equatorial) can be calculated from the values in table 4.7.1 and is approximately 5.0 kcal/mole. That means that the conformer with the <i>tert</i>-butyl group axial is approximately 3.3 kcal/mol (5.0 kcal/mol - 1.7 kcal/mole) less stable than the conformer with the <i>tert</i>-butyl group equatorial. This means that 1-<i>tert</i>-butyl-1-methylcyclohexane will spend the majority of its time in the more stable conformation.

Disubstituted Cyclohexanes: The Relative Stability of <i>cis</i> and <i>trans</i> Isomers

The situation is more complex when the effect of conformations on the relative stability of <i>cis</i> and <i>trans</i> disubstituted cyclohexanes is analyzed. Remember, configurational stereoisomers do not interconvert without breaking bonds, whereas conformational isomers normally interconvert rapidly by the ring flip process.

Let's apply a similar analysis to the <i>cis</i> and <i>trans</i> stereoisomers of 1,2-dimethylcyclohexane.

In <i>cis</i>-1,2-dimethylcyclohexane, one methyl group is axial and one methyl group is equatorial in both ring flip conformers, so neither conformer is more stable than the other. It is important to note, that this molecule cannot get both methyl groups axial without breaking bonds to make a new molecule.
In trans-1,2-dimethylcyclohexane, one conformer has both methyl groups axial and the other has both methyl groups equatorial. The conformer with both methyl groups axial is 3.4 kcal/mole (2 x 1.7 kcal/mol) less stable than the conformer with both methyl groups equatorial. Obviously, the equilibrium will favor the conformer with both methyl groups in the equatorial position.

To decide whether the cis or trans isomer of 1,2-dimethylcyclohexane is more stable, compare the relative energy of the most stable conformer of cis-1,2-dimethylcyclohexane to the most stable conformer of trans-1,2-dimethylcyclohexane. The trans-1,2-dimethylcyclohexane has the most stable conformer, so it is the more stable isomer.

Does this mean that the trans isomer of a disubstituted cyclohexane is always more stable than the cis isomer? Let's examine both the cis and trans isomers of 1,3-dimethylcyclohexane and find out.

As can be seen in the structures above, cis-1,3-dimethylcyclohexane's most stable conformer has both methyl groups equatorial, while trans-1,3-dimethylcyclohexane always has one methyl group is equatorial and one methyl group axial. This means that the cis isomer 1,3-dimethylcyclohexane is more stable than the trans isomer. And that is opposite what we found for 1,2-dimethylcyclohexane.

As practice, you should do a similar conformational analysis of the cis and trans isomers of 1,4-dimethylcyclohexane. You should find that the trans isomer of 1,4-dimethylcyclohexane is more stable than the cis isomer.
Summary

The relative stabilities of the cis and trans isomers of disubstituted cyclohexanes depends upon which isomer has the most stable conformer. The most stable isomer for disubstituted cyclohexanes is summarized below.

<table>
<thead>
<tr>
<th>substitution type</th>
<th>most stable isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-disubstituted cyclohexanes</td>
<td>trans</td>
</tr>
<tr>
<td>1,3-disubstituted cyclohexanes</td>
<td>cis</td>
</tr>
<tr>
<td>1,4-disubstituted cyclohexanes</td>
<td>trans</td>
</tr>
</tbody>
</table>

Exercises

Questions

Q4.8.1

For the following molecules draw the most stable chair conformation and explain why you chose this as an answer

1 = trans-1,2-dimethylcyclohexane

2 = cis-1,3-dimethylcyclohexane

Solutions

S4.8.1

1 – The most stable conformation would be to have the methyl groups axial reducing steric interaction

2 – The most stable conformation would be to have the groups equatorial this would reduce the strain if they were axial
Contributors

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