

4.8: CONFORMATIONS OF DISUBSTITUTED CYCLOHEXANES

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

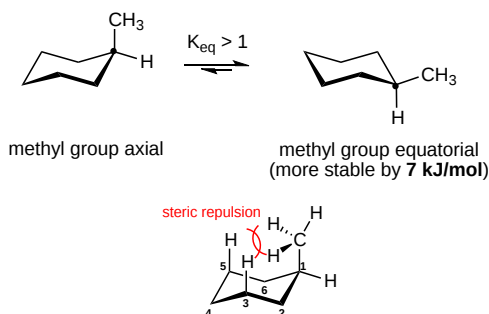
STUDY NOTES

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 chair 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. This is true for all monosubstituted cyclohexanes. The chair conformation which places the substituent in the equatorial position will be the most stable and be favored in the ring flip equilibrium.



DISUBSTITUTED CYCLOHEXANES

Determining the more stable chair conformation becomes more complex when there are two or more substituents attached to the cyclohexane ring. To determine the stable chair conformation, the steric effects of each substituent, along with any additional steric interactions, must be taken into account for both chair conformations.

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

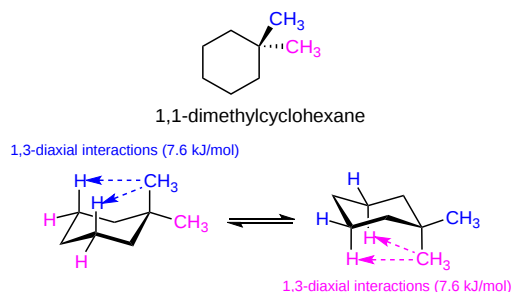
- Substituents prefer equatorial rather than axial positions in order to minimize the steric strain created of 1,3-diaxial interactions.
- The more stable conformation will place the larger substituent in the equatorial position.

1,1-DISUBSTITUTED CYCLOHEXANES

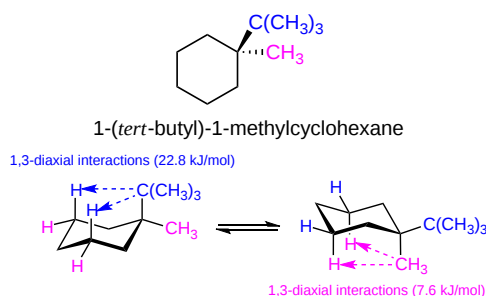
The more stable chair conformation can often be determined empirically or by using the energy values of steric interactions previously discussed in this chapter. Note, in some cases there is no discernable energy difference between the two chair conformations which means they are equally stable.

1,1-dimethylcyclohexane does not have *cis* or *trans* isomers, because both methyl groups are on the same ring carbon. Both chair conformers have one methyl group in an axial position and one methyl group in an equatorial position giving both the same relative stability. The steric strain created by the 1,3-diaxial interactions of a methyl group in an axial position (versus equatorial) is 7.6 kJ/mol (from Table 4.7.1), so both conformers will have equal amounts of steric strain. Thus, the equilibrium between the two conformers does not

favor one or the other. Note, that both methyl groups cannot be equatorial at the same time without breaking bonds and creating a different molecule.

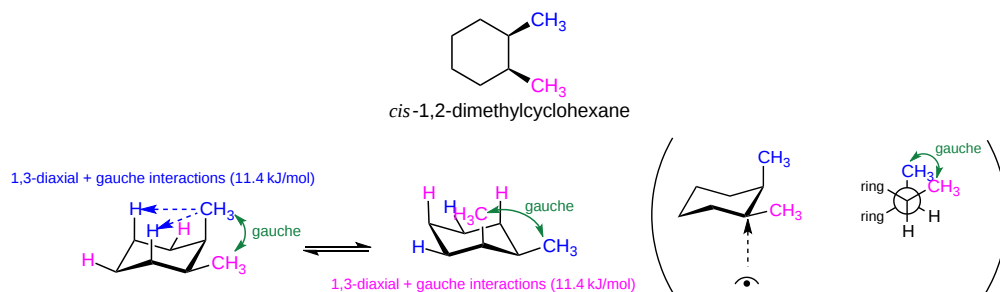


However, if the two groups are different, as in 1-*tert*-butyl-1-methylcyclohexane, then the equilibrium favors the conformer in which the larger group (*tert*-butyl in this case) is in the more stable equatorial position. The energy cost of having one *tert*-butyl group axial (versus equatorial) can be calculated from the values in table 4.7.1 and is approximately 22.8 kJ/mol. The conformer with the *tert*-butyl group axial is approximately 15.2 kJ/mol (22.8 kJ/mol - 7.6 kJ/mol) less stable than the conformer with the *tert*-butyl group equatorial. Solving for the equilibrium constant *K* shows that the equatorial is preferred about 460:1 over axial. This means that 1-*tert*-butyl-1-methylcyclohexane will spend the majority of its time in the more stable conformation, with the *tert*-butyl group in the equatorial position.

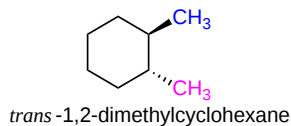


CIS AND TRANS STEREOISOMERS OF 1,2-DIMETHYLCYCLOHEXANE

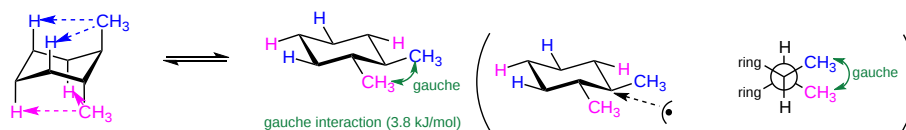
In *cis*-1,2-dimethylcyclohexane, both chair conformations have one methyl group equatorial and one methyl group axial. As previously discussed, the axial methyl group creates 7.6 kJ/mol of steric strain due to 1,3-diaxial interactions. It is important to note, that both chair conformations also have an additional 3.8 kJ/mol of steric strain created by a *gauche* interaction between the two methyl groups. Overall, both chair conformations have 11.4 kJ/mol of steric strain and are of equal stability.



In *trans*-1,2-dimethylcyclohexane, one chair conformer has both methyl groups axial and the other conformer has both methyl groups equatorial. The conformer with both methyl groups equatorial has no 1,3-diaxial interactions however there is still 3.8 kJ/mol of strain created by a *gauche* interaction. The conformer with both methyl groups axial has four 1,3-Diaxial interactions which creates 2×7.6 kJ/mol (15.2 kJ/mol) of steric strain. This conformer is (15.2 kJ/mol - 3.8 kJ/mol) 11.4 kJ/mol less stable than the other conformer. The equilibrium will therefore favor the conformer with both methyl groups in the equatorial position.

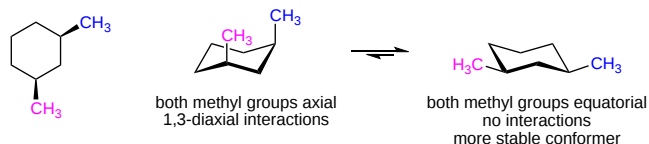


two 1,3-diaxial interactions (15.2 kJ/mol)

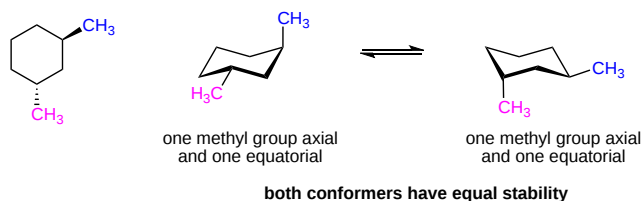


CIS AND TRANS STEREOISOMERS OF 1,3-DIMETHYLCYCLOHEXANE

A similar conformational analysis can be made for the *cis* and *trans* stereoisomers of 1,3-dimethylcyclohexane. For *cis*-1,3-dimethylcyclohexane one chair conformation has both methyl groups in axial positions creating 1,3-diaxial interactions. The other conformer has both methyl groups in equatorial positions thus creating no 1,3-diaxial interaction. Because the methyl groups are not on adjacent carbons in the cyclohexane rings gauche interactions are not possible. Even without energy calculations it is simple to determine that the conformer with both methyl groups in the equatorial position will be the more stable conformer.



For *trans*-1,3-dimethylcyclohexane both conformations have one methyl axial and one methyl group equatorial. Each conformer has one methyl group creating a 1,3-diaxial interaction so both are of equal stability.



SUMMARY OF DISUBSTITUED CYCLOHEXANE CHAIR CONFORMATIONS

When considering the conformational analyses discussed above a pattern begins to form. There are only two possible relationships which can occur between ring-flip chair conformations:

- 1) AA/EE: One chair conformation places both substituents in axial positions creating 1,3-diaxial interactions. The other conformer places both substituents in equatorial positions creating no 1,3-diaxial interactions. This diequatorial conformer is the more stable regardless of the substituents.
- 2) AE/EA: Each chair conformation places one substituent in the axial position and one substituent in the equatorial position. If the substituents are the same, there will be equal 1,3-diaxial interactions in both conformers making them equal in stability. However, if the substituents are different then different 1,3-diaxial interactions will occur. The chair conformation which places the larger substituent in the equatorial position will be favored.

Substitution type	Chair Conformation Relationship
<i>cis</i> -1,2-disubstituted cyclohexanes	AE/EA
<i>trans</i> -1,2-disubstituted cyclohexanes	AA/EE
<i>cis</i> -1,3-disubstituted cyclohexanes	AA/EE
<i>trans</i> -1,3-disubstituted cyclohexanes	AE/EA
<i>cis</i> -1,4-disubstituted cyclohexanes	AE/EA
<i>trans</i> -1,4-disubstituted cyclohexanes	AA/EE

✓ EXAMPLE 4.8.1

For *cis*-1-chloro-4-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *cis*-1,4-disubstituted cyclohexanes should have two chair conformations each with one substituent axial and one equatorial. Based on this, we can surmise that the energy difference of the two chair conformations will be based on the difference in the 1,3-diaxial interactions created by the methyl and chloro substituents.

1,3-diaxial interactions (7.6 kJ/mol)



1,3-diaxial interactions (2.0 kJ/mol)

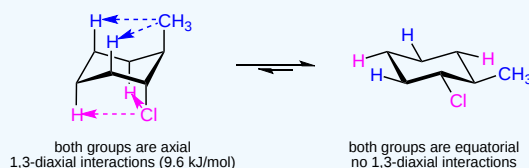
As predicted, each chair conformer places one of the substituents in the axial position. Because the methyl group is larger and has a greater 1,3-diaxial interaction than the chloro, the most stable conformer will place it in the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol - 2.0 kJ/mol) 5.6 kJ/mol more stable than the other.

✓ EXAMPLE 4.8.2

For *trans*-1-chloro-2-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *trans*-1,2-disubstituted cyclohexanes should have one chair conformation with both substituents axial and one conformation with both substituents equatorial. Based on this, we can predict that the conformer which places both substituents equatorial will be the more stable conformer. The energy difference of the two chair conformations will be based on the 1,3-diaxial interactions created by both the methyl and chloro substituents.

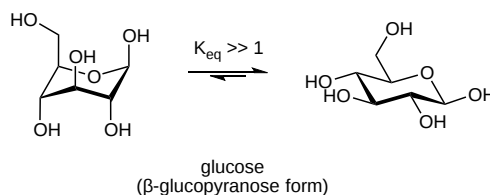


As predicted, one chair conformer places both substituents in the axial position and the other places both substituents equatorial. The more stable conformer will place both substituents in the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol + 2.0 kJ/mol) 9.6 kJ/mol more stable than the other.

CONFORMATIONAL ANALYSIS OF COMPLEX SIX MEMBERED RING STRUCTURES

Cyclohexane can have more than two substituents. Also, there are multiple six membered rings which contain atoms other than carbon. All of these systems usually form chair conformations and follow the same steric constraints discussed in this section. Because the most commonly found rings in nature are six membered, conformational analysis can often help in understanding the usual shapes of some biologically important molecules. In complex six membered ring structures a direct calculation of 1,3-diaxial energy values may be difficult. In these cases a determination of the more stable chair conformer can be made by empirically applying the principles of steric interactions.

A later chapter will discuss how many sugars can exist in cyclic forms which are often six membered rings. When in an aqueous solution the six carbon sugar, glucose, is usually a six membered ring adopting a chair conformation. When looking at the two possible ring-clip chair conformations, one has all of the substituents axial and the other has all the substituents equatorial. Even without a calculation, it is clear that the conformation with all equatorial substituents is the most stable and glucose will most commonly be found in this conformation.



✓ EXAMPLE 4.8.3

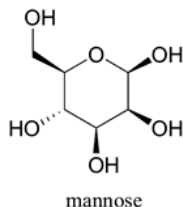
The six carbon sugar, fructose, in aqueous solution is also a six-membered ring in a chair conformation. Which of the two possible chair conformations would be expected to be the most stable?

Solution

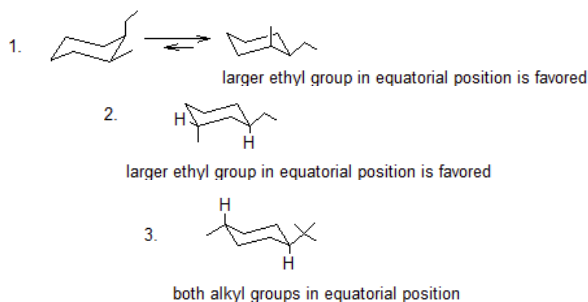
The lower energy chair conformation is the one with three of the five substituents (including the bulky $-\text{CH}_2\text{OH}$ group) in the equatorial position (pictured on the right). The left structure has 3 equatorial substituents while the structure on the right only has two equatorial substituents.

EXERCISES

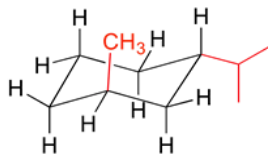
1. Draw the two chair conformations for *cis*-1-ethyl-2-methylcyclohexane using bond-line structures and indicate the more energetically favored conformation.
2. Draw the most stable conformation for *trans*-1-ethyl-3-methylcyclohexane using bond-line structures.
3. Draw the most stable conformation for *trans*-1-*t*-butyl-4-methylcyclohexane using bond-line structures.
4. Draw the most stable conformation for *trans*-1-isopropyl-3-methylcyclohexane.
5. Can a 'ring flip' change a *cis*-disubstituted cyclohexane to *trans*? Explain.
6. Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.



SOLUTIONS



4.



The bulkier isopropyl group is in the equatorial position.

5. No. In order to change the relationship of two substituents on a ring from *cis* to *trans*, you would need to break and reform two covalent bonds. Ring flips involve only *rotation* of single bonds.

6.

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 equatorial reducing steric interaction

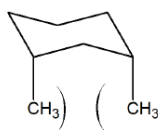
2 – The most stable conformation would be to have the groups equatorial this would reduce the strain if they were axial



1



2



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