7.3 MONOSUBSTITUTED CYCLOHEXANES. CONFORMATIONAL ANALYSIS

A substituent group in a substituted cyclohexane, such as the methyl group in methyl cyclohexane, can be in either an equatorial or an axial position.

These two compounds are not identical, yet they have the same connectivity, so they are stereoisomers. Because they are not enantiomers, they must be diastereomers. Like cyclohexane itself, substituted cyclohexanes such as methylcyclohexane also undergo the chair interconversion. As Fig. 7.6 (p. 278) shows, axial methylcyclohexane and equatorial methylcyclohexane are interconverted by this process. Note in this interconversion that a down methyl remains down and an up methyl remains up. (Demonstrate this to yourself with models!) Because this process is rapid at room temperature, methylcyclohexane is a mixture of two conformational diastereomers (Sec. 6.10A). Because diastereomers have different energies, one form is more stable than the other.

Equatorial methylcyclohexane is more stable than axial methylcyclohexane. In fact, it is usually the case that the equatorial conformation of a substituted cyclohexane is more stable than the axial conformation. Why should this be so?

Examination of a space-filling model of axial methylcyclohexane (Fig. 7.7, p. 278) shows that van der Waals repulsions occur between one of the methyl hydrogens and the two axial hydrogens on the same face of the ring. Such unfavorable interactions between axial groups are called 1,3-diaxial interactions. These van der Waals repulsions destabilize the axial conformation relative to the equatorial conformation, in which such van der Waals repulsions are absent.
Figure 7.6 The chair interconversion results in an equilibrium between equatorial (left) and axial (right) conformations of methylcyclohexane. The conversion is shown with two different ring perspectives. Notice in this interconversion that a down methyl remains down and an up methyl remains up.

Figure 7.7 The equilibrium between axial and equatorial conformations of methylcyclohexane is shown with (a) Lewis structures, (b) ball-and-stick models, and (c) space-filling models. The hydrogens involved in 1,3-diaxial interactions in the axial conformation are shown in color, and the interactions themselves are indicated with red brackets.
As Fig. 7.8 shows, the energy (enthalpy) difference between axial and equatorial conformations of methylcyclohexanes is 7.4 kJ mol\(^{-1}\) (1.8 kcal mol\(^{-1}\)). Because there are two 1,3-diaxial interactions in methylcyclohexane, each interaction is responsible for one-half of the enthalpy difference, or 3.7 kJ mol\(^{-1}\) (0.9 kcal mol\(^{-1}\)). We’ll find that we can use this value in predicting the relative energies of other methyl-substituted cyclohexanes. In other words, each methyl–hydrogen 1,3-diaxial interaction in a cyclohexane derivative raises the enthalpy by 3.7 kJ mol\(^{-1}\) (0.9 kcal mol\(^{-1}\)).

As shown in Fig. 7.9, the 1,3-diaxial interaction of a methyl group and a hydrogen in axial-methylcyclohexane looks a lot like the van der Waals interaction between methyl hydrogens in gauche-butane. The energy cost of this interaction in gauche-butane is 2.8 kJ mol\(^{-1}\) (Fig. 2.5, p. 54). Because there are two such 1,3-diaxial interactions in axial-methylcyclohexane, the gauche-butane analogy would predict an energy cost of \(2 \times 2.8 = 5.6\) kJ mol\(^{-1}\). The actual value, 7.4 kJ mol\(^{-1}\), is in fair agreement with this prediction. For this reason, 1,3-diaxial methyl–hydrogen interactions in cyclohexane derivatives are sometimes called gauche-butane interactions.

The energy cost of placing a methyl group in the axial position of a cyclohexane ring is reflected in the relative amounts of axial and equatorial methylcyclohexanes present at equilib-

![Figure 7.8 Relative enthalpies of axial and equatorial methylcyclohexane.](image)

![Figure 7.9 The relationship between the axial conformation of methylcyclohexane and gauche-butane. One gauche-butane part of methylcyclohexane is highlighted, and the corresponding van der Waals repulsion is shown with a colored bracket. The second gauche-butane interaction in methylcyclohexane is shown with the gray bracket.](image)
As you will see when you work Problem 7.2, methylcyclohexane contains very little of the axial conformation at equilibrium.

The investigation of molecular conformations and their relative energies is called **conformational analysis**. We have just carried out a conformational analysis of methylcyclohexane. The conformational analyses of many different substituted cyclohexanes have been performed. As might be expected, the 1,3-diaxial interactions of large substituent groups are greater than the interactions in methylcyclohexane. For example, the equatorial conformation of tert-butylcyclohexane is favored over the axial conformation by about 20 kJ mol\(^{-1}\) (about 5 kcal mol\(^{-1}\)).

This means that a sample of tert-butylcyclohexane contains a truly minuscule amount of the axial conformation. (See Problem 7.3.)

### Separation of Chair Conformations

The two chair conformations of a monosubstituted cyclohexane are diastereomers. If these conformations could be separated, they would have different physical properties. In the late 1960s, C. Hackett Bushweller, then a graduate student in the laboratory of Prof. Frederick Jensen at the University of California, Berkeley, cooled a solution of chlorocyclohexane in an inert solvent to \(-150^\circ\text{C}\). Crystals suddenly appeared in the solution. He filtered the crystals at low temperature; subsequent investigations showed that he had selectively crystallized the equatorial form of chlorocyclohexane!

When the equatorial form was "heated" to \(-120^\circ\text{C}\), the rate of the chair interconversion increased, and a mixture of conformations again resulted. Similar experiments have been carried out with other monosubstituted cyclohexanes.

### PROBLEMS

7.2 The \(\Delta G^\circ\) difference between the axial and equatorial conformations of methylcyclohexane (7.3 kJ mol\(^{-1}\), 1.74 kcal mol\(^{-1}\); see Fig. 7.8) is about the same as the \(\Delta H^\circ\) difference. Calculate the percentages of axial and equatorial conformations present in one mole of methylcyclohexane at 25 \(^\circ\text{C}\). (\textit{Hint:} See Study Problem 7.1.)

7.3 Using the information in the previous problem and in Eq. 7.7, contrast the relative amounts of axial conformations in samples of methylcyclohexane and tert-butylcyclohexane.

7.4 (a) The axial conformation of fluorocyclohexane is 1.0 kJ mol\(^{-1}\) (0.25 kcal mol\(^{-1}\)) less stable than the equatorial conformation. What is the energy cost of a 1,3-diaxial interaction between hydrogen and fluorine?
(b) Estimate the energy difference between the gauche and anti conformations of 1-fluoropropane.

\[ \text{H}_2\text{C}—\text{CH}_2—\text{CH}_2—\text{F} \]

1-fluoropropane

7.5 Suggest a reason why the energy difference between conformations of ethylcyclohexane is about the same as that for methylcyclohexane, even though the ethyl group is larger than a methyl group.

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**7.4 DISUBSTITUTED CYCLOHEXANES**

### A. Cis–Trans Isomerism in Disubstituted Cyclohexanes

Consider a typical disubstituted cyclohexane, 1-chloro-2-methylcyclohexane.

![Image of 1-chloro-2-methylcyclohexane]

In one stereoisomer of this compound, both the chloro and methyl groups are in equatorial positions. This compound is in rapid equilibrium with a conformational diastereomer in which both the chloro and methyl groups assume axial positions.

![Image of trans-1-chloro-2-methylcyclohexane]

Either conformation (or the mixture of them) is called trans-1-chloro-2-methylcyclohexane. The designation “trans” is used with cyclic compounds when two substituents have an up–down relationship.

![Image of cis-1-chloro-2-methylcyclohexane]

Notice that the up–down relationship is unaffected by the chair interconversion.