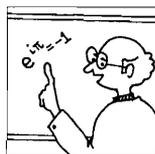# Classroom

In this section of *Resonance,* we invite readers to pose questions likely to be raised in a classroom situation. We may suggest strategies for dealing with them, or invite responses, or both. "Classroom" is equally a forum for raising broader issues and sharing personal experiences and viewpoints on matters related to teaching and learning science.

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Conformational Analysis of Cyclohexanes Diastereoisomerism in Disubstituted Cyclohexanes

The cycloalkanes most commonly found in nature, viz., in some alkaloids, steroids and terpenoids contain six membered rings because they can exist in a completely strain free chair conformation. The fundamental understanding of the conformations of cyclohexane and the structures of molecules containing cyclohexane ring was developed by Derek H R Barton and Odd Hassel, who shared the Nobel Prize in 1969. An enormous amount of experimental and theoretical evidence is available on the conformational analysis of these compounds. In this article, distinguishing the conformations of the diastereomers and their relative stabilities are discussed in brief.

The substituents on the chair form of cyclohexane are bonded in two different directions with respect to the plane of the ring. The bonds which are nearly parallel to the principal molecular axis are the axial bonds, written as vertical lines, alternately pointing upward and downward, i.e., above and below the plane of the ring. The other six bonds known as the equatorial bonds are nearly perpendicular to the axial bonds, close to the equatorial plane of the ring and are directed away from the ring (*Figure* 1).
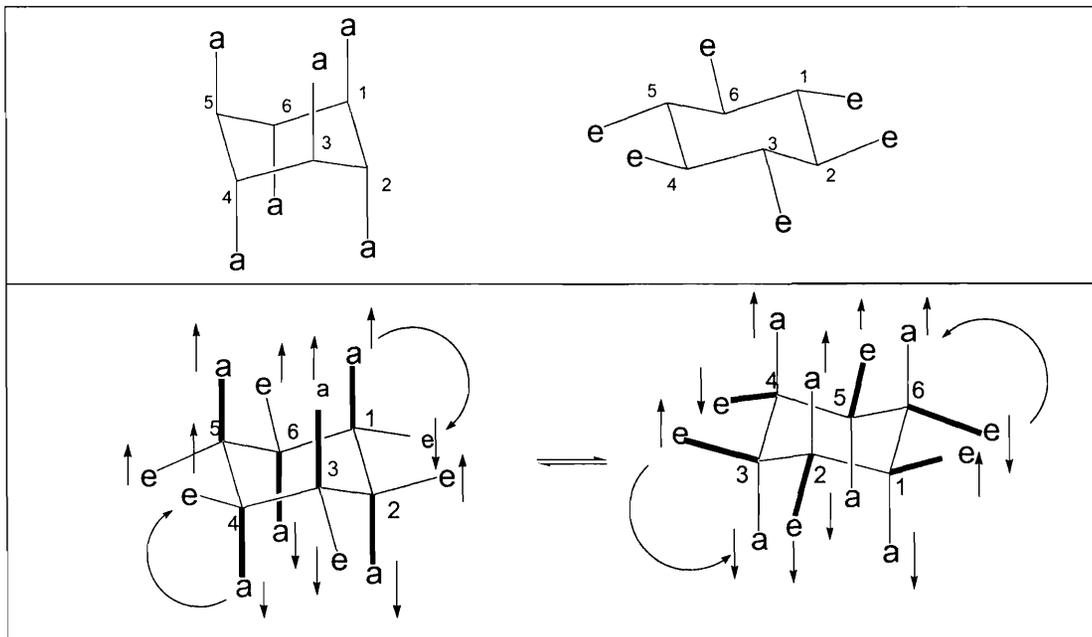
Figure 1 (top).
Figure 2 (bottom).

Each carbon has an axial bond and an equatorial bond, which are in opposite directions. When the axial bond is up, the equatorial bond is down and if the axial bond is down, the equatorial bond is up. The two axial bonds and the two equatorial bonds on the adjacent positions are in the opposite directions (*Figure 2*).

The ring inversion from one chair form to another takes place by flipping of the ring carbons. This occurs by twisting (restricted rotation) of the bonds, and results in the interchange of the positions of the axial and equatorial bonds.

In monosubstituted cyclohexanes, the substituent preferentially occupies the equatorial position, which is on the exterior part of the ring. Substitution on the axial position leads to interactions
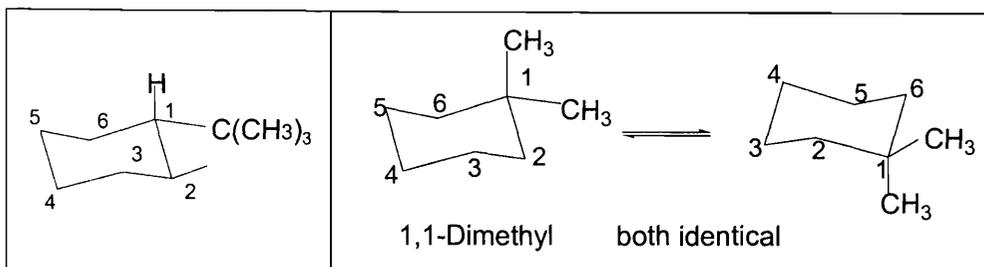
Figure 3.

a-methyl

e-methyl
more stable

1,1-Dimethyl   both identical
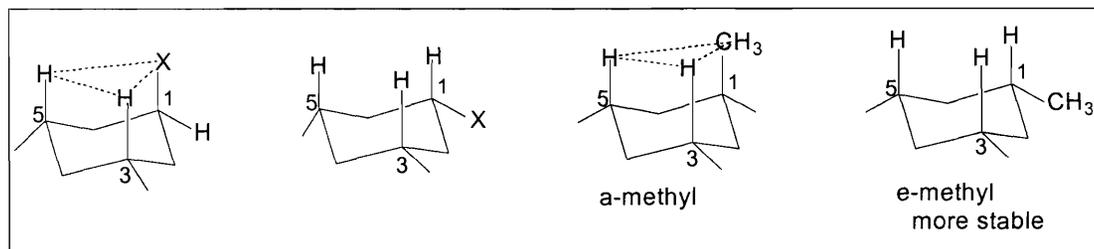
Figure 4 (left).
Figure 5 (right).

with the 1,3-diaxial hydrogens present on the same side of the ring. Hence, the equatorially substituted cyclohexane is more stable and is the preferred conformation (*Figure* 3). The ratio of the two conformers is variable depending on the size of the substituent. For example, while the two conformers for methylcyclohexane exist in unequal amounts, t-butyl cyclohexane exists invariably in a single conformation with the bulky t-bultyl group occupying the equatorial position (*Figure* 4).

Disubstituted Cyclohexanes and Diastereoisomerism

1,1-Disubstituted cyclohexanes:

The two identical groups, like in 1,1-dimethylcyclohexane, occupy an equatorial and an axial position in both conformations. Hence, both are equally stable and so identical (*Figure* 5).

When two different substituents are present, the bulkier one preferentially occupies the equatorial position, e.g., 1-methyl-1-cyclohexanol (*Figure* 6).

The conformation with the larger methyl group in the equatorial position is more stable, so the two conformers are present in
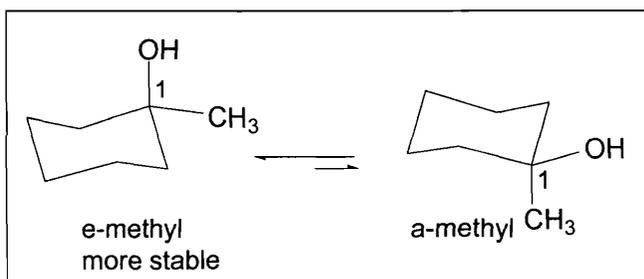

e-methyl   a-methyl CH_3
more stable

Figure 6.

unequal amounts. Because the substituents are present in different positions, the two conformations are diastereomers. However, since they interconvert very fast, they cannot be separated.

The two interconvertible chair forms of 1,2-, 1,3- and 1,4- disubstituted cyclohexanes exist as cis and trans diastereomers. Distinguishing the cis and trans isomers in the chair conformations is often confusing which can be cleared by looking in the direction of the axial and equatorial bonds. Hence, writing these bonds in a proper plane of the conformation is important.

Substitution Pattern and Cis/Trans Isomerism

The corresponding cis- and trans- 1,2- and 1,4- disubstituted cyclohexanes have the same substitution patterns while it is reverse for the 1,3-compounds (*Figure* 7).

Substitution	Position	Isomer	Preferred conformation
1,2- & 1,4-	e,e & a,a	Trans	e,e
	e,a & a,e	Cis	both identical
			(if the substituents are identical)
1,3-	e,e & a,a	Cis	e,e
	e,a & a,e	Trans	(if the substituents are identical)

The trans isomers of 1,2- and 1,4- disubstituted cyclohexanes with diequatorial substituents are more stable than the corresponding cis isomers with the e,a- and a,e- substitutions, as the group in the axial position gives rise to 1,3-diaxial interactions. In the 1,3-disubstituted cyclohexanes, the cis isomer with diequatorial substitution is more stable than the e,a- and a,e- trans conformation, because of the 1,3-interactions in the latter[1].

There are certain examples where the conformation of a molecule can be frozen (locked) into a single conformation by a large alkyl group. The t-butyl group in 4-t-butyl cyclohexanol is large enough to lock the conformation in a single chair form. This group occupies only the equatorial position in all other t-butylcyclohexanols also (*Figure* 8).
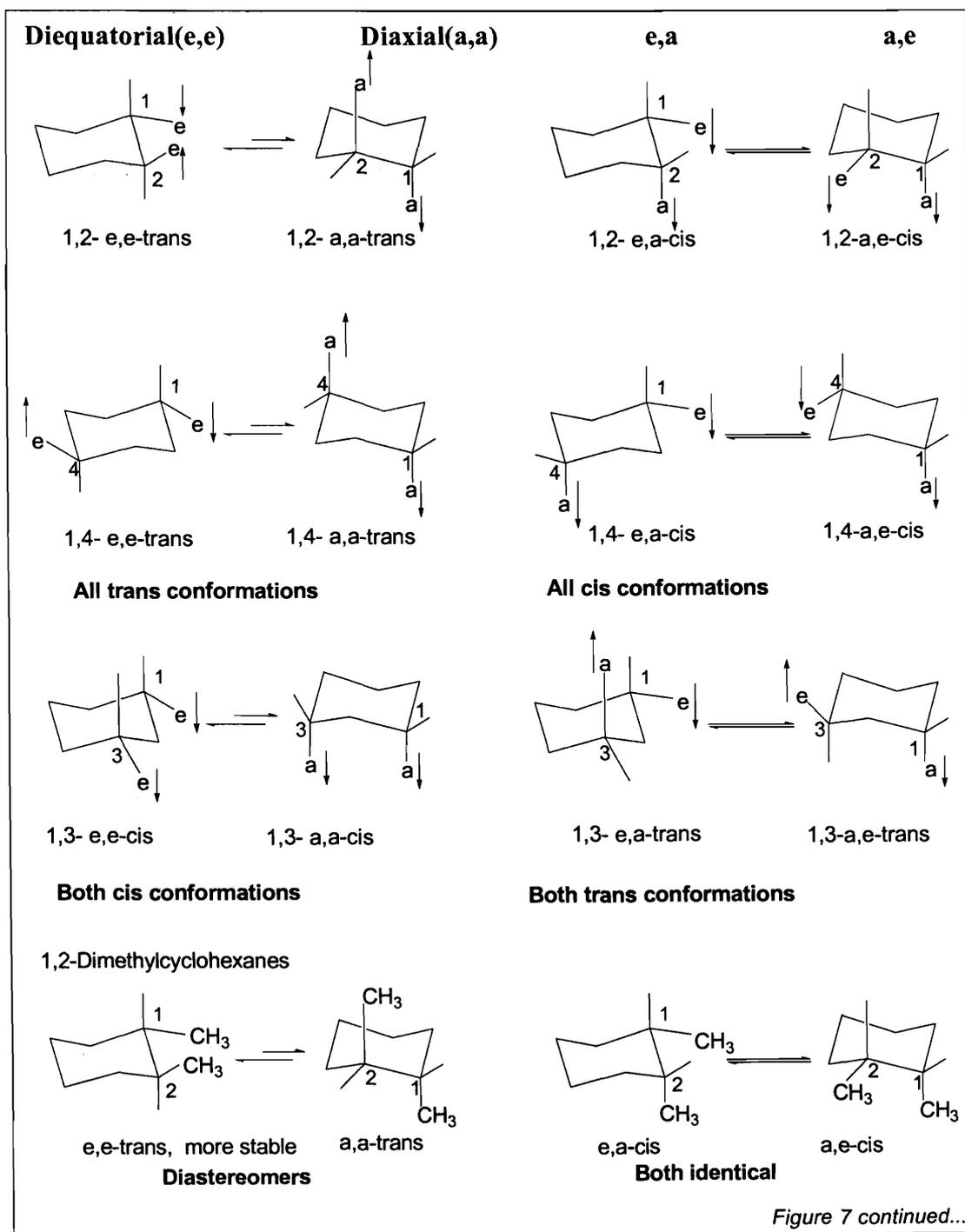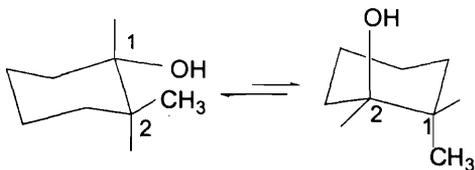
The conformation with the maximum number of equatorial substitutions will be more stable. Ring inversion does not change the cis and trans relationships of the substituents.

Figure 7.

Diequatorial(e,e) **Diaxial(a,a)** **e,a** **a,e**

1,2- e,e-trans   1,2- a,a-trans   1,2- e,a-cis   1,2-a,e-cis

1,4- e,e-trans   1,4- a,a-trans   1,4- e,a-cis   1,4-a,e-cis

All trans conformations   **All cis conformations**

1,3- e,e-cis   1,3- a,a-cis   1,3- e,a-trans   1,3-a,e-trans

Both cis conformations   **Both trans conformations**

1,2-Dimethylcyclohexanes

e,e-trans, more stable   a,a-trans   e,a-cis   a,e-cis
Diastereomers   **Both identical**

Figure 7 continued...

2-Methylcyclohexanols

e,e-trans, more stable   a,a-trans
methyl larger than hydroxy
Diastereomers
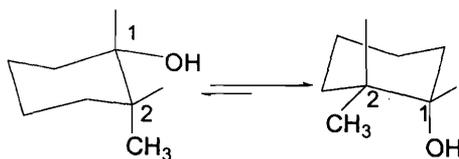
e,a-cis   a,e-cis
              more stable
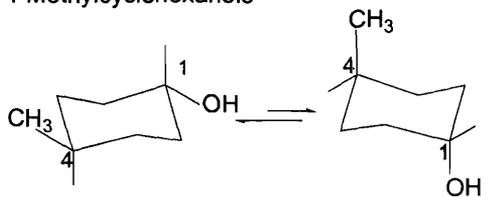**Diastereomers**

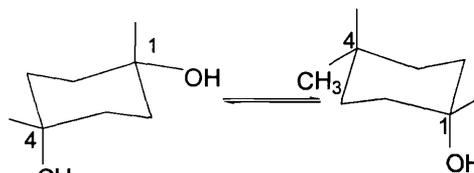1,4-Dimethylcyclohexanes
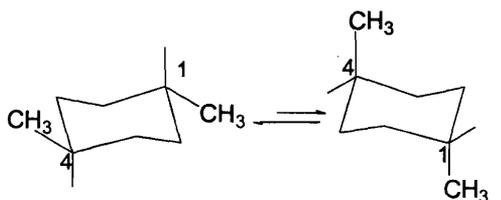
e,e-trans, more stable   a,a-trans
Diastereomers
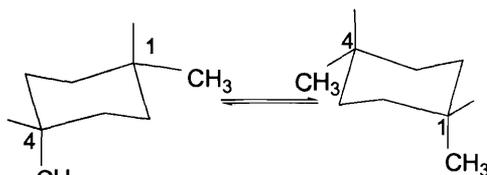
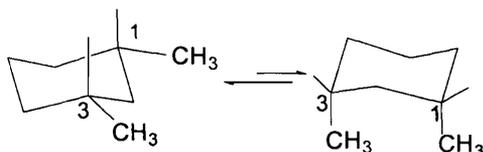e,a- cis   a,e-cis
Both identical

4-Methylcyclohexanols

e,e-trans, more stable   a,a-trans
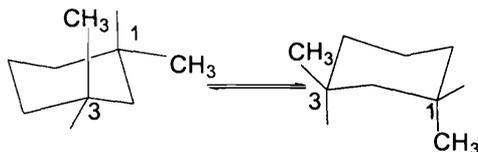**Diastereomers**

e,a- cis   a,e-cis, more stable
Diastereomers

1,3-Dimethylcyclohexanes

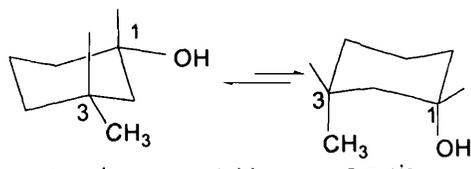e,e-cis, more stable   a,a-cis
Diastereomers

e,a-trans   a,e-trans
Both identical

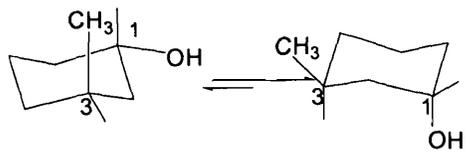*Figure 7 continued...*

Figure 7 continued...

3-Methylcyclohexanols

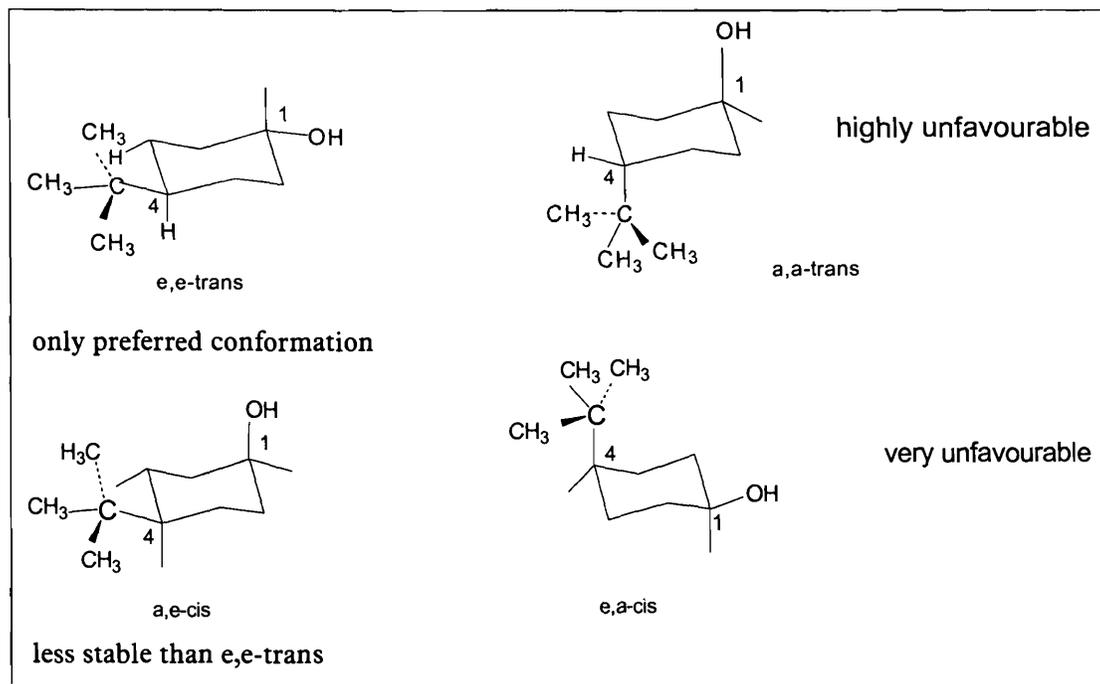e,e-cis, more stable   a,a-cis

Diastereomers

e,a-trans   a,e-trans ,more stable

Diastereomers

However, with two such bulky groups, ring distortion takes place. In the chair conformation of 1,4-di-t-butylcyclohexane the bulky t-butyl groups even in diequatorial positions cannot avoid steric interactions with the adjacent hydrogens. Hence, the molecule prefers to pucker into a twist boat form so that these groups are away from all the adjacent hydrogens. In the twist boat form, the groups are not exactly equatorial as in the chair conformation, but are directed away from the ring and are known as the pseudoequatorial positions (*Figure* 9).

Figure 8.

e,e-trans

only preferred conformation

highly unfavourable

a,a-trans

a,e-cis

less stable than e,e-trans
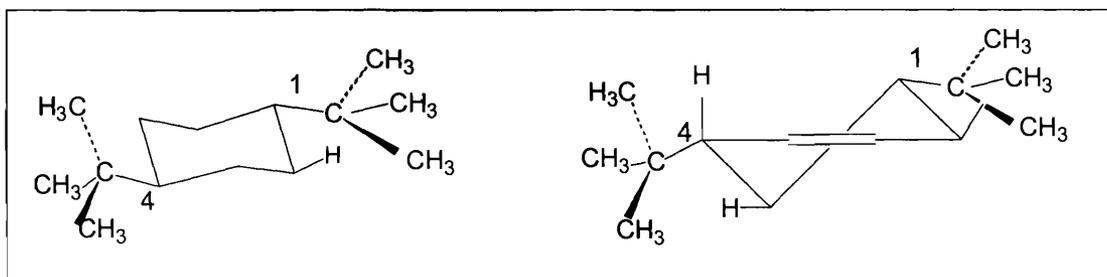
very unfavourable

e,a-cis

Figure 9.

Another factor which predominates in deciding the stability of the conformations is the intramoleculer H-bonding e.g. in the 1,3- and 1,4- dihydroxy cyclohexanes. The diaxial chair conformation of cis-1,3-dihydroxycyclohexane is preferred due to stabilization by intramolecular H-bonding, as the two hydroxy groups are closer, while this is not possible in the diequatorial form.

More interesting is the example of cis-1,4-dihydroxycyclohexane where the unfavourable boat form is the preferred conformation due to intramolecular H-bonding and the molecule exists in only one form.
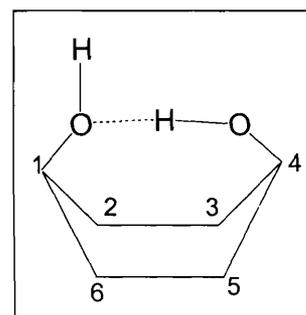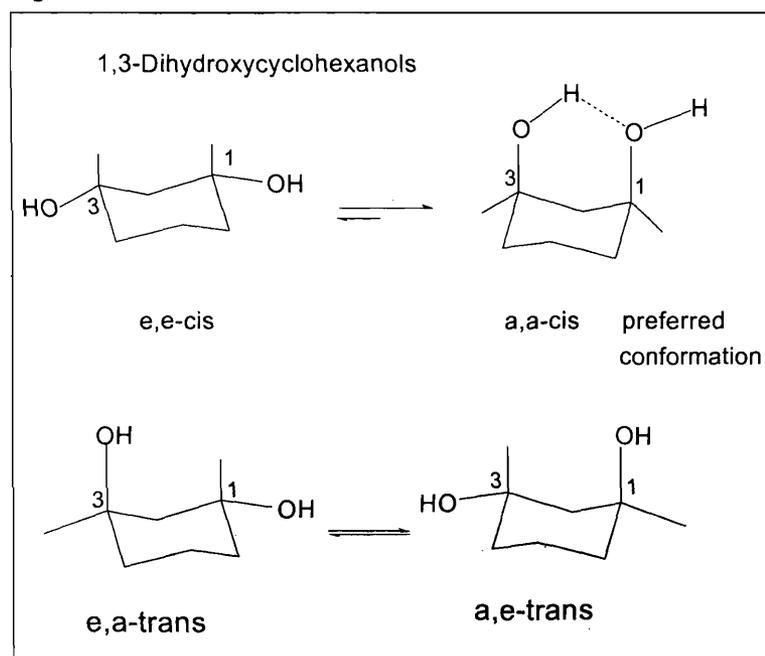

Figure 11.

Figure 10.

Suggested Reading

[1] E L Eliel, S H Wilen and L N Mander, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, 1994.
[2] D Nasipuri, *Stereochemistry of Organic Compounds*, second edition New Age International Publishers, 1996.