4   Cyclohexane

Aims

In this chapter you will first learn the conformational analysis of cycloalkanes with smaller numbers of carbon atoms, from cyclopropane (C_3) to cyclopentane (C_5). Compared to alkanes with equivalent numbers of carbon atoms, rotations about the single bond in smaller cycloalkanes are much less flexible due to their cyclic structure.

The most important feature of cyclohexane is that all ∠C-C-C have the tetrahedral angle (109°28'). It has two chair and two boat conformers, and the two chair forms interconvert with each other *via* boat forms. Many natural products contain cyclohexane-like structures as their components, and this fact makes the study of cyclohexane particularly important.

In addition, you will learn how the stereochemistry of cyclohexane is widened by substituted cyclohexanes. The conformational analysis of methyl- and dimethyl-cyclohexanes will be very good examples to promote your study of this point.

New terms and concepts

cycloalkane
ring inversion
*axia*l bond
equatorial bond
chair form
boat form
population of conformer
*cis-trans* isomerism (cyclic compounds)
1,3-diaxial interaction

Goals of this chapter

After you master this chapter successfully, you will be able to do the following:
1   to build up molecular models of cyclohexane in a chair or in a boat form. To compare the relative stability of these two conformers based on the butane-gauche interaction.
2   to understand the ring inversion of cyclohexane and axial-equatorial exchange that accompanies this inversion.
3   to explain the relative stability of conformers of substituted cyclohexanes in terms of the larger stability of the equatorial conformer and the 1,3-diaxial interaction.

## 4.1   Cyclohexane; chair form and boat form

In the past, chemists believed that cycloalkanes, including cyclohexane, were planar like benzene (see below). Since the ∠C-C-C bond angle of the sp^3 hybridized carbon chain is 109°28', cycloalkanes will suffer some strain if they are planar.

60°	90°	108°	120°
cyclopropane	cyclobutane	cyclopentane	cyclohexane
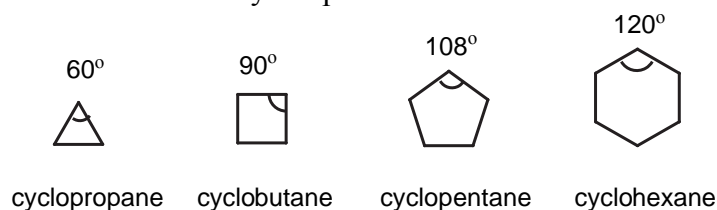
All cycloalkanes, except cyclopentane, become unstable because of this strain (**Baeyer's strain theory**). According to this theory, the most stable cycloalkane is cyclopentane, and cyclohexane is

the next.

Although this theory could explain the high reactivity of cyclopropane, it gradually became clear that cyclohexane would be more stable if a nonplanar structure is assumed. Under this assumption, the $\angle$C-C-C bond angle of cyclohexane could maintain the tetrahedral angle. Because of the cyclic nature, the number of structures cyclohexane can take is much fewer than its acyclic analog hexane. There is, however, a flip-flop of the ring as the rotation about the C-C bond of cyclohexane takes place. The movement of the ring can most conveniently be defined by the torsion angle made by the four successive carbon atoms (a butane unit). If we choose C1~C4 (**1**) as the butane unit, the torsion angle can be defined as shown in **2**. You should confirm the discussion above by using a molecular model.

1   **2**
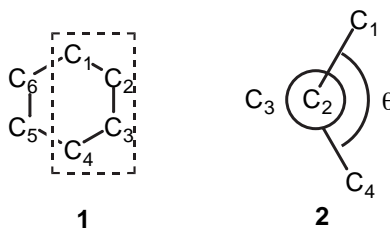
Q4.1

Are there any restrictions on the angle θ made by the four successive carbon atoms of cyclohexane?☐

Q4.2

In order to understand the stereochemistry of cyclohexane, how many "butane units" should be taken into consideration?☐

A4.1

In the case of butane, θ can be any value from 0° to 360° (or –180° to +180 °). In the case of cyclohexane, there is a severe restriction on θ. The allowed value is *ca*. 90° as a maximum. Such a conformation as *ap* is impossible.☐

If the torsion angle-energy diagram for C_1~C_4, "butane unit" of cyclohexane, is essentially identical with that of butane (Fig. 2.4), then the staggered form **3** (which is referred to as "**butane gauche unit**") should be more stable than the eclipsed form **4**.

3   **4**
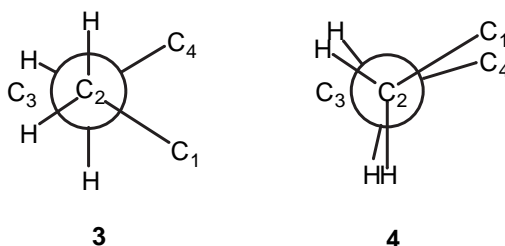
If a given cyclohexane contains six butane-gauche units, it should be the most stable conformer when all bond angles are tetrahedral.

Q4.3

Draw a perspective view of cyclohexane with six butane-gauche units. Confirm, with the aid of a molecular model, that all bond angles are tetrahedral.☐
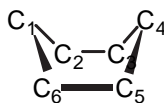
A4.2

6 units; C_1~C_4, C_2~C_5, C_3~C_6, C_4~C_1, C_5~C_2 and C_6~C_3. With these all torsion angles in

cyclohexane can be examined.◻

The conformer of cyclohexane **5** or **5'** is called the **chair form**, which is the most stable one.

There is another conformer of cyclohexane **6** or **6'** in which all bond angles are tetrahedral. This conformer is called the **boat form**.


6   **6'**

Q4.4

Carry out the conformational analysis of **6** with reference to six "butane units". Compare its stability with the chair form.◻

A4.3
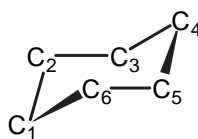
5   **5'**

◻

Q4.5

Draw the Newman projections of **5** and **6** viewed along the direction of the C_2-C_3 and C_6-C_5 bonds◻

A4.4

In **6**, there are two butane-eclipsed units (C_1-C_2-C_3-C_4 and C_1-C_6-C_5-C_4). The other butane units are all staggered. Hence the energy difference between **5** and **6** can be approximated as the energy difference between the butane in the gauche form and the butane in the eclipsed form, *i.e.*, 21 x 2 = 42 kJ mol^{-1}.◻

A4.5
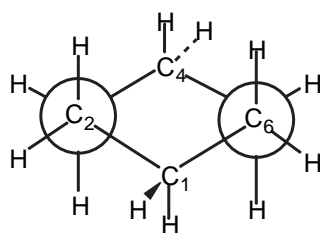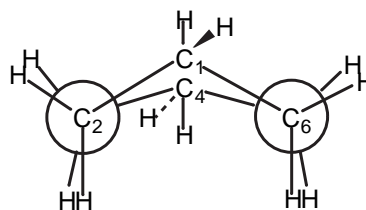
Chair form **7**   Boat form **8**

◻

It is rather tricky to portray two hydrogen atoms bonded to C_1 and C_4, which are beyond the scope of the rules for drawing Newman projections. Here the flying-wedge drawing has been partly employed.


S4.1 Cyclohexane: chair form and boat form.
chair form: consists of six butane-gauche units
boat form: consists of four butane-gauche units and two butane-eclipsed units

---

Now let us consider twelve hydrogen atoms of cyclohexane. Of the two C-H bonds for each

carbon atom, one is perpendicular to the pseudo-plane made by the six carbon atoms, and the other parallel to it. If we asume that cyclohexane resembles the earth, the chain of six carbon atoms may be accepted as the equator. Based on this analogy, the C-H bond perpendicular to the equator (hence parallel to the axis of the earth) is called an **axial bond**, and that parallel to the equator an **equatorial bond**. An atom or a group of atoms bonded to the these bonds are referred to as axial atoms (groups) or equatorial atoms (groups), respectively.

axial-Hydrogen **9**   equatorial-Hydrogen **10**
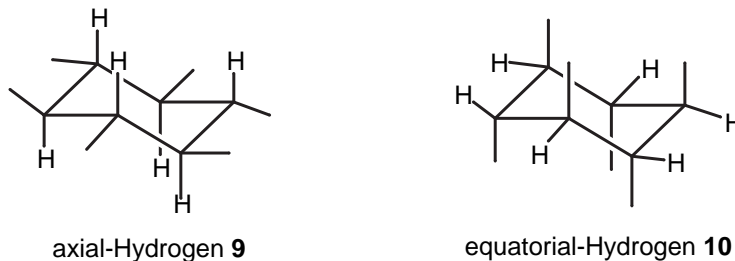
There are two ways to portray a cyclohexane in the perspective view. With one way, the C_2-C_3-C_5-C_6 plane is horizontal (as in **5**). This way is advantageous when making a comparison with a boat form. With the other way, the C_2-C_3-C_5-C_6 plane is slightly tilted so that the axial bonds are perpendicular (as in **9**). This method is convenient when it is important to differentiate between the axial and the equatorial.

4.2   Ring inversion of cyclohexane

The relation between a chair cyclohexane and a boat cyclohexane can be most conveniently examined with the aid of a molecular model (Fig. 4.1). If you lift up the leg of **11** (*i.e.*, C_1) gently, you will obtain a boat cyclohexane **12** (process i). Notice that rotation about the C-C bonds takes place at the same time. This chair-boat interconversion is referred to as the **ring inversion** of cyclohexane. This phenomenon is a type of the **chemical exchange**.
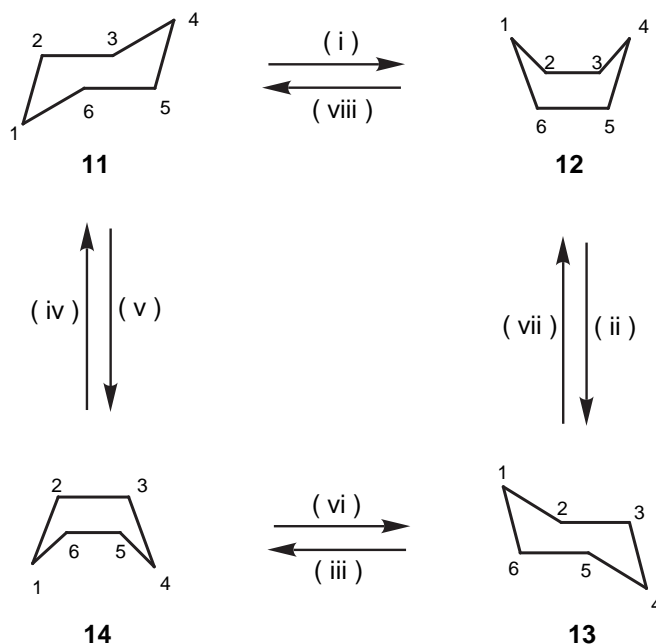

Figure 4.1 Inversion of a cyclohexane ring

In addition to process (i) (**11** → **12**), there is another process (v) having equal probability to lead to the other boat form (**11** → **14**). The boat form **12** can be reconverted to **11** by pulling down the bow (or the stern) (C_1) (process viii) or converted to another chair **13** by pulling down the stern

(or the bow) (C_4) (process ii).

The second chair **13** can be converted to boat **14** by pulling down the support C_1 (process iii) or to boat **12** by lifting up the leg C_4 (process vii). The boat form 14 can similarly be converted to two chairs **11** or **13** (processes iv and vi). Since the energy barrier of the boat $\rightleftarrows$ chair interconversion is low, the process **11** $\rightleftarrows$ **12** $\rightleftarrows$ **13** $\rightleftarrows$ **14** takes place very easily at ambient temperature.

Q4.6

With the help of a molecular model of the carbon skeleton (no hydrogen atoms attached), confirm that chair forms **11** and **13**, and boat forms **12** and **14** are identical.☐

In the case of cyclohexane, the two chair forms **11** and **13**, obtained by the ring inversion, were proved identical as far as the shape of the carbon skeleton is concerned. Can you say, however, that these two are strictly identical? Your belief will waver if you make a chair form with six axial hydrogen atoms **15**. By inversion notice that the second chair form **16** has six equatorial hydrogen atoms rather than six axial hydrogen atoms. Similarly, a chair form with six equatorial hydrogen atoms **17** is converted to the second chair form with six axial hydrogen atoms, **18**.
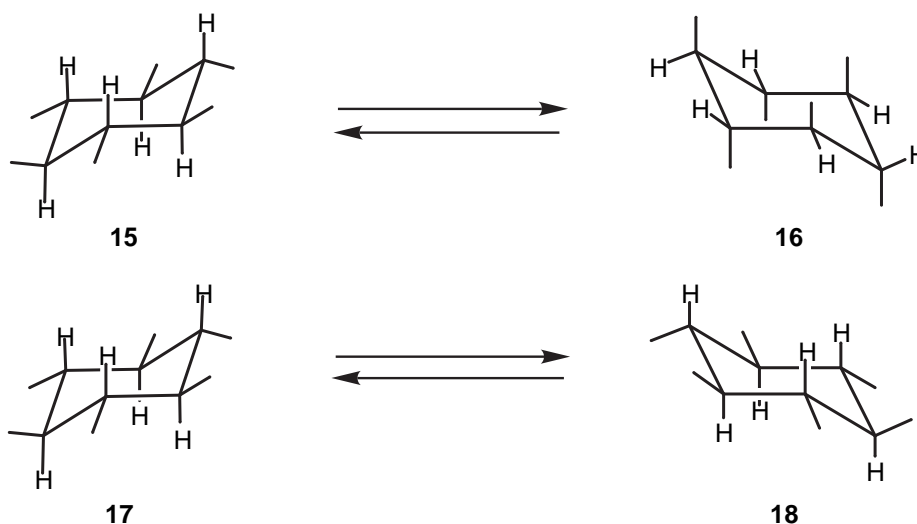

Figure 4.2 Axial-equatorial exchange by ring inversion

Inversion of a chair form of cyclohexane will not reproduce the exactly identical chair form. If we neglect hydrogen atoms, **11** and **13** are identical. However, **15** or **17** are not identical with **16** or **18** if hydrogen atoms are taken into consideration. If we can differentiate axial hydrogen atoms from equatorial hydrogen atoms, cyclohexane **19** is not identical with cyclohexane **20** that is formed from **19** by ring inversion. This fact will be greatly clarified after you have studied substituted cyclohexanes.
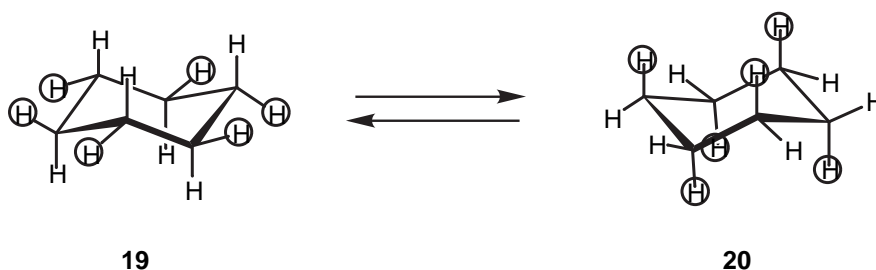
S4.2 Ring inversion of cyclohexane

Ring inversion: a chair cyclohexane is converted to another chair form *via* a boat form.
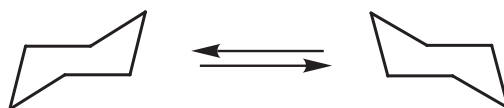
S4.3 Axial, equatorial

axial: the direction perpendicular to the molecular plane: to be converted to equatorial by ring inversion

equatorial; the direction parallel to the molecular plane: to be converted to axial by ring inversion

| axial | equatorial |
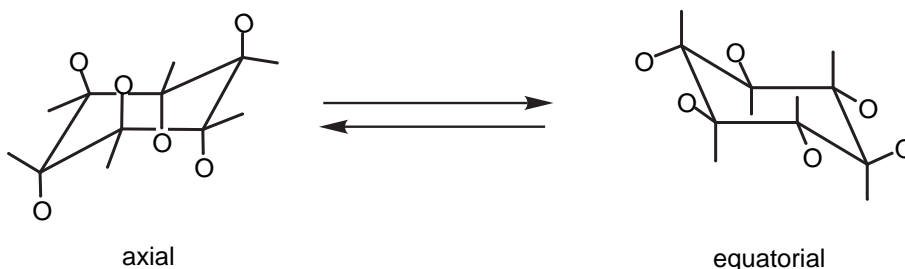
Q4.7

Which of the following three statements is acceptable as a description of cyclohexane?
(a) A 50:50 mixture of chair cyclohexane and boat cyclohexane
(b) Only as one of the chair forms
(c) A 50:50 mixture of two chair forms.☐

A4.6

You had better make two of **11**, and convert these to **12** and **14** to compare.☐

A4.7

(c). Strictly speaking, however, a small amount of boat forms may coexist. The answer is correct if we can assume that the population of the boat form is negligibly small.

There is another point to be considered. It is difficult to differentiate between (b) and (c). What we can observe experimentally is that there is only one type of cyclohexane, that is, a chair cyclohexane. At room temperature, the chair-chair interconversion takes place *ca*. 100,000 times s^{-1}. Even at a very low temperature (-67°C), the frequency is *ca*. 100 times s^{-1}.☐

4.3 Ring inversion of substituted cyclohexanes

Methylcyclohexane, which is obtained by replacing one of the hydrogen atoms of cyclohexane with a methyl group, is a very intriguing compound. The two chair forms of methylcyclohexane are not identical as is the case with cyclohexane itself. The equatorial methyl derivative **21** and the axial methyl derivative **22** form a pair of stereoisomers (Fig. 4.3)
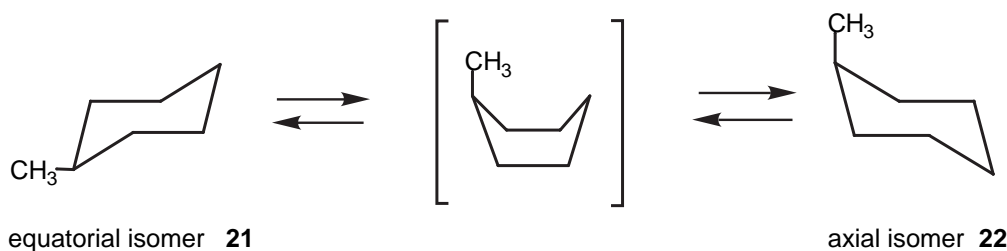

equatorial isomer **21**   axial isomer **22**

Figure 4.3 Ring inversion of methylcyclohexane

The two chair forms of cyclohexane **11** and **13** are identical, but the two chair forms of methylcyclohexane **21** and **22** are stereoisomers. Then, how would you characterize the difference between **21** and **22**? Return to cyclohexane and examine the twelve hydrogen atoms, preferably with the aid of a molecular model. The interatomic distances among the three axial hydrogen atoms bonded to C_1, C_3 and C_5 are relatively short. If one of those three hydrogen atoms, *e.g.*, the hydrogen atom bonded to C_1, is substituted by a large group such as methyl, the distance between the methyl group and the axial hydrogen atoms bonded to C_3 or C_5 become much shorter and generate a large steric interaction. This interaction is called the **1,3-diaxial interaction**. This will make the energy of the axial methylcyclohexane higher than that of the equatorial one.

S4.4 1,3-diaxial interaction
Steric hindrance (repulsion) between two axial substituents at C_1 and C_3 (or equivalent relation) of chair cyclohexane.
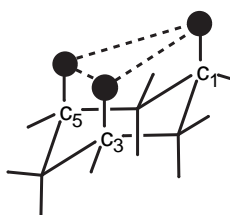
Q4.8
Explain the reason why axial methylcyclohexane **22** is unstable as compared with equatorial methylcyclohexane **21** in terms of gauche and butane-eclipsed units. Estimate the energy difference between **21** and **22**. □

Q4.9
It was found by experiments that the free energy difference ΔG between **21** and **22** is 7.5 kJ mol^{-1}. Calculate the population of each isomer at (a) 27°C and (b) -100°C. □

A4.8
The most significant difference is that the butane unit C_3-C_2-C_1-CH_3 is gauche for equatorial methylcyclohexane **23** while it is antiperiplanar (trans) for **24**. In other word, **23** has more energy than **24** has by twice the difference between butane-gauche and butane- antiperiplanar units, *i.e.*, 2 x 4 = 8 kJ mol^{-1}. □

Q4.10
t-Butylcyclohexane is obtained by substituting one of the hydrogen atoms of cyclohexane with a bulky substituent *t*-butyl group $(CH_3)_3C$-. It is known that this compound exists solely as an equatorial isomer, and that no ring inversion takes place. Why? □

A4.9
The population of the axial isomer is (a) 4.8 %, (b) 0.55%. The lower the temperature, the less the population of the unstable isomer is. □

A4.10
Because of its bulkiness, the 1,3-diaxial interaction between the axial *t*-butyl group and the atom (or group of atoms) in their relevant position is extremely large if the *t*-butyl group becomes axial. In fact the axial *t*-butyl group at C_1 will collides with the axial hydrogen atoms at C_3 or C_5. □

4.4   Substituted cyclohexanes

If there is no ring inversion of cyclohexane, or if the conformers of cyclohexane are averaged by ring inversion, there is only one isomer for methylcyclohexane. In fact, ring inversion does exist, and there are two isomers for methylcyclohexane, axial and equatorial isomers. Thus, the number of isomers of substituted cyclohexanes will vary whether or not the "averaging" by the ring inversion is taken into consideration.

If we admit averaging of cyclohexane ring by inversion, we need not worry about the chair and boat forms of cyclohexane. Cyclohexane may be regarded as a planar molecule. Methylcyclohexane can be written as **25** or **26**. We may differentiate the upper and lower sides of the plane, but adopting this procedure is to admit that one side is the axial side and the other the equatorial side.


25   **26**
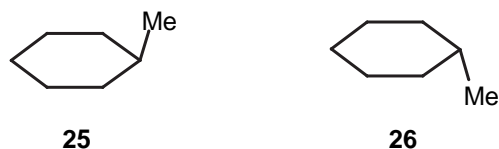
If we admit averaging, there is one isomer **27** for 1,1-dimethylcyclohexane, and there are two isomers **28** and **29** for 1,2-dimethylcyclohexane. **28** is the *cis* isomer and **29** is the *trans* isomer.

1,1-dimethyl-   1,2-dimethyl-

cis   *trans*

27   **28**   **29**
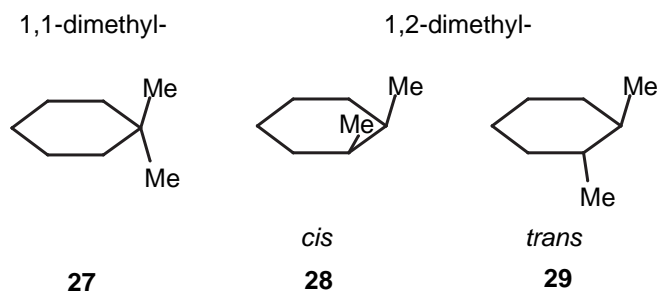
<mark>Q4.11</mark>
When "averaging" by ring inversion is considered, how many isomers are there for 1,3- and 1,4-dimethylcyclohexane?☐

However, if averaging by ring inversion is not accepted, or if **21** and **22** of methylcyclohexane are regarded as isomers, the situation will be different. The case of 1,1-dimethylcyclohexane is rather special. For this compound, the number of isomers is one whether or not averaging is accepted. By ring inversion, **27**ae is converted to the identical molecule **27**ea .

27ae   **27**ea
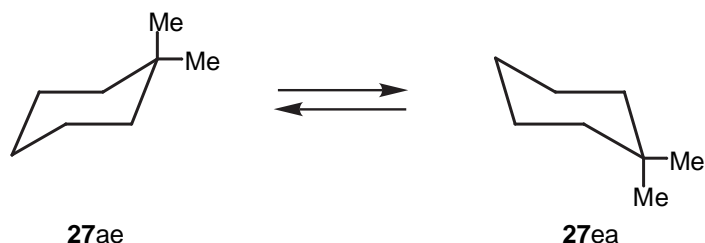
The situation is different for 1,2-dimethylcyclohexane. There are two *trans* isomers; one with two equatorial methyl groups (**34**ee), which, by ring inversion, turn into the other isomer with two axial methyl groups (**34**aa). **34**ee and **34**aa are different compounds in the same sense that **21** and **22** are different. Hence the population should not be 50:50, and it is expected that **34**aa has a much larger energy due to the double 1,3-diaxial interaction of two axial methyl groups, and the equilibrium indicated below should largely be shifted to the left side.

34ee   **34**aa
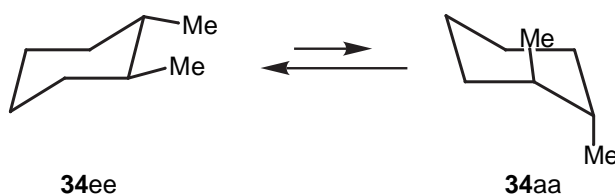
How about the *cis* isomer? How is **35**ea related to **35**ae? As for the conformation of methyl groups is concerned, the two compounds have the same stereochemistry and hence the same energy. The equilibrium below should be 50:50. Detailed analysis of the structure of two compounds with the aid of a molecular model will reveal an important point, which will be discussed later.

35ea   **35**ae
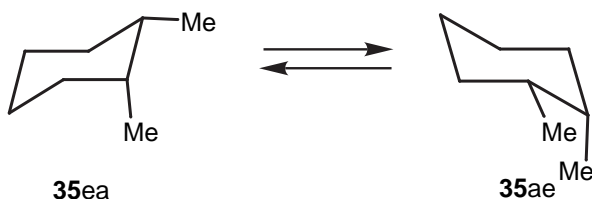
Q4.12

Following the example of **34** and **35**, develop a conformational analysis of *cis*- and *trans*-1,3-dimethylcyclohexane **36** and **37**. ☐

A4.11

The results are similar with 1,2-dimethylcyclohexane. There are *cis* and *trans* isomers for each.
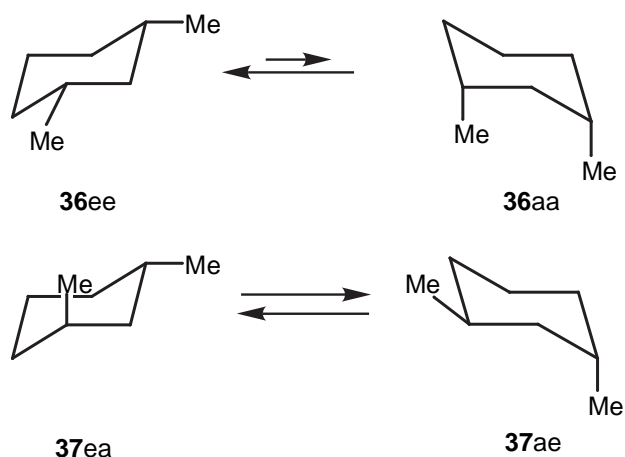

cis   trans   cis   trans

30   **31**   **32**   **33**

☐
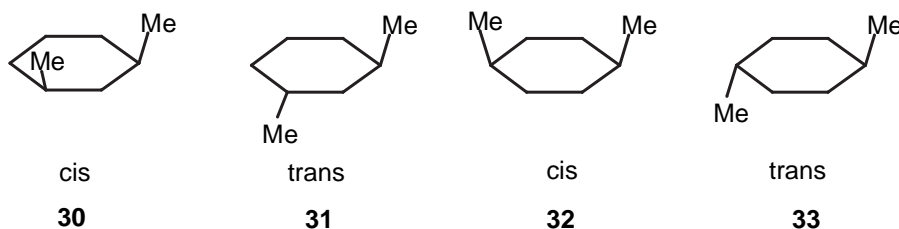
Q4.13

Develop a conformational analysis of *cis*- and *trans*-1,4-dimethylcyclohexane **38** and **39** in a similar manner. ☐

A4.12

In the case of the *cis* isomer **36**, the equilibrium should be shifted to the **36ee**. Wih the *trans* isomer **37**, conformation of the two methyl groups is equal for **37**ea and **37**ae. Hence the equilibrium remains 50:50.

36ee   **36**aa
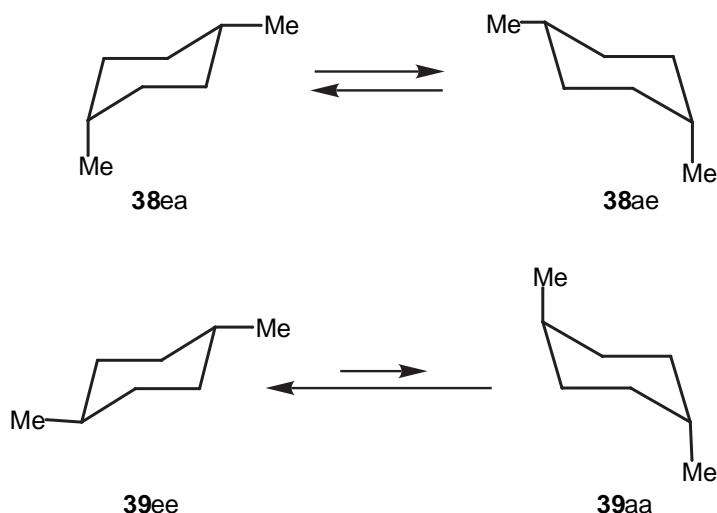
37ea   **37**ae

Q4.14

Estimate the number of butane-gauche unit in each conformer of dimethylcyclohexane, and discuss the relative stability using these data.

A4.13

In the case of the *cis* isomer **38**, the equilibrium ea ⇄ ae should be 50:50 while for the *trans* isomer **39**, the equilibrium **39**ee ⇄ **39**aa should shift to the left.

38ea   **38**ae

39ee   **39**aa

The larger the number of butane-gauche units, the more unstable the conformer. Especially in *cis*-1,3-isomer **36**aa, an 1,3-diaxial interaction between two methyl groups is involved., and expected to be the least stable among these nine stereoisomers.

Q4.15

Decalin $C_{10}H_{18}$ is the perhydro derivative of naphthalene, and consists in two cyclohexanes that share one edge. If the cyclohexanes in decallin remain in a chair conformation, how many stereoisomers are possible for decalin?

A4.14

| *trans*-1,2	aa	4	*trans*-1,3	ae = ea	2	*trans*-1,4	aa	4
	ee	1	*cis*-1,3	aa	4		ee	0
cis-1,2	ae = ea	3		ee	0	*cis*-1,1	ae = ea	2

Q4.16

There is some resemblance between the structure of decalin and that of 1,2-

dimethylcyclohexane. Confirm that the *cis* isomer **41** is susceptible to a ring inversion like that of *cis*-1,2-dimethylcyclohexane, but that such an inversion is impossible for the *trans* isomer **40**. Explain.☐

A4.15

2. One is *trans*-decalin **40** and the other *cis*-decalin **41**.It will be very instructive if you carefully study, preferably with the aid of a molecular model, the stereochemistry of the fused part (*i.e.*, the shared edge), and compare the stereochemistry with that of 1,2-dimethylcyclohexane.


40   **41**
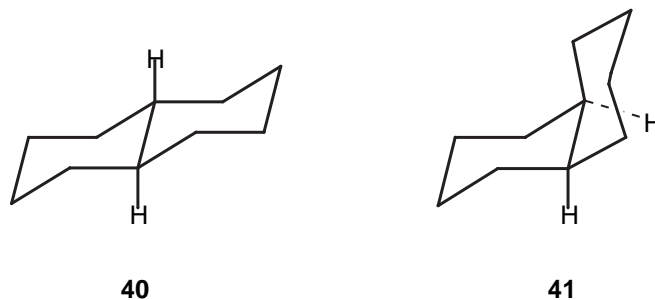
☐
A4.16

The reason why the ring inversion is impossible for the *trans* isomer **40** is that it is an ee $\rightleftarrows$ aa inversion. The inversion of the *cis* isomer is an ea $\rightleftarrows$ ae inversion. You should confirm these point with a molecular model.

41a   **41b**

☐
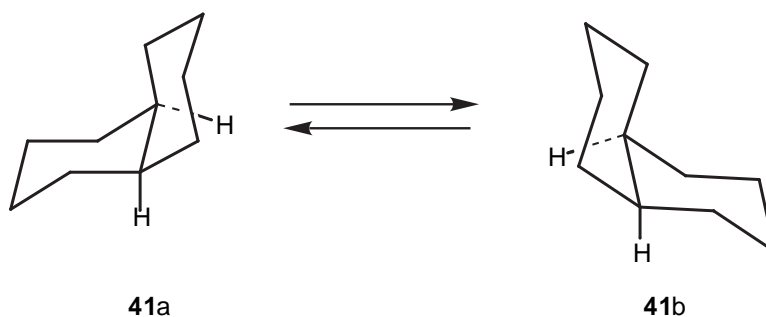
4.5   Cyclopropane, cyclobutane, cyclopentane

Among cycloalkanes C_nH_{2n}, all of these with C = 3~5, that is, cyclopropane **42**, cyclobutane **43** and cyclopentane **44**, have ∠C-C-C bond angles that deviated from the tetrahedral angle.

Cyclopropane **43** has a high chemical reactivity, but its ring is rigid and there is no ring inversion. As expected, 1,2-dimethylcyclopropane has two isomers, the *cis* isomer **45** and the *trans* isomer **46**.

42   **43**   **44**

45   **46**
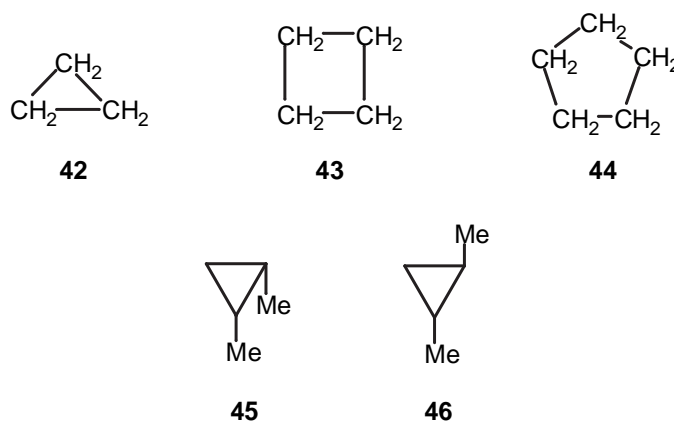
Q4.17

Write down the structure of all isomers of cyclopropane dicarboxylic acid $C_3H_4(COOH)_2$.

For many years cyclobutane **43** was regarded as a square molecule. It is now known that at least in the gas and liquid phases, **43** has a folded structure, and consequently a ring inversion **43a** ⇄ **43b**, similar to that of cyclohexane, takes place.

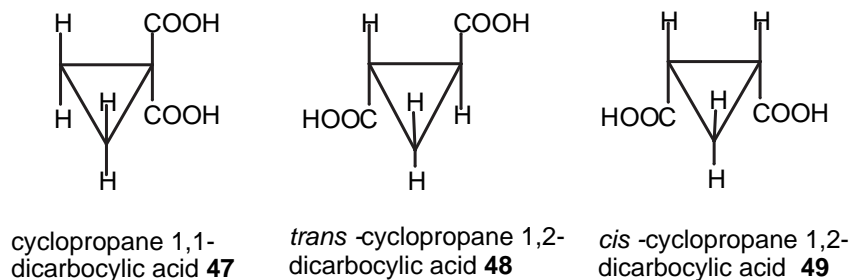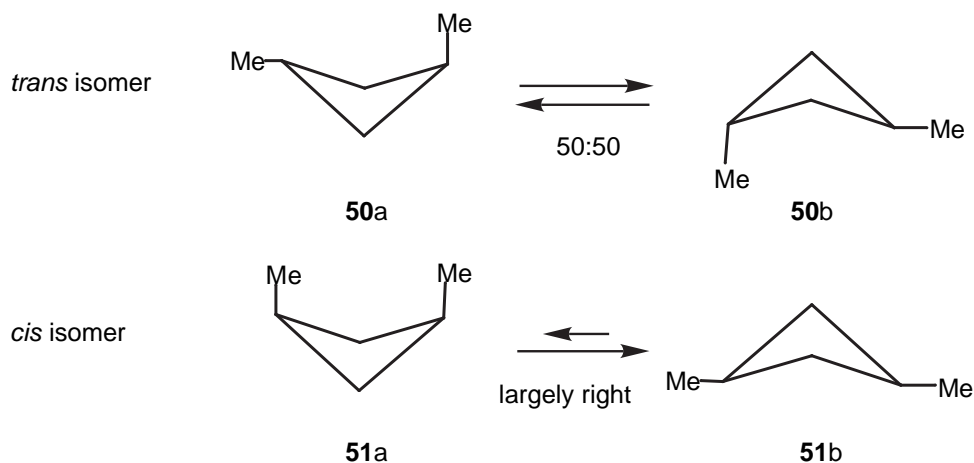**43a**   **43b**
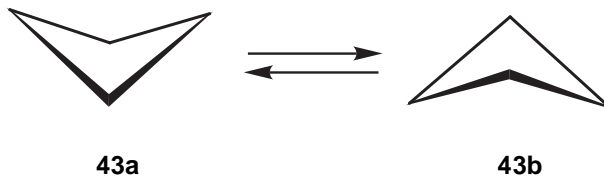
Q4.18

Explain the ring inversion of *trans*- and *cis*-1,2-dimethylcyclobutane. Predict which direction the equilibrium will shift for each isomer.

A4.17

The idea is much the same as with the case of dimethylcyclohexane: two methyl groups on the same carbon atoms or on the different carbon atoms.
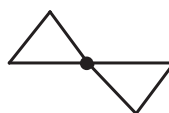
cyclopropane 1,1-dicarbocylic acid **47**   *trans*-cyclopropane 1,2-dicarbocylic acid **48**   *cis*-cyclopropane 1,2-dicarbocylic acid **49**

A4.18

trans isomer

50a   50:50   **50b**

cis isomer

51a   largely right   **51b**

Cyclopentane **44** is also a nonplanar molecule, and like cyclobutane, it has a folded, envelope type structure **52** or half-chair structure **53**. For **52**, there is no flip-flop of the triangle part, and instead, a process in which the carbon at the tip of the triangle alternates one after the other. In the envelope form, four carbon atoms, and in the half-chair form, three carbon atoms define a plane.

52   **53**