REVIEW

Organic Stereochemistry

Part 4[1])

Isomerisms about Single Bonds and in Cyclic Systems

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This *Part* introduces and illustrates conformational isomerism, the pharmacological implications of which will be the focus of *Part 6*. As noted by *Roberts* [1], *conformation* is sometimes referred to by chemists as the '*fourth C-word*' describing the structure of organic molecules, the other three being *composition*, *constitution*, and *configuration* (see also *Part 1*).

The *concept* of conformational isomerism was *created* (or shall we say that the *phenomenon* of conformational isomerism was *discovered*) by *Derek H. R. Barton* and *Odd Hassel*. These two distinguished chemists shared the *Nobel* Prize in Chemistry 1969 '*for their contributions to the development of the concept of conformation and its application in chemistry*' [1][2]. An excellent summary of their epoch-making work can be found in their *Nobel* lectures [3][4]. As noted by *Allinger* and *Eliel* [5], the work that earned them this recognition is compiled in no more than a dozen publications each. Among these, two stand out as the foundation stones of the concept of conformation [6][7].

As defined by *Barton*, '*the word 'conformation' is used to denote differing strainless arrangements in space of a set of bonded atoms. In accordance with the tenets of classical stereochemistry, these arrangements represent only one molecular species*' [7]. This definition applies to '*free*' rotation around single bonds. However, a careful reading of this definition suggests that it may also include inversion at *unstable stereogenic centers*, when such inversion does not imply bond cleavage and reforming. This is the case of stereogenic centers bearing one free electron pair, as exemplified in *Part 2*, *Figs. 2.3* and *2.4*, namely *chiral carbanions*, **2.7**, *oxonium compounds*, **2.11**, *tertiary amines*, **2.14**, and *tertiary amides*, **2.15**. Interestingly, the *IUPAC* (*International Union of Pure and Applied Chemistry*) has reached the following consensual definition of conformers: '*The spatial arrangement of the atoms affording distinction between stereoisomers which can be interconverted by rotations about formally single bonds. Some authorities extend the term to include inversion at trigonal pyramidal centres and other polytopal rearrangements*' [8]. Our energy-based discrimination between configurational and conformational isomers presented in *Part 1*, *Fig. 1.15*, derives from this consensual definition.

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[1]) For the other *Parts*, see *Helv. Chim. Acta* **2013**, *96*, 1 – 3.

Fig. 4.1. For convenience and clarity, the concept and applications of conformational isomerism discussed in this *Part* are divided into *a*) the concept of *torsional isomerism around single bonds*, and *b*) the *stereochemistry of cyclic systems*, where conformational and configurational aspects are too intimately intertwined to allow a separate treatment. A number of useful textbooks and reviews, both classical and more recent, gives ample space to conformational issues [9–20].

We begin with a brief reminder of the *thermodynamics* of conformational isomerism, and go on to explain and illustrate the conventions and *graphical representations* used for conformers. Examples are then examined, first involving conformational isomerism around single bonds in unconjugated systems. The simplest compound to begin with is ethane, followed by more complex cases documenting the *attractive or repulsive role of substituents*. A further structural factor that can influence the conformation behavior is the presence of a double or triple bond, or an aromatic ring in the vicinity of a strainless rotating single bond. A phenomenon called *hyperconjugation* may occur in such cases.

A comparable progression from simple to more complex structures is followed in our treatment of cyclic systems. Here, the path goes from *carbocycles* to *heterocycles* (essentially aza- and oxa-heterocycles). The last section is dedicated to *fused and bridged cyclic systems*. The latter have a more or less marked level of rigidity, implying that configurational aspects may predominate over conformational ones.

The pharmacological implications of the concepts discussed here will be presented in *Part 6*.

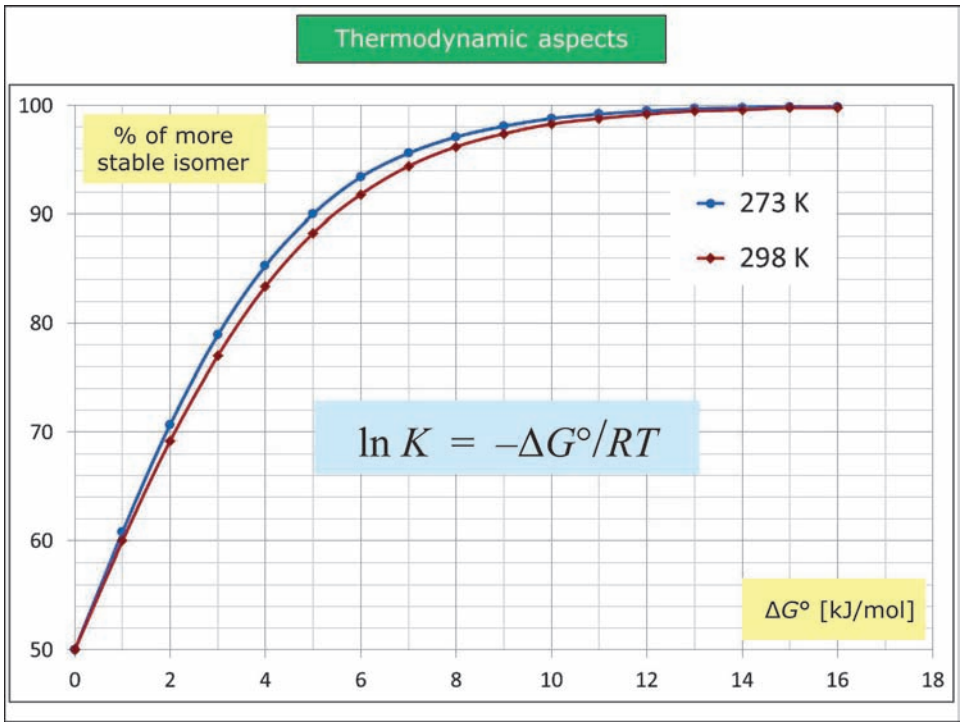


Fig. 4.2. Isomers generated by rotation around a single bond are, in most cases, separated by an energy barrier of several kilojoules per mole, which corresponds to extremely rapid rates of interconversion. Thus, barriers of 20, 40, and 60 kJ/mol (*ca.* 5, 10, and 20 kcal/mol, resp.) correspond to rate constants of interconversion of *ca.* 10^9, 10^5, and 10^2 s^{-1}, respectively.

The *energy difference* between rotational isomers, *rotamers*, are relatively small, *i.e.*, on the order of a few to several kJ/mol. It is this difference that is the key factor in determining the *rotamer composition* of a flexible compound at a given temperature. In turn, this conformational composition may be a major factor that influences the reactivity, especially the biochemical reactivity, of a given compound. The difference ΔG° in conformational *Gibbs* energy (also known as free energy) for the case $M \rightleftharpoons N$ is related to the conformational equilibrium constant K (or *conformational ratio*) by the equation shown, yielding the Boltzmann *distribution* (also called the *Gibbs* distribution). Note that this equation applies to *all dynamic equilibria*, not only conformational ones. If either K or ΔG° is known, the percentage of the more stable conformer at a given temperature can be calculated. It can be seen in the *Figure* that an energy difference of 10 kJ/mol (*ca.* 2.4 kcal/mol) at 25° corresponds to an isomer composition of 98.2 : 1.8. Comprehensive tabulations covering a wide range of temperatures were published together with a wealth of other conformational data [21]; plots calculated for a wide range of temperature are also available [22].

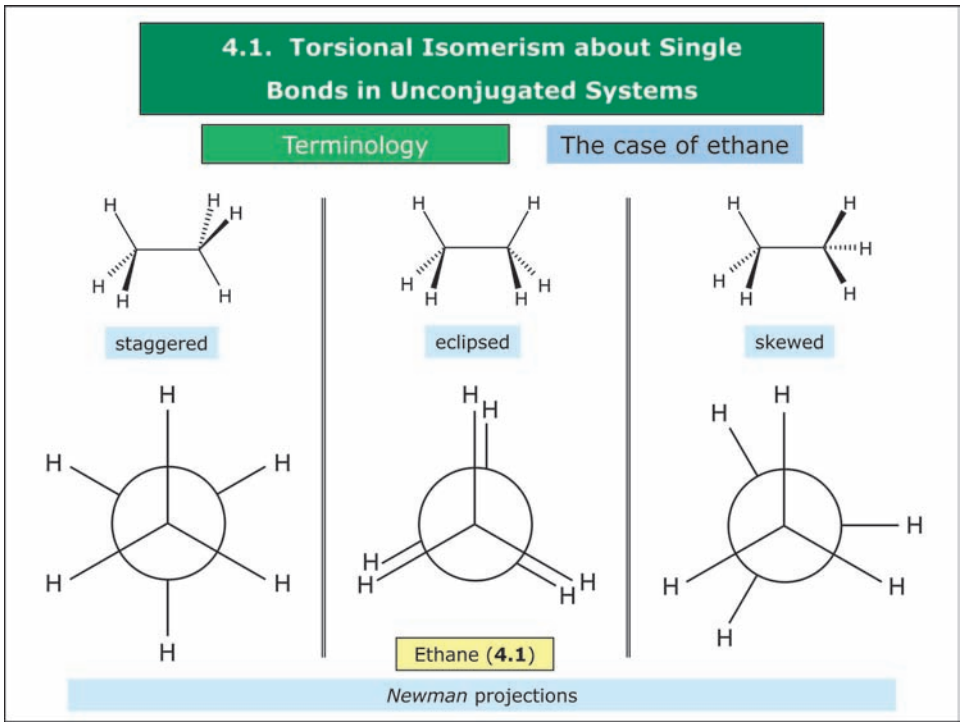


Fig. 4.3. We now consider rotation around *single bonds linking unconjugated centers*, or centers which can be regarded as unconjugated (*i.e.*, in (C_{sp^3}–C_{sp^3} bonds, C_{sp^3}–heteroatom bonds, and heteroatom–heteroatom bonds). The classical way to start a discussion on conformational isomerism and the terminology used is with *ethane* (**4.1**), a simple but rich model. Internal rotation around the C–C bond is best seen when using Newman *projections* [23], as shown here by comparing the latter with perspective drawings. Assuming the proximal (frontal) C-atom and its three H-atoms to be stationary, the distal (rear) atoms are left free to rotate. The geometric variable here is the *torsion angle* τ (Greek *tau*) *also written as* θ (Greek *theta*), which can assume any absolute value between 0 and 180°. Note that, in chemical terminology [8], the term *dihedral angle* φ (Greek *phi*, sometimes written as Φ, capital *phi*) is often used synonymously, both the torsion angle and the dihedral angle being defined as the angle between the two planes formed by atoms A–X–Y and atoms X–Y–B, respectively. Here and in other *Parts* of this Work, we prefer to refer to *torsion angles* when considering the range 0° to ±180°, and *we convert torsion angles to dihedral angles* when considering the unsigned 0° to 360° range in energy plots and elsewhere. For example, a value of $\tau = -90°$ corresponds to $\varphi = 270°$ (see also *Fig. 4.5*).

An infinite number of rotational isomers of ethane are conceivable, but two are remarkable, namely the *eclipsed* and *staggered* ones, where the torsion angle has a value of 0° and 60°, respectively. The innumerable intermediate rotamers are called *skewed*.

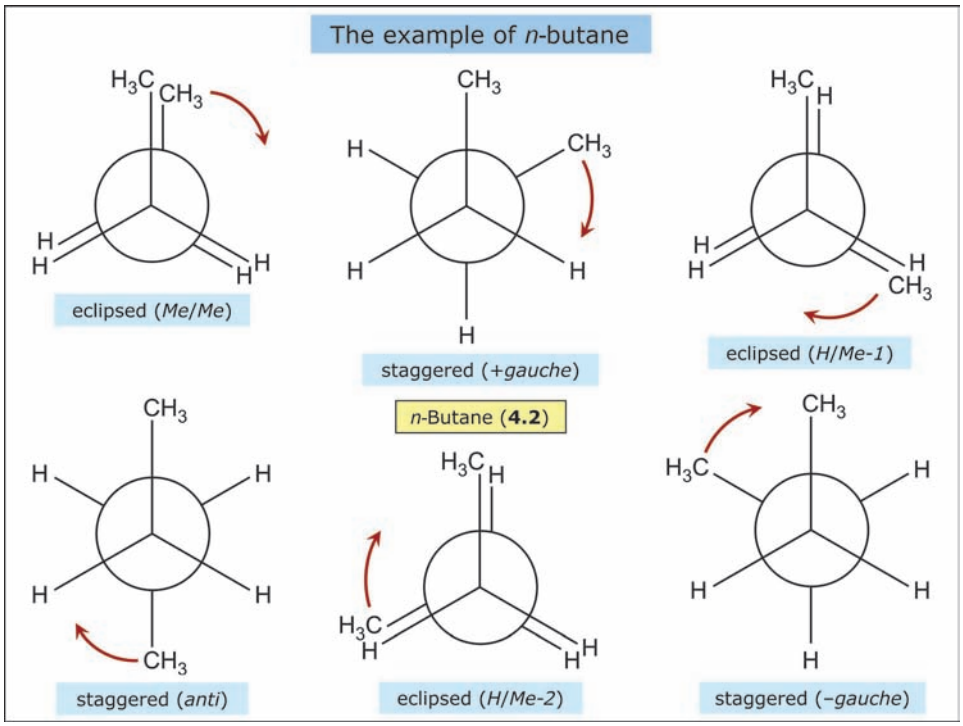
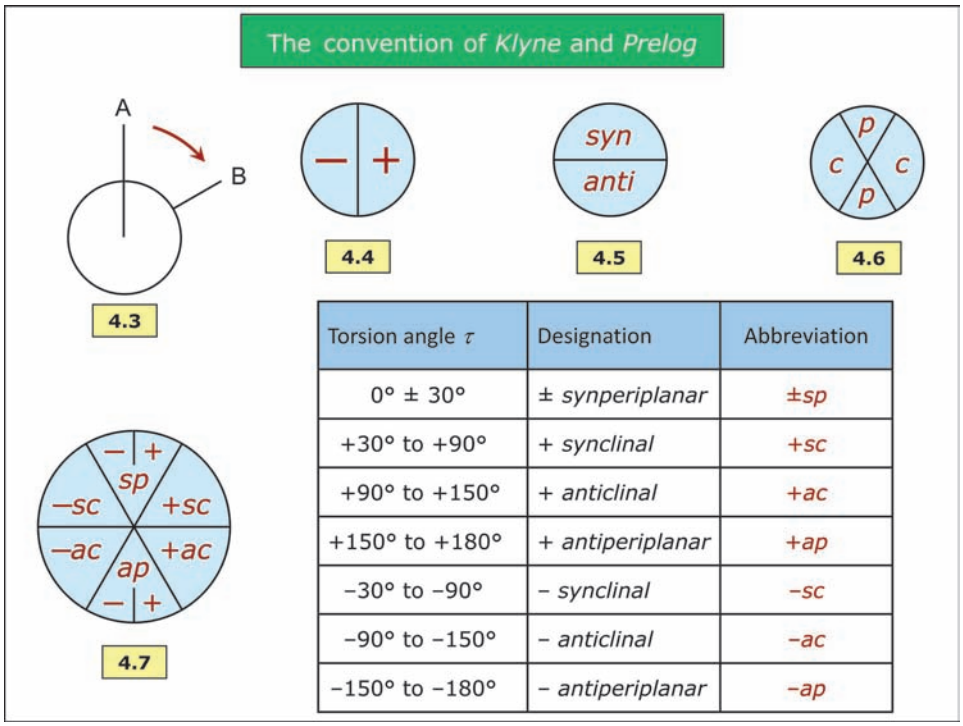


Fig. 4.4. The molecule of n-*butane* (**4.2**) provides a more complex example. Despite the fact that this molecule has three strainlessly rotating C–C bonds, only the central C–C bond is considered here. Beyond the innumerable skewed conformations that exist and are not discussed here, the molecule presents *three eclipsed* and *three staggered* conformations. Our walk around the circle begins with the singular Me/Me eclipsed rotamer. Keeping the *proximal* Me group and H-atoms stationary, the *distal* C-atom, and its geminal Me group and H-atoms are *rotated clockwise* (red arrow) by 60° steps as shown. The *staggered conformers* are the low-energy ones as we shall see in *Fig. 4.6*; they are commonly known as the *anti* rotamer and the two *gauche* rotamers. Remarkably, the + *gauche*- and the − *gauche* rotamers (also designated as *G1* and *G2*, resp.) are *non-superimposable mirror images* of each other. They are thus *chiral conformers*. The same is true for two eclipsed forms, *i.e.*, *H/Me-1* and *H/Me-2*. Indeed, the staggered *G1* and eclipsed *H/Me-1* conformers have (*P*)-helicity, whereas staggered *G2* and eclipsed *H/Me-2* conformers have (*M*)-helicity (see *Part 3*).



Torsion angle τ	Designation	Abbreviation
0° ± 30°	± *synperiplanar*	±*sp*
+30° to +90°	+ *synclinal*	+*sc*
+90° to +150°	+ *anticlinal*	+*ac*
+150° to +180°	+ *antiperiplanar*	+*ap*
−30° to −90°	− *synclinal*	−*sc*
−90° to −150°	− *anticlinal*	−*ac*
−150° to −180°	− *antiperiplanar*	−*ap*

Fig. 4.5. The terminology used above to designate the conformers of ethane and *n*-butane is *unambiguous but clumsy* to discriminate between eclipsed and staggered rotamers, and *incomplete* for intermediate conformations. A useful convention proposed by *Klyne* and *Prelog* [24] has been recommended to complement the common one [8]. As shown, the convention begins by specifying one *proximal* and one *distal* group, namely the *two fiducial groups* designated here as A and B (**4.3**). These groups are selected from the substituents carried by the two single bonded atoms (X–Y) according to the following criteria:

- If all substituents are different, the sequence rule is applied.
- If two substituents on X and/or Y are identical, the one which is unique is chosen independently of the sequence rule.
- If all substituents are identical, the one providing the smallest torsion angle is chosen.

When viewing A–X–Y–B along X–Y as shown in **4.3**, the *torsion angle* is defined by the angle formed by the segments A–X and Y–B[2]). The sign of the angle is defined by the sense of the (shortest) rotation which brings A to overlap with B; the angle is positive for a clockwise rotation, and negative for a counterclockwise one ((*P*)- and (*M*)-helicity, resp.). This definition of the *torsion angle* permits a clear description of the A–X–Y–B angle.

The convention based on the torsion angle divides the circle into several fields as shown in **4.4**, **4.5**, and **4.6**. Combining their labels yields the various designations abbreviated in **4.7** and made explicit in the *Table*.

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[2]) Strictly speaking, this operational definition is valid only in the 2D space of a *Newman* projection, in contrast to the rigorous definition in 3D space given in *Fig. 4.3*.

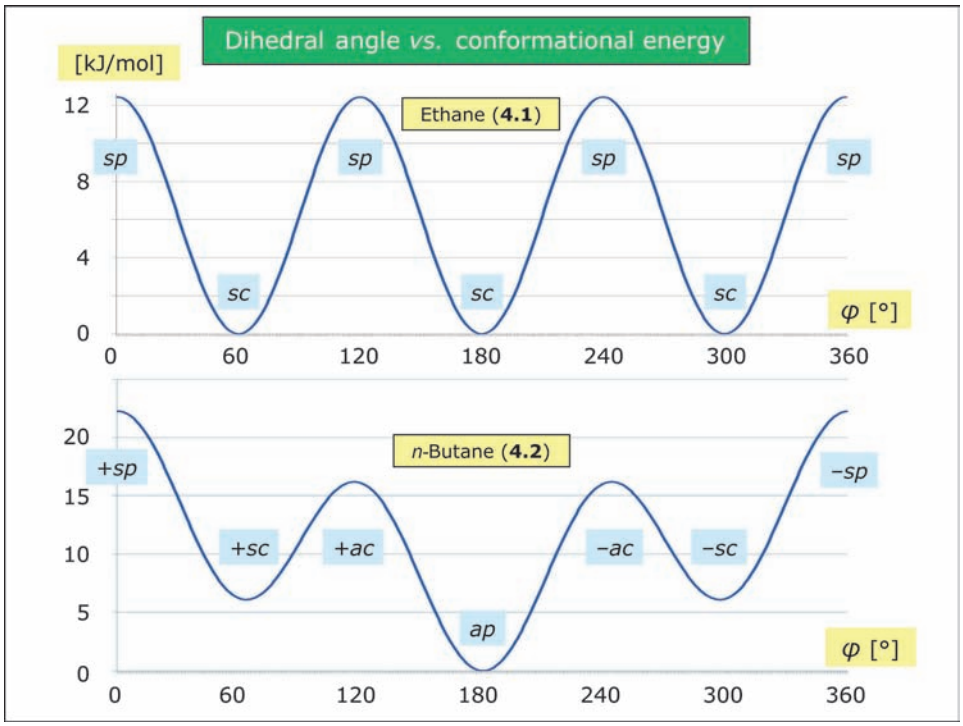


Fig. 4.6. Having underlined some definitions and conventions, we may now take a look at the dynamic behavior of flexible molecules, namely the variation of their *conformational energy* with the dihedral angle.

In *ethane* (**4.1**), three *sc (synclinal) conformations* are encountered during a rotation of 360°. These conformers are the *low-energy, staggered* ones. They are identical, have identical internal energy content, and no criterion allows their discrimination. The same is true for the three *sp* (*synperiplanar*) conformations; these again are identical, and their internal energy is in fact the *torsional barrier* of ethane, whose value is very close to 12 kJ/mol[3]). An early assumption that this torsional barrier has steric causes has turned out to be wrong, if only because the H-atoms are barely within contact distance. It is now known that the barrier is caused by a stabilizing *hyperconjugation* (*cf. Fig. 4.17*) in the staggered conformer [27].

As we saw in *Fig. 4.4*, the conformational behavior of n-*butane* (**4.2**) is more complex than that of ethane due to the two terminal Me groups[3]). Most importantly, two types of information can be derived from plots such as this one [28]. First, one can examine the *energy difference(s) between minima*, which, to a very large extent, determine(s) the *relative populations* (*i.e.*, percentages) of rotamers (see *Fig. 4.2*). Thus, three *low-energy conformers* are seen in the plot of the conformational energy of

[3]) The conformational profiles were determined by a Grid search as implemented in the VEGA program, systematically rotating the monitored torsion and generating 360 rotamers (1 per degree) whose total energy was determined by PM6 semi-empirical calculations [25][26].

n-butane, namely the single *anti* (*antiperiplanar* in the alternative convention) conformer and the two chiral *gauche* (*synclinal*) rotamers. The former is the *global minimum conformer*, since it avoids a Me/Me interaction. The *synclinal* rotamers, in contrast, are the local minima, the two Me groups being *gauche* and thus experiencing only a slight steric repulsion. The difference in free energy between the *anti* and the *gauche* forms depends to some extent on conditions (vacuum or solvent, *etc.*) and methods (experimental or computational); our approach yielded value close to 6 kJ/mol.

The second type of information provided by such plots are the *torsional barriers* which separate the minima. The barrier between the *anti* conformer and the *anticlinal* conformers (*i.e.*, the eclipsed *H/Me*) is close to 16 kJ/mol due to two H/Me interactions). The direct transition between the *synclinal* and *synperiplanar* conformers (*i.e.*, the eclipsed *Me/Me*) is close to 22 kJ/mol due to a marked steric strain between the two Me groups[3]). The main interest in energy barriers is the fact that rate constants of interconversion between rotamers can be calculated from them (see caption of *Fig. 4.2* for some estimates).

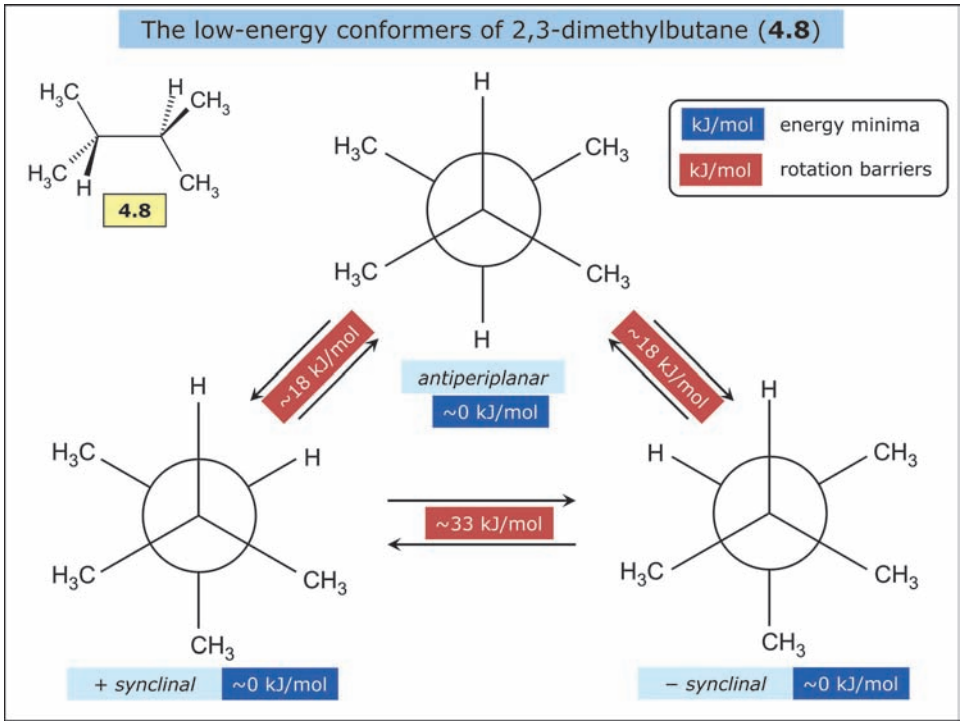


Fig. 4.7. The above examples and discussions have centered on A–X–Y–B systems, where X and Y are CH_2. Compounds with a *higher degree of substitution* on the two central C-atoms are expected to show a more complex conformational behavior depending on both the substitution pattern and the nature of substituents [29].

A simple yet informative example in this context is offered by *2,3-dimethylbutane* (**4.8**) [12]. The *anti* conformer (*antiperiplanar*) isomerizes to the two *gauche* forms

(*synclinal*) *via* a barrier of *ca.* 18 kJ/mol involving three eclipsed interactions, namely two H/Me and one Me/Me. The direct conversion of one *gauche* rotamer to the other must overcome two Me/Me eclipsed interactions, hence its higher barrier.

With regards to the *relative energy of the three staggered conformers*, it is interesting to note that they have almost identical internal energies, meaning that they are equivalent minima, and that they exist in close-to-equal proportions.

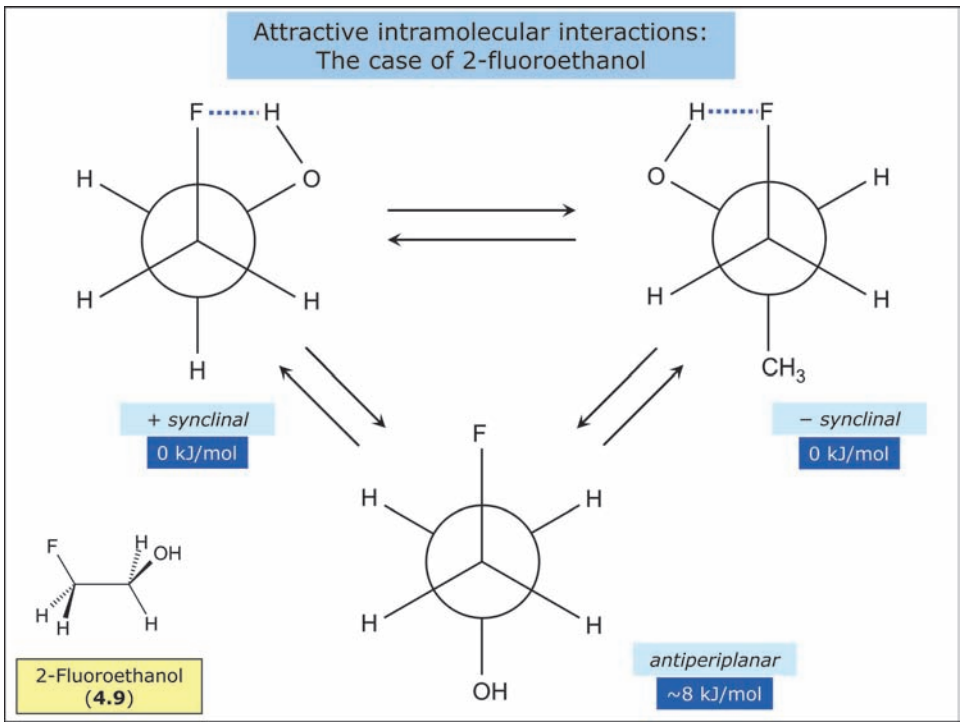


Fig. 4.8. Formation of attractive intramolecular interactions can explain a conformational preference differing from that of our previous examples [12][30][31]. This is seen in the two enantiomeric *synclinal* forms of *2-fluoroethanol* (**4.9**), where an intramolecular H-bond can stabilize the *gauche* forms compared to the *anti* form [32]. The difference is quite large (*ca.* 8 kJ/mol). It is smaller in, *e.g.*, *2-chloroethanol* (*ca.* 4 kJ/mol), probably due to the larger bulk of the Cl- compared to the F-atom.

Note also that any discussion of the relative stability of rotamers based on consideration of pure staggered conformers is a mere approximation. Indeed, torsion angles of 60° are assumed, but it is known that marked deviations do exist. Also, bond-length and bond-angle distortions tend to distribute the strain, formally generated by the *gauche* interactions, over the entire molecule. For a realistic assessment of rotamer stability, one must, therefore, consider all structural aspects.

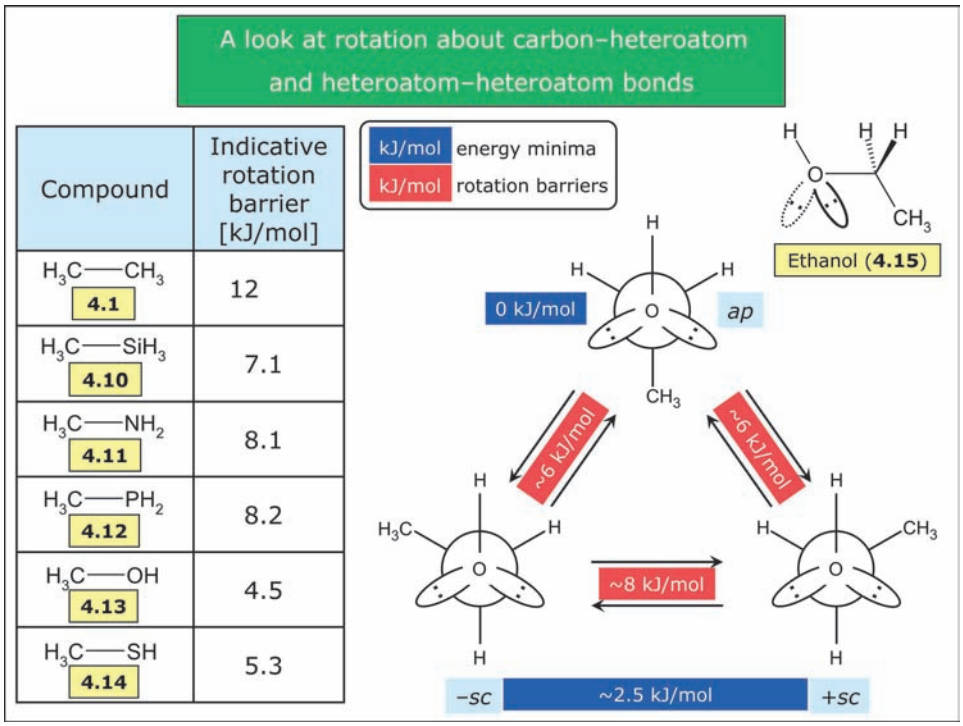


Fig. 4.9. Having discussed rotation about C_{sp^3}–C_{sp^3} bonds, we now turn our attention toward some *C_{sp^3}–heteroatom bonds*. Their rotation barriers are usually low, unless strong nonbonded intramolecular interactions between substituents become predominant. The factors governing the indicative values compiled in the *Table* include the length of the central bond, the number of H/H interactions, and other electronic factors such as the electron density of H-atoms and exchange interactions between C–H and X–H orbitals [12]. As seen, the rotation barrier of methylsilane (**4.10**), methylamine (**4.11**), methylphosphine (**4.12**), methanol (**4.13**), and methanethiol (**4.14**) are in the range of 4–8 kJ/mol, *i.e.*, lower than the barrier of ethane (**4.1**).

Ethanol (**4.15**) provides a more complex example than methanol (**4.13**). Explicit drawing of the two *lone pairs of electrons* at the O-atom allows a more realistic grasp of intramolecular interactions. Viewing the molecule along its O–C bond reveals three staggered conformers, namely the *anti* rotamer (*ap*) and the two mirror-image *gauche* forms (*sc*) [33]. The former is the *global minimum*, but its energy difference with the local minima (the two *gauche* forms) is minute, as are the rotation barriers. This is seen in the approximate values indicated in the *Figure*.

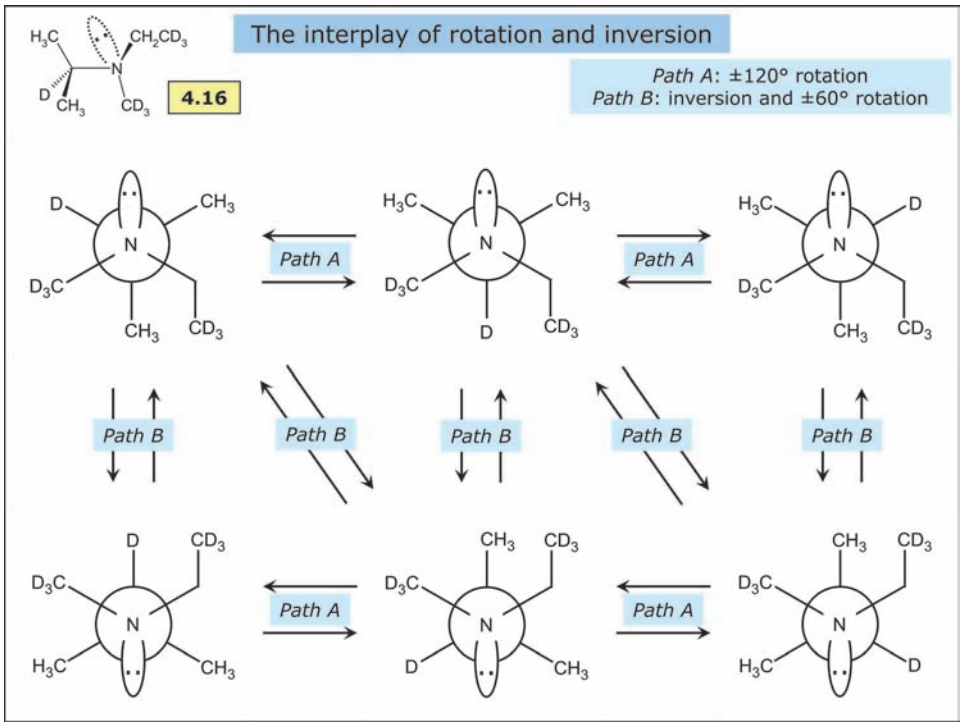


Fig. 4.10. Because the inversion barrier at a N-atom is higher than the rotation barrier in C–N (*e.g.*, *Fig. 4.9*) and N–N bonds, rotation in such systems may be concurrent with or hidden by *nitrogen inversion* in experimental investigations [34]. A particularly informative example is that of the sevenfold deuterated (*isopropyl methyl)ethylamine* **4.16** [35]. This compound features three C–N bonds (*i.e.*, three rotors), implying a complex *conformational hypersurface* further complicated by nitrogen inversion. The *Figure* focuses on a small area in this hypersurface showing *rotation* about the (^{i}Pr)C–N(Et,Me) bond (upper row) and *nitrogen inversion* (lower row).

Under adequate conditions of solvent and very low temperature, the two isomerization phenomena of rotation and inversion could be observed by dynamic NMR spectroscopy. The rotation about the (^{i}Pr)C–N(Et,Me) bond (and/or about the N–CH_2 bond, since the two could not be distinguished) was found to have a barrier of *ca.* 23 kJ/mol, whereas N inversion required *ca.* 30 kJ/mol. An even more intricate example will be presented in the next *Figure*.

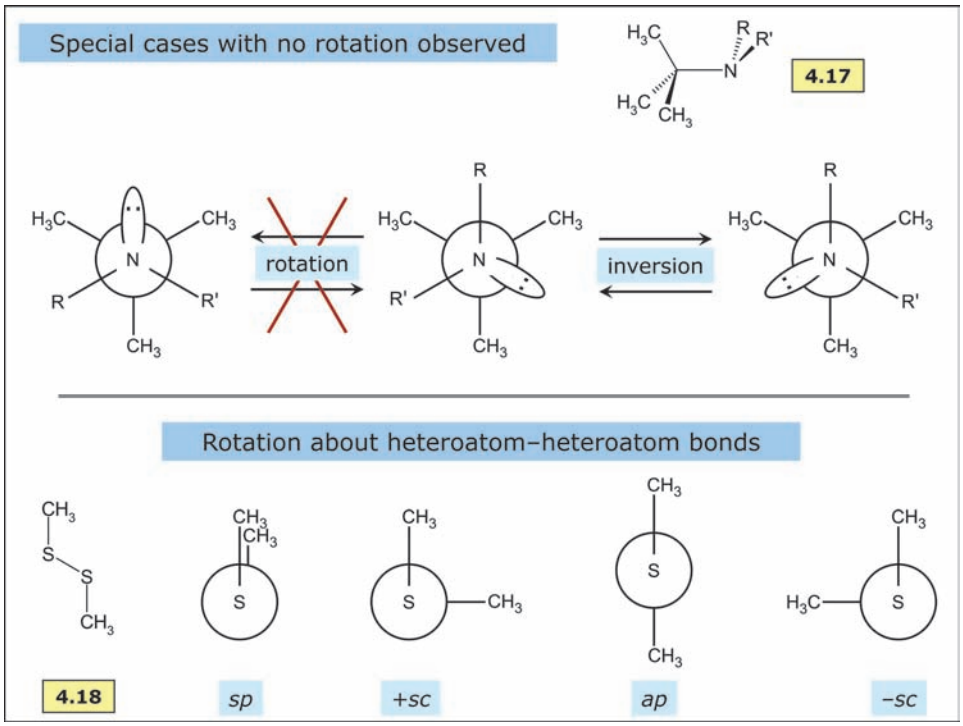
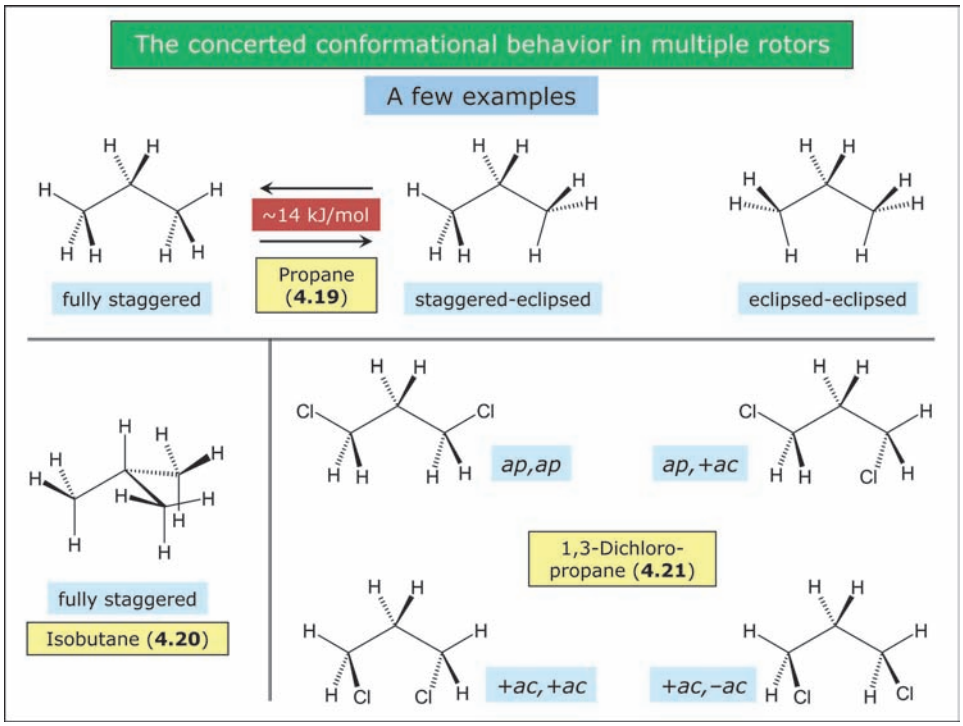


Fig. 4.11. *Tertiary amines* containing an *N-tert*-butyl group, as shown here with the *generic structure* **4.17**, represent a case where no C–N bond rotation but only N inversion was observed [36].

Coming briefly to *rotation about heteroatom–heteroatom bonds*, we note that it is influenced by destabilizing interactions between the electron pairs [37]. Such interactions appear to play a marked role in controlling the conformational behavior of *peroxides*, *hydrazines*, and *hydroxylamines*. An interesting and simple example is provided by *dimethyl disulfide* (**4.18**) [38]. Its lowest-energy rotamers have a torsion angle of $85-90^\circ$ (*i.e.*, the enantiomeric rotamers $+sc$ and $-sc$). These are separated by a *trans*-barrier (*ap*) of *ca.* 9 kJ/mol and an eclipsed barrier (*sp*) of *ca.* 30 kJ/mol.



Figs. 4.12 and 4.13. In a molecule, a *strainlessly rotating bond* (including its substituents) is called a *rotor*. Most molecules feature several rotors, yet our presentation up to this point was focused on a single rotor even when considering multirotor molecules. We now take a more global view.

When several rotors are present in a molecule, they show some degree of concertedness in their rotation. Taking *propane* (**4.19**) as an example [12][28][32], its preferred conformation is the fully staggered one. The experimentally observed rotation barrier of *ca.* 14 kJ/mol involves rotation of one Me group only, and leading to the staggered-eclipsed conformer. The barrier created by the eclipsed-eclipsed form was not observed.

When increasing substitution in a homologous series of compounds, a regular increase in rotation barrier is observed, *e.g.*, ethane, propane, *isobutane* (**4.20**). The preferred conformation of the latter is the fully staggered one (shown here), and the rotation barrier of one Me group is *ca.* 16 kJ/mol. Similar trends are observed in the series mono-, di-, and trimethylamine; methanol and dimethyl ether; methanethiol and dimethyl sulfide. This phenomenon is accounted for by repulsive interactions between the H-atoms of the various Me groups. A further role is played by an interaction between Me groups which takes the form of a stabilization, if the central atom is a π-donor (*e.g.*, an O-atom), or a destabilization, if the central atom is a π-acceptor [12][39]. In general, a methylene chain exhibits some tendency to exist as the fully extended conformer (*ap,ap,ap,…*). However, it may not be the predominant conformer, because its statistical weight is small as compared to the sum of all other conformers.

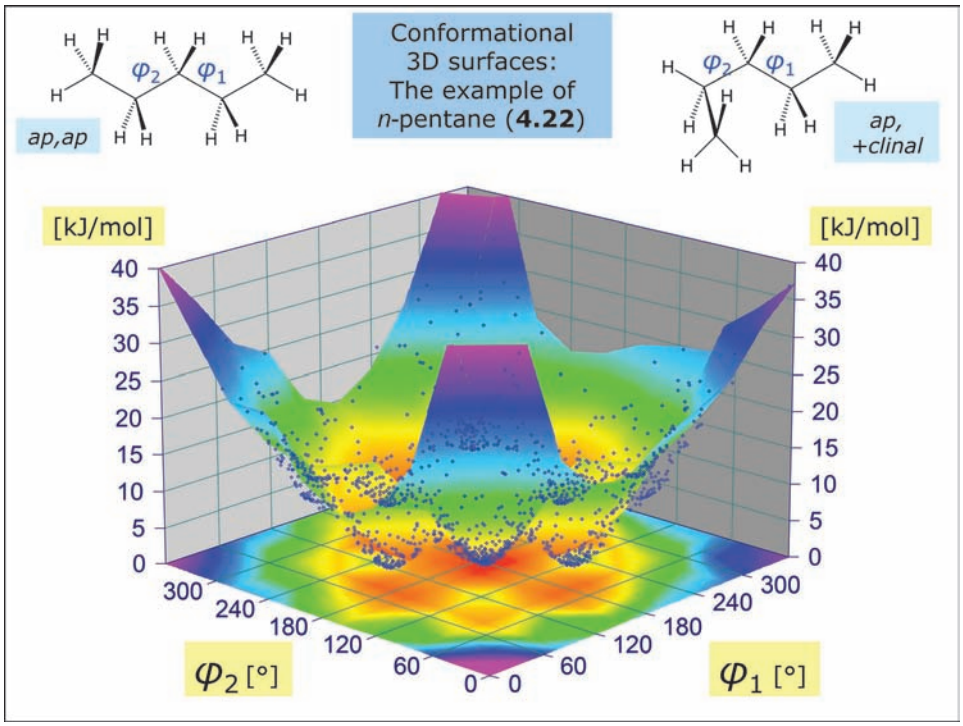


Fig. 4.13

In the case of n-*pentane* (**4.22**; *Fig. 4.13*), the (*ap,ap*)-conformer (also designated *T.T* = *trans,trans*) is somewhat favored over the (*ap,clinal*)-form (also known as *trans, gauche* = *T.G*). This example has also been chosen to provide the reader with a graphical feeling of the complex conformational behavior of multirotor molecules. Allowing only the rotation of the two central C–C bonds (as measured by the *dihedral angles* φ_1 and φ_2 covering the 0° to 360° rotation), one obtains a 3D surface whose vertical axis represents the relative energy of the conformers[4]). In this example, the *global minimum* is seen at $\varphi_1 \sim \varphi_2 \sim 180°$ (*ap,ap*). Just a few kJ/mol higher, one finds *four local minima* of equal energy, namely around 180°/90° (*ap,* + *clinal*); around 180°/270° (*ap,* − *clinal*); around 90°/180° (+ *clinal,ap*); and around 270°/180° (− *clinal,ap*). Other local minima of higher energy are also seen.

The number of possible conformers increases markedly in substituted alkanes. Taking *1,3-dichloropropane* (**4.21**) as an example, the energy minima are *ap,ap* (statistical weight 1×); *ap,* ± *ac* (4×); + *ac,* + *ac* and − *ac,* − *ac* (1× each); and + *ac,* − *ac* and − *ac,* + *ac* (1× each). As opposed to *n*-alkanes, the (+ *ac,* + *ac*)- and (− *ac,* − *ac*)-conformers predominate over the (*ap,ap*)-form. In contrast, the (+ *ac,* − *ac*)- and (− *ac,* + *ac*)-conformers are improbable on steric grounds. Many results for amines and alcohols have been compiled [33].

[4]) The 3D-conformational surface was generated by a Grid search (as implemented in the VEGA program [25]), systematically rotating the monitored rotors and generating 1296 rotamers (36 per rotor, in 10° steps). The total energy of each conformer was determined by PM6 semi-empirical calculations.

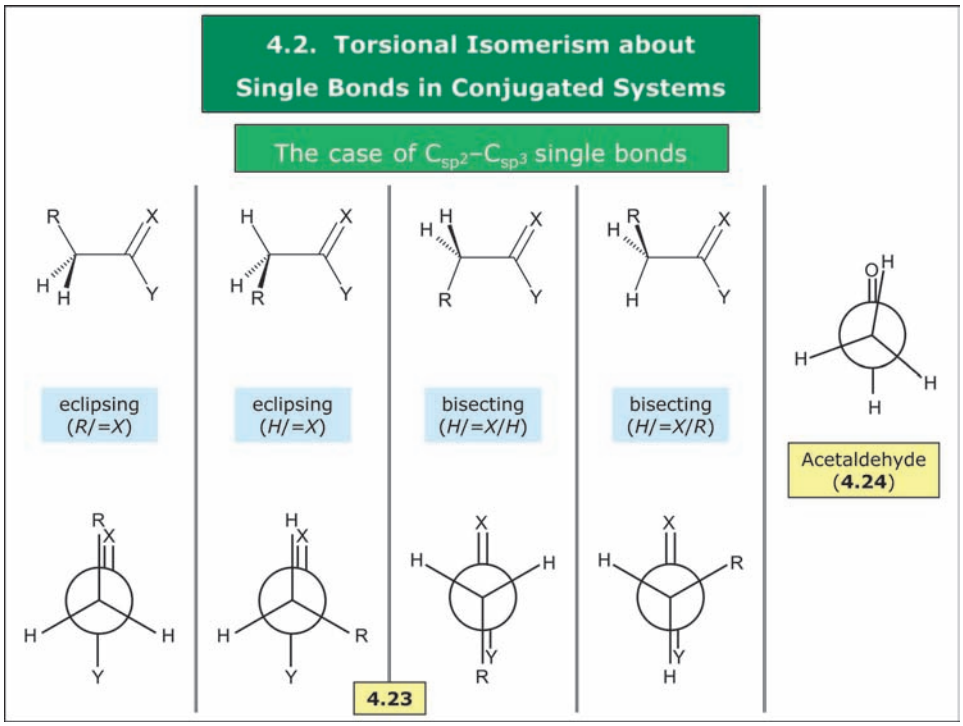
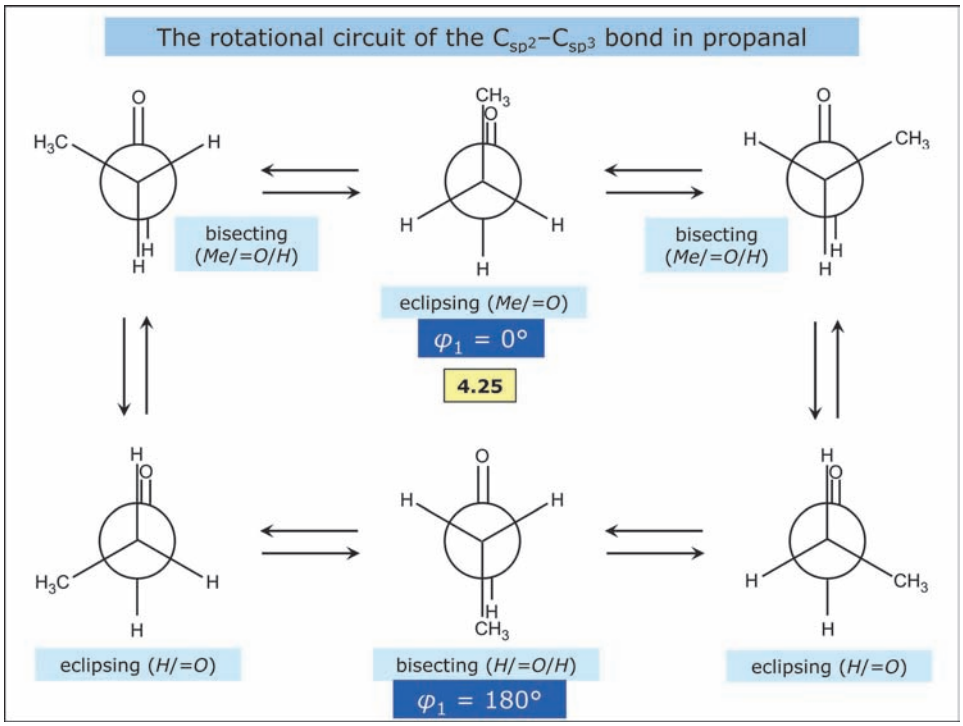


Fig. 4.14. Due, in particular, to resonance effects, the presence of sp^2-hybridized C-atoms considerably influences the rotational behavior of molecules about single bonds. We shall consider successively C_{sp^2}–C_{sp^3}, C_{sp^2}–C_{sp^2}, and C_{sp^2}–heteroatom bonds.

Rotational isomerism about *C_{sp^2}–C_{sp^3} single bonds* can be discussed in terms of the rotamers illustrated here with the *generic structure* **4.23** [12][40]. These four rotamers can be designated relatively to the double bond, which can eclipse either H-atom or substituent on the adjacent C_{sp^3} atom, or can bisect either of their angles. Specifying which H-atom or substituent is involved renders the labels explicit, if somewhat clumsy, as shown. A well-studied class of compounds are the *aliphatic aldehydes* (X = O; Y = H). Thus, *acetaldehyde* (**4.24**) has a small threefold rotation barrier (close to 5 kJ/mol), the preferred conformation being an eclipsing one with a slight twist of *ca.* 9° as illustrated.

In general, it appears that aldehydes exist mainly as *R/O* and *H/O* eclipsed forms, with the former predominating. Bulky substituents R tend to shift the equilibrium between the two forms, and the influence of the solvent is dependent on the nature of the substituent [40].



Figs. 4.15 and 4.16. Here, we take a closer look at the conformational behavior of aldehydes, using *propanal* (**4.25**) as an example. This molecule is in fact a double rotor, but we begin a depiction of the torsional circuit about its *C_{sp^2}–C_{sp^3} single bond*, taking 60° steps from 0° to 360°. In three of the resulting rotamers, the C=O bond is eclipsed by either the C–Me bond (once) or a C–H bond (twice). In the three other rotamers, the C=O bond is bisecting two C–H bonds (once), while in the two others it bisects a C–Me and a C–H bond.

Reasoning in terms of the energy profile of the sole C_{sp^2}–C_{sp^3} rotor does not provide a realistic energy. We thus turn to a 3D energy surface (*Fig. 4.16*) combining the ordinate (kJ/mol) with the two horizontal axes (φ_1 and φ_2 covering the 0° to 360° range). The surface can be compared to three hammocks slung side-by-side. The three barriers separating the 'hammocks' correspond to the eclipsed values of the φ_2 dihedral angle. The minima of the three 'hammocks' correspond each to a fully staggered value of the φ_2 angle (60°, 180°, and 300°). Each such 'hammock' has its energy minimum at $\varphi_1 = 180°$ and its maxima at $\varphi_1 = 0°/360°$.

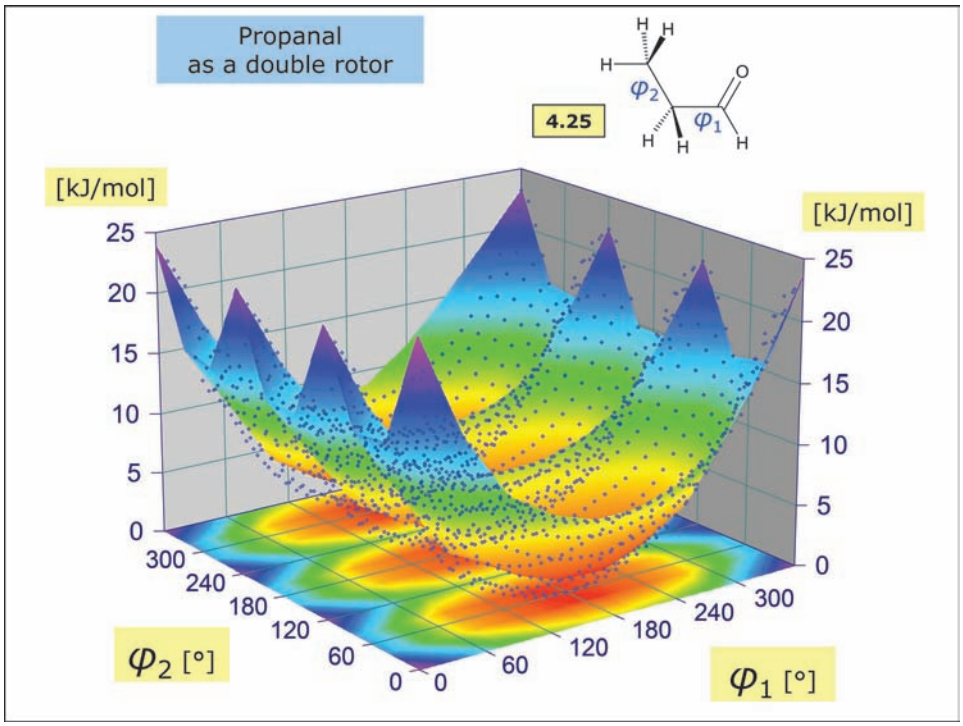

Propanal
as a double rotor
4.25
[kJ/mol]
25
20
15
10
5
0
300
240
180
120
60
0
φ_2 [°]
[kJ/mol]
25
20
15
10
5
0
0
60
120
180
240
300
φ_1 [°]

Fig. 4.16

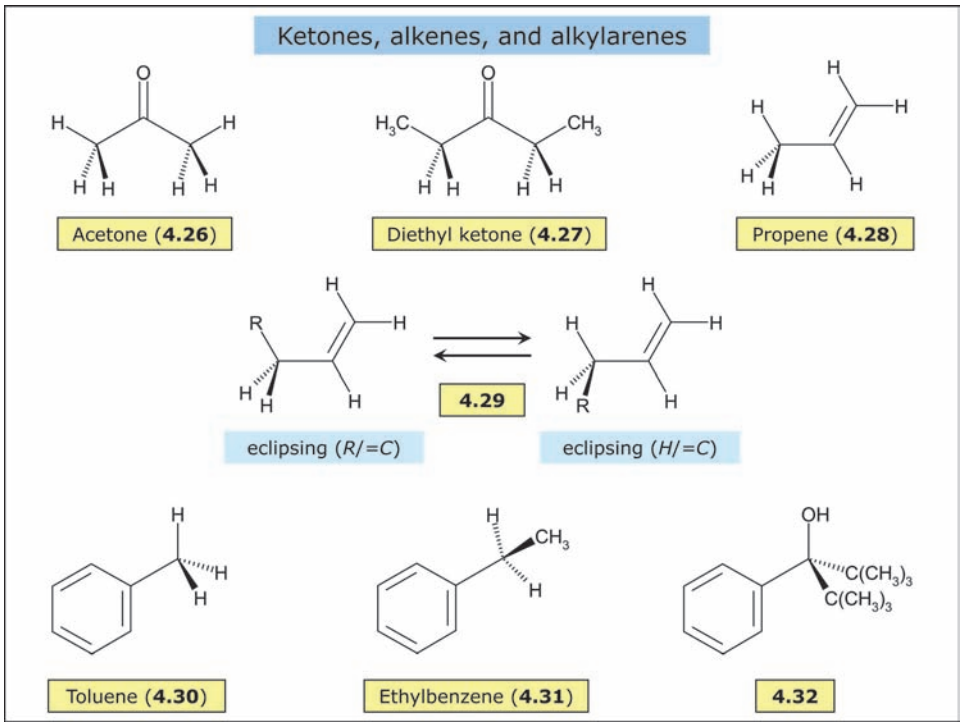


Fig. 4.17. In agreement with the behavior of aldehydes, *aliphatic ketones* exist predominantly as eclipsed rotamers. The preferred conformer of *acetone* (**4.26**) is the one shown here, namely the eclipsing *H/O/H* one, the rotation barrier being *ca.* 3 kJ/mol [40]. Similarly, the preferred conformer of *diethyl ketone* (**4.27**) is the eclipsing *Me/O/Me* one.

Alkenes containing the propenyl moiety (*i.e.*, **4.23** in *Fig. 4.14*; X being CH_2 or CHR′ or CR′R″) show close similarities to the carbonyl compounds discussed above. For example, the preferred conformation of *prop-1-ene* (**4.28**) has a terminal H-atom eclipsing the C=C bond, while the rotation of the Me group has a barrier of *ca.* 8 kJ/mol [12][40]. In *3-substituted prop-1-enes*, **4.29**, three low-energy conformations now exist due to the loss of symmetry caused by the 3-substituent. One of the rotamers is achiral and has the C=C bond eclipsing the 3-substituent; the two other rotamers have a H-atom eclipsing the C=C bond, the position of the 3-substituent here defining the $+ac$- and $-ac$ conformer. These two chiral conformers are usually slightly preferred over the (*R/=C*)-eclipsing form, except when the substituent, is for example, F or MeO [12][40].

Benzene derivatives are structurally close to the above compounds, as exemplified by *toluene* (**4.30**). Its preferred conformation has a H-atom eclipsing the π-system, the barrier of rotation being extremely low (some J/mol) due to the presence of a *sixfold rotation barrier*. In a molecule such as toluene, an eclipsed conformation is to be found after every 60° rotation step, and no noteworthy relief of conformational strain can be obtained by a rotation of only 30°. In other words, the barrier is minute because no

lower-energy rotamers exist [12][41]. But should the side chain be lengthened as in *ethylbenzene* (**4.31**), the preferred conformer now has the C–Me bond perpendicular to the aromatic ring. When the Me group in toluene is substituted with bulky groups, the rotation barrier may become quite large; for example, it is close to 80 kJ/mol in compound **4.32**.

The conformational behavior about *C_{sp^2}–C_{sp^3} bonds compared to C_{sp^3}–C_{sp^3} bonds* has received due attention [27][40–44]. Thus, main factors controlling conformation in the former are one-electron attractive interactions, whereas they are two-electron repulsive interactions in the latter. Furthermore, the energy of the one-electron attractive interactions decreases with decreasing electron density in the Me group. In both prop-1-ene (**4.28**) and acetaldehyde (**4.24**), the electron density in the methyl C–H bonds interacts with the π-electron density, and this interaction is called *hyperconjugation*. As the Me group rotates, its σ- and π-electron loss to the C=C bond varies, the preferred conformation showing minimal loss, *i.e.*, maximal electron density and, therefore, maximal one-electron attractive interactions.

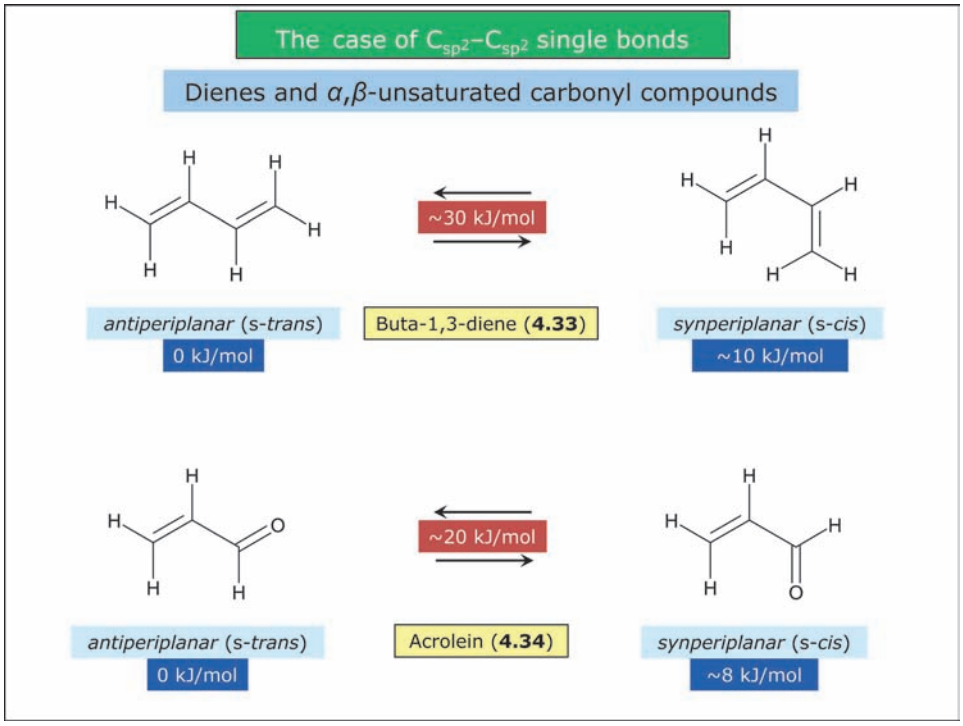
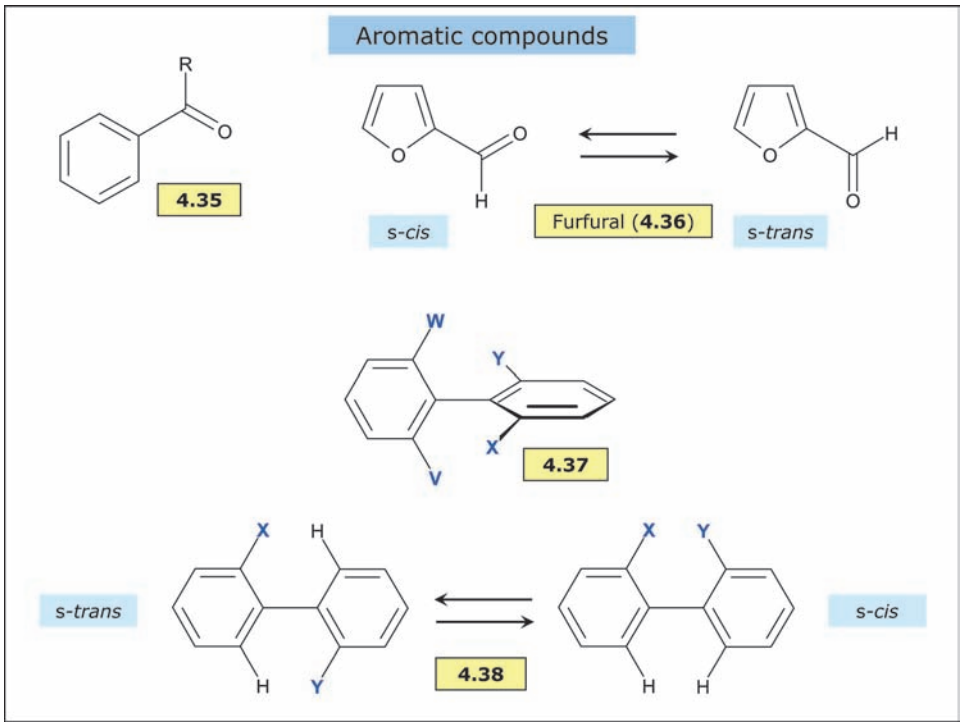


Fig. 4.18. The factors controlling conformational behavior around *C_{sp^2}–C_{sp^2} bonds* differ from those involved in rotational isomerism about C_{sp^2}–C_{sp^3} bonds. In both cases, however, they are of an electronic nature. It is well-known that the two C=C bonds experience *conjugation* across the single bond, and that this phenomenon is maximal when the system is planar [12][32][44–46]. In general, rotation around C_{sp^2}–C_{sp^2} single bonds will result in a marked preference for planar conformations, with out-of-plane and in particular perpendicular transition states.

In many systems, two planar conformations exist, namely those having the two C=C bonds *trans* or *cis* across the single bonds. These two rotamers are referred to as s-*trans* (*antiperiplanar*) and s-*cis* (*synperiplanar*), respectively. The letter 's' here stands for 'single bond', the latter having in fact a *partial* π *character* caused by conjugation. In simple compounds such as *buta-1,3-diene* (**4.33**) and *acrolein* (**4.34**) used here as examples, the s-*trans*-rotamer is favored over its s-*cis*-isomer for mere steric reasons [47]. Substitution at some of the C-atoms may render the s-*trans*-conformer more crowded and reverse the conformational preference.



Figs. 4.19 and 4.20. The partial double-bond character of the C_{sp^2}–C_{sp^2} single bond in *aromatic carbonyl compounds* is relatively modest compared to analogous systems, implying a lower rotation barrier [46]. Their preferred conformation is heavily influenced by interactions between ring substituents and the carbonyl side chain [48]. In the absence of such interactions, the coplanar rotamer is preferred as shown here for *benzaldehyde* (**4.35**; R = H). *Acetophenone* (**4.35**; R = Me) is also coplanar or very nearly so.

While there is only one coplanar form for compounds having the generic structure **4.35**, this is no longer true in the presence of a substituent in the 2- or 3-position, or in some heteroaromatic analogs. Thus, the degeneracy of the two planar forms is broken in *furfural* (= furan-2-carbaldehyde; **4.36**), which exists mainly as an s-*cis*-rotamer and an s-*trans*-one [49]. In the absence of dominant solvation factors, the s-*cis*-form is the

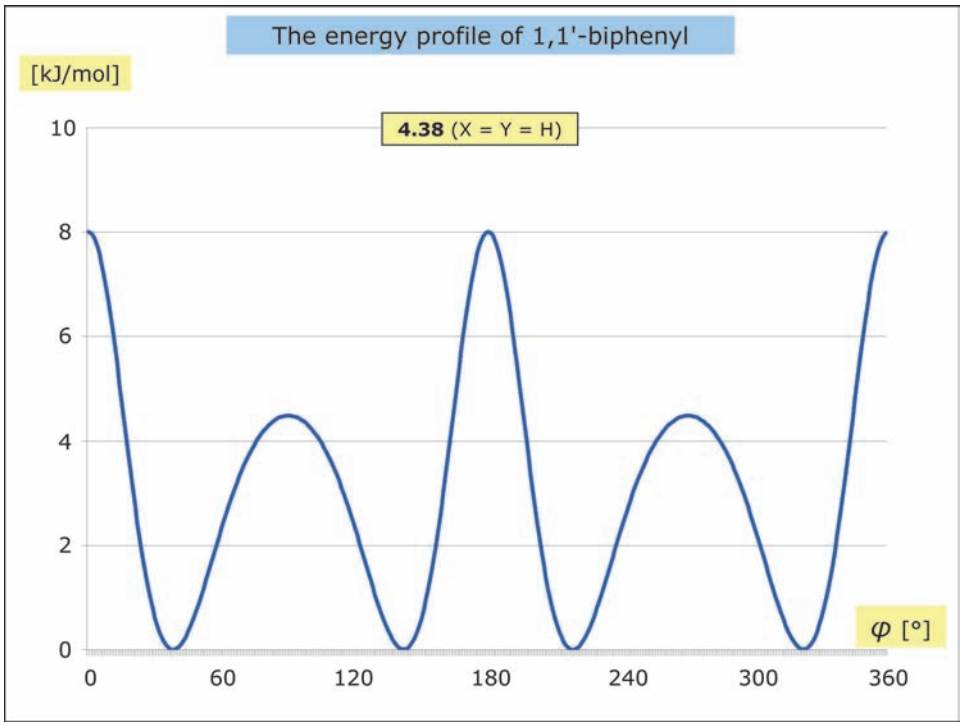
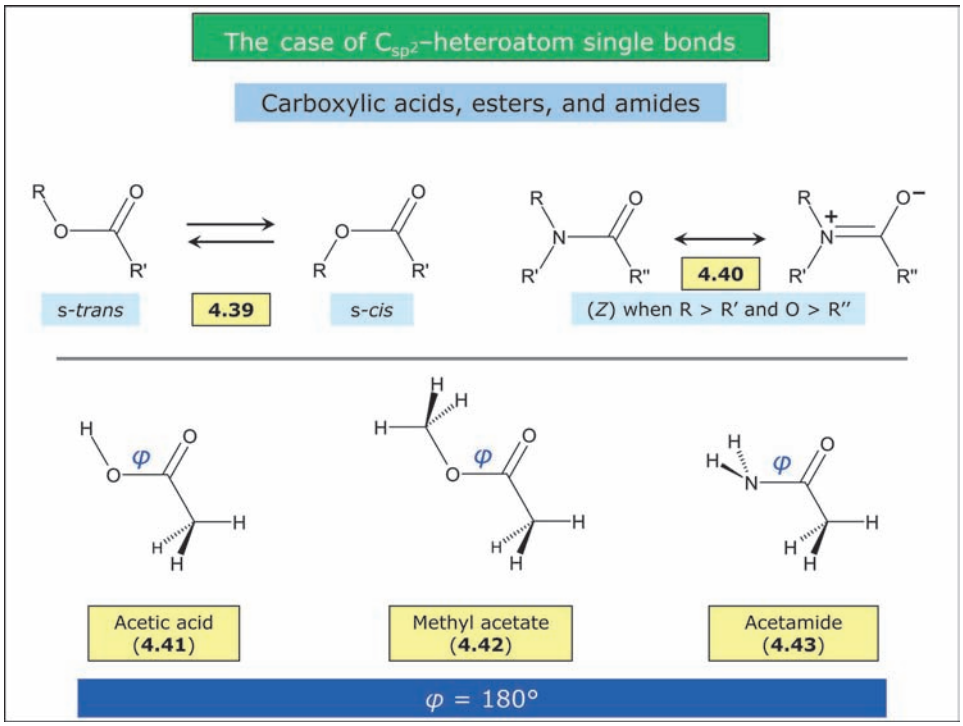


Fig. 4.20.

preferred one, because it minimizes charge repulsion between the two O-atoms. Only in polar media is the charge repulsion sufficiently diminished to stabilize the s-*trans*-form (by *ca.* 4 kJ/mol in the pure liquid).

1,1′-Biphenyls offer a case of particular interest. *1,1′-Biphenyl* itself (**4.37**; V = W = X = Y = H) experiences two opposing forces, namely resonance stabilization favoring a coplanar conformation, and steric interactions between the *ortho*-H-atoms which favor *clinal* conformations. As shown by the energy profile of 1,1′-biphenyl (*Fig. 4.20*), the energy minima are symmetrically located at dihedral-angle (φ) values of 40°, 135°, 225°, and 320°, with the highest energy barrier (*ca.* 8 kJ/mol) at 0° and 180° (= 360°), and a smaller barrier at 90° and 270°. These results were obtained by semi-empirical molecular orbital calculations[3]) and are comparable to those from *ab initio* calculations [50].

The presence of ring substituents and mainly *ortho*-substituents (*cf.* **4.37**) influences the low-energy conformations and even more the rotation barrier. The rotation of *2,2′-disubstituted 1,1′-biphenyls*, **4.38**, involves two diastereoisomeric transition states both planar, namely the s-*trans*-form and the s-*cis*-form; the former shows less severe crowding. Their rotation barrier is relatively high, close to 60 kJ/mol in 2,2′-dimethoxy-1,1′-biphenyl (**4.38**; X = Y = MeO) and 75 kJ/mol in 2,2′-dimethyl-1,1′-biphenyl (**4.38**; X = Y = Me) [14]. These values lie in the fuzzy zone separating conformational and configurational isomerism, as discussed in *Part 3* in connection with *axial chirality*, hindered rotation, and *atropisomerism*.



Figs. 4.21 and 4.22. We now come to *C_{sp^2}–heteroatom bonds*. Rotation around such bonds is usually a higher-energy process than rotation around C_{sp^2}–C_{sp^3} single bonds, due to conjugation and to the resulting partial double-bond character of the pivot bond. If we consider first *C_{sp^2}–O single bonds*, we encounter compounds such as phenols and aromatic ethers, and esters. A comparable tendency toward planarity is found in uncrowded phenols and aromatic ethers.

Carboxylic acids, **4.39** (R = H), and *esters*, **4.39** (R = alkyl), exist as two preferred planar (or near-planar) rotamers, namely the *s*-trans-*form* where the R and R′ groups are *antiperiplanar* ($\tau = 180°$), and the *s*-cis-*form* where R and R′ are *synperiplanar* ($\tau = 0°$) [12][32]. Torsional isomerism around *C_{sp^2}–N single bonds* exists in amides, imides, anilines, and others. Partial delocalization of the C=O bond causes the *amide bond* to acquire a *partial double-bond character*, as represented by its resonance structures, and hence to prefer a planar or near-planar conformation, **4.40**. Another consequence of this observed electron delocalization is to render the amide N-atom nonbasic. The importance of the partial double-bond character is well illustrated by the relative high barrier of rotation of amides (*ca.* 70–80 kJ/mol), as seen in *Fig. 4.22*. The height of this barrier decreases slightly with increasing bulk of the substituents [51].

An energy profile of *acetic acid* (**4.41**), *methyl acetate* (**4.42**), and *acetamide* (**4.43**) is shown in *Fig. 4.22* [52][3]). The s-*trans*- and the s-*cis*-forms of methyl acetate are seen to be equivalent and to be separated by a barrier of *ca.* 20 kJ/mol. This is not the case for acetic acid where the s-*cis*-form is clearly preferred. Note, however, that the generic structure **4.39** does not give a complete view of the conformational issues raised by

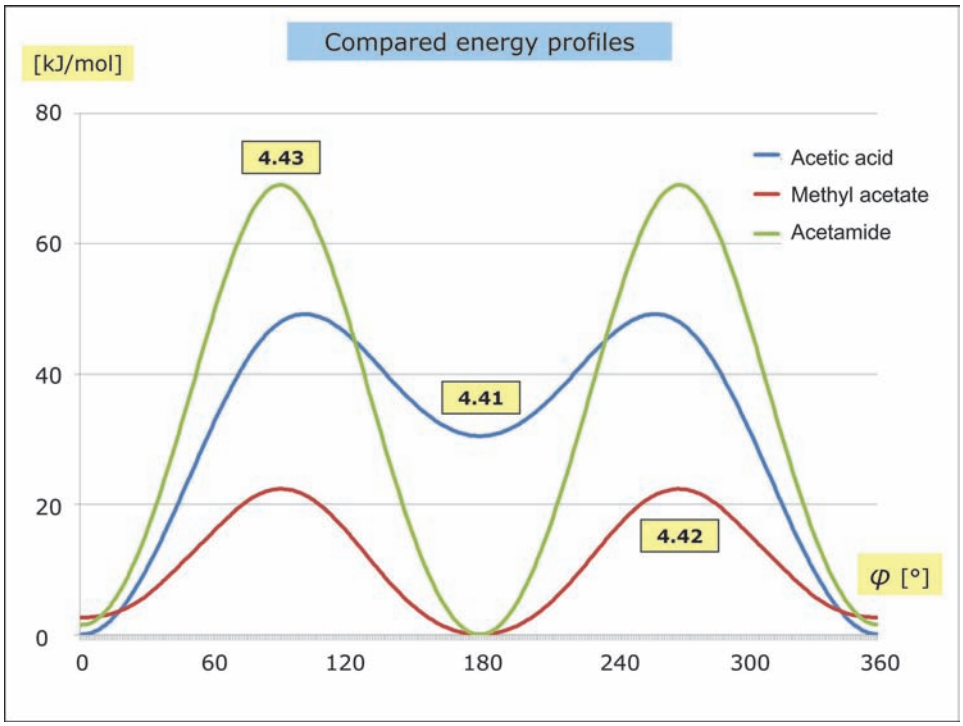


Fig. 4.22.

alkyl esters. As easily deduced from the triple-rotor structure of *methyl acetate* (**4.41**), several low-energy conformers must exist even in a simple ester such as this one.

When the two *N*-substituents, R and R′, in *amides* are different, two planar rotamers exist whose designation may not be devoid of ambiguity. The s-*cis* and s-*trans* descriptors are confusing, and the recommended procedure for tertiary amides is to use the (*E*,*Z*)-convention (see *Part 3*) based on the sequence rule and on the partial double-bond character of the amide bond [8]. In the case of *N*-monosubstituted amides (**4.40**; R′ = H), the (*Z*)-rotamer predominates by *ca.* 4 kJ/mol, or more, over the (*E*)-form [12][53]. In the case of *N*-disubstituted amides with dissimilar substituents of comparable bulk, marked isomeric predominance is lost.

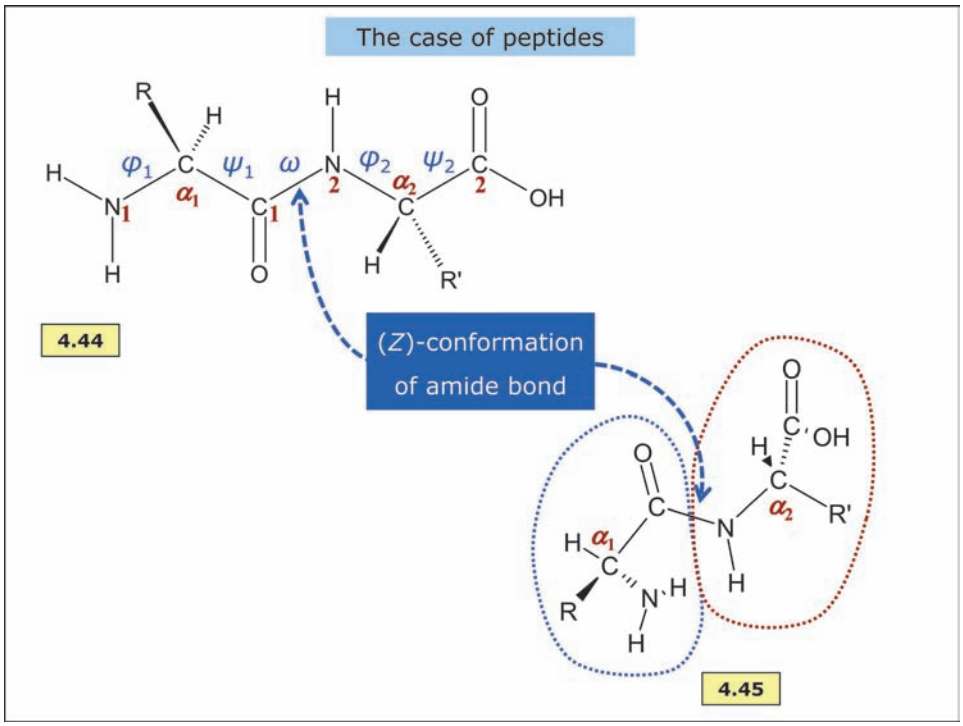
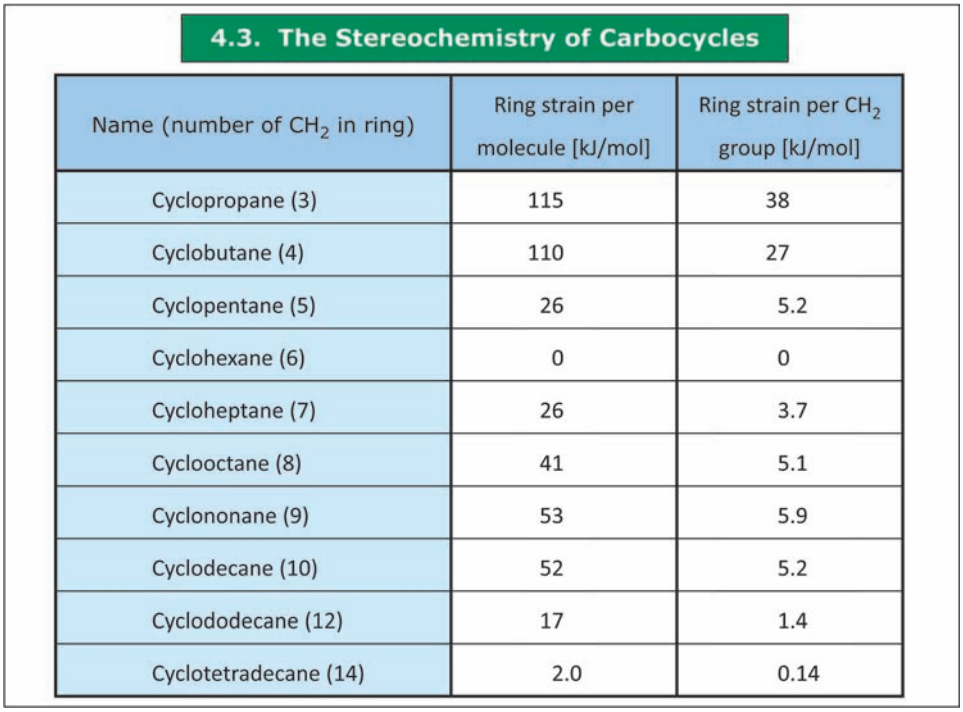


Fig. 4.23. Amide bonds have a particular significance in *biochemistry*, being the main components of the backbone of *proteins* and other *peptides* [54–56]. A specific notation system is used to label torsion angles in peptides, as illustrated here with the *generic dipeptide* **4.44**. The *residues,* beginning with the *N-terminus*, are labeled as 1, 2 *etc.* The *backbone* C_{sp^3}*-atoms* are designated as C_α, while the N-atoms and the carbonyl C-atoms share the number of their residue (see *red labels* in **4.44**). The *blue labels* refer to the torsion angles, ω (*omega*) being the torsion angle of the peptide bond with partial double-bond character. The angles *phi* (φ) and *psi* (ψ) refer to the bonds between N and C_α and between C_α and C_1, respectively.

The structure **4.45** represent a *generic* L,L*-dipeptide* whose conformation is the one it would have as part of a *peptidic* α*-helix* (see *Part 3*). The peptide bond has an ω angle of *ca.* 0° and (*Z*)-conformation. In residue 1, the C–H and C=O bonds (angle ψ) are nearly eclipsing, and the same holds in residue 2 in which, furthermore, the N–H and C–R′ bonds (angle φ) are also eclipsing. A large database of backbone-dependent rotamers is available [20][57].



4.3. The Stereochemistry of Carbocycles

Name (number of CH_2 in ring)	Ring strain per molecule [kJ/mol]	Ring strain per CH_2 group [kJ/mol]
Cyclopropane (3)	115	38
Cyclobutane (4)	110	27
Cyclopentane (5)	26	5.2
Cyclohexane (6)	0	0
Cycloheptane (7)	26	3.7
Cyclooctane (8)	41	5.1
Cyclononane (9)	53	5.9
Cyclodecane (10)	52	5.2
Cyclododecane (12)	17	1.4
Cyclotetradecane (14)	2.0	0.14

Fig. 4.24. Cyclic systems show some specific stereochemical characteristics that justify a separate treatment, if only because the concepts of conformational isomerism, diastereoisomerism, and enantiomerism, are inseparable in such treatments.

Chain cyclization generates a strain which can be determined by comparing the heats of combustion per CH_2 group for the cyclic and linear analog. The main contribution to *ring strain* are the Baeyer *strain* (bond-angle strain) and the Pitzer *strain* (strain of *gauche* and eclipsing bonds). In *small rings* (three- and four-membered), the *Baeyer* strain is especially marked, but is less or negligible in *common rings* (five- to seven-membered), *medium rings* (eight- to eleven-membered), and *large rings* (twelve-membered and more). In all systems, *Pitzer* strain operates and will tend to be relieved by deviations of the C-skeleton from planarity. In larger rings, *transannular interactions* also contribute to the relative strain. The *Table* compiles rounded off values of the ring strain in *unsubstituted cycloalkanes* [12][58–63].

Cyclic molecules will obviously tend to adopt the conformation(s) minimizing all strain contributions. In these energy minima, the remaining strain is optimally distributed between the various contributions (bond-length and bond-angle deviations, *Pitzer* strain, and other nonbonded interactions). Cyclic systems usually exhibit several possible conformations whose interconversion can occur by two distinct processes, *i.e.*, cycle reversal and pseudorotation. *Ring reversal* (sometimes inadequately called 'inversion') involves a relatively high-energy transition state (some kJ/mol) occurring with modification of bond angles and all other strains. *Pseudorotation* is a lower-energy process which does not involve bond-angle variations but only changes in *Pitzer* strain and other nonbonded interactions. Conformers which can be transformed by pseudorotation are called *flexible*; those which can only undergo reversal are called *rigid*.

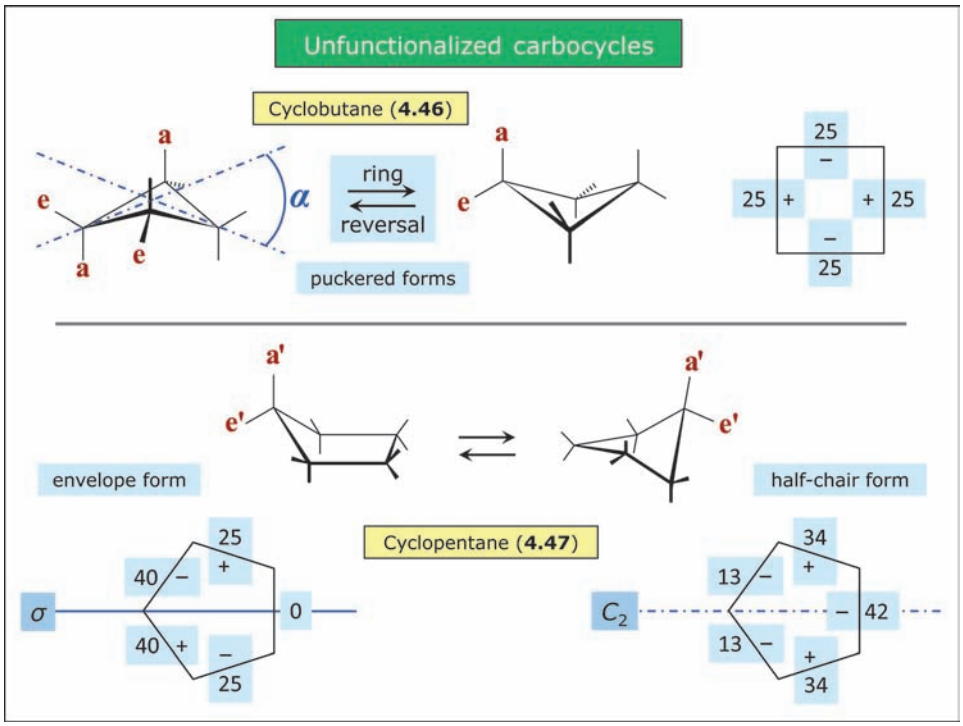
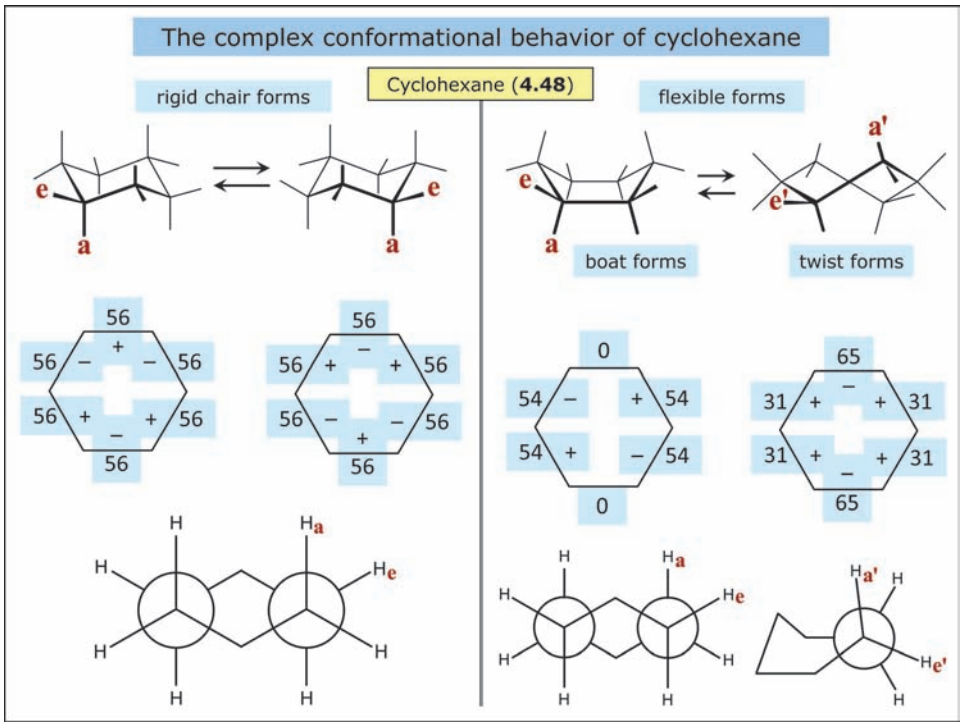


Fig. 4.25. Unsubstituted *cyclopropane* attracts no stereochemical interest as it is planar by definition. The first homolog displaying conformational mobility is *cyclobutane* (**4.46**), whose preferred conformation is the *puckered form* shown here. This means that one C-atom is out of the plane of the other three C-atoms. The value of the *puckering angle* α is *ca.* 35°, which corresponds to torsion angles of $\pm 25°$ as pictured in the conventional representation shown. Unsubstituted cyclobutane undergoes *ring reversal* to generate an identical conformer, a process comparable to the wing motion of a butterfly [64–68]. *Ring reversal* is a conformational change which transforms a ring conformation by inverting (changing the sign) of all its torsion angles. In other words, it is an interconversion between two forms of the same type having torsion angles of the same absolute values but of opposite signs. Given the relative high energy of cyclobutane's ground state (*Fig. 4.24*), the energy necessary to reach the *planar transition state* is minute (*ca.* 5–6 kJ/mol). This implies that the planar form may be detectably populated in some derivatives.

Our representation of cyclobutane also identifies two positions at each C-atom, namely an *axial* and an *equatorial* one, commonly abbreviated as a and e, respectively [69]. As shown, ring reversal transforms the axial bonds into equatorial ones, and inversely, and only in the case of substituted cyclohexanes will the two puckered forms be distinguishable. As discussed later, substituting any position markedly influences the conformational behavior of the molecule. Also, a specific description of the *puckering concept*, used in designating *puckered forms*, will be presented later (*Figs. 4.39–4.43*).

In *cyclopentane* (**4.47**), the bond angles have values close to the optimum, implying that the strain in the molecule arises from bond opposition and is partly relieved by *puckered* conformations [70][71]. Two flexible forms of cyclopentane exist. In the so-called *envelope form*, one C-atom projects out of the plane of the four others; this conformer has C_s symmetry (presence of a plane of symmetry σ). The other flexible conformer is the *half-chair (or twist) form* in which three neighboring C-atoms are coplanar, while the other two are above and below the plane, respectively, and equidistant from it. This conformer has C_2 symmetry.

In *unsubstituted cyclopentane*, the envelope and half-chair conformers undergo interconversion through intermediate conformations with no symmetry. As depicted in *Fig. 4.39*, if in the envelope form the out-of-place C-atom (arbitrarily designated C(1)) is moved together with an adjacent C-atom, a half-chair is obtained (C(1) above, C(2) below the plane). Continuing the motion generates another envelope form with C(1) in the plane and C(2) below it, and so on. Ten indistinguishable envelope forms and ten indistinguishable half-chair forms undergo interconversion by this process of *pseudo-rotation*. Indeed, it is not the molecule that rotates but the out-of-plane deformation, like a wave on a water surface. This pseudorotational circuit is essentially of constant strain and, therefore, free; there are no energy minima and maxima. However, the fully planar conformation is less stable by *ca.* 20 kJ/mol. As a result of this flexibility, the position of exocyclic bonds can no longer be considered as strictly axial and equatorial, as is the case in cyclobutane and cyclohexane. It is thus customary in cyclopentane (and in cycloheptane) to distinguish between pseudo-equatorial (e′) and pseudo-axial (a′) bonds [8][69].



Figs. 4.26 and 4.27. A significant example of isomerism is offered by *cyclohexane* (**4.48**). Its preferred conformer is the *chair form* characterized in 1943 by *Hassel* [4–6]. An ideal chair form would have torsion angles of 60° and C–C–C bond angles of 109.5°. Because the normal C–CH_2–C bond angle is 112.4°, the angle strain for the ideal chair form would be *ca.* 4 kJ/mol. Also, a bond angle of 112.4° corresponds to torsion angles of 52°, with a *Pitzer* strain of *ca.* 3 kJ/mol. The real cyclohexane chair, therefore, balances these strains with bond angles of 111° and *torsion angles of 56°*. In the hexagonal representation of cyclohexane, only the sign of the torsion angles is sometimes given; their absolute value may be omitted when it is 56°.

The chair conformers of cyclohexane show *equatorial and axial exocyclic bonds.* This form is a *rigid* one which must undergo *ring reversal* to be transformed to other conformers, in particular to another chair. For cyclohexane itself, the two chair forms are indistinguishable, but a careful inspection reveals that the reversal process changes all equatorial bonds into axial ones, and *vice versa*. The reversible ring reversal process underlying chair–chair conversion is a complex and relatively high-energy one, with a barrier in the order of 40–50 kJ/mol. A detailed description of this process is available [68][72].

Cyclohexane also exists as *flexible forms*, namely the *boat form* and the *twist form* (or *skew-boat*). In fact, the flexible forms give rise to a large number of conformers by continuous variation of their torsion angles – there existing 38 energetically possible conformers, the so-called canonical forms. The boat and twist forms represent the local energy maxima and minima, respectively, of the flexible form, with the former *ca.*

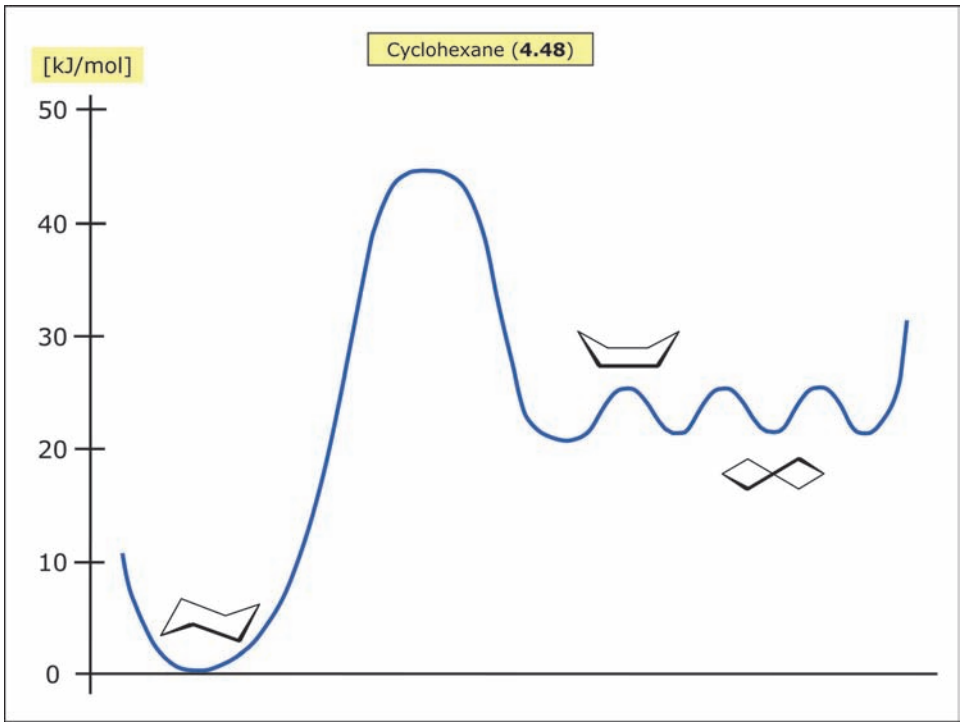


Fig. 4.27.

25 kJ/mol and the latter *ca.* 20 kJ/mol above the global energy minimum of the chair form. An indicative energy plot of the conformational profile of cyclohexane is shown in *Fig. 4.27.*

The boat forms, like the chair forms, possess only equatorial and axial bonds. In contrast, the exogenous bonds in the twist forms are designated as *pseudo-equatorial* (e′) and *pseudo-axial* (a′).

Increasing the number of CH_2 groups in carbocyclic systems results in the possibility of additional conformers [64][68][70]. Thus, *cycloheptane* has two families of conformers interconvertible by pseudorotation, namely the chair and twist-chair forms on the one hand, and the boat and twist-boat forms on the other. The twist-chair is the preferred conformation. As for *cyclooctane*, its conformers have been classified into three families of interconvertible symmetric forms. The first family contains two forms, the familiar crown (all torsion angles of 92°, with regularly alternating sign) and a lower-energy form (D_2). The interconvertible symmetric forms of the second family are the familiar chair form, another D_2 form of lower energy, a centrosymmetric form, and a boat-chair form (the lowest-energy member of all the symmetric forms of cyclooctane). In the third family, there is a boat form plus a tub form (the highest-energy member). Given the relatively low transition barriers from one family to the others, cyclooctane exists as a mobile and complex mixture of conformers.

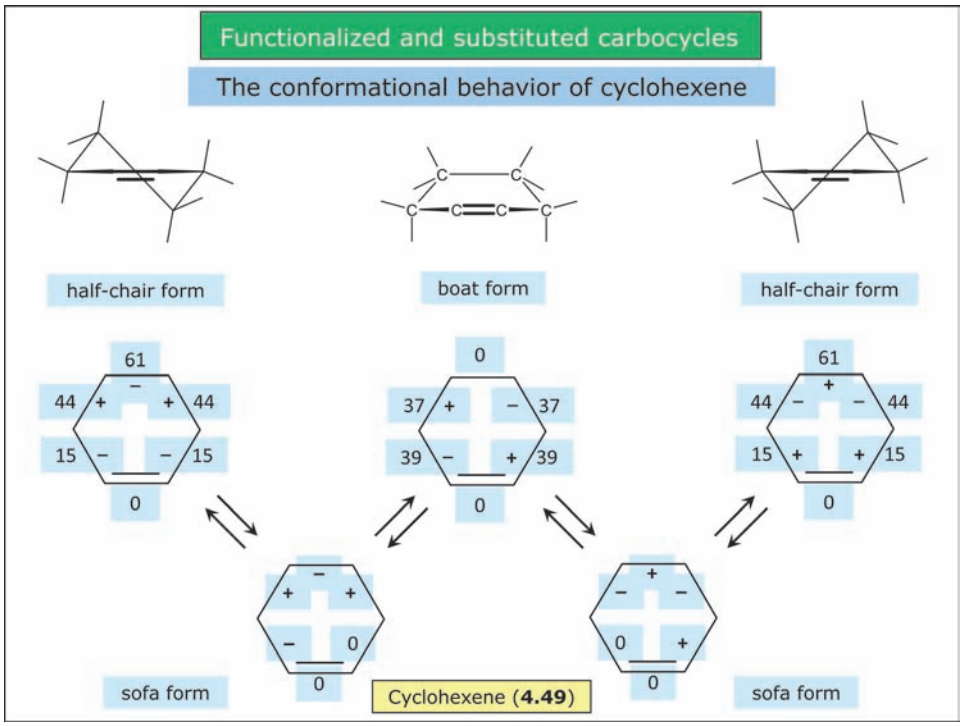
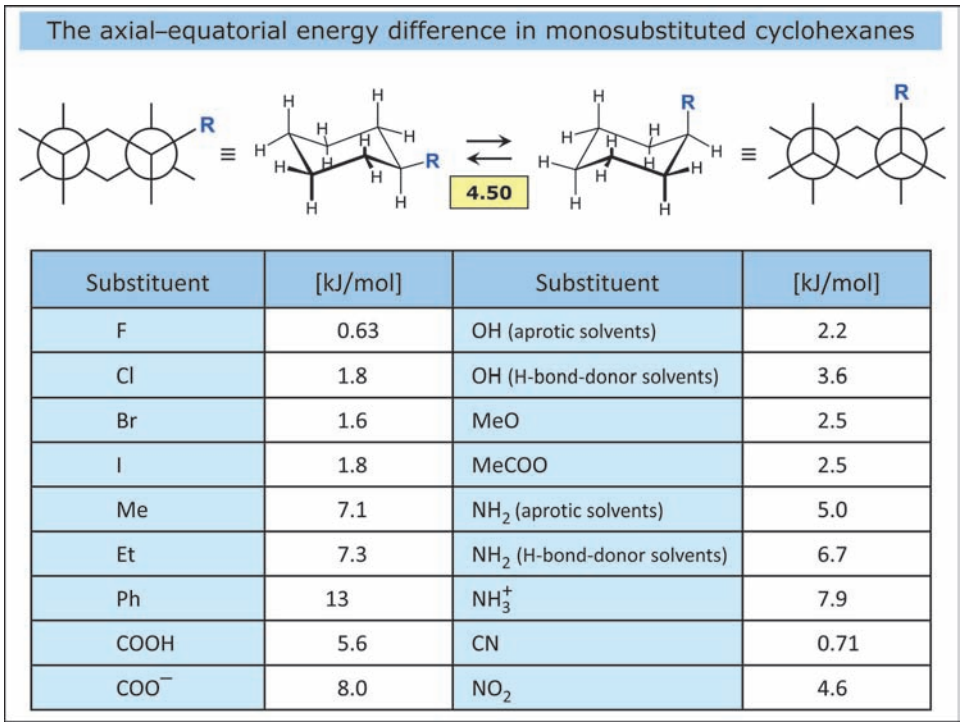


Fig. 4.28. Introduction of a *double bond* into an carbocycle considerably flattens the molecule. Taking *cyclohexene* (**4.49**) as an example of a functionalized carbocycle, it appears that its C-atoms 1, 2, 3, and 6 have long been considered as exclusively coplanar. In this situation, the most stable forms are the two *enantiomeric half-chair* conformers. They undergo interconversion *via* a transition state which is the *boat form* having an energy of *ca.* 25 kJ/mol above the global minimum [68][72]. The indicative values of their torsion angles are shown in the hexagonal representations just underneath the perspective drawings.

A slight twisting of the C=C bond was later found to be energetically feasible, allowing the so-called *sofa forms* at just *ca.* 3 kJ/mol above the global minimum. However, these forms do not correspond to local minima but are *transitional conformations* in the half-chair-to-boat interconversion path. For this reason, only the signs of the torsion angles are indicated.



Substituent	[kJ/mol]	Substituent	[kJ/mol]
F	0.63	OH (aprotic solvents)	2.2
Cl	1.8	OH (H-bond-donor solvents)	3.6
Br	1.6	MeO	2.5
I	1.8	MeCOO	2.5
Me	7.1	NH_2 (aprotic solvents)	5.0
Et	7.3	NH_2 (H-bond-donor solvents)	6.7
Ph	13	NH_3^+	7.9
COOH	5.6	CN	0.71
COO^-	8.0	NO_2	4.6

Fig. 4.29. As suggested earlier, *monosubstituted cyclohexanes*, **4.50**, can occur in two isomeric chair forms, the substituent being equatorial or axial as illustrated here. The energy barrier between the two forms is usually in the range of 40 – 50 kJ/mol and is thus comparable to the barrier in cyclohexane itself (*Fig. 4.27*). Furthermore, the energy difference between the chair and boat forms is again comparable to that of cyclohexane. What is relevant here, however, is the energy difference between the two isomeric chair forms. As a rule, monosubstituted cyclohexane will tend to prefer the chair form with the substituent in the equatorial position, but a few exceptions do exist [73]. The indicative values provided in this *Figure* are means from large sets of data obtained under different experimental conditions [74][75].

Classically, steric arguments are put forward to explain the equatorial preference of the substituent. However, inspection of the *Figure* shows the steric factor to play a partial role only, since electronic and solvent effects, in particular hydration of polar groups, have a notable effect. For example, Cl and Me substituents have comparable volumes yet differ markedly in their equatorial preference. Also, ionized substituents have a somewhat stronger influence than their neutral form.

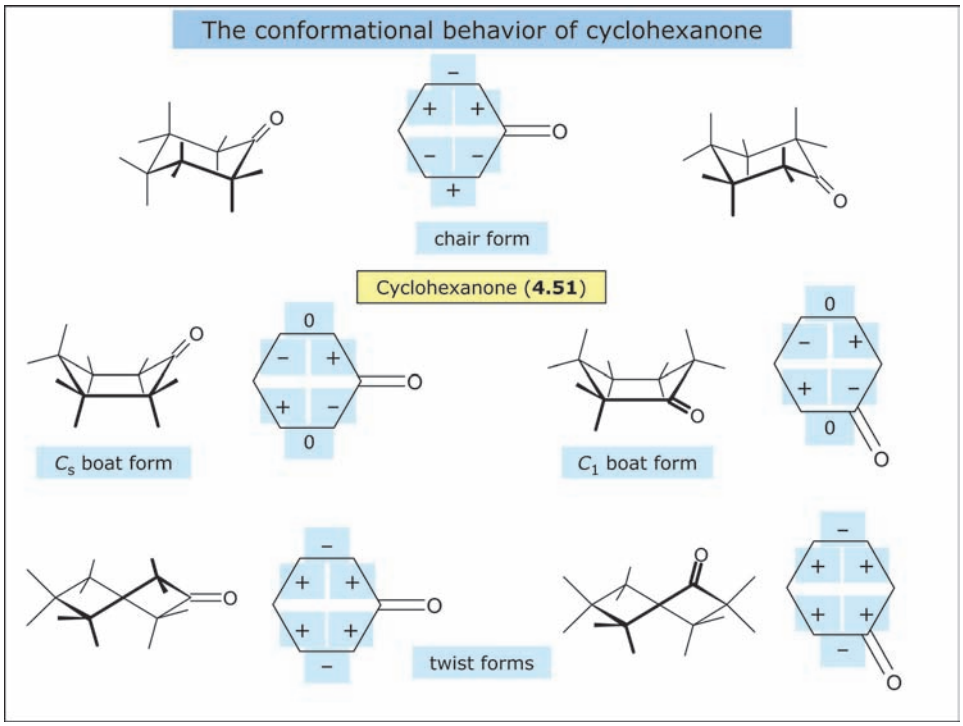


Fig. 4.30. Monosubstituted carbocycles including an endocyclic C_{sp^2}-atom call for a specific discussion. An example of such compounds is *cyclohexanone* (**4.51**) where minor distortions exist as compared to cyclohexane. Like the latter, and in contrast to monosubstituted cyclohexane derivatives, the two chair forms are indistinguishable. Because the barrier of rotation around a C_{sp^2}–C_{sp^3} bond is intrinsically lower than around a C_{sp^3}–C_{sp^3} bond, cyclohexanone shows increased flexibility in the part of the ring containing the C=O group [68]. The barrier of chair inversion is *ca.* 20–25 kJ/mol. Cyclohexanone can further adopt two distinct *boat conformations*, one with a *plane of symmetry* (C_s boat) and the other devoid of it (C_1 boat). Two distinct *twist conformations* also exist, both without a plane of symmetry. These boat and twist conformers have energy contents of *ca.* 23, 17, 13, and 17 kJ/mol above that of the chair form. The hexagonal representation of cyclohexanone conformers is simplified here to focus only on the signs of the torsion angles.

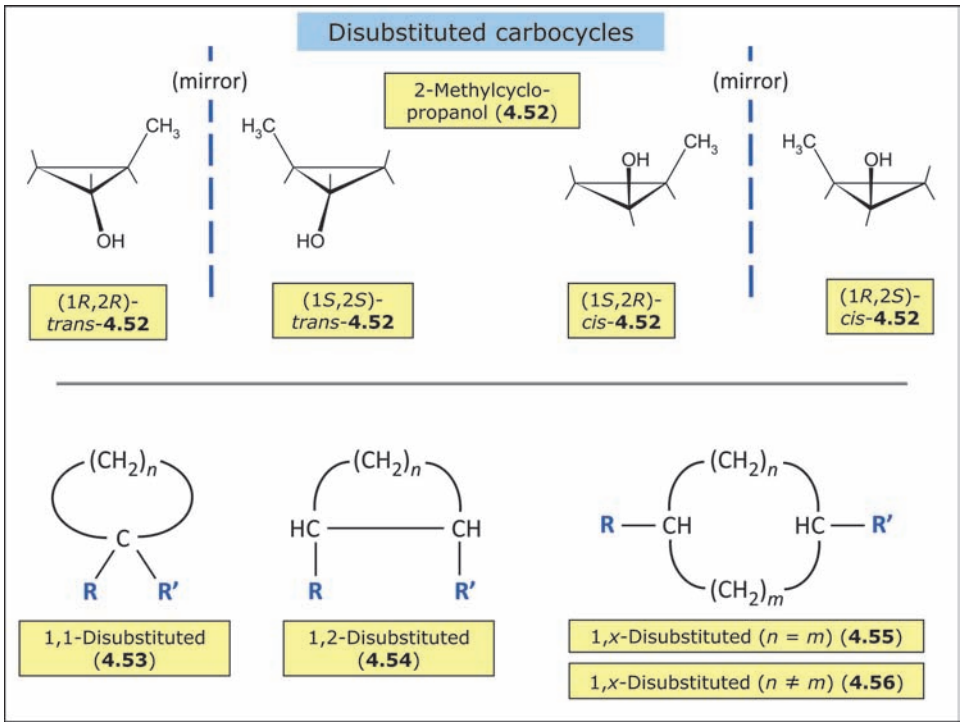
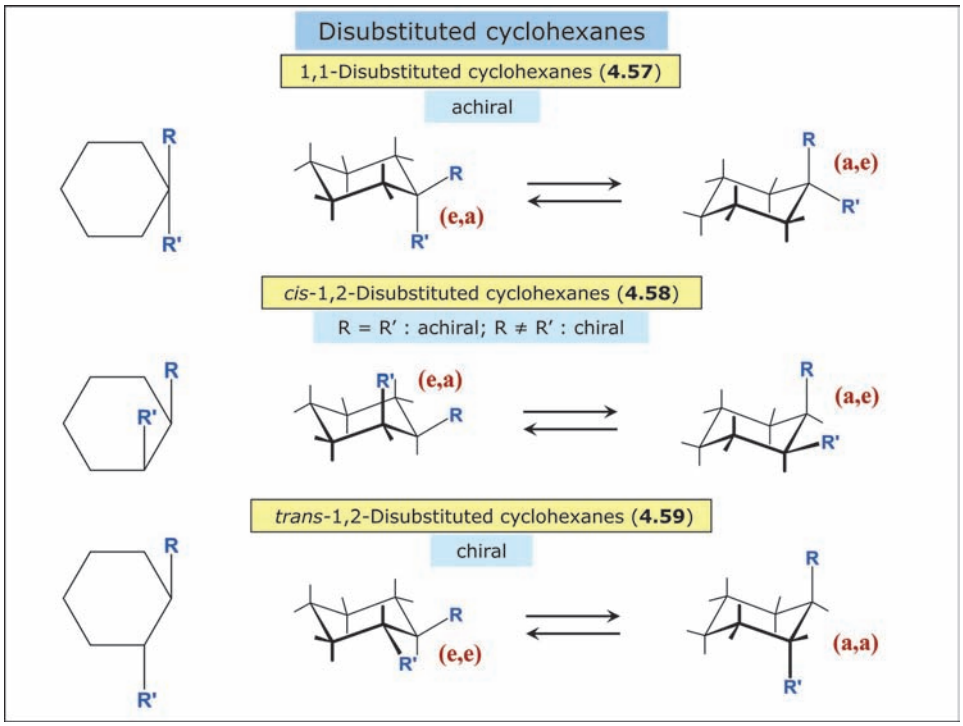


Fig. 4.31. Di- and polysubstituted cyclic systems differ from monosubstituted cycles in that they also generate *configurational isomerism* in addition to conformational isomerism, as suggested by the title of this *Part*. Consider, for instance, *2-methylcyclopropanol* (**4.52**) selected here as a compound devoid of conformational isomerism. This molecule contains two stereogenic C-atoms and exists as *four stereoisomers* in accordance with the rules discussed for acyclic systems (*Parts 2* and *3*). The *two enantiomeric* trans-*isomers* have the two substituents on either side of the plane of the cycle, whereas the *two enantiomeric* cis-*isomers* have their substituents on the same side. Thus, and to repeat what has been discussed in *Part 3*, each of the four stereoisomers of **4.52** is enantiomeric with one, and one only, of the three other stereoisomers, and diastereoisomeric with the remaining two.

In the case of geminal substituents on a carbocycle (*i.e.*, *1,1-disubstituted carbocycles*, **4.53**), a plane of symmetry exists, meaning that the molecule is achiral. In the case of *1,2-disubstituted carbocycles* having *two different substituents*, **4.54**, the same configurational characteristics as seen in **4.52** exist. In *disubstituted carbocycles* where the two substituents R and R′ are at any two C-atoms, **4.55** and **4.56**, the condition for the existence of two stereogenic centers and four stereoisomers is that the two branches of the cycle differ (*i.e.*, **4.56**). When the two branches are identical, *i.e.*, **4.55**, the molecule contains a plane of symmetry which causes the two enantiomeric pairs to degenerate into two achiral diastereoisomers, namely a *cis*- and a *trans*-isomer.



Figs. 4.32 and 4.33. Let us now consider disubstituted carbocycles in both their *configurational and conformational aspects*, using *cyclohexane derivatives* as examples. Each of the cases considered here is illustrated with a planar representation together with the two distinct chair conformers the compound exists in, and we begin with *configurational aspects*. Thus, *1,1-disubstituted cyclohexanes*, **4.57**, are achiral as mentioned above.

1,2-Disubstituted derivatives and *1,3-disubstituted derivatives* can be either *cis*-configured, **4.58** and **4.60**, respectively, or *trans*-configured, **4.59** and **4.61**, respectively [76]. The cis-*isomers* having identical substituents have a plane of symmetry and are thus achiral; in contrast, the cis-*isomers* with different substituents are chiral. The trans-*isomers* are always chiral, because there is no plane of symmetry in such molecules. The *1,4-disubstituted cyclohexanes* also occur as *cis*- and *trans*-isomers, **4.62** and **4.63**, respectively, and they are always achiral due to their plane of symmetry. While the conformational behavior of these compounds cannot alter their configurational features (see below), it may nevertheless markedly affect their spectral properties and (bio)chemical reactivity.

Regarding the *conformational aspects* of disubstituted cyclohexanes, only chair conformers have been drawn, although it is known that a few cyclohexane derivatives preferentially adopt non-chair conformations, *e.g.*, cyclohexane-1,4-dione, *trans*-1,3- and *cis*-1,4-di(*tert*-butyl)cyclohexane [72]. With regards to the chair conformers shown in the two *Figures*, one needs to discriminate between two groups of isomers. 1,1-Disubstituted cyclohexanes, **4.57**, exist in an $axial + equatorial \rightleftharpoons equatorial + axial$

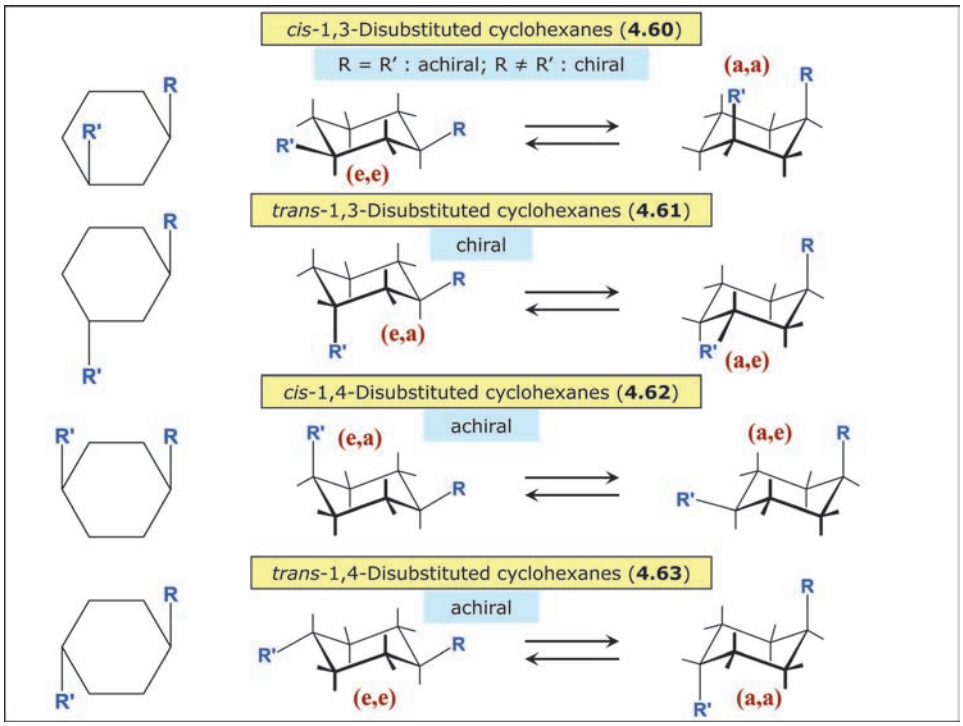


Fig. 4.33.

equilibrium, their preferred conformations depending mostly on the balanced contributions of the two substituents. The same is true for the other isomers experiencing the same type of equilibrium, namely the *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-disubstituted cyclohexanes, **4.58**, **4.61**, and **4.62**, respectively.

The isomers which experience a *diequatorial* $\rightleftharpoons$ *diaxial equilibrium* are *trans*-1,2-, *cis*-1,3-, and *trans*-1,4-disubstituted cyclohexanes, **4.59**, **4.60**, and **4.63**, respectively. Here, both substituents will tend to adopt an equatorial position (see *Fig. 4.29*). However, an additional effect arises from the different interactions between the substituents themselves in the diaxial and diequatorial conformers. As a result, interactions between the substituents also contribute to the conformational energy. In *trans*-1,2-dichlorocyclohexane, **4.59** ($R = R' = Cl$), for example, the Cl/Cl *gauche* interaction destabilizes the diequatorial conformer.

To summarize, we are reminded that the cis *and* trans convention has found its most legitimate use in describing the *relative configuration* of substituents on ring systems. As we saw earlier in this *Part*, the *cis*/*trans* convention is no longer used in the description of conformational isomerism in rotors, except for some conjugated systems where planar conformations can be described by the descriptors s-*cis* and s-*trans* (see above). As for isomerism about double bonds, we saw in *Part 3* how the *cis*/*trans* convention can be confusing as compared to the (*E*,*Z*)-convention.

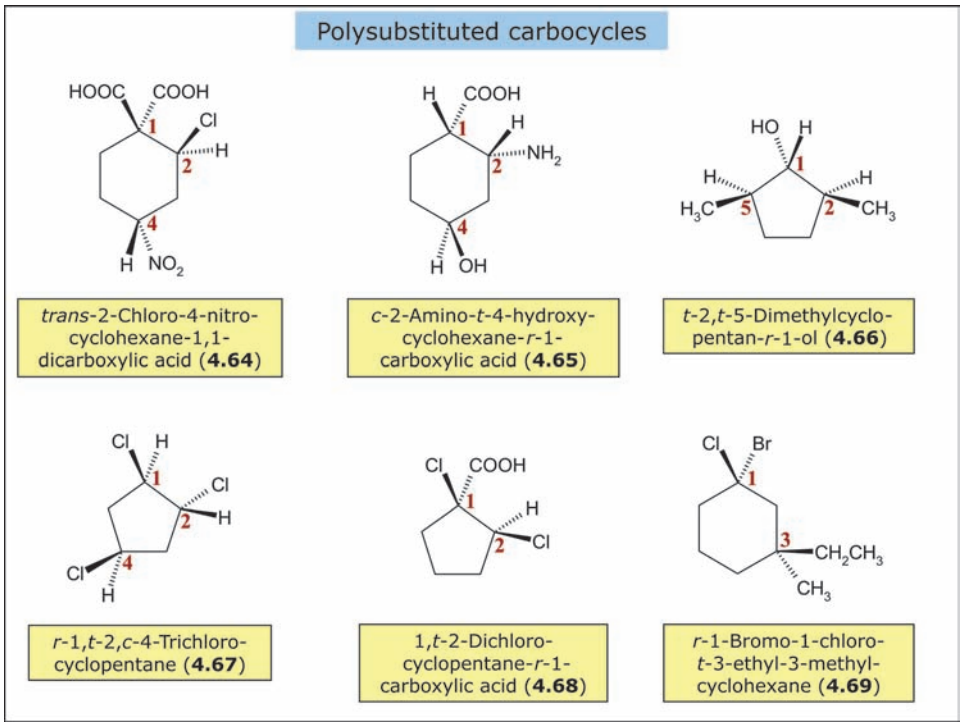


Fig. 4.34. Up to now, the presentation focused on disubstituted carbocycles. As recommended by the *IUPAC*, when '*one substituent and one hydrogen atom are attached at each of two positions of a monocycle, the steric relations of the two substituents are expressed as* cis *or* trans*, followed by a hyphen and placed before the name of the compound*' [8e]. This rule can also be applied when there are four substituents, two of them being identical and geminal, as illustrated by trans-*2-chloro-4-nitrocyclohexane-1,1-dicarboxylic acid* (**4.64**).

In the common cases of *more than two substituents attached to the ring*, the use of *cis* and *trans* requires the definition of a *reference substituent*. This is done by choosing the substituent with the lowest locant as the reference substituent and adding '*r*-' before the locant. The relation of the other substituents relative to the reference is then expressed by adding '*c*-' or '*t*-' (for *cis* and *trans*, resp.) before their locants [8e]. For example, compound **4.65** and its enantiomer are c-*2-amino*-t-*4-hydroxycyclohexane*-r-*1-carboxylic acid*. Similarly, compound **4.66** is t-*2,*t-*5-dimethylcyclopentan*-r-*1-ol*. Compound **4.67** is a more complicated example due to a danger of ambiguous numbering; the correct numbering according to *IUPAC* rules [8e] leads to r-*1,*t-*2,*c-*4-trichlorocyclopentane*, whereas the alternative numbering would yield *r*-1,*t*-2,*t*-4.

When two different substituents are attached at the same position of a monocycle, the lowest-numbered substituent named as *suffix* becomes the reference group, *e.g.*, *1,*t-*2-dichlorocyclopentane*-r-*1-carboxylic acid* (**4.68**). If none of the substituents is named as suffix, *i.e.*, if there is no principal functional group, that substituent (in the lowest-numbered pair when applicable) preferred by the sequence rule becomes the reference group, *e.g.*, r-*1-bromo-1-chloro*-t-*3-ethyl-3-methylcyclohexane* (**4.69**).

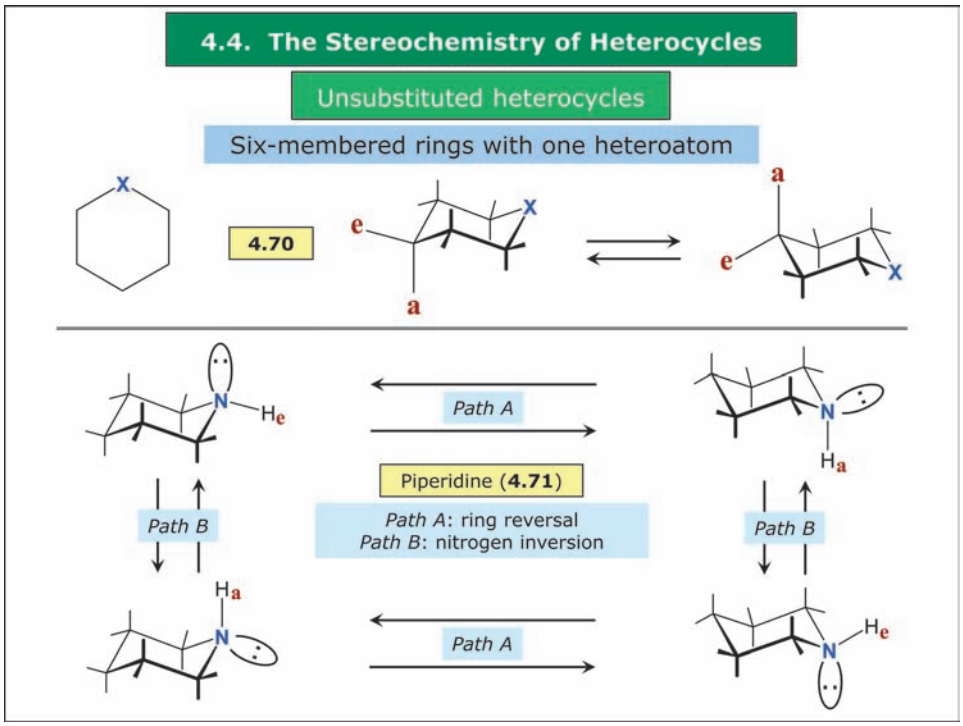


Fig. 4.35. Replacing a C-atom with a N- or O-atom in a saturated cycle has only a modest influence on the geometry. Indeed, C–C bond lengths (1.54 Å) show modest difference from C–N (1.47 Å) or C–O (1.43 Å) lengths; also, C–C–C, C–N–C , and C–O–C bond angles are usually in the range of $112° \pm 0.5°$. Replacing a C-atom with a S-, P-, or Si-atom has a more profound influence due to their relatively longer bond lengths (d(C–S): 1.82 Å; d(C–P): 1.84 Å, and d(C–Si): 1.87 Å). Furthermore, the C–S–C bond angle is relatively closed (*ca.* 100°). Non-negligible *distortions* are thus expected when comparing heterocycles containing these atoms with their C-analogs.

Baeyer *strain* in O- and N-containing heterocycles will be essentially the same as in the corresponding carbocycle, while it may be larger in S-containing heterocycles. Bond-opposition strain of *gauche* and eclipsed conformations (Pitzer *strain*) will differ between carbocycles and heterocycles. Also, solvation energies may in some cases be larger in heterocycles and hence may show marked solvent dependency.

Six-membered rings offer perhaps the most useful comparison between hetero- and carbocycles. When the endocyclic atom in the *six-membered heterocycle* **4.70** is either O (*i.e.*, *oxane* or tetrahydropyran) or S (*i.e.*, *thiane*), the process of chair–chair equilibrium converts the unsubstituted ring into its superimposable image, while all axial and equatorial positions are interchanged. The same holds for *silinane* (=silacyclohexane; **4.70**; $X = SiH_2$), which is identical to cyclohexane with respect to the number of exocyclic positions.

The behavior of *piperidine* (**4.71**; also **4.70** with X = NH) differs from that of the above compounds since *chair–chair reversal* (*Path A*) results in *two achiral*

diastereoisomeric conformers having the H-atom at N(1) in an axial or equatorial position, respectively. The two diastereoisomeric conformers can also interconvert by *nitrogen inversion* (*Path B*). Ring inversion and nitrogen inversion are competitive processes, and are often difficult to distinguish experimentally. The fact that the products of both processes are not distinguishable is a further argument to consider the low-energy nitrogen inversion as a conformational rather than configurational process (see *Part 1*) [12][14][64][68][70–73][77][78].

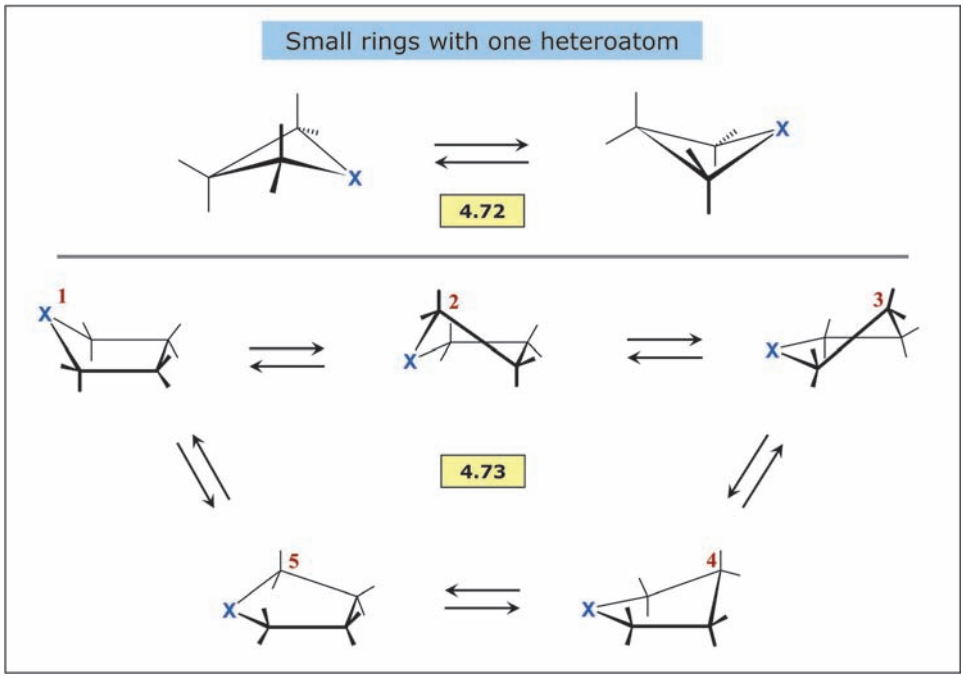


Fig. 4.36. In four-membered heterocycles, the barrier of ring reversal from one puckered form to the other is quite sensitive to the nature of the heteroatom. *Siletane* (=silacyclobutane; **4.72**; X = SiH_2) and *azetidine* (**4.72**; X = NH) have a barrier comparable to that of cyclobutane (**4.46**; *ca.* 5–6 kJ/mol; see *Fig. 4.25*). In contrast, the barrier is low in *thietane* (**4.72**; X = S) and *oxetane* (**4.72**; X = O; *ca.* 3 and < 1 kJ/mol, resp.) [65]. The barrier is thus significantly lower when the heteroatom bears no exocyclic atom (H in the present case). The difference between oxetane and thietane can be explained by the smaller C–S–C valency angle compared to the C–O–C angle (see *Fig. 4.35*).

Unlike six-membered heterocycles, but like cyclopentane, *five-membered heterocycles* (**4.73**) are pseudorotational systems assuming a continuous set of conformations. The heteroatom can occupy distinct positions in the envelope and half-chair forms, as illustrated here with a pseudorotational circuit showing only the five possible envelope forms (all viewed from the same angle, the out-of-plane atom being numbered). The absence of well-defined energy maxima and minima leaves only a theoretical interest in the discrimination of conformers [12][66–68][70][71][79][80].

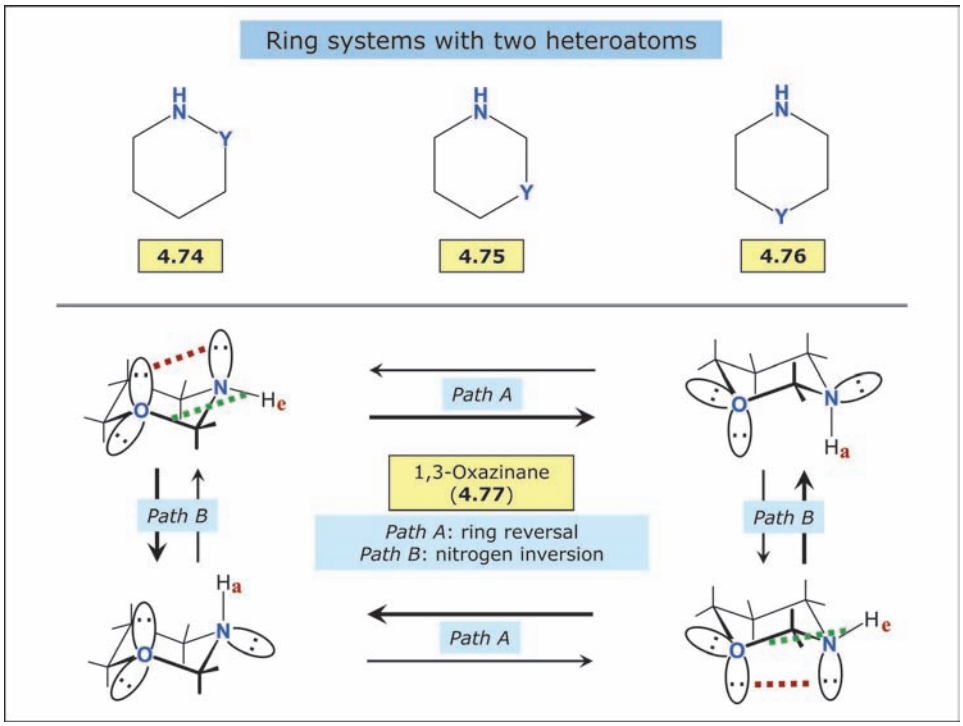


Fig. 4.37. The conformational complexity of heterocycles will increase with the number of endocyclic heteroatoms. A well-studied class is that of *six-membered cycles containing two heteroatoms*. Here, we mention piperidine analogs bearing an endocyclic heteroatom in position 2 (*e.g.*, *1,2-oxazinane*; **4.74**; Y = O), in position 3 (*e.g.*, *hexahydropyrimidine*; **4.75**; Y = NH), and in position 4 (*e.g.*, *morpholine*; **4.76**; Y = O). *1,3-Oxazinane* (**4.77**; Y = O) offers an interesting example of the marked conformational effect resulting from electronic interactions between the two geminal, electron-rich heteroatoms. Indeed, a strong preference has been found for the N–H bond to be axial, in contrast to piperidine itself (*cf.* **4.71** in *Fig. 4.35*) where the N–H bond has a slight tendency (by *ca.* 1 kJ/mol), at least in apolar media, to be equatorial [77][81]. This may be attributed, at least in part, to an electrostatic repulsion between two electron lone pairs when the N–H bond is equatorial (red dotted line). The axial preference of the N–H bond may also indicate an attractive *gauche* interaction between the polar N–H axial bond and the C(2)–O bond (green dotted line).

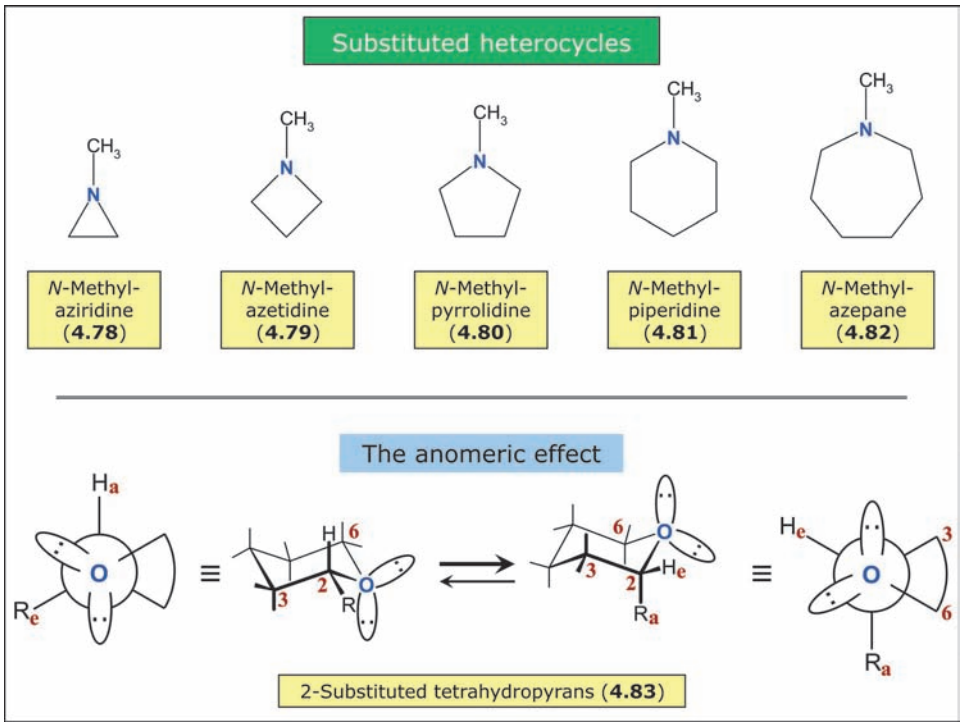


Fig. 4.38. In substituted heterocycles, the interaction between endocyclic heteroatom(s) and exocyclic substituent(s) may have marked conformational consequences. Thus, N-heterocycles may carry *N*-substituents whose behavior differs from those of substituents in other ring positions. The general configurational lability of N-atoms can generate *diastereoisomeric conformations* without ring reversal, as already exemplified with N–H axial *vs.* equatorial bonds in piperidine (**4.71**) and 1,3-oxazinane (**4.77**; Y = O). However, this is not a general rule, as several cases of *configurational stability* of N are known. Looking at nitrogen inversion in *N*-substituted, three- to seven-membered azacycloalkanes, it was found that N-*methylaziridine* (**4.78**), N-*methylazetidine* (**4.79**), N-*methylpyrrolidine* (**4.80**), N-*methylpiperidine* (**4.81**), and N-*methylazepane* (**4.82**) have approximate values of N-inversion of 80, 40, 35, 35, and 30 kJ/mol, respectively [82][83]. In other words, the N-inversion barrier in *N*-methylaziridine (**4.78**) implies a fair degree of configurational stability. The regular decrease in N-inversion barrier in this series of homologs reflects the progressive decrease in bond-angle strain in compounds **4.78** to **4.82**. But many other factors may influence a barrier of N-inversion, *e.g.*, the steric bulk and electronegativity of the substituent, and electronic conjugation within the ring as modified by the presence of a second heteroatom.

As already seen above, the preferred position of an *N*-substituent is usually found to be the equatorial one, but the axial *vs.* equatorial difference is small. In the case of *O- or S-containing heterocycles*, some electron-rich substituents at C(2) show an unusual conformational behavior. Indeed, a halogen atom, or an O- or S-containing substituent at C(2) will tend to markedly prefer an *axial position*, a propensity known as the *anomeric effect* [73][79][84], which is a significant phenomenon in the conformational behavior of carbohydrates, as exemplified later. The magnitude of the anomeric effect

has been defined as the difference in free energy between the axial and the equatorial conformers, plus the ordinary conformational preference of the 2-substituent. For 2-substituted 4-methyltetrahydrofurans, the anomeric effect was found to be close to 11 kJ/mol for Cl, and smaller (*ca.* 4–6 kJ/mol) for OH, O–alkyl, and O–acyl.

The causes of the anomeric effect are of electronic nature and have led to many speculations. A simple but incomplete approximation considers dipole–dipole repulsions as favoring the axial conformer. An oversimplified but suggestive representation using *2-substituted tetrahydro-2*H*-pyrans* (**4.83**) shows two *gauche* interactions between the equatorial electron-rich 2-substituent and the O-atom lone pairs of electrons, but only one such interaction when the 2-substituent is axial. For a better visualization, each conformer is represented twice, once in perspective drawing and once in *Newman* projection looking at the molecule along the O–C(2) bond.

Experimentally, it has consistently been found that the endocyclic distance between the O-atom and C(2) is shorter than the O–C(6) distance, indicating mixing of the O nonbonding orbitals with the C(2)–H and C(2)–R antibonding orbitals. For symmetry reasons, this electron donation can be effective only from the axial O lone pair into the C–R orbitals of an axial (*anti*) substituent R.

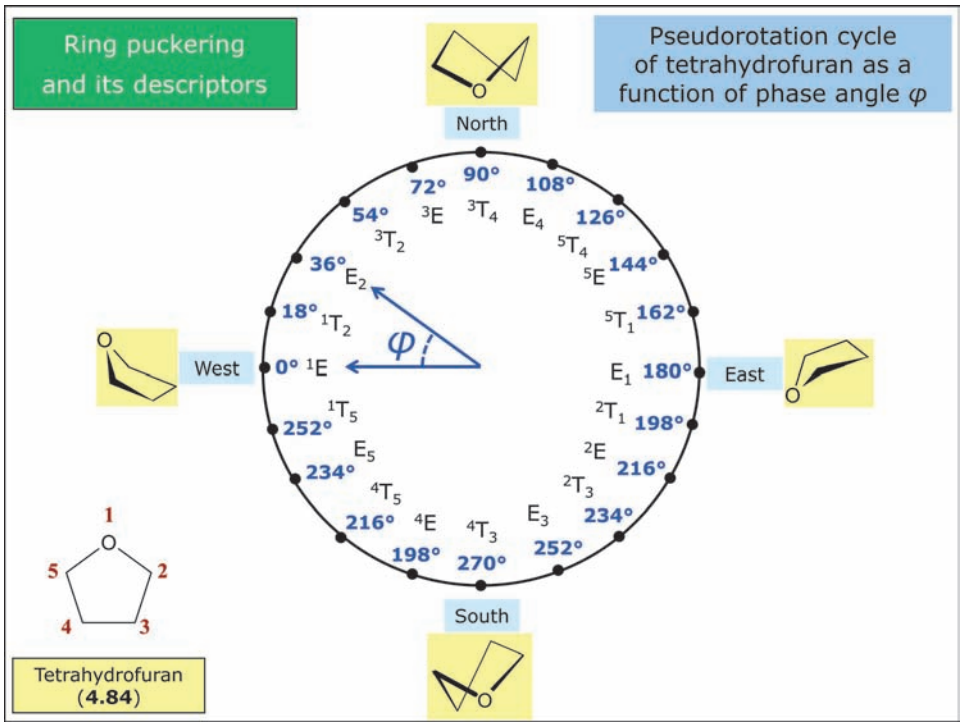


Fig. 4.39. Earlier (*Fig. 4.25*), we mentioned the puckered form of cyclobutane, namely its conformer with one of the ring atoms lying out of the plane of the three other ring atoms. Puckered forms also occur for four-membered saturated heterocycles, as well as for larger carbocycles and heterocycles. Describing the *ring puckering* of such heterocycles is an important problem in biochemistry and has led to the creation of

special *descriptor systems*. Indeed, the concept of ring puckering has been widely used to characterize nonplanar conformations of heterocycles. It was first introduced in 1947 [85] to describe the pseudorotation of the nonplanar cyclopentane conformations and was then generalized in the 1970s[5]). The description is based on the *vertical deviations of each ring atom* with respect to a mean plane which cuts through the geometrical center of the ring and is uniquely defined irrespective of atom numbering. In other words, the ring-puckering descriptors indicate how a given cyclic conformation deviates from planarity. Leaving aside the mathematical treatment of the equations required to compute the ring-puckering descriptors, it should be noted that the number of such descriptors increases with ring size and can be represented on a (hyper)sphere of $(N-3)$ dimensions for an N-membered ring.

Although the ring-puckering concept can be applied to all rings regardless of their size (apart from the three-membered rings which, by definition, are always planar and do not have out-of-plane vibrations), such an approach finds its most relevant applications in describing the conformational profile of five-membered and six-membered heterocycles. Specifically, the puckering of *five-membered rings* is defined by *two independent descriptors*, namely φ, *representing the phase angle of pseudorotation*, and q, *the amplitude of puckering*. Since q is nearly constant, the ring puckering can be suitably described by considering the phase angle φ only. The puckering of six-membered rings is described in the next *Figure*.

Tetrahydrofuran (**4.84**) can be taken as a useful example to illustrate the application of ring-puckering descriptors with clear links to the conformations of *furanose sugars*. In detail, the puckering of five-membered rings can be represented by a pseudorotation cycle (or wheel), as illustrated here for the conformers of tetrahydrofuran. According to the *IUPAC* recommendations[6]), the *pseudorotation cycle of tetrahydrofuran* reveals an alternating sequence of ten envelope (E) conformations and ten twist (T) conformations in steps of 18°, plus one planar geometry (for $q=0$). When considering the cycle as the face of a compass, the conformations can be subdivided into *West-type conformers* (around $\varphi=0°$), when the ring assumes envelope geometries, and the O-atom occupies the apex above the mean plane, *East-type conformers* (around $\varphi=180°$) for envelope geometries, where the O-atom occupies the apex below the mean plane, as well as *North-type conformers* (φ *ca.* 90°) and *South-type conformers* (φ *ca.* 270°), when the ring assumes twist geometries, and the largest dihedral angle corresponds to the C(3)–C(4) bond.

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[5]) In the same period as *Cramer* and *Pople* [86], *Pickett* and *Strauss* proposed an alternative method to describe ring puckering, based on a symmetry-adapted set of coordinates, indicating the deviation of the molecule from a planar regular structure [87].

[6]) A superscript (number) before the symbol 'E' indicates that the apex atom is above the mean plane, a subscript behind 'E', that the apex atom is below the mean plane. For the twist conformers, there is always a superscript before and a subscript behind 'T', indicating the atoms of the bond with the largest dihedral angle where the first atom is above and the second atom below the mean plane.

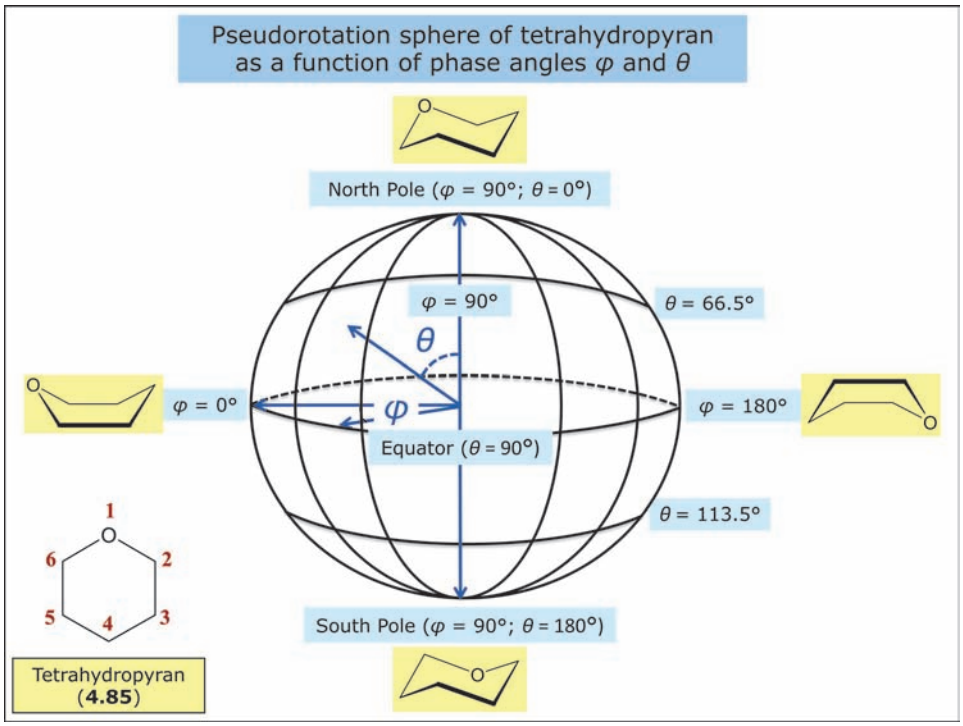


Fig. 4.40. In analogy with five-membered rings, the puckering of *six-membered rings* is defined by *three independent descriptors*, namely φ and θ representing the *phase angles of pseudorotation*, and q the amplitude of puckering. Again, and since the *puckering amplitude* (q) is nearly constant, the ring puckering can be suitably described by considering the phase angles only. With this simplification, the puckering of six-membered rings can be represented by a pseudorotation sphere. This is illustrated here with *tetrahydro-2*H*-pyran* (**4.85**), which is the ring system of *pyranose sugars.*

As represented by the pseudorotation sphere (to be viewed as the terrestrial globe), tetrahydropyran can assume chair conformations which correspond to the Poles (*North Pole:* $\varphi = 90°$; $\theta = 0°$; *South Pole* $\varphi = 90°$; $\theta = 180°$) and boat conformations which lie on the *Equator line.* Besides the Polar conformations ($\theta = 0°$ and 180°), the θ angle assumes only three other values ($\theta = 66.5°$, 90°, and 113.5°). For each θ value, it is possible to define a set of tetrahydropyran conformations differing by 30° steps in the φ angle. In the Equatorial line ($\theta = 90°$), there is an alternating sequence of boat and twist (or skew-boat) conformations, while both *Tropical lines* ($\theta = 66.5°$ and 113.5°) are characterized by an alternating sequence of half-chair and envelope geometries. Overall, this globe defines a total of 38 energetically possible *'canonical' conformations:* two chairs, six boats, six twists, twelve half-chairs, and twelve envelopes[7]). In theory, there is also a planar conformation (when $q = 0$), which, however, is energetically unrealistic.

[7]) Also for the conformations of six-membered rings, *IUPAC* recommends use of superscripts and subscripts to describe the atoms above and below the mean plane, thus providing an immediate image of the conformations. For an exhaustive description of all canonical geometries, see [88].

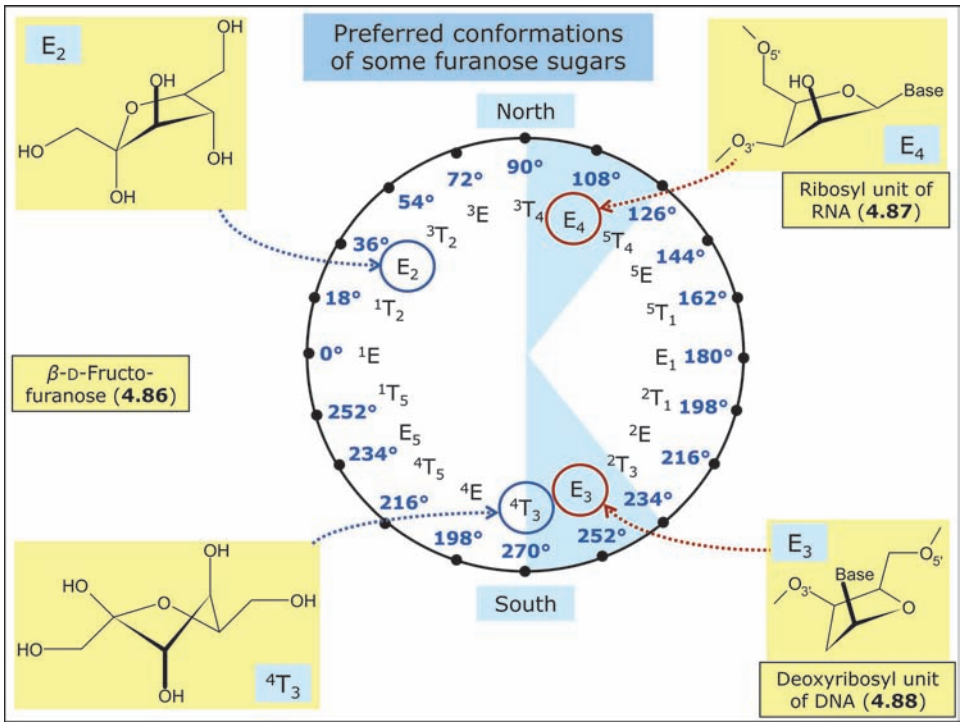


Fig. 4.41. In the previous *Figures*, the major tetrahydropyran and tetrahydrofuran conformers were described by ring-puckering descriptors regardless of their *energy profile*. Nevertheless, it is clear that there are only a limited number of favored conformations for each ring system depending on both its substituents and environment. In particular, the preferred geometries of a given sugar ring are affected by the various interactions that its OH groups can elicit, thus resulting in a significant puckering variability. Such a conformational versatility plays a critical role in the transition states found along the reaction paths catalyzed by several enzymes and influences the conformational behavior of all *biopolymers* including sugar units (*e.g.*, polysaccharides and nucleic acids) [89a]. On extensive review on the conformational analysis of furanosides has been published very recently [89b].

Regarding *furanose sugars*, the *Figure* depicts the example of *β*-D-*fructofuranose* (**4.86**) which mostly assumes E_2 geometries. These are stabilized by several intramolecular H-bonds and allow the anomeric OH group to be maintained in the axial positions. In contrast, the *β*-D-fructofuranosyl moiety in crystalline sucrose adopts the $^4T_3$ twist form, illustrating the marked influence environment can have on sugar conformation [90].

A noteworthy application to conformation issues in furanoses is exemplified by nucleic acids in which the different puckerings of the *ribosyl unit in RNA*, **4.87**, and the *deoxyribosyl unit in DNA*, **4.88**, influence the overall folding of RNA and DNA helices. As evidenced by the reported pseudorotation cycle, very few of the possible furanose conformations are allowed energetically in nucleic acids. In particular, the conforma-

tions assumed by the ribosyl and deoxyribosyl units are confined to well-defined regions about E_4 (*North-type conformations*) and E_3 (*South-type conformations*), respectively [91]. The two conformations have a marked influence on the distance separating two adjacent phosphate groups, which is significantly lower in the E_4 (North-type) geometries (5.9 Å *vs.* 7.0 Å). This structural difference, in turn, causes RNA to adopt a more folded conformation (the so-called '*A-type helix*') when compared to the more extended conformation preferentially assumed by DNA (the so-called '*B-type helix*'; see *Part 3*). Note, however, that DNA can also assume A-type conformations as, for example, in the transient DNA–RNA hybrids that occur during transcription [92]. Interestingly, the conformations that sugars assume in nucleic acids are significantly different compared to those observed for other furanose sugars in solution. This difference is due to the fact that the sugar puckering in nucleic acids is strongly influenced by the base (purine or pyrimidine) substituent, while the anomeric effect plays a key role in influencing the conformation of the free furanoses.

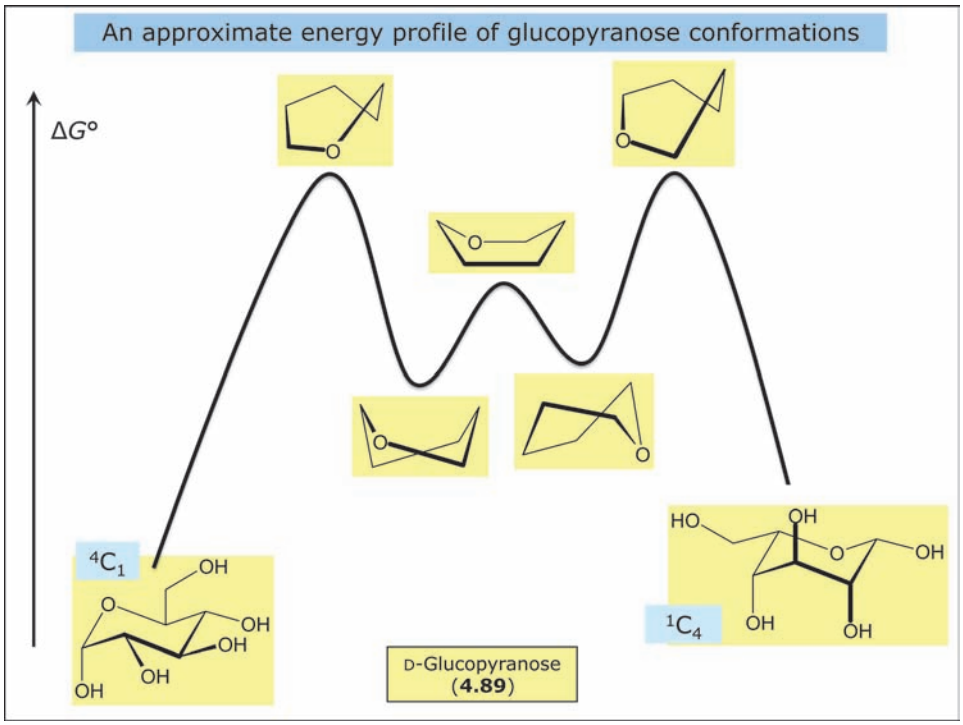


Fig. 4.42. This *Figure* offers an artist's view of the energy profile for the D-*glucopyranose ring* (**4.89**), emphasizing that the relations between free-energy profile and ring puckering are necessarily more complex than those of ribose [93][94]. A first consideration is that the two chair conformers differ in their free-energy value, the $^4C_1$ conformer being the preferred one. Such a difference may be due to the anomeric effect, since in this geometry the OH group at the anomeric center is in its favored axial

position, while, in the other chair $^1C_4$ geometry (located at the South Pole), it is shifted to a disfavored equatorial position. Interestingly, the anomeric effect is not restricted to chair conformers but influences the right part of the energy profile which is characterized by conformations where the OH group at the anomeric C-atoms occupies axial or pseudoaxial positions. Other factors that favor the $^4C_1$ geometry include *a*) the *Hassel–Ottar* effect which operates when the $HOCH_2$ moiety is not surrounded by other OH groups on the same side (*syn-axial* or *syn-equatorial*), *b*) the Δ2 effect which accounts for the repulsion between vicinal *gauche* OH groups, and *c*) intramolecular H-bonds [95].

Furthermore, the *Figure* shows a putative pathway connecting the two chair conformers[8]) and underlines an energy ranking (envelope > boat > twist > chair) common to most six-membered saturated rings, even though it can be vastly affected by the environment. For example, recent studies showed that cellobiohydrolase I, an enzyme involved in the hydrolysis of cellulose polysaccharides, induces changes in D-glucose puckering by stabilizing ^4E and $^4H_3$ conformations in its catalytic cavity. Allegedly, such a conformational rearrangement drives the substrate toward the transition state of the hydrolysis reaction [97].

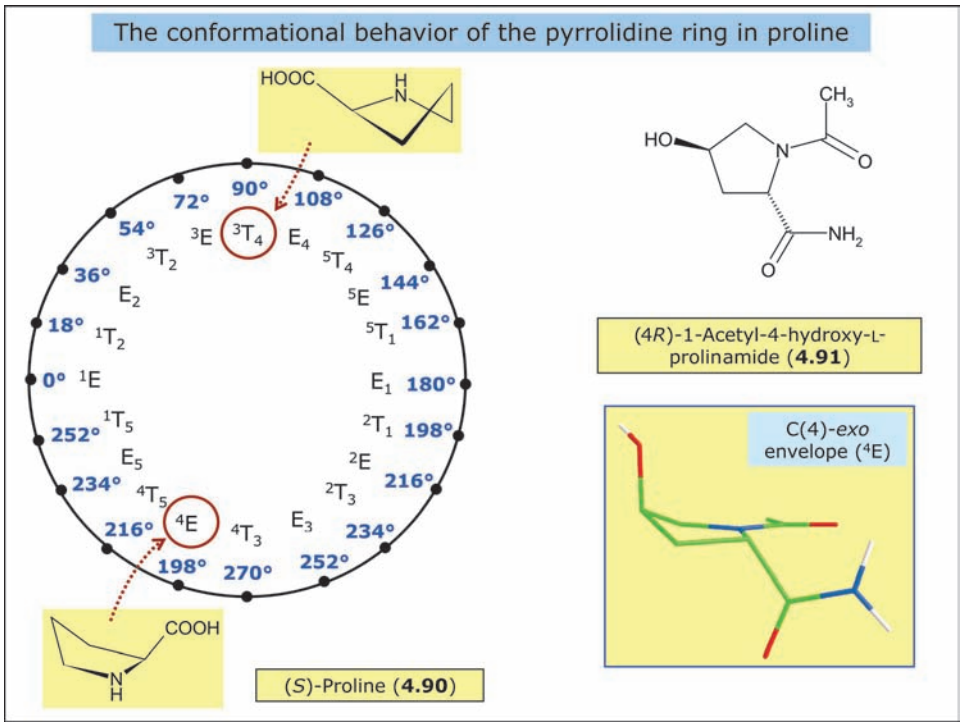


Fig. 4.43. The previous *Figures* outlined some remarkable applications of the puckering concept in describing and classifying *sugar conformations*. Here, we turn our

[8]) Also, the pathways connecting the favored conformations of D-glucopyranose are clearly influenced by solvent and other conditions; all possible trajectories were schematically represented by *Stoddart* in a 2D scheme known as *Stoddart*'s diagram [96].

attention to the utility of this concept in protein folding, in which the pyrrolidine ring in *proline* (**4.90**) plays a marked role. In proline, the pseudorotation cycle of the pyrrolidine ring features an equilibrium between two predominant forms, namely the C(4)-endo *twist* ($^3T_4$) and the C(4)-*exo* envelope (^4E) conformers, also referred to as 'down' and 'up', respectively [98]. In unsubstituted proline, its twist form is the preferred one, while in proteins adjacent residues can influence its puckering propensity. In detail, the main factor controlling pyrrolidine puckering within proteins is the arrangement of the vicinal peptide bonds. Indeed, peptide bonds with (*E*)-conformation (see *Figs. 4.22* and *4.23*) favor the C(4)-*exo* envelope (^4E) over the twist C(4)-*endo* ($^3T_4$) geometry, while the latter is the preferred conformation with peptide bonds with (*Z*)-conformation. The pathways connecting the two favored geometries depend on the molecular environment and often involve a transitional envelope, although planar geometries can also be encountered in these itineraries. Thus, specific protein environments can stabilize transitional geometries rather than the canonical up and down forms, and indeed a recent analysis on 241 PDB proteins revealed the presence of 65 planar conformations out of the 2197 monitored prolines [99].

A detailed analysis of proline residues in crystalline protein structures revealed no clear puckering preference between up and down geometries. An exception was *hydroxyproline* as found in polyprolyl chains where the pyrrolidine ring preferentially assumes envelope geometries. This is shown here with *(4*R*)-1-acetyl-4-hydroxy*-L-*prolinamide* (**4.91**) as a model molecule of 4-hydroxyprolyl residues in proteins. In other words, pyrrolidine conformation in such residues is not affected statically by protein folding, but assists dynamically backbone conformational changes such as (*Z*/*E*)-isomerization, with a clear interdependence between phase angle and backbone torsions [100].

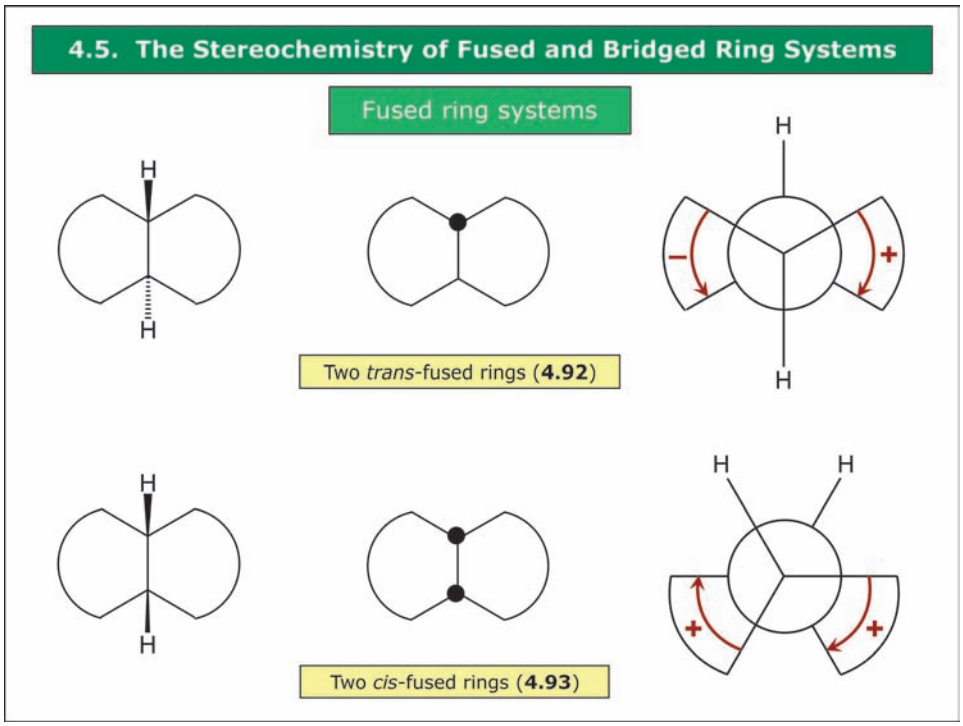


Fig. 4.44. We now come to the last section in this *Part* and deal with the *stereochemistry of cyclic systems containing two or more fused or bridged rings*. Two fused rings have the property of sharing two endocyclic atoms, as opposed to bridged rings which have more than two common atoms [8–16][18][19].

Configurational and conformational aspects both play important roles in the stereochemistry of fused bi- and polycycles. Thus, configurational isomerism results from the fusion of two alicyclic rings. Considering first the general case of two rings of undefined size, it can be seen that the two angular H-atoms can be either *trans*, **4.92**, or *cis*, **4.93**, relative to each other. The two stereoisomeric molecules resulting from either a *trans* or a *cis* fusion may be represented in different ways as shown; replacing an '*up*' bond and its H-atom with a full dot is not favored by the *IUPAC* [8] but may be useful at times. The application of the torsion angle concept to describe *cis*- and *trans*-junctions will be presented in *Fig. 4.46*.

The two C-atoms engaged in ring fusion (*i.e.*, at *valley positions*) may be symmetrically or dissymmetrically substituted depending on the symmetry properties of the molecule. In other words, they may or may not be stereogenic centers depending on the rest of the molecule. But in either case, the cis/trans *diastereoisomerism* displayed by bicyclic fused systems is comparable to cases of disatereoisomerism in disubstituted carbocycles (*Figs. 4.31–4.33*) and does not involve new stereochemical principles.

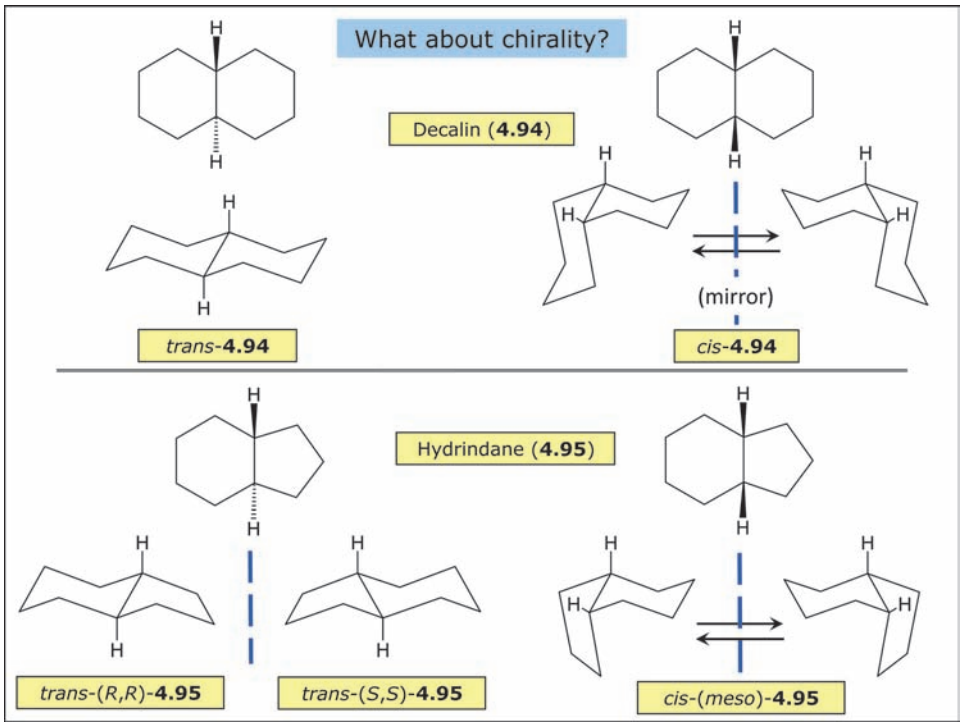


Fig. 4.45. The stereochemical aspects of fused rings systems are not limited to configurational diastereoisomerism, but may also cover configurational and even conformational enantiomerism. Taking *decalin* (= decahydronaphthalene; **4.94**) as an example, this compound occurs as two *configurational diastereoisomers*, namely *trans*-decalin and *cis*-decalin, which differ in their *conformational behavior*. If we consider only the low-energy chair-chair conformations and not the higher-energy boat-chair and boat-boat forms, it has been shown that *trans*-decalin is conformationally rigid. In contrast, *cis*-decalin occurs as two *enantiomeric conformers* separated by a barrier of reversal of *ca.* 50 – 60 kJ/mol [101]. If, in decalin, either ring is considered as substituent of the other, the *trans*-isomer displays a diequatorial pattern, whereas the *cis*-isomer is axial-equatorial. Also, the latter differs from the former by three *gauche n*-butane interactions. *cis*-Decalin, therefore, has a higher energy content than *trans*-decalin.

Hydrindane (= octahydro-1*H*-indene; **4.95**) is an interesting molecule because it results from the fusion of two rings of different size, and also because it represents a portion (rings *C* and *D*) of the *steroid nucleus* to be presented later. The dissimilarity of the two rings causes the two C-atoms engaged in ring fusion to be stereogenic. Since they carry identical ligands, the molecule will occur as two stable *trans*-enantiomers and a *meso*-isomer. As with the decalins, the *trans*-hydrindanes are conformationally rigid molecules, whereas *cis*-hydrindane is flexible and occurs as a pair of *enantiomeric conformers*. The free energy of activation of the ring reversal is *ca.* 25 – 30 kJ/mol [71][102].

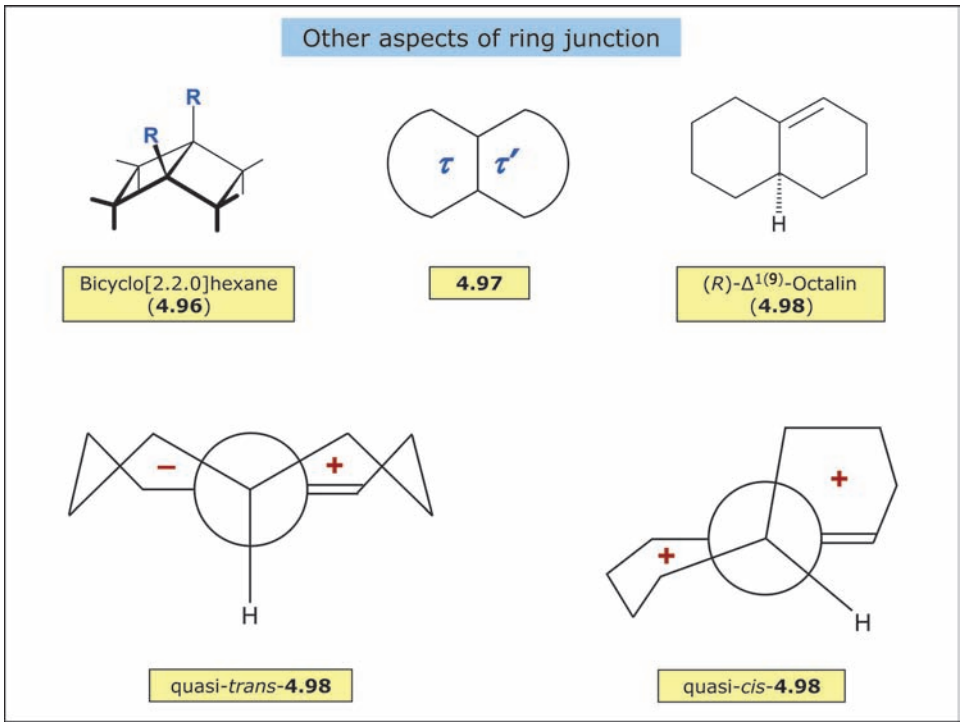


Fig. 4.46. An important point to note is that the *cis*/*trans*-isomerism resulting from ring fusion is impossible on steric grounds for the smallest rings (three- and four-membered). Thus, only the *cis*-form of *bicyclo[2.2.0]hexane* (**4.96**) is known, the *trans*-junction being rendered prohibited by steric strain [65].

The *concept of torsion angle* can be gainfully used to describe the stereochemistry of ring junction [68]. A ring fusion can thus be defined by two torsion angles of junction (τ and τ'), *i.e.*, the torsion angle of each ring with the common bond taken as the central bond (**4.97**). This application has been anticipated in *Fig. 4.44* which shows a *trans*-junction, characterized by two torsion angles of opposite signs, while a *cis*-junction is characterized by two positive signs.

Here, we extend this application to the case of a ring junction involving a trigonal C-atom, as exemplified by one of the positional isomers of *(*R*)-Δ1(9)-octalin* (=(4a*R*)-1,2,3,4,4a,5,6,7-octahydronaphthalene; **4.98**). This molecule has one stereogenic C-atom (the tetrahedral C-atom engaged in ring fusion) and is chiral. The conformational flexibility of the molecule allows its occurrence in two *distinct groups of conformers*, as shown. Those having torsion angles of junction of opposite signs are termed quasi-*trans* by analogy with examples presented earlier. When the torsion angles are of same sign, the conformers are designated as quasi-*cis*. The latter appear of slightly higher energy than the former due to the marked opening of the τ' angle [68].

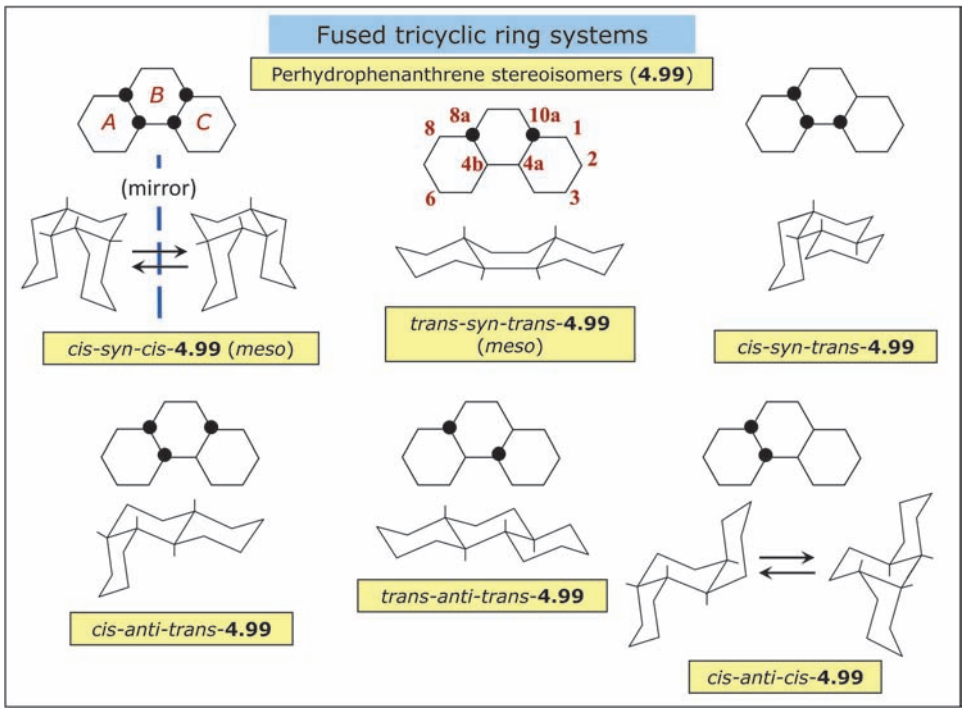
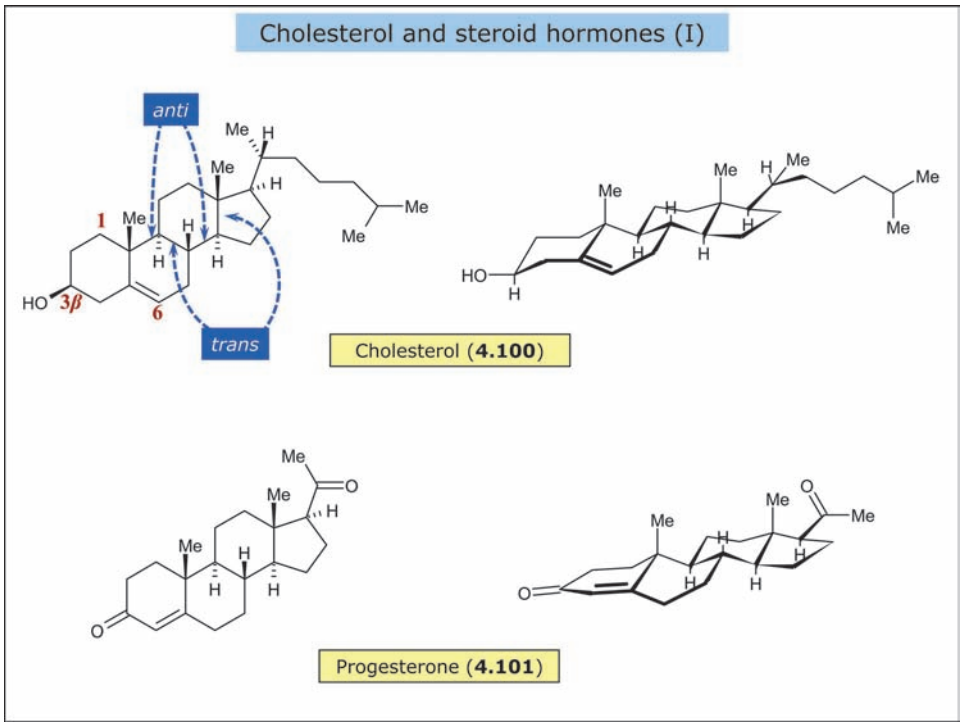


Fig. 4.47. *Fused tricyclic systems* must be considered from two viewpoints, namely the relationship between two adjacent (fused) rings, and the steric relationship between the two non-adjacent (external) rings. Perhydrophenanthrene (**4.99**) is an interesting model compound of great stereochemical richness. Four *stereogenic centers* are apparent (4a, 4b, 8a, 10a, *i.e.*, the C-atoms involved in ring fusion) and the molecule occurs as ten *stereoisomers* (*two* meso-*forms* and *four pairs of enantiomers*). The fusion of rings *A* and *B*, and that of rings *B* and *C*, are described by the same *cis-trans* notation discussed above. The relation between rings *A* and *C* is described by considering the relative position of the H-atoms at C(4a) and C(4b). The prefixes *syn* and *anti* are used when these H-atoms are on the same or opposite side, respectively; the terms *cisoid* and *transoid*, respectively, are also allowed [8]. The two *meso*-forms are the *cis-syn-cis*- and *trans-syn-trans*-isomers, since a plane of symmetry is evident. The four other forms are chiral, only one enantiomer per pair being shown [10].

The relative energy of perhydrophenanthrene stereoisomers is best discussed when considering the *preferred conformations* and their number of equatorial and axial bonds at the C-atoms engaged in ring fusion. The isomer of lowest energy is thus the *trans-anti-trans*-form which has *four equatorial bonds*. Isomers of higher energy (*ca.* 12 kJ/mol) are the *cis-syn-cis*- and *cis-anti-trans*-forms (*three equatorial* and one axial bond). Two isomers have *two equatorial* and two axial bonds (*cis-syn-cis*- and *cis-anti-cis*-form), while the isomer of highest energy is the *trans-syn-trans*-form in which the central ring is forced to a boat conformation.

The isomers of perhydrophenanthrene having no or just one *cis*-junction are *conformationally rigid*; two *cis*-junctions render the molecule flexible. As a result, the *cis-syn-cis*-form is a mixture of *two enantiomeric conformers*, while the *cis-anti-cis*-form undergoes isomerization between *two diastereoisomeric conformers*.



Figs. 4.48 and 4.49. These two *Figures* illustrate an important biochemical and pharmacological application of the stereochemistry of fused rings. On the left, they show the 2D structure of the compounds to be discussed, whereas *perspective drawings* are presented on the right-hand-side.

The endogenous compounds to be discussed are known as steroid hormones, and they are derived from *cholesterol* (= 3β-cholest-5-en-3-ol; **4.100**) [103][104]. The skeleton of this compound is known as *cholestane* and contains 27 C-atoms, namely the tetracyclic gonane skeleton, the C(18)H_3 and C(19)H_3 (*i.e.*, Me(18) and Me(19)) groups, and a side chain of eight C-atoms. The point of interest in our context is the tetracyclic system and its configuration. In this conventional representation, the substituents can point either upward or downward, these positions being known as β or α, respectively, a notation that, under such conditions, describes *absolute configurations.*

There are four ring junctions in cholesterol which can be described by the *cis-trans/syn-anti* convention, as shown. The same is true for the female gestagen hormone *progesterone* (**4.101**) and the male hormone *testosterone* (**4.102**). In contrast, the highly active testosterone metabolite *5α-dihydrotestosterone* (**4.103**) features five such junctionmodes which are described as *trans-anti-trans-anti-trans.* Because the *A* ring in *17β-estradiol* (**4.104**; a female estrogen hormone) is aromatic, there are only three junction modes to consider in this molecule, and these are *trans-anti-trans.* The saturated six-membered rings in these molecules are in a chair conformation, implying that their substituents can be located in an axial or equatorial position. Six-membered rings containing one C=C bond, or one or more C_{sp^2}-atoms adopt more flattened con-

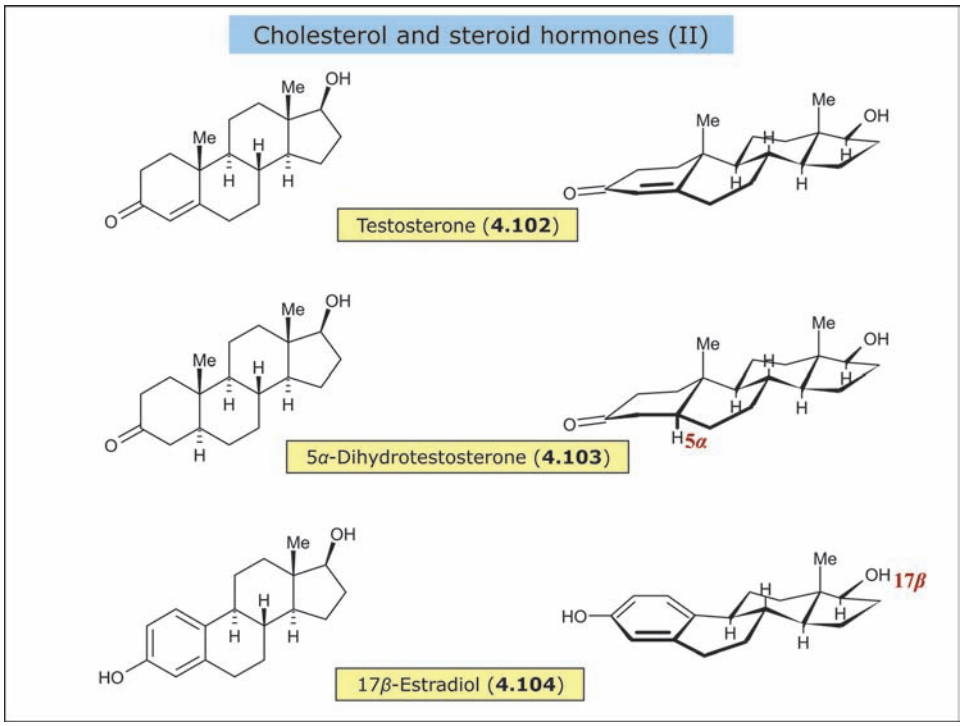
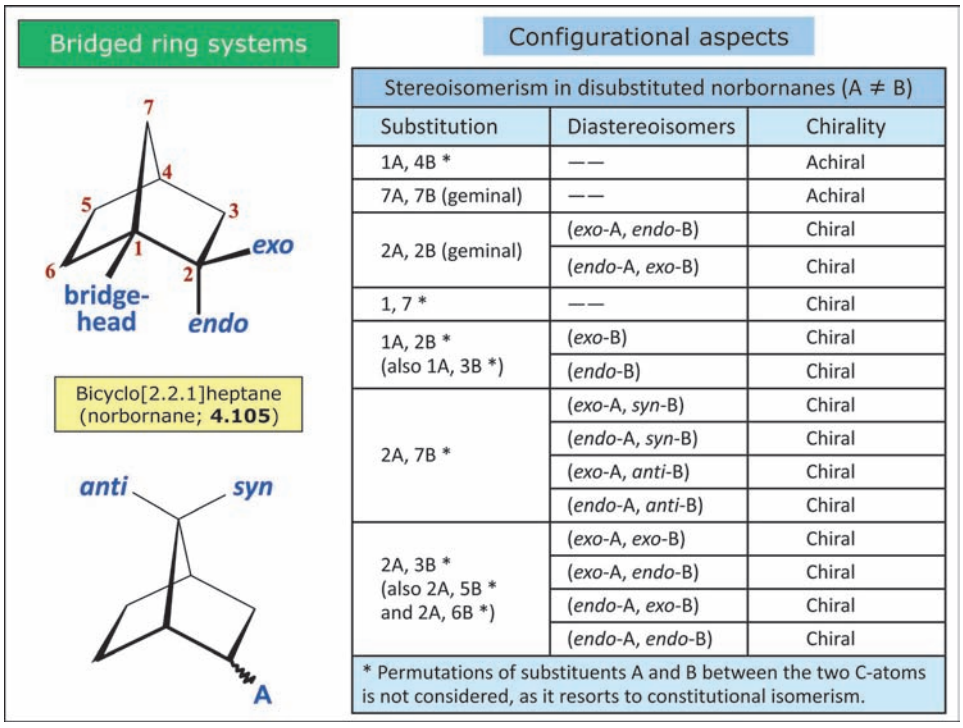


Fig. 4.49.

formations. The cyclopentane ring in these steroids (ring *D*) occurs in a half-chair or open-envelope conformation. All these stereochemical features are critical in the recognition of the compounds by their receptors and enzymes. In addition, we can conclude from the above that the biosynthetic pathways of steroid hormones have evolved to produce the stereoisomers of lowest energy and highest rigidity.



Configurational aspects

Stereoisomerism in disubstituted norbornanes (A ≠ B)

Substitution	Diastereoisomers	Chirality
1A, 4B *	——	Achiral
7A, 7B (geminal)	——	Achiral
2A, 2B (geminal)	(*exo*-A, *endo*-B)	Chiral
	(*endo*-A, *exo*-B)	Chiral
1, 7 *	——	Chiral
1A, 2B * (also 1A, 3B *)	(*exo*-B)	Chiral
	(*endo*-B)	Chiral
2A, 7B *	(*exo*-A, *syn*-B)	Chiral
	(*endo*-A, *syn*-B)	Chiral
	(*exo*-A, *anti*-B)	Chiral
	(*endo*-A, *anti*-B)	Chiral
2A, 3B * (also 2A, 5B * and 2A, 6B *)	(*exo*-A, *exo*-B)	Chiral
	(*exo*-A, *endo*-B)	Chiral
	(*endo*-A, *exo*-B)	Chiral
	(*endo*-A, *endo*-B)	Chiral

* Permutations of substituents A and B between the two C-atoms is not considered, as it resorts to constitutional isomerism.

Fig. 4.50. As mentioned above, *bridged ring systems* are characterized by their rings being joined by more than two common atoms [8][12]. In medicinal chemistry and other fields of chemistry, bridged ring systems are often prepared as 'rigid' analogs of simpler cyclic or acyclic molecules. By blocking various functional groups in selected positions, they allow a rational approach to topology-dependent chemical, biochemical and pharmacological properties. Here, we look at some of their *configurational characteristics* using *norbornane* (= *bicyclo[2.2.1]heptane*; **4.105**) as example. This molecule appears as a cyclohexane ring forced in a strained boat structure by a methylene ($-CH_2-$) bridge. A substituent at C(2), C(3), C(5), or C(6) is designated as *exo* or *endo*, respectively, depending on its equatorial or axial position relative to the boat skeleton. The position of substituent at C(1) or C(4) is unequivocal and is designated as *bridgehead*.

There is considerable *configurational restriction* in norbornane and analogous systems [12]. Norbornane monosubstituted at C(1) or C(7) has a plane of symmetry and does not display stereoisomerism. When *substituted at C(2)*, norbornane has three stereogenic centers, but for steric reasons C(1) and C(4) behave as a single element of chirality. Four stereoisomers occur in this case, namely (+)- and (−)-*endo*, and (+)- and (−)-*exo*. In *disubstituted or polysubstituted norbornanes*, various possibilities arise from the non-identity of the positions C(7), C(1) *vs.* C(4), C(2) *vs.* C(3), and C(5) *vs.* C(6). The resulting stereochemical complexity of bridged ring systems is illustrated here with disubstituted norbornanes. The *Table* does not include positional isomers and distinguishes between cases of diastereoisomerism and enantiomerism; it is best understood by examining molecular models.

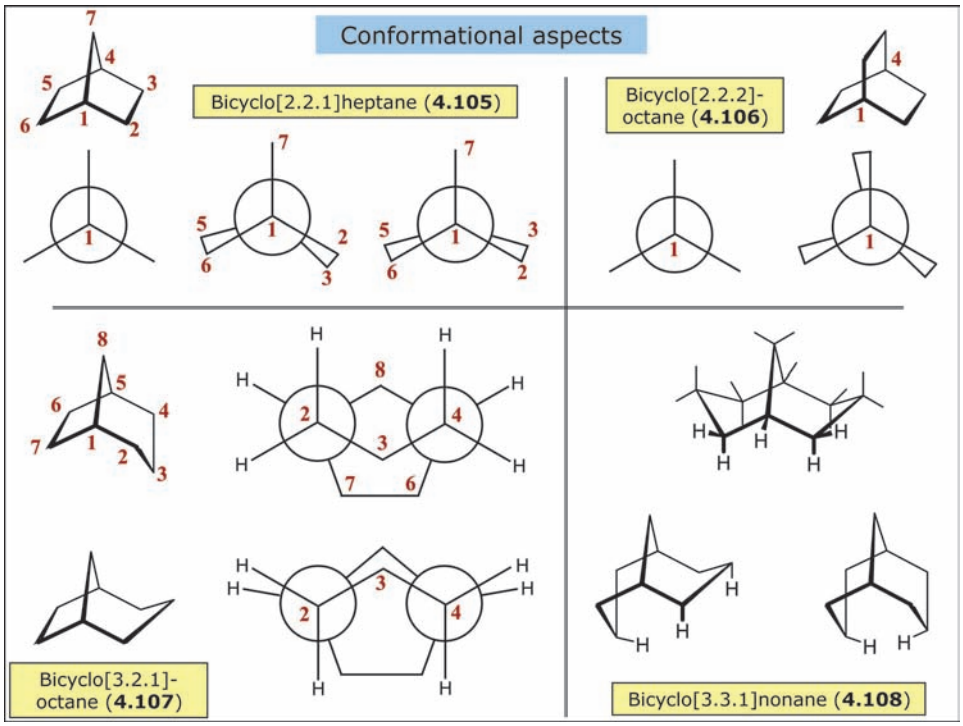


Fig. 4.51. The conformational rigidity of bridged systems mentioned earlier is a relative notion. Only the smaller, highly strained homologs are genuinely rigid, since, in these molecules, ring deformations originate only from vibrations in bond lengths and angles. A minor extent of conformational freedom is apparent in *norbornane* (**4.105**). This molecule has strict $\mathbf{C}_{2v}$ symmetry, but variously substituted derivatives occur in twisted conformations, as represented in the two projections shown [71][9]). Although the measured angles of twist are minor (some degrees), they imply that a slight distortion of the $\mathbf{C}_{2v}$-conformer requires little energy.

Bicyclo[2.2.2]octane (**4.106**) in its totally eclipsed form has $\mathbf{D}_{3h}$ symmetry. The molecule possesses a broad energy minimum for twisting around the C(1)–C(4) axis [60][105]. The resulting twisted conformer and its enantiomeric form have $\mathbf{D}_3$ symmetry, with also a modest angle of twist (7° to 15°), and they are favored over the totally eclipsed form by only a fraction of 1 kJ/mol.

As compared to the above molecules, conformational freedom is increased in *bicyclo[3.2.1]octane* (**4.107**), *bicyclo[3.3.1]nonane* (**4.108**), and similar compounds [60][106][9]). For example, the chair-chair conformer in bicyclo[3.3.1]nonane is favored over the boat-boat form by *ca.* 6 to 10 kJ/mol.

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[9]) The projections of bicyclo[2.2.1]heptane (**4.105**) and bicyclo[2.2.2]octane (**4.106**) resemble *Newman* projections, but differ from them in that the molecules are not viewed along an actual bond, but by placing the C(4)-atom just behind the C(1)-atom. Such projections, although non-conventional, can nevertheless allow an informative representation of intramolecular relations. In contrast, the projections of the two conformers of bicyclo[3.2.1]octane (**4.107**) are proper *Newman* projections along the C(2)–C(1) and C(4)–C(5) bonds.

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Received August 14, 2012