Chapter 2
Conformational Analysis of Monosaccharides

Molecules are dynamic assemblies of atoms chemically linked by single or multiple bonds. Hence, all atoms as well as groups of atoms are in perpetual motion, vibrating and rotating about chemical bonds. The deformation of chemical bonds due to vibration (stretching, wagging, etc.) of atoms is quantized and it is not the subject of conformational analysis. However, the rotation of atoms about the single bonds is the subject of conformational analysis.

Conformation of a molecule can be defined as a spatial arrangement of its atoms (or ligands) in a molecule that is obtained by free rotations about single bonds. Hence, the conformations are interconvertible by rotation about the single bonds.

When an atom that carries no substituent rotates about a single bond that links it to another atom, which does or does not carry a substituent, the rotation will not change the spatial arrangement of atoms in that molecule and therefore there will be no change in conformation due to rotation, as shown in Fig. 2.1 for molecules of hydrogen (*1*), chlorine (*2*), and water (*3*).

1 *2* *3*

Fig. 2.1

Hence, these rotations of atoms in a molecule are not the subject of conformational analysis.

The rotation of two atoms about a single bond that connects them will, however, result, in the course of time, in formation of many nonidentical spatial arrangements of atoms in a molecule, if both atoms carry at least one substituent. Each individual spatial arrangement of atoms or group of atoms in a molecule obtained *via* the free rotation is called the *conformation* of that molecule.

Thus, for example, in hydrogen peroxide (Fig. 2.2) the rotation of oxygen atoms about the oxygen–oxygen single bond could theoretically produce an "infinite" number of conformations. However, even though the hydrogen atom is very small, some conformations will be favored over the others because the rotational barrier is not small (1.1 kcal/mol [1, 2]). Various conformations of hydrogen peroxide in

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Fig. 2.2 are represented with the so-called "sawhorse" (perspective) formulas (upper raw) and with the so-called Newman′s projections (lower raw) (the relative position of the two hydrogen atoms is looked upon along the oxygen–oxygen bond). It was found by millimeter-wave spectroscopy [3] and by ab initio calculation [4] that the gauche coformation *6* is the favored conformation (dihedral angle between the hydrogens is ca. 120°).

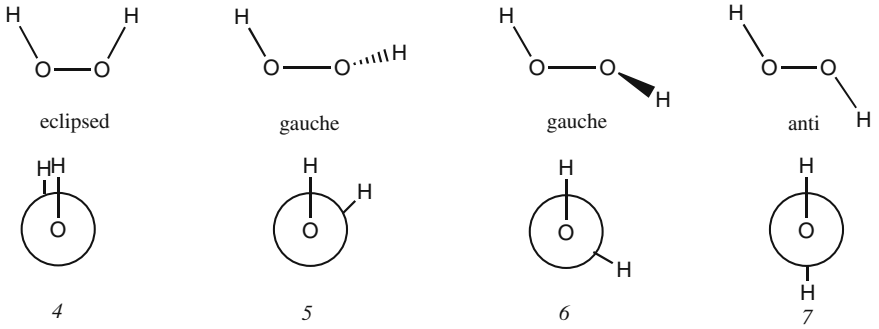


Fig. 2.2

Conformational Analysis of Acyclic Hydrocarbons

The rotation of two methyl groups of ethane about the C–C single bond (Fig. 2.3) should theoretically produce also an "infinite" number of conformations if the rotation about the C–C bond was completely free. However, due to a nonbonded interaction between the hydrogen atoms on two adjacent methyl groups (known as

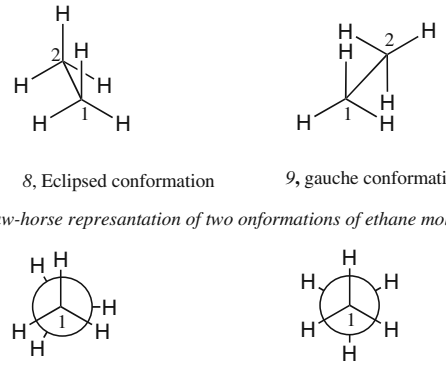
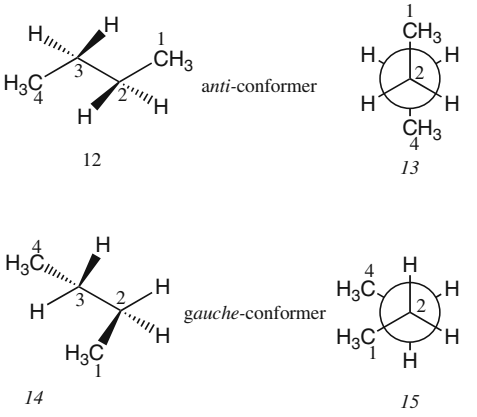


Fig. 2.3

torsional or *Pitzer strain* [1]) the rotation about the C–C bond in ethane molecule is not completely free [3] because in the *eclipsed* conformation the interaction between the hydrogen atoms is larger (ca. 2.89–2.93 kcal/mol [1–8]) than in the *gauche* conformation, since the inter-atomic distance between the vicinal hydrogen atoms of the two neighboring methyl groups in eclipsed conformation (torsional angle 0°) is significantly shorter (2.26 Å) than in the gauche conformation (torsional angle 60°) (2.50 Å). Since the conformational energy of *8*, *10* is higher than that of *9*, *11* the *gauche* conformation will be preferred in the conformational equilibrium mixture of ethane. In Fig. 2.3 only two conformations of ethane molecule are shown – the least stable *eclipsed* conformation (*8* and *10*) (it has the highest internal energy of all possible ethane conformations because the hydrogen atoms are closest to each other) and the most stable *gauche* (*9* or *11*) conformation because it has the lowest internal energy of all possible ethane conformations (the hydrogen atoms are at the greatest distance from each other).

It should be, however, noted that the steric (van der Waals) interactions actually account for less than 10% of the rotational barrier in ethane, since the hydrogen atoms of two methyl groups are barely within the van der Waals distance. Electrostatic interactions of the weakly polarized C–H bonds are negligent, too. The principal interaction responsible for the rotational barrier in ethane is, according to Pitzer [9], the overlap resulting in repulsion [10] of bond orbitals in the eclipsed conformation; changes in electronic structure other than those required by the changes in C–H bond overlaps are of minor importance for the existence of the barrier [9]. The existence of rotational barrier in ethane, according to Bader et al. [11] is explained by the increase of the C–C bond length during the transition from the gauche (staggered) conformation to the eclipsed one; this increase is more than 10 times larger than the accompanying decrease in the C–H separation.



12 13

14 15

Fig. 2.4

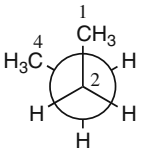
When two carbon atoms linked by a single bond carry larger atoms or group of atoms as substituents, then the conformational energy difference of *gauche* and

eclipsed conformations becomes much larger. This difference becomes even greater if substituents are polar or if they are even electrically charged, because in addition to the nonbonded (van der Waals) interactions there now will also be present dipolar and/or electrostatic interactions between the neighboring substituents.

Since, it is well established that molecules tend to assume their most stable conformations in which the magnitude and the number of unfavorable stereoelectronic interactions are at the minimum, then all possible *eclipsed* conformations may be safely eliminated from discussions because they will not be present in conformational mixtures in significant amounts to influence the chemical behavior of a given molecule.

It should be pointed out that of all possible *gauche* conformations there is only one in which the dihedral angle between the two largest substituents is 180°. This conformation is called *anti* or antiperiplanar [12] (*ap*) conformation and is always the preferred conformation.

This is now a good place to briefly describe Klyne–Prelog proposal [12] for describing the stereochemistry across a single bond in terms of torsional angle, τ, between the ligands such as, for example, between the two methyl groups in *n*-butane. When $\tau = 60°$ the conformer is *gauche* (*staggered* or *skewed*) but according to Klyne–Prelog proposal it is either ±*syn*-clinal (±sc) *(16*, *17*) or ±*anti*-clinal (±ac)(*18*, *19*) (Fig. 2.5). When torsional (dihedral) angle between the two methyl groups is between +30° and +90° the conformer is +*syn*-clinal (+sc), and if it is between –30° and –90°, the conformer is –*syn*-clinal (–sc). When the torsional (dihedral) angle between the two methyl groups is between +90° and +150° the conformer is +*anti*-clinal (+ac) and if it is between –90° and –150° the conformer is –*anti*-clinal (–ac). When torsional angle between two methyl groups is between



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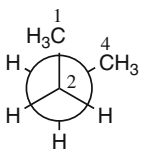

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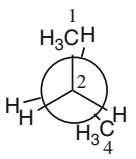

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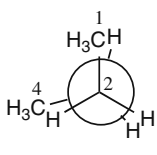

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–*syn*-clinal conformer + *syn*-clinal conformer + *anti*-clinal conformer –*anti*-clinal conformer

All four conformers are *gauche*, *staggered*, or *skew* conformers

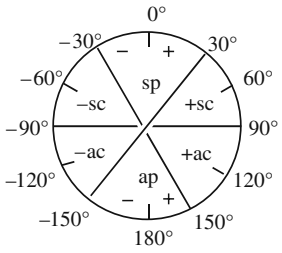

Fig. 2.5

–30° and +30° the conformer is ±*syn*-periplanar (±sp) and if it is between –150° and +150° the conformer is ±*anti*-periplanar (±ap). When torsional (dihedral) angle between two methyl groups is 0° the conformer is eclipsed and when the torsional (dihedral) angle between two methyl groups is 180° the conformer is *trans* or *anti*.

In aliphatic hydrocarbons, such as *n*-butane, for example, where only steric (van der Waals) interactions are involved, the *anti*-conformer is significantly preferred, over the *gauche* conformers, since the two methyl groups (the largest substituents on the C2 and C3 carbon atoms) are furthest apart (Fig. 2.4). The *anti*/*gauche* conformer ratio in *n*-butane is, at room temperature, almost 2:1 as determined by NMR spectroscopy.

Consequently, the polymethylene hydrocarbons tend to adopt planar *zigzag* conformation in which all carbon atoms lie in one plane (Fig. 2.6). In this conformation, all carbon atoms (the largest "substituents" in *n*-butane subunits) are in the *anti*-orientation (C1–C4, C2–C5, C3–C6, etc.). The small 1,3-nonbonding interactions between the hydrogen atoms (C_2H-C_4H, C_3H-C_5H, etc.) are the only destabilizing interactions. Unlike the acyclic hydrocarbons, each carbon atom of an acyclic monosaccharide has in addition to a hydrogen atom one large substituent which is most often hydroxyl group, but it can also be an amino, thio, or other group or an atom. In this case, if the acyclic form of a carbohydrate adopts the *zigzag* conformation then depending on a monosaccharide one or more 1,3-nonbonded interactions are possible between two larger ligands (oxygen atoms, for example).

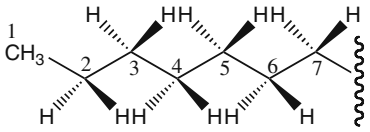

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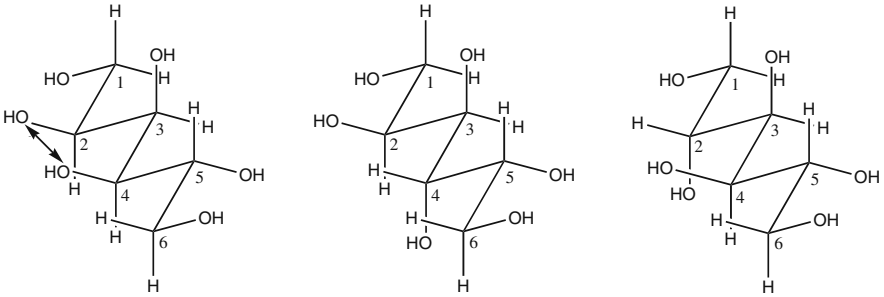
Fig. 2.6

Conformational Analysis of Acyclic (Aldehydo) Forms of Monosaccharides

The conformation of acyclic aldehydo sugars cannot be studied in solutions due to their spontaneous cyclization and formation of hemiacetals. However, derivatization of the C4 and the C5 hydroxyl groups (by alkylation or acylation) or derivatization of the aldehydo group of a monosaccharide (by formation of dialkylacetals or dialkyldithioacetals) prevents the hemiacetal formation permitting thus the conformational studies to be conducted in solution. To avoid derivatization the carbonyl group of a monosaccharide can simply be reduced with complex metal hydrides and the obtained sugar alcohol – *alditol* can then be used for conformational studies.

If D-glucitol (*21*), D-galactitol (*22*), and D-mannitol (*23*) (the alditols obtained by reduction of D-glucose, D-galactose, and D-mannose) are represented in their zigzag conformations (Fig. 2.7) it can be seen that only in D-glucitol there is one large 1,3-nonbonded interaction (both steric and dipolar) between the C2 and the C4 hydroxyl groups. This interaction destabilizes this conformation by 1.5 kcal/mol. In all three *zigzag* conformations there is present a number of much weaker 1,3-*syn*–axial interactions (we will explain the term "1,3-*syn*–axial interac-



21, D-Glucitol *22,* D-Galactitol *23,* D-Mannitol

Fig. 2.7

tion" when we discuss the conformational analysis of pyranoid forms of monosaccharides). In D-glucitol there are four 1,3-*syn*–axial interactions (two between the C3 oxygen and the C1 and C5 hydrogens, one between the C5 oxygen and the C3 hydrogen, and one between the C4 oxygen and the C6 hydrogen) that destabilize this conformation by additional 1.8 kcal/mol (one *syn*–axial interaction between an oxygen and hydrogen atom destabilizes the given conformation by 0.45 kcal/mol). In D-galactitol (*22*) there are six 1,3-*syn*–axial interactions between the oxygen and hydrogen atoms (two between the C3 oxygen and the C1 and C5 hydrogens, two between the C4 oxygen and the C2 and C6 hydrogens, one between the C5 oxygen and the C3 hydrogen, and one between the C2 oxygen and C4 hydrogen destabilizing this conformation by a total of 2.70 kcal/mol). In D-mannitol (*23*) there are also six such interactions present (one between the C2 oxygen and the C4 hydrogen, two between the C3 oxygen and the C1 and C5 hydrogens, two between the C4 oxygen and the C2 and C6 hydrogens, and one between the C5 oxygen and C3 hydrogen) destabilizing this conformation by 2.70 kcal/mol.

Unlike D-galactitol and D-mannitol, which in solution exist predominantly in planar *zigzag* conformation, as shown [13] by ^{1}H NMR spectroscopy and in crystalline state by X-ray crystallography [14–18] D-glucitol adopts the so-called *sickle* (bent) conformation [14], in which the C2 and the C5 carbon atoms are in the *gauche* rather than in the *anti*-orientation (Fig. 2.8), to avoid the destabilizing *syn*–axial interaction between the C2 and the C4 hydroxyl groups (*21* in Fig. 2.7).

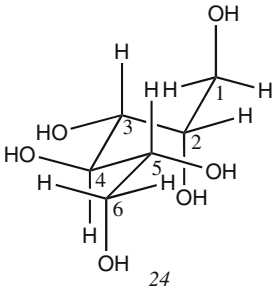


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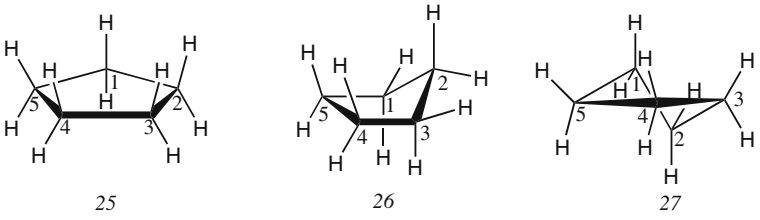
Fig. 2.8

Conformational Analysis of Cyclic (Lactol, Hemiacetal) Forms of Monosaccharides

Furanoses

The conformational analysis of furanoid forms of sugars is closely related to the conformational analysis of substituted cyclopentanes because they are both five-membered ring systems. For that reason we will start our discussion on conformational analysis of furanoid form of monosaccharides by briefly discussing the conformational analysis of cyclopentane first.

The cyclopentane can assume three distinct conformations: planar *25*, envelope *26*, and twist *27* conformation (Fig. 2.9), together with an infinite number of conformations that lie in the conformational interconversion path of cyclopentane.



25 planar *26* enevelope *27* twist

Fig. 2.9

The deviation of the endocyclic C–C bond angle of 108° in planar conformation of cyclopentane (*25* in Fig. 2.9) from tetrahedral valence angle of 109.5° of a carbon atom is relatively small (1.5°) and cannot have noticeable effect on the energy content of cyclopentane due to the Baeyer ring strain. Yet if one compares the heat of combustion per CH_2 group of acyclic hydrocarbons (157.5 kcal/mol) [19] and cyclohexane (157.4 kcal/mol) with that of cyclopentane (158.7 kcal/mol) it is

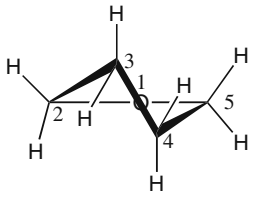
estimated that the energy content of cyclopentane is higher by 6–7 kcal/mol than that of both *n*-pentane or the five-carbon fragment of cyclohexane. Since this higher internal energy of cyclopentane cannot be related to Baeyer ring strain, it was suggested by Pitzer [20–22] that the energy content of cyclopentane must be due to sterically unfavorable arrangement of adjacent methylene groups. As can be seen from Fig. 2.9 in the planar conformation *25* all 10 hydrogen atoms are completely eclipsed as well as all five-ring carbons. If one accepts the value of ca. 1 kcal/mol as the magnitude of unfavorable interaction energy between two eclipsed hydrogen atoms in ethane molecule, the internal energy of the planar conformation of cyclopentane should be greater than 10 kcal/mol. However it is 6–7 kcal/mol suggesting that in order to minimize these destabilizing interactions the cyclopentane adopts a *puckered* (a nonplanar) conformation which can be either the *envelope 26* conformation (also called the C_2 conformation – named after the symmetry point group) or the *twist* conformation *27* (also called the *half-chair* or the C_s conformation – named after symmetry point group) (Fig. 2.9). By adopting the envelope conformation the total torsional strain is only 60% of total torsional strain of planar conformation because of the presence of only six pairs of eclipsed hydrogens. According to Pitzer the cyclopentane ring is puckered to such an extent that one carbon sticks out about 0.2 Å from the plane containing the other four carbon atoms [20, 21]. The more recent calculations [22, 23] have shown that the energy minimum of cyclopentane molecule is attained when one carbon atom takes up the position 0.5 Å out of plane containing the other four carbon atoms. The carbon atom protruding from the plane is not fixed in that position [20, 21] but it "rotates around the ring" by an up and down motion of all five methylene carbons; this motion has been termed "*pseudorotation*" the result of which is the adoption of an infinite number of intermediate conformations.

In twist conformation the three neighboring carbons lie in one plane, while the other two are twisted, one lies below and the other above that plane, and they are equidistant from the plane containing the other three carbons. Since the twist conformation has only four pairs of eclipsed hydrogen atoms the total torsional strain of this conformation is 40% of the torsional strain of planar conformation. Difference in energy between the envelope and the twist conformations is very small, the envelope form being more stable by 0.5 kcal/mol.

Puckering of cyclopentane ring has been experimentally confirmed (a) thermodynamically from entropy measurements [24–27] and (b) by electron scattering [28]. Since the puckering of cyclopentane ring is not fixed and the energy barrier for conformational inter-conversions via pseudorotation is small (less than 0.6 kcal/mol at room temperature) no definite conformational energy minima and maxima can be observed for cyclopentane.

Most of what is said for cyclopentane is applicable to the conformational analysis of tetrahydrofuran. Calculation on tetrahydrofurans suggests [22] that the molecule exists in *twist* (half-chair) form with the maximum puckering occurring at carbon atoms 3 and 4, away from the heteroatom (*28* in Fig. 2.10). The replacement of one cyclopentane carbon with an oxygen atom decreases the Pitzer strain but introduces additional Baeyer strain into the molecule because the valence

angle of oxygen atom is 104.45°, whereas the endocyclic valence angle of planar cyclopentane ring is 108°.



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Tetrahydrofuran in twist conformation

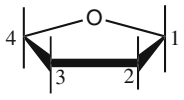
Fig. 2.10

The introduction of substituents into either cyclopentane or tetrahydrofuran dramatically limits the number of possible conformations that they may adopt due to the increase of energy barriers for conformational interconversions.

The proof that furanoses do exist in nonplanar conformations has been obtained from X-ray crystallographic studies as well as from NMR spectroscopy studies in solutions.

Depending on the nature and location of its substituents, the furanose ring was shown to adopt both the C_s and the C_2 conformation [29–33]. Bulky substituents are taking up the most staggered ("equatorial") position, at the most staggered carbon atom. The oxygen atom most likely takes up the least staggered position in the furanose ring. Lemieux [34] has discussed, in considerable depth, the conformational behavior of furanoses based on the assumption that they adopt the C_s conformations.

Nonbonded interactions between the *cis*-1,2-substituents on furanoid ring are relieved by puckering of a planar conformation to the C_2 conformation by displacing the C_2 or C_3 carbons from the plane containing the other four atoms [35–40] (Fig. 2.11) or to the C_s conformation (Fig. 2.10). Hence it may be concluded that E conformations with the C_2 or C_3 carbons displaced from the plane of the ring (i.e., ^2E, E_2, ^3E, E_3) are the most stable conformations (for instance, *31* corresponds to ^2E conformation). In addition, electronegative substituents at carbon atoms other than C_1 will prefer to take up quasi-equatorial or isoclinal orientations. The C_1 electronegative substituents will tend to assume quasi-axial orientation.



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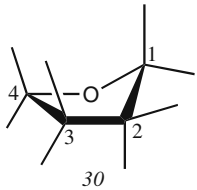

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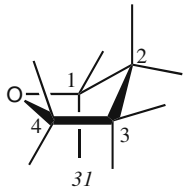

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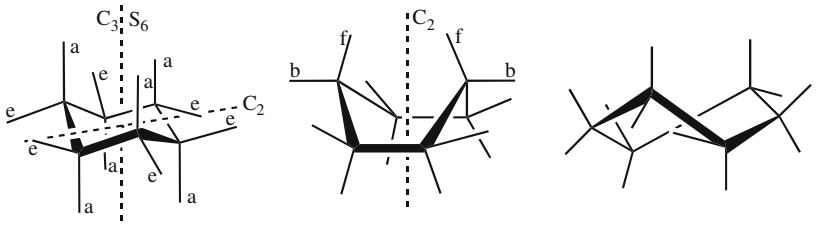
Fig. 2.11

The conformational analysis of furanoses is plagued by two insurmountable difficulties: (a) the flexible nature of the five-membered ring which is not allowing the accurate evaluation (or calculation) of interaction energies between the ring substituents and (b) difficulties in accurately determining the concentration of furanose forms in solutions at equilibrium.

Pyranoses

Although carbohydrate pyranoid rings are slightly flattened compared to cyclohexane rings and have no elements of symmetry, the conformational analysis of pyranoses is intimately related to the conformational analysis of cyclohexane. Therefore, we will begin our discussion of conformational analysis of pyranoses by briefly discussing the conformational analysis of cyclohexane first.



32 chair conformation

33 boat conformation

34 Skew-boat conformation

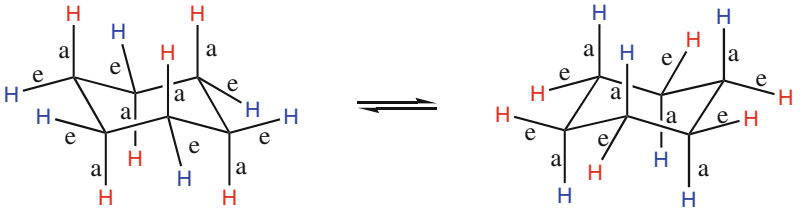
Fig. 2.12

Cyclohexane may exist in three distinct conformations (Fig. 2.12): *chair 32*, *boat 33*, and *twist-boat* (or *skew-boat*) *34* conformations. The *chair* conformation is relatively stiff and has the following elements of symmetry: C_3 axis of symmetry that coincides with the S_6 rotation–reflection axis of symmetry, three C_2 axis of symmetry, three planes of symmetry, and a center of symmetry. The *boat* conformation is flexible and has one C_2 axis of symmetry and two planes of symmetry, whereas the *skew-boat* (or *twist-boat*) *conformation* is flexible and has no symmetry elements.

Cyclohexane in chair conformation *32* has two geometrically different sets of hydrogens: six hydrogens are oriented parallel to the S_6 (that is also the C_3) axis of the molecule and are called *axial* (*a*) hydrogens and the six hydrogen atoms that alternate about the so-called "equatorial" plane that is a plane perpendicular to the S_6 (C_3) axis and are called *equatorial* (*e*) hydrogens. In the boat conformation (*33* in Fig. 2.12) there are two pairs of hydrogens that are very different from the other eight. These are the four hydrogens that are attached to two carbons that lie out of the plane of other four carbons of the boat conformation. The two hydrogens that point away from the ring and are almost parallel to the plane containing the four carbon atoms are said to be in *bowsprit* (*b*) orientation; the two hydrogens that are pointed toward the ring are said to be in *flagpole* (*f*) orientation. From other eight

hydrogens four are equatorial and the other four pseudo-axial. Although the boat conformation is free from Baeyer (ring) strain, there is eclipsing of eight hydrogen atoms that are part of the planar part of the six-membered ring causing elevated torsional strain; in addition to that there is also a severe van der Waals interaction between two hydrogen atoms in the *flagpole* orientation. As a result, the boat conformation is calculated to be 6.9 kcal/mol less stable than the chair conformation [41]. To avoid these unfavorable interactions the boat adopts the *skew-boat* conformation *34* by pseudo-rotation around its ring C–C bonds (Fig. 2.12). Its energy has been calculated to be 5.3 kcal/mol, i.e., 1.6 kcal/mol less than the boat conformation, but still 5.3 kcal/mol higher than the energy of the chair conformation.

Although relatively rigid, the cyclohexane *chair* conformation *35* is able to *flip* over to the alternate chair conformation *36*, as illustrated in Fig. 2.13. After flipping over, the hydrogen atoms of a cyclohexane that were axial (red in the left conformation) became equatorial and vice versa, the hydrogens that were equatorially oriented in the left conformation (blue hydrogens) became axial in the right conformation.



35 Interconversion of two alternate chair conformations *36*

Fig. 2.13

The interconversion of the two-cyclohexane chair conformations (*37* ⇌ *42*) (Fig. 2.14) involves the formation of a *half-chair conformation 38* in the transition state (first step), which (in the second step) collapses either into flexible twist-boat conformation (*39*, *40*) or back to the initial conformation *37*. The *twist-boat* conformation 39 is in dynamic equilibrium with the boat conformation *40*; in this conformational mixture the *twist-boat* conformation is at the energy minimum and the boat conformation is at the energy maximum (energy difference between these two forms is estimated to be 1.0–1.5 kcal/mol). The conversion of a *twist-boat* conformation into an alternate chair conformation *42* requires the formation of the corresponding alternate *half-chair* conformation *41* in the second transition state. Figure 2.14 illustrates the chair–alternate chair (*37* ⇌ *42*) interconversion via the half-chair *38* and alternate half-chair *41* transition state intermediates.

The activation energy of chair-to-chair interconversion (the barrier of the ring inversion in cyclohexane) has been experimentally determined by variable temperature NMR studies [42, 43] and calculated by force field method [42, 44, 45]. The obtained $\Delta G^{\#}$ values for the barrier was found to vary from 10.1 to 10.25 kcal/mol at temperatures between –50 and –70°C. Calculated and experimentally determined values are in good agreement.

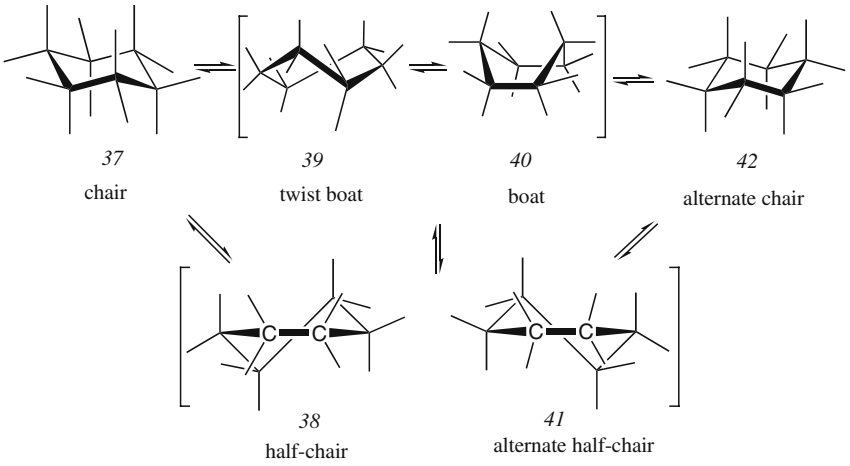


Fig. 2.14

Substitution of one hydrogen atom in cyclohexane with a "bulky" substituent dramatically changes the described situation. The most stable chair conformation of a mono-substituted cyclohexane is the one in which the substituent takes up the equatorial orientation.

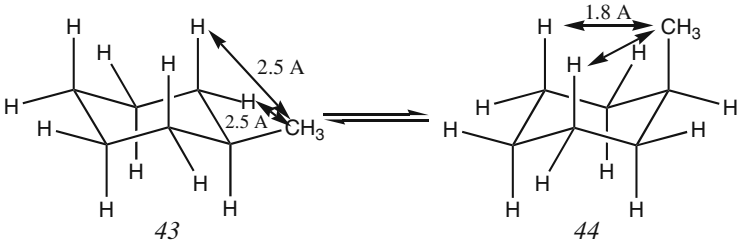


Fig. 2.15

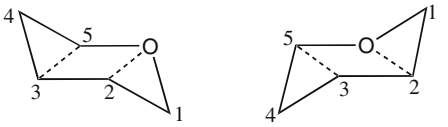
The reason for this is the unfavorable nonbonding interaction between the axial substituent and the two 1,3-*syn*–axial hydrogen atoms. For example 1,3-*syn*–axial interaction between an axial methyl group and the two axially oriented hydrogen atoms in methylcyclohexane (*44* in Fig. 2.15) is 1.6–1.8 kcal/mol suggesting that at conformational equilibrium (Fig. 2.15) the conformation having methyl group equatorially oriented (*43* in Fig. 2.15) will strongly predominate (*43*:*44* = 19:1; i.e., 95–5%). Disubstituted and polysubstituted cyclohexanes are even more restrictive in number of possible conformations.

Replacing one carbon atom of a cyclohexane ring with an oxygen atom, converting thus the cyclohexane to tetrahydropyran, introduces several very important changes. First, the six-membered ring of a pyranoid sugar is somewhat flattened compared to the cyclohexane due to the shorter C–O bond as compared to C–C

bond (1.43 Å vs. 1.53 Å, respectively) and due to the larger endocyclic C–O–C valence angle (112–114°) as compared to C–C–C valence angle (109°) of cyclohexane. Consequently the nonbonding interactions in pyranoid forms of sugars are slightly different than in cyclohexane. Second, the chair conformers of pyranoid rings are asymmetric. Third, for all pyranoid forms of sugars two distinct chair conformations are possible whereby very often one is much more stable than the other.

When describing various pyranoid conformations the following conventions are commonly used:

1. Conformations are designated: C, for the chair, B for the boat, S for the twist-boat, and H for the half-chair conformation.
2. A reference plane must always be chosen so that it contains four of the ring six atoms. If an unequivocal choice is impossible, as with the chair and twist-boat conformers, the reference plane is chosen so that the lowest numbered carbon in the ring is displaced from this plane.
3. Ring atom(s) that lie(s) above the reference plane (numbering clockwise from above) is/are written as superscript(s) and precede(s) the letter designating the conformation, while the ring atom(s) that lie(s) below the reference plane is/are written as subscript(s) and follow the letter designating the conformation.



45 $^4C_1$ conformation

46 $^1C_4$ conformation

Fig. 2.16

Thus as shown in Fig. 2.16, the reference plane for the two possible chair conformations of a pyranoid ring is chosen so that they contain O, C2, C3, and C5 atoms. When the C1 atom is below and the C4 atom above the reference plane the chair conformation is designated as $^4C_1$; when the C1 atom is above and the C4 atom below the reference plane, it is designated as $^1C_4$. Since enantiomeric conformers have different descriptors the $^4C_1$ (D) conformer is the enantiomer of $^1C_4$ (D) conformer. For this reason conformational descriptors should always be used in reference to either the D- or the L-series. This can be illustrated with the $^4C_1$ and $^1C_4$ conformers of methyl α-D- and α-L-ribopyranosides (*47* and *48*, respectively) (Fig. 2.17).

An alternative method to ascribe the descriptors $^4C_1$ and $^1C_4$ to two pyranoid conformers is as follows: when the atom numbering is clockwise (looking from the above) and the plane containing the C2, C4, and O5 (ring oxygen) is above the plane containing C1, C3, and C5 carbons, the ring conformer is $^4C_1$ (*49*); similarly, when the atom numbering is anticlockwise (looking from the above) and the plane

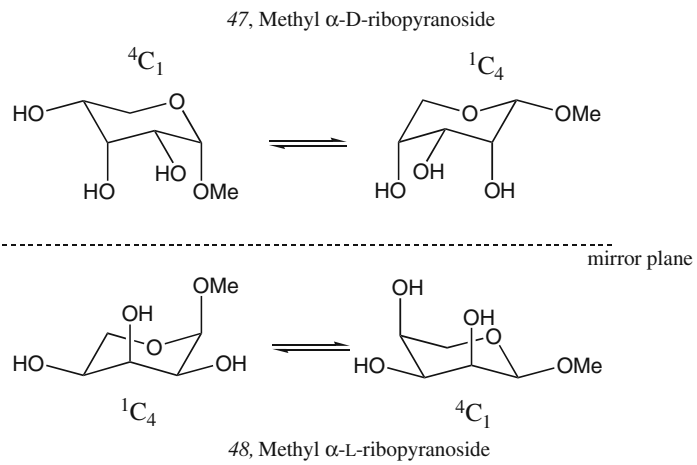


Fig. 2.17

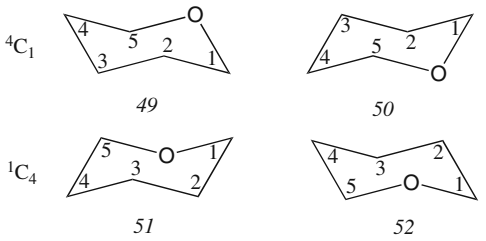
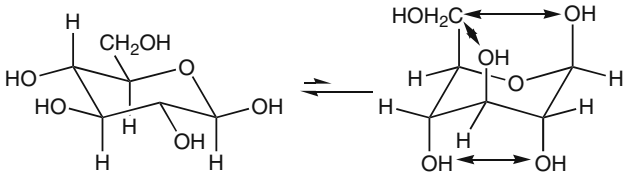


Fig. 2.18

containing the C2, C4, and O5 (ring oxygen) is below the plane containing the C1, C3, and C5 carbon atoms, the conformer is again $^4C_1$ (*50*). However, when the atom numbering is clockwise (looking from above) and the plane containing the C1, C3, and C5 carbon atoms is above the plane containing the C2, C4, and O5 (ring oxygen) the conformer is $^1C_4$ (*51*). The conformer is again $^1C_4$ (*52*), when numbering is anticlockwise and the plane containing the C1, C3, and C5 carbon atoms is below the plane containing C2, C4, and O5 (ring oxygen) (Fig. 2.18).

The hydroxymethyl group (the C6 carbon) of a hexopyranose will always assume the equatorial orientation because it is, as the largest substituent on a pyranoid ring, subjected to largest nonbonded steric interactions with other ring substituents. Consequently, whether a glycopyranose will adopt the $^4C_1$ or the $^1C_4$ conformation will depend on in which conformation the hydroxymethyl group is equatorially oriented. Thus, in D-series the hydroxymethyl group is oriented equatorially in $^4C_1$ conformation, whereas in L-series the hydroxymethyl group is oriented equatorially in $^1C_4$ conformation.

For example, β-D-glucopyranose normally exists in $^4C_1$ conformation, with the largest substituent (hydroxymethyl group) equatorially oriented (*53* in Fig. 2.19). In

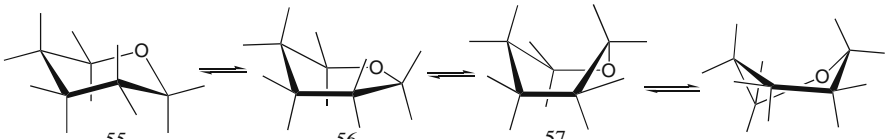


53 *54*

$^4C_1$ Conformation of β-D-glucopyranose $^1C_4$ Conformation of β-D-glucopyranose

Fig. 2.19

the $^1C_4$ conformation the hydroxymethyl group of β-D-glucopyranose will be axially oriented and subjected to two strong 1,3-*syn*–axial interactions with the C1 and the C3 hydroxyl groups (*54*); in addition, the axially oriented C2 hydroxyl group will be involved in 1,3-*syn*–axial interaction with the C4 hydroxyl group additionally destabilizing this conformation (Fig. 2.19).



55 *56* 57 *58*

Fig. 2.20

By analogy to conformational interconversions of cyclohexane rings, the $^4C_1$ and the $^1C_4$ conformers of a pyranoid sugar can also undergo interconversion. This is shown in Fig. 2.20. The rigid $^4C_1$ chair pyranoid conformer converts, via a transition state that resembles a half-chair conformation, to flexible boat and twist-boat conformations which can then either convert back, via the same transition state, to initial $^4C_1$ conformation or to a rigid $^1C_4$ conformation. Six different twist-boat conformers and six different boat conformers may be identified in the course of boat/twist-boat pseudorotation pathway of a pyranoid ring (Fig. 2.21). However, similar to the cyclohexane ring, twist-boat conformers are found to be much less stable than $^4C_1$ and $^1C_4$ chair conformations and their presence in conformational equilibria can be considered in most instances negligible.

Calculation of Conformational Energies of Pyranoses

The prediction of conformational properties of pyranoid form of a monosaccharide can be done only if the relative free energies of two chair forms are known. Angyal [35, 46, 47] has developed a semiempirical method for obtaining the values of these relative free energies by taking both steric and electronic interactions into consideration [48].

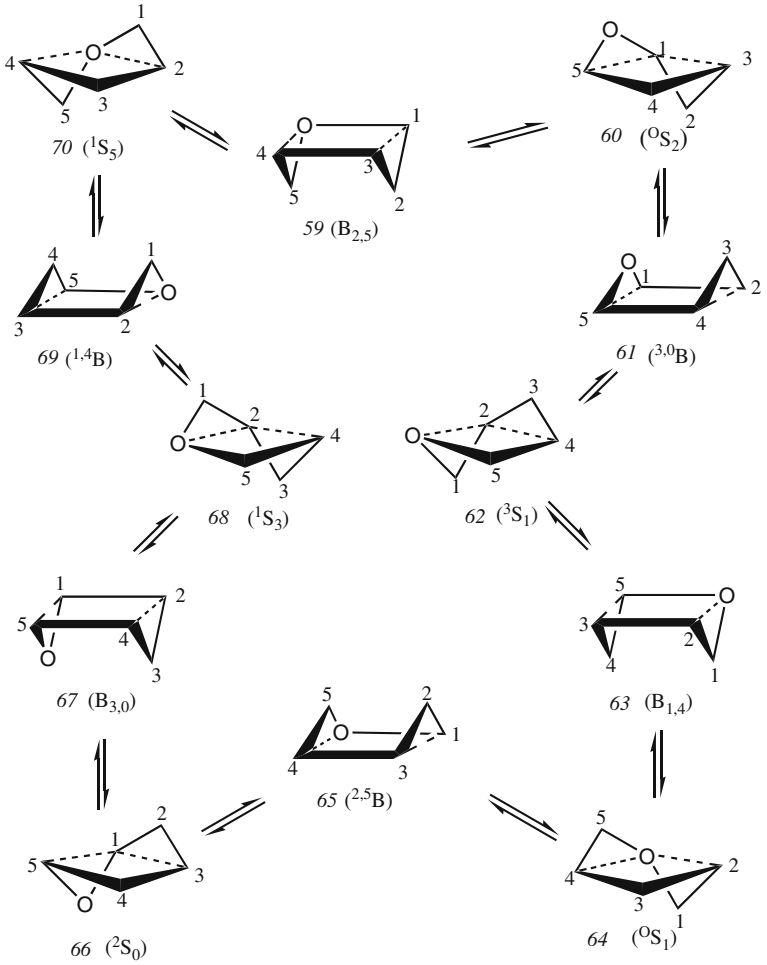


Fig. 2.21

The numerical values for nonbonding interactions in pyranoid structures of monosaccharides were obtained from conformational studies of cyclitols and some model pyranose sugars.

However, this semi-quantitative calculation of relative free energy of cyclitols and pyranoses in aqueous solutions is based on a number of assumptions, of which the following three are the most important.

1. *The pyranose and the cyclohexane rings have the same geometry*. This is only partially true since the replacement of one ring carbon with an oxygen results in considerable flattening of the six-membered ring due to (1) shorter C–O bonds (they are ca. 10% shorter than C–C bonds, i.e., 1.42 Å vs. 1.54 Å, respectively)

and (2) due to larger endocyclic O–C–O bond angle (112–114°) with regard to the endocyclic C–C–C bond angle (109°).

2. *In aqueous solutions the intramolecular hydrogen bonds do not play any role in conformational equilibria.*
3. *The relative free energy of conformers can be obtained by simple addition of (1) energies of various nonbonded interactions between ligands, (2) energies of electronic interactions, and (3) entropy differences*. The assumption is made that *the contributions of these individual thermodynamic quantities are independent of each other.*

Although none of the above assumptions is strictly true, the success of this approach in practice suggests that the errors introduced by making these assumptions are quite small.

If the energy contributions due to bond length deformation strain and bond angle bending strain are considered to be negligible, then only two types of nonbonded interactions are important for the conformational analysis of hexopyranoses:

(1) 1,3-*Syn*–axial nonbonded interactions between *syn*–axial ligands (excluding the *syn*–axial interaction between two hydrogen atoms). This interaction is designated as X_a:Y_a.
(2) 1,2-Nonbonded interactions between ligands on two vicinal (adjacent) carbon atoms that are in *gauche* conformation (again excluding the *gauche* interaction between two hydrogen atoms). This interaction is designated as X_1:Y_2.

The standard conformational free energy difference between two conformers can be calculated from the conformational equilibrium constant according to the equation:

$$\Delta G_X^0 = -RT \ln K \tag{1}$$

where ΔG_X^0 is the standard conformational free energy difference, R is the universal gas constant (1.98726 cal/deg mol), T is the absolute temperature in Kelvin, and K is the equilibrium constant.

The most of interaction energies in pyranoid forms of sugars were determined by studying the equilibrium composition of tridentate borate complexes of cyclohexitols having three hydroxyl groups in *cis*-1,3,5 relationship (this arrangement is not possible in sugar pyranoid forms (Fig. 2.22)).

The formation of tridentate complex involves the initial inversion of more stable chair form *71*, in which the three hydroxyl groups are equatorially oriented, to the alternative chair conformation *72*, in which they are all axial (Fig. 2.22). This conformation is then capable to form the borate complex. Tridentate complexes are formed in the 1:1 ratio from their components (cyclitols and borate) and are strong acids, unlike borate complexes with vicinal diols that are weak acids (the acid strength of the latter complexes is comparable to boric acid). Consequently, the formation of tridentate complex lowers the pH of borate solutions. The boric

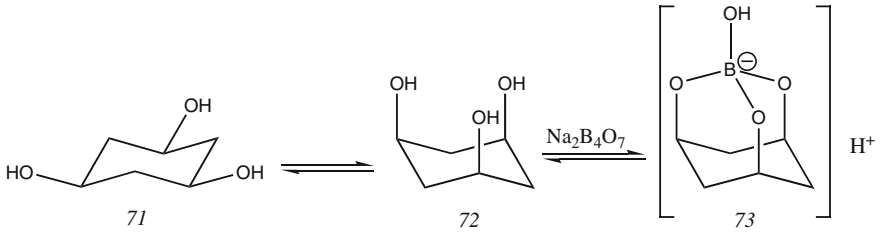


Fig. 2.22

acid itself is a weak Lewis acid with little tendency to form tetrahedral borate anion $B(OH)_4^-$, because its planar form is considerably stabilized by resonance involving the limiting structures $H^+O{=}B^-(OH)_2$. From the change in pH of the borate solution caused by successive addition of a cyclitol, the equilibrium constant K of complex formation can be calculated (Equation (1)) [49]

$$K = [\text{Complex}^-]/[\text{Borate}^-][\text{Cyclitol}] \tag{2}$$

The equilibrium constants for the formation of borate complexes with *scyllo*-quercitol *74, myo*-inositol *75*, *epi*-quercitol *78, epi*-inositol *79*, *cis*-quercitol *82*, and *cis*-inositol *83* are shown in Figs. 2.23 and 2.24.

Since the equilibrium constants of tridentate borate formation depend on nonbonded interactions in the complex, the values of interaction energies can be calculated from K. In order to do so, two assumptions were made:

(1) Free energy of formation of tridentate anion from axial *cis*-1,3,5-hydroxyl groups and borate ion is independent of the nature of other substituents on cyclohexane ring
(2) Free energies of conformational isomers are additive functions of energy terms associated with the presence of nonbonded interactions, that is, the occurrence of one interaction in a molecule does not affect the magnitude of another one

The stability of the complex depends on steric orientation of free hydroxyl groups in the complex: the more these are in the axial position, the less stable the complex is. Since the equilibrium constants of tridentate borate formation depend on nonbonded interactions of the free hydroxyl groups, the values of these interaction energies were calculated from equilibrium constants (Figs. 2.23, 2.24, and 2.25).

The interaction energies are calculated in the following way. The energies of each nonbonded interaction in individual cyclitols, and in the tridentate borate complexes, are listed and separately added up. For borate complexes a term is added to account for the free energy change on formation of the tridentate borate complex from the three hydroxyl groups; and the difference between the totals for each cyclitols and for its borate complex is equated with the experimentally determined free energy

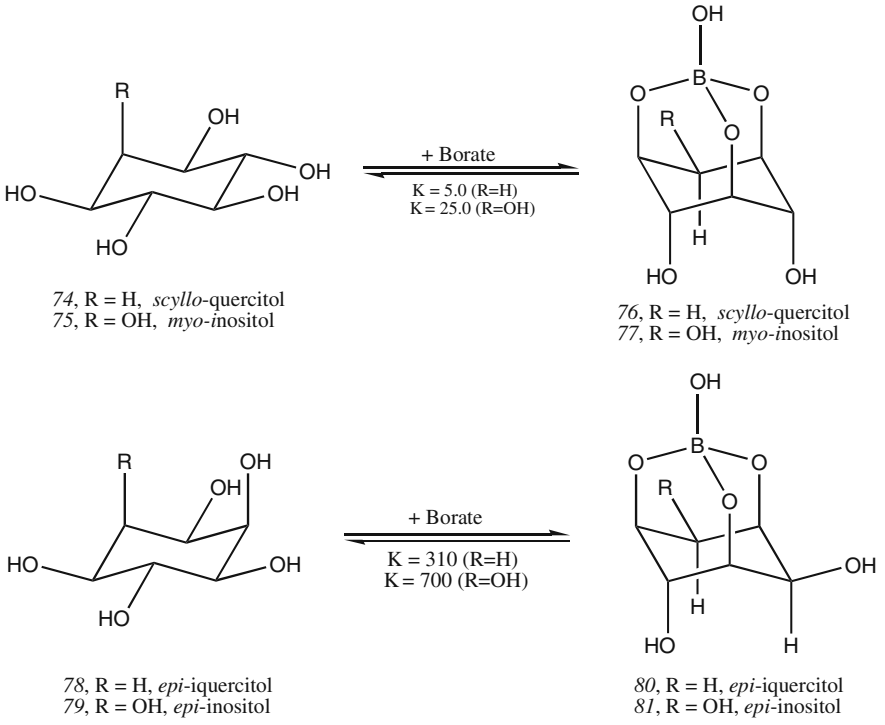


Fig. 2.23

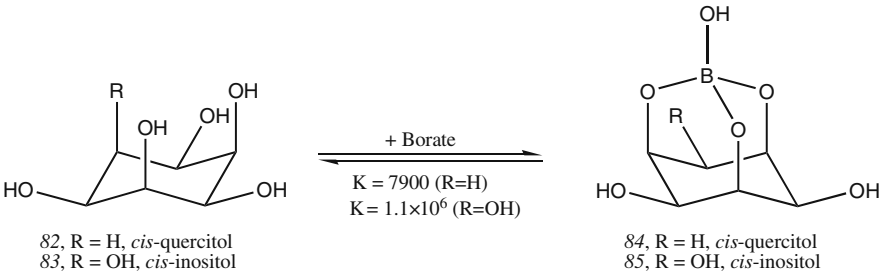
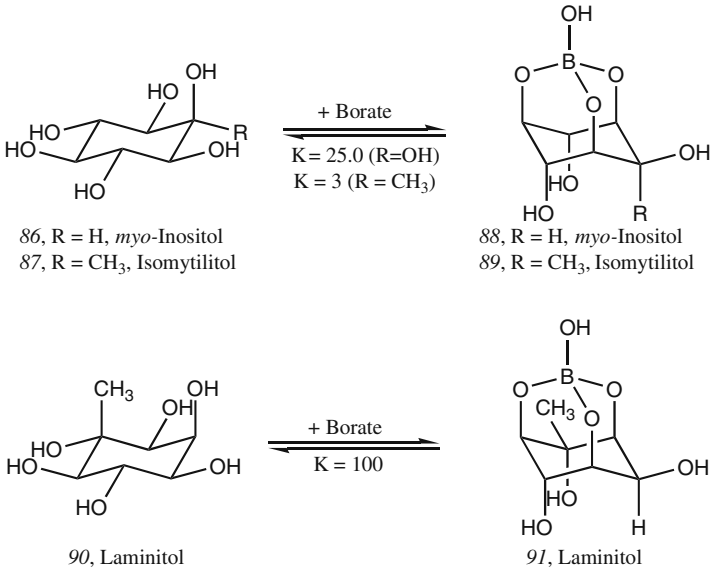


Fig. 2.24

difference (calculated from $\Delta G^0 = -RT \ln K$). A series of equations resulted from which all unknown quantities were calculated [50, 51] (Table 2.1).

Thus, for example, from Fig. 2.23 we see that for *scyllo*-quercitol *74* the equilibrium constant K for the complex formation with borate is 5. This corresponds to ΔG^0 value of –0.95 kcal/mol. Since ΔG^0 is equal to the difference between the sum of nonbonded interactions in the complex *76* which is $2(O_a{:}H_a) + (O_a{:}O_a)$ and the



86, R = H, *myo*-Inositol
87, R = CH_3, Isomytilitol

88, R = H, *myo*-Inositol
89, R = CH_3, Isomytilitol

90, Laminitol

91, Laminitol

Fig. 2.25

Table 2.1 The values for 1,2-*gauche* and 1,3-*syn*–axial interactions between the ligands on a pyranoid ring (excluding the interactions between hydrogen atoms)

Interaction	ΔG^0 (kcal/mol at 25°C)
O_1:O_2	0.35
C_1:O_2	0.45
O_a:H_a	0.45
C_a:H_a	0.9
O_a:O_a	1.9
C_a:O_a	2.5*
Anomeric effect	0.55–3.2**
Δ2 effect	1.36

* Determined at 40°C
** Value of 0.55 kcal/mol is for free sugars; for OMe it is 0.9 kcal/mol, and for 1-halogens higher.

sum of nonbonded interactions in *scyllo*-quercitol *74* which is $4(O_1{:}O_2)$, one can write

$$\Delta G^0 = 2(O_a{:}H_a) + (O_a{:}O_a) + \Delta G^0_F - 4(O_1{:}O_2) = -0.95\,\text{kcal/mol}$$

In analogous fashion, another five equations can be written for the other five cyclitols from Figs. 2.23 and 2.24, and the set of six simultaneous equations can be solved for $(O_1{:}O_2)$, $(O_a{:}H_a)$, $(O_a{:}O_a)$, and $\Delta G^0{}_F$. The value found for $\Delta G^0{}_F$ is –2.5 kcal/mol.

In order to determine the interaction energies of hydroxymethyl group that is needed for the calculation of conformational energies in pyranoid rings, it was assumed that conformational energy of hydroxymethyl group is not very different from conformational energy of methyl group in aqueous solvents. Preliminary experiments [52] have indicated that interactions of the methoxymethyl group are approximately of the same value as those of methyl group. Based on this one can safely assume that this would also apply to the hydroxymethyl group.

The values for carbon–oxygen [(C_a:O_a) and (C_1:O_2)] and carbon–hydrogen (C_a:H_a) interactions were determined similarly as was done previously, only the methyl cyclitols were used for the formation of tridentate borate complexes such as *myo*-inositol *86*, isomytilitol *87*, and laminitol *90* (Fig. 2.25). From equilibrium constants and the sums of nonbonded interactions in cyclitols and their corresponding tridentate borate complexes conformational free energies were again calculated. The obtained values are listed in Table 2.1.

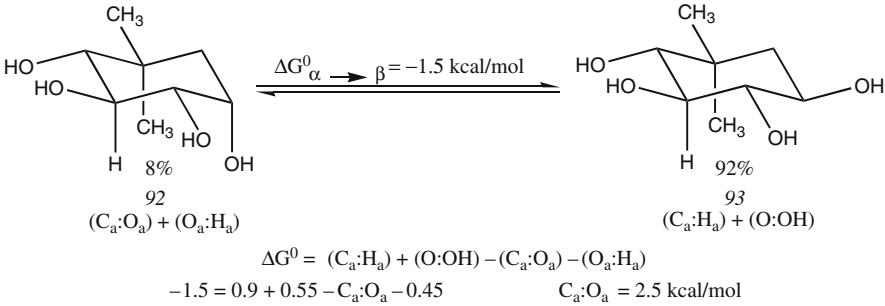


Fig. 2.26

It should be noted that the 1,2-interactions between the two vicinal oxygen atoms (equatorial–equatorial or axial–equatorial) are considered to be identical.

Alternatively, from a study of the equilibrium in aqueous solution between the α- and β-anomers of 6-deoxy-5-C-methyl-D-*xylo*-hexopyranose value of 2.5 kcal/mol was obtained for the (C_a:O_a) (Fig. 2.26).

The value for (C_a:H_a) is assumed to be one-half the conformational energy of a methyl group, i.e., 0.9 kcal/mol ($-\Delta G^0_{\text{methyl}} = 1.8$ kcal/mol [52]).

In addition to nonbonding interaction energies that have been so far determined there is another stereoelectronic interaction that has to be taken into account when calculating the free energies of pyranoses and that is the so-called "anomeric effect." The existence of this stereoelectronic effect was first recognized by Edwards [53] but it was given its name and exhaustively studied by Lemieux [54] and has become the subject of study of many investigators (this topic will be discussed later to a much greater detail). It is related to the composition of equilibrium mixtures of free sugars in aqueous solutions which seemed to be in violation of the classical postulates of conformational analysis of cyclohexane. The aqueous solution of D-glucose, for example, contains at equilibrium 36% of α-D-glucose and 64% of the

β-D-glucose, corresponding to a free energy difference of only 0.35 kcal/mol, in spite of the fact that there are in α-D-glucose two O_aH_a interactions each one raising the free energy of α-D-glucose by 0.45 kcal/mol for a total of 0.9 kcal/mol. Furthermore, the conformational mixture of cyclohexanol at equilibrium contains 77% of conformer with equatorial hydroxyl group *94* and 23% of conformer with axially oriented hydroxyl group *95* corresponding to a free energy difference of 0.8 kcal/mol [55] (Fig. 2.27).

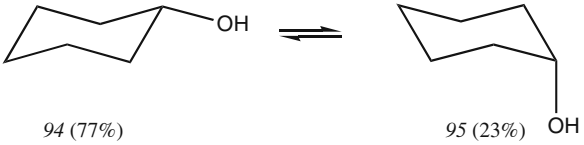


Fig. 2.27

It should be noted that the reported *A*-values in the literature for the hydroxyl group vary significantly and depend upon the method used for its determination. Thus for example, from esterification studies Eliel [56] determined that the *A*-value for OH is 0.5 kcal/mol, whereas Subotin et al. [57] found from ^{13}C NMR studies of cyclohexanol equilibrium at low temperatures (–80°C) the *A*-value for hydroxyl group to be 1.02 kcal/mol.

Figure 2.28 illustrates how the value for the anomeric effect (O:OH) was determined. As can be seen the anomeric effect is lowest for sugars having the C2 hydroxyl group equatorially oriented and highest for sugars having the C2 hydroxyl group axially oriented. The 2-deoxy sugars have the anomeric effect between these two extremes.

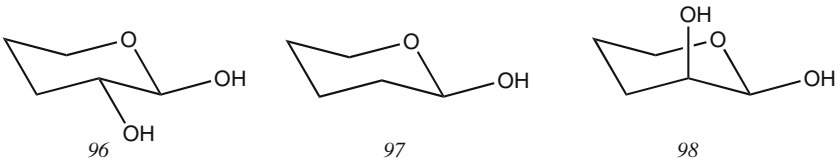
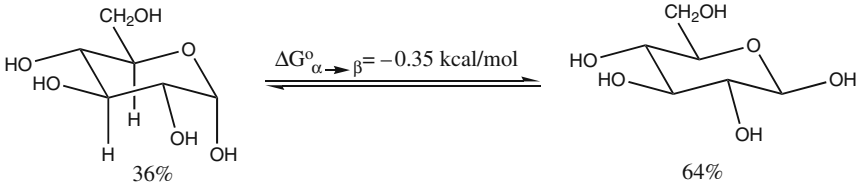


Fig. 2.28

Since the C2 carbon of 2-deoxy sugars bears no electronegative substituent (hydroxyl oxygen) which can interfere with the electronic properties of the C1 carbon and thus with the anomeric effect, then 0.85 kcal/mol can be taken as the value for the anomeric effect. The introduction of an equatorial electronegative substituent at the C2 carbon (hydroxyl group) decreases the value of anomeric effect (O:OH = 0.55 kcal/mol), whereas the introduction of an axial electronegative substituent (hydroxyl group) at the C2 carbon of a hexopyranoside increases the value of the anomeric effect (O:OH = 1.0 kcal/mol) (Fig. 2.29).

D-Glucopyranose

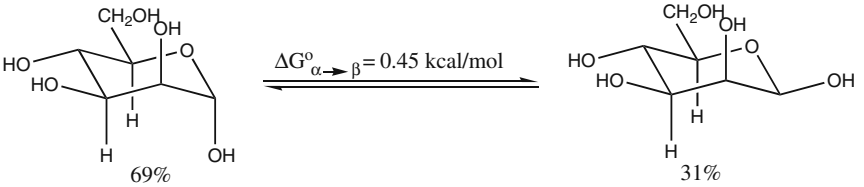


36% 64%

Interactions: 2 (O_a:H_a) Interactions: (O:OH)

ΔG^o = (O:OH) – 2 (O_a:H_a) –O.35 = (O:OH) – 0.9 (O:OH) = 0.55 kcal/mol

D-Mannopyranose

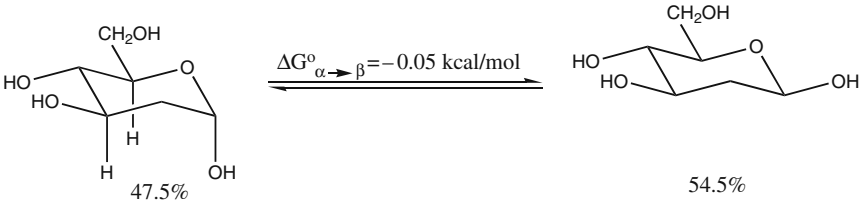


69% 31%

Interactions: 2 (O_a:H_a) Interactions: (O:OH) + (O_1:O_2)

ΔG^0 = (O:OH) + (O_1:O_2) – 2 (O_a:H_a) 0.45 = (O:OH) + 0.35 – 0.9 (O:OH) = 1.0 kcal/mol

2-Deoxy-D-glucopyranose



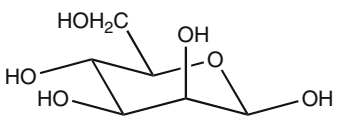
47.5% 54.5%

Interactions: 2 (O_a:H_a) Interactions: (O:OH)

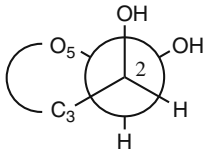
ΔG^0 = (O:OH) – 2 (O_a:H_a) – 0.05 = (O:OH) – 0.9 O:OH) = 0.85 kcal/mol

Fig. 2.29

The increased values for the anomeric effect of sugars having the C2 hydroxyl group axially oriented, as, for example, in D-mannose, was originally considered as a separate electronic interaction and was named by Reeves [58, 59] Δ2 effect. The originally suggested explanation for the high value of the anomeric effect of D-mannose was that the C2 axial hydroxyl group in β-D-mannopyranose lies parallel and coplanar with the resultant dipole of the C1–O5 and the C1–O1 oxygens (*100* in Fig. 2.30) introducing thus an additional destabilization.



99



100

Fig. 2.30

If both the C2 and C3 carbons bear an axial hydroxyl group they are considered [47] to cancel out each other and the value of 0.85 kcal/mol is used for the anomeric effect.

In Table 2.2 are given the compositions of the equilibrium mixtures of aldoses after dissolution in water as determined by NMR [61].

The equilibrium compositions of the sugars in solutions are affected by temperature, by the nature of solvent, and by the presence of substituents. In less polar solvents than water, the anomeric effect increases favoring the α-pyranose over the β-pyranose form if the sugar belongs to D-series and is in $^4C_1$ conformation. Aldoses with an axial C2 hydroxyl group (mannose, lyxose) contain much higher proportion

Table 2.2 Predominant conformations of D-aldohexo- and D-aldopentopyranoses in aqueous solution

Aldose	Conformation found by		Calculated interaction energies (kcal/mol)	
	NMR [63–65]	Calculation [66]	C1	1C
α-D-Allose	C1	C1	3.9	5.35
β-D-Allose	C1	C1	2.95	6.05
α-D-Altrose	C1, 1C	C1, 1C	3.65	3.85
β-D-Altrose	C1	C1	3.35	5.35
α-D-Glucose	C1	C1	2.4	6.55
β-D-Glucose	C1	C1	2.05	8.0
α-D-Mannose	C1	C1	2.5	5.55
β-D-Mannose	C1	C1	2.95	7.65
α-D-Gulose		C1	4.0	4.75
β-D-Gulose	C1	C1	3.05	5.45
α-D-Idose	C1, 1C	C1, 1C	4.35	3.85
β-D-Idose		C1	4.05	5.35
α-D-Galactose	C1	C1	2.85	6.3
β-D-Galactose	C1	C1	2.5	7.75
α-D-Talose	C1	C1	3.55	5.9
β-D-Talose		C1	4.0	8.0
α-D-Ribose	C1, 1C	C1, 1C	3.45	3.55
β-D-Ribose	C1, 1C	C1, 1C	2.5	3.1
α-D-Arabinose	1C	1C	3.2	2.05
β-D-Arabinose		C1, 1C	2.9	2.4
α-D-Xylose	C1	C1	1.95	3.6
β-D-Xylose	C1	C1	1.6	3.9
α-D-Lyxose	C1, 1C	C1, 1C	2.05	2.6
β-D-Lyxose	C1	C1	2.5	3.55

of the α-pyranose form in dimethyl sulfoxide than in water, whereas sugars with an equatorial C2 hydroxyl group (glucose, xylose) have approximately the same equilibrium composition in both solvents [62, 63].

The conformations of aldohexopyranoses, in aqueous solutions, are, as seen from the data in Table 2.2, controlled mainly by the orientation of hydroxymethyl group, which is the bulkiest substituent and as such tends to assume the equatorial position. Hence, all of the β-D-anomers are predominantly in the C1 ($^4C_1$) conformation, because in the 1C ($^1C_4$) form there is a large *syn*–axial interaction between the axial hydroxymethyl and the axial anomeric hydroxyl groups, as shown in Fig. 2.18. This interaction is absent from 1C conformation of α-anomers but most of them also prefer the C1 conformation; only α-D-idopyranose exists predominantly in the 1C form; the aqueous solutions of α-D-altropyranose and α-D-gulopyranose have substantial proportions of both chair forms at equilibrium.

In the absence of a hydroxymethyl group at C5, the conformations of the aldopentopyranoses are controlled by the orientation of the hydroxyl groups. Thus, the D-arabinopyranoses favor the 1C form, α-D-lyxopyranose and α-D-ribopyranose are conformational mixtures, and the other pentoses are predominantly in the C1 form.

A relationship between the percentage of the more stable conformer at equilibrium, equilibrium constant *K*, and standard free energy difference at 25°C for an equilibrium of isomers A ⇌ B is given in Table 2.3.

Table 2.3 Relationship between the percentage of more stable isomer, equilibrium constant and standard free energy difference

% of more stable isomer	K	ΔG^0 (kcal/mol)
50	1.00	0
60	1.50	0.119
70	2.33	0.502
80	4.00	0.973
90	9.00	1.302
95	19.00	1.744
98	49.00	2.306
99.9	999.0	4.092
99.99	9999	5.456

As it can be seen the difference in free energies between two conformers of 0.973 kcal/mol results in fourfold excess of the more stable isomer in the equilibrium mixture.

Computational studies of carbohydrate structures were reported by many groups [67–78]. The early studies were based partly on experimental data, and partly on ab initio calculations, usually at the Hartree–Fock level. The experimental data, though reliable, were normally determined in solutions, very often in water, or some other hydroxylic solvents, with sugar concentrations most often unknown. Hence, one must be concerned about solvation effects in the interpretation of these data. An additional difficulty was that ab initio calculations of carbohydrates required the use of a fairly large basis set in order to obtain what is hoped to be the chemical accuracy.

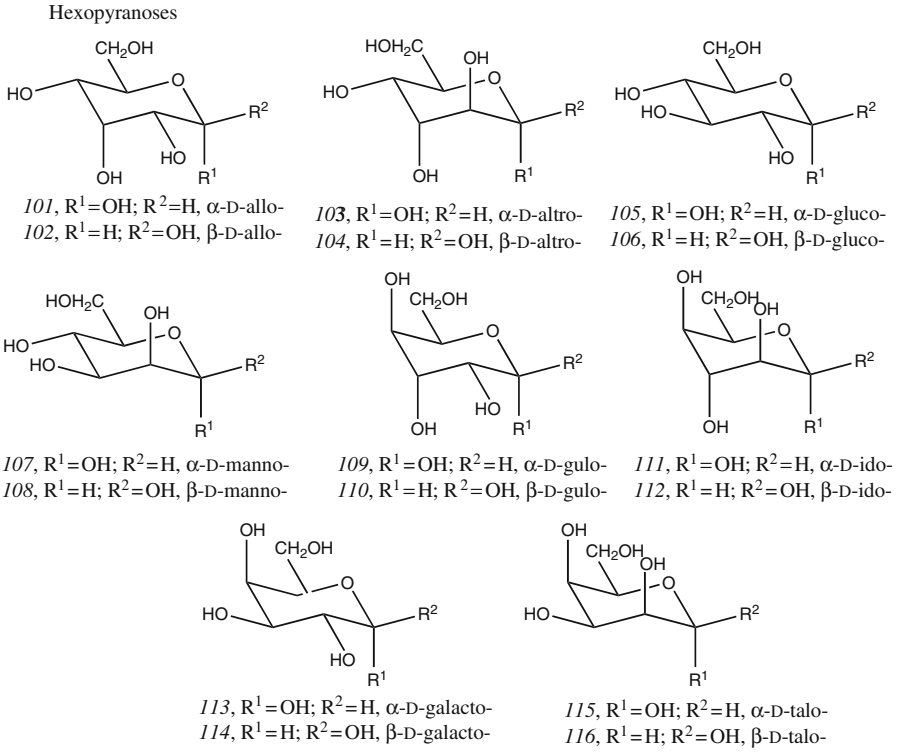


Fig. 2.31 Structures of hexopyranoses depicting the orientations of their secondary hydroxyl groups

Figure 2.31 shows the preferred conformations for aldohexopyranoses in aqueous solution as determined by NMR spectroscopy [60]. Allinger et al. [79] have reported the ab initio calculations of 84 conformations of 12 different sugars (hexoses), in both pyranose and furanose forms. They used the same MM4 force field calculation that they used for the calculation of simple alcohols and ethers, but for carbohydrates they had to make some important additions to take into the account the anomeric affect, gauche effect, and the Δ2-effect which are all present in sugars but not in simple alcohols and ethers (Fig. 2.32).

Fig. 2.32

The Δ2-effect is energetically important only in a few sugars, such as β-D-altropyranose *104*, β-D-mannopyranose *108*, β-D-idopyranose *112,* and β-D-talopyranose *116* (Fig. 2.31) and tends to stabilize the α anomer relative to β, by about 1.36 kcal/mol. It should be noted that a recent study found no evidence that Δ2-effect plays an important role in determining the conformational properties of sugars [80].

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