Organic Synthesis with Carbohydrates

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Preface

The carbohydrates or saccharides constitute the most abundant group of compounds found in nature. They are structurally very diverse and are endowed with a wealth of stereochemical properties. Saccharides are available in cyclic and acyclic forms, can have different chain lengths and oxidation and reduction states, and can be substituted with a wide range of functionalities. Furthermore, monosaccharides can be linked together through glycosidic linkages to give oligo- or polysaccharides. Many saccharides are readily and cheaply available and provide an attractive, renewable source of material.

Not surprisingly, these compounds are important starting materials in organic synthesis, and there are thousands of research papers and numerous industrial processes in which carbohydrates feature prominently.

This book provides broad coverage of the use of carbohydrates in organic synthesis, at postgraduate student level. Each chapter describes established and widely used methods and approaches, but also covers recent and promising reports. Many citations to the primary literature are provided. It is hoped, therefore, that this book will also be of use to synthetic organic chemists and carbohydrate chemists in academic and industrial laboratories.

The authors recognise that one book cannot cover all aspects of synthetic carbohydrate chemistry. Part A focuses on monosaccharide chemistry, complex oligosaccharides and glycoconjugate synthesis. For a long time, this area of chemistry was the domain of a small and specialised group of researchers. In the early eighties, it became apparent that oligosaccharides are involved in many important biological processes, such as cell-cell recognition, fertilisation, embryogenesis, neuronal development, viral and bacterial infections and tumour cell metastasis. Consequently, the preparation of complex glycoconjugates became part of mainstream organic chemistry and it is now part of the undergraduate or postgraduate chemistry curriculum in many universities. Chapter one covers important properties of saccharides, such as configuration, conformation, the anomeric effect and equilibrium composition in solution. This basic knowledge is key to many of the discussions that follow. The next two chapters detail the use of protecting groups in carbohydrate chemistry and the preparation of functionalised monosaccharides. Chapters four and five deal with glycosidic bond chemistry, preparation of complex oligosaccharides and the synthesis of glycopeptides.

Part B discusses enantioselective natural product synthesis from monosaccharides. Nowadays, most natural product syntheses are performed in an asymmetric manner. This development is due principally to the realisation that enantiomers may have very different biological properties: one of them may have the desired property, while the other may be potentially harmful, or at least undesirable. Many methods are available for obtaining compounds in an optically pure form. However, each method involves, at a particular stage, a chiral molecule obtained from a natural source, either by using a chiral starting material or chiral auxiliary, or by employing a chiral catalyst. Carbohydrates have been used extensively as chiral starting materials but they have also been utilised as chiral auxiliaries and ligands of chiral catalysts. The examples covered in chapters six to eighteen illustrate the use of carbohydrates in the synthesis of a wide range of natural products. In many cases, the origin of the starting material cannot be recognised in the final product. These chapters demonstrate how the rich stereochemistry of carbohydrates can be used efficiently to install chiral centres into target compounds. To ensure that this material is suitable for teaching, emphasis is placed on retrosynthetic analysis as well as on mechanistic explanations for key and novel reactions.

Geert-Jan Boons and Karl J. Hale

Contents

PART A: STRUCTURE AND SYNTHESIS OF SACCHARIDES AND GLYCOPROTEINS

Part A

Structure and Synthesis of Saccharides and Glycoproteins

1 Mono- and oligosaccharides: structure, configuration and conformation

G.-J. Boons

1.1 Introduction

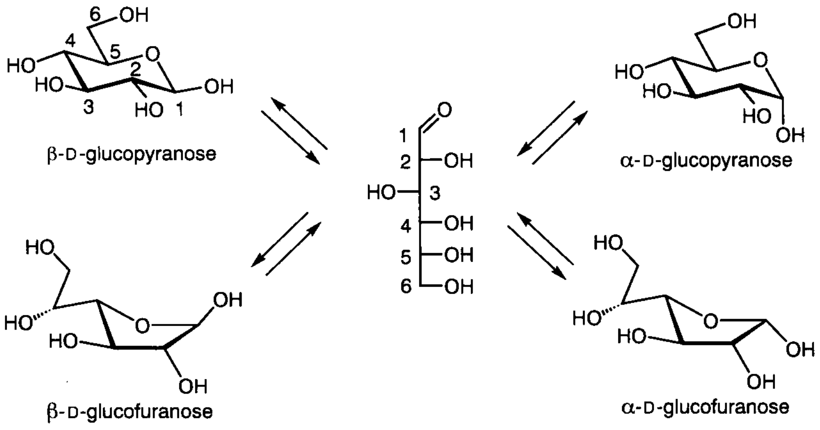
Carbohydrates constitute the most abundant group of natural products. This fact is exemplified by the process of photosynthesis, which alone produces 4×10^{14} kg of carbohydrates each year. As their name implies, carbohydrates were originally believed to consist solely of carbon and water and thus were commonly designated by the generalised formula $C_x(H_2O)_y$. The present-day definition[1] is that 'the carbohydrates' are a much larger family of compounds, comprising monosaccharides, oligosaccharides and polysaccharides, of which monosaccharides are the simplest compounds, as they cannot be hydrolysed further to smaller constituent units. Furthermore, the family comprises substances derived from monosaccharides by reduction of the anomeric carbonyl group (alditols), oxidation of one or more terminal groups to carboxylic acids or replacement of one or more hydroxyl group(s) by a hydrogen, amino or thiol group or a similar heteroatomic functionality. Carbohydrates can also be covalently linked to other biopolymers, such as lipids (glycolipids) and proteins (glycoproteins).

Carbohydrates are the main source of energy supply in most cells. Furthermore, polysaccharides such as cellulose, pectin and xylan determine the structure of plants. Chitin is a major component of the exoskeleton of insects, crabs and lobsters. Apart from these structural and energy storage roles, saccharides are involved in a wide range of biological processes. In 1952, Watkins disclosed that the major blood group antigens are composed of oligosaccharides.[2] Carbohydrates are now implicated in a wide range of processes[3] such as cell–cell recognition, fertilisation, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organisation into specific tissues, viral and bacterial infections and tumour cell metastasis. It is not surprising that saccharides are key biological molecules since by virtue of the various glycosidic combinations possible they have potentially a very high information content.[4]

In this chapter, the configurational, conformational and dynamic properties of mono- and oligosaccharides will be discussed and, in general, reference is made to reviews that cover these aspects. These properties, as described in the discussion which follows, are not placed in a historical context.

1.2 Configuration of monosaccharides[5,6]

Monosaccharides are chiral polyhydroxy carbonyl compounds, which often exist in a cyclic hemiacetal form. Monosaccharides can be divided into two main groups according to whether their acyclic form possesses an aldehyde (aldoses) or keto group (ketoses). These, in turn, are further classified, according to the number of carbon atoms in the monomeric chain (3–10) into trioses, tetroses, pentoses, hexoses, etc. and the types of functionalities that are present. D-Glucose is the most abundant monosaccharide found in nature and has been studied in more detail than any other member of the family. D-Glucose exists in solution as a mixture of isomers. The linear form of glucose is energetically unfavourable relative to the cyclic hemiacetal forms. Ring closure to the pyranose form occurs by nucleophilic attack of the C(5) hydroxyl on the carbonyl carbon atom of the acyclic species (Scheme 1.1). Hemiacetal



Scheme 1.1 Different forms of D-glucose.

ring formation generates a new asymmetric carbon atom at C(1), the anomeric centre, thereby giving rise to diastereoisomeric hemiacetals which are named α and β anomers depending on whether the C(1) substituent resides on the bottom or top of the sugar ring. Cyclisation involving O(4) rather than O(5) results in a five-membered ring structurally akin to furan and is therefore designated as a furanose.

Accordingly, the six-membered pyran-like monosaccharides are termed pyranoses.

All the common hexoses contain four asymmetric centres in their linear form and therefore 2^4 (16) stereoisomers exist which can be grouped into eight pairs of enantiomers. The pairs of enantiomers are classified as D and L sugars. In the D sugars the highest numbered asymmetric hydroxyl group [C(5) in glucose] has the same configuration as the asymmetric centre in D-glyceraldehyde and, likewise, for all L sugars the configuration is that of L-glyceraldehyde (Figure 1.1). The acyclic and pyranose forms of the D-aldoses are depicted in Figures 1.2 and 1.3, respectively.

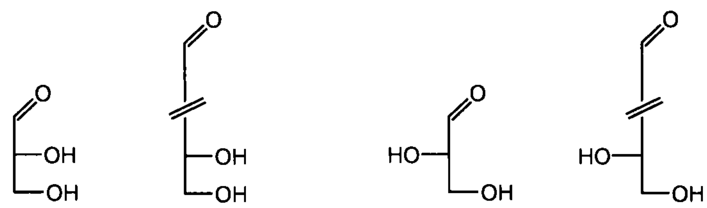


Figure 1.1 D and L sugars.

Monosaccharides have been projected in several ways, the Fischer projection being the oldest (Figure 1.4). In the Fischer projection, the monosaccharides are depicted in an acyclic form and the carbon chain is drawn vertically, with the carbonyl group (or nearest group to the carbonyl) at the top. Each carbon atom is rotated around its vertical axis until all of the C—C bonds lie below a curved imaginary plane. It is only when the projection of this plane is flattened that it can be termed a Fischer projection. In the α anomer the exocyclic oxygen atom at the anomeric centre is formally *cis*, in the Fischer projection, to the oxygen of the highest-numbered chiral centre [C(5) in glucose]; in the β anomer the oxygens are formally *trans*.

Haworth introduced his formula to give a more realistic picture of the cyclic forms of sugars. The rings are derived from the linear form and drawn as lying perpendicular to the paper with the ring oxygen away from the viewer and are observed obliquely from above. The chair conformation gives a much more accurate representation of the molecular shape of most saccharides and is the preferred way of drawing these compounds. It has to be noted that the Mills formula and zig-zag depiction are particularly useful for revealing the stereochemistry of the carbon centres of the sugars.

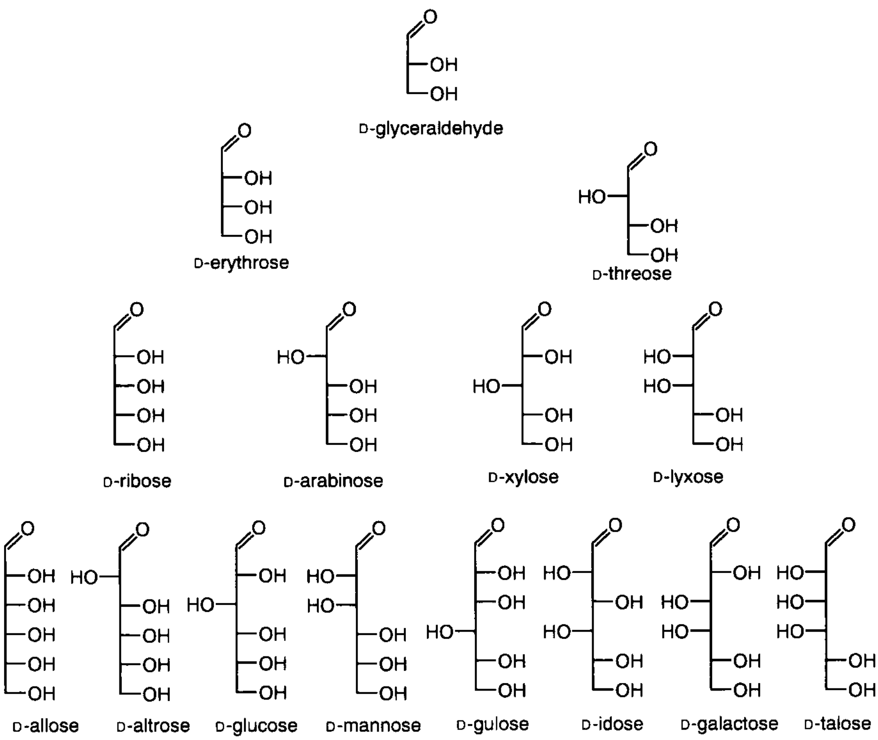


Figure 1.2 Acyclic forms of the D-aldoses.

Apart from the monosaccharides depicted in Figure 1.3, many other types are known. Several natural occurring monosaccharides have more than six carbon atoms and these compounds are named the higher carbon sugars. L-Glycero-D-manno-heptose is such a sugar and is an important constituent of lipopolysaccharides (LPS) of Gram-negative bacteria (Figure 1.5).

Some saccharides are branched and these types are found as constituents of various natural products. For example, D-apiose occurs widely in plant polysaccharides. Antibiotics produced by the micro-organism *Streptomyces* are another rich source of branched chain sugars.

As already mentioned, the ketoses are an important class of sugars. Ketoses or uloses are isomers of the aldoses but with the carbonyl group occurring at a secondary position. In principle, the keto group can be at each position of the sugar chain, but in naturally occurring ketoses the keto group, with a very few exceptions, is normally at the 2-position. D-Fructose is the most abundant ketose and adopts mainly the pyranose form.

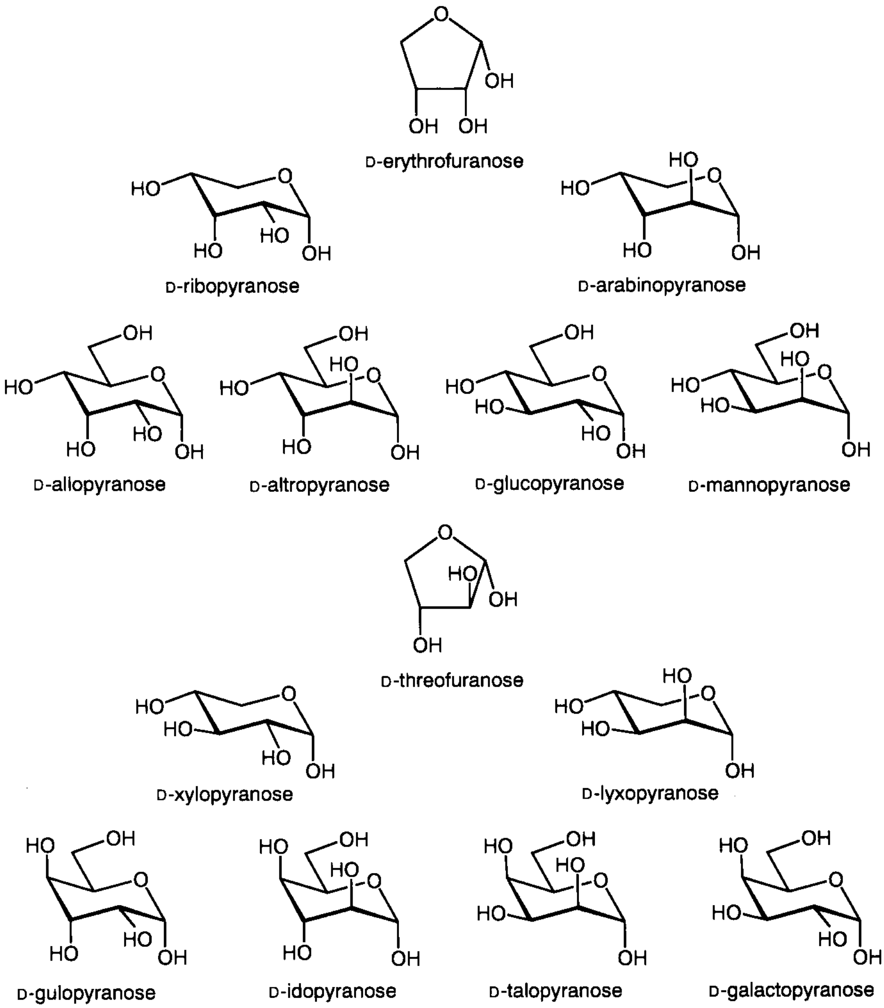


Figure 1.3 Cyclic forms of α-D-aldoses.

The uronic acids are aldoses that contain a carboxylic acid group as the chain-terminating function. They occur in nature as important constituents of many polysaccharides. The ketoaldonic acids are another group of acidic monosaccharides, and notable compounds of this class are 3-deoxy-D-manno-2-octulosonic acid (Kdo) and *N*-acetyl neuraminic acid (Neu5Ac). Kdo is a constituent of LPS of Gram-negative bacteria and links an antigenic oligosaccharide to Lipid A. *N*-Acetyl-neuraminic acid is found in many animal and bacterial polysaccharides and is critically involved in a host of biological processes.

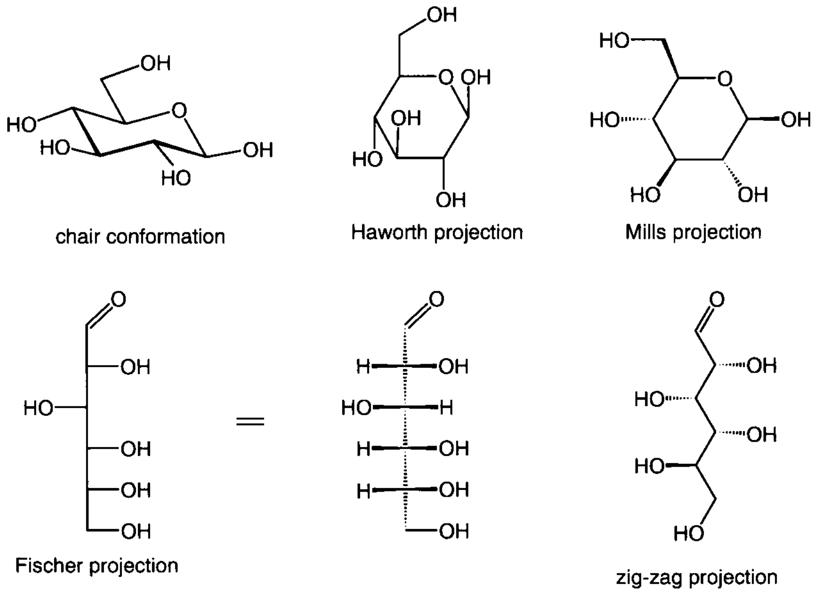


Figure 1.4 Different projections of D-glucopyranose.

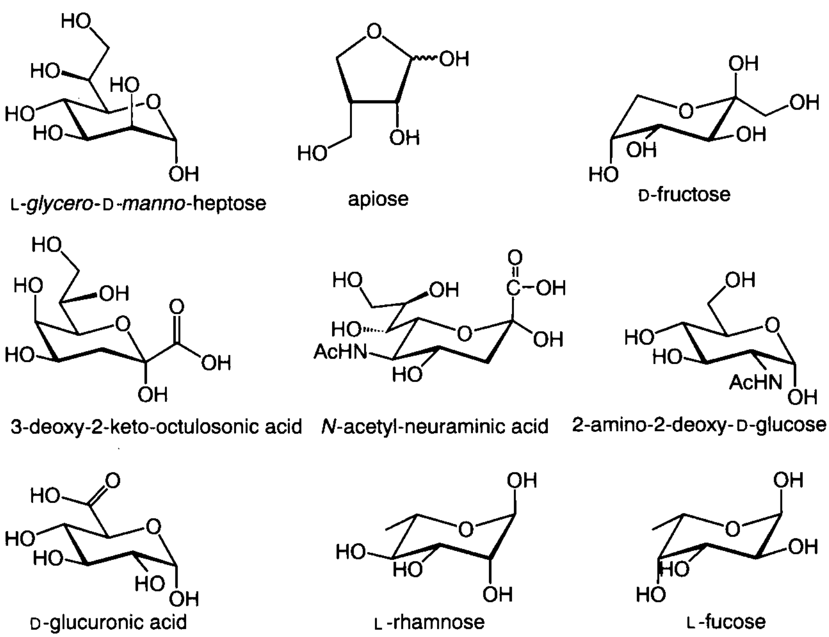


Figure 1.5 Some naturally occuring monosaccharides.

Monosaccharides may possess functionalities other than hydroxyls. Amino sugars are aldoses or ketoses which have a hydroxyl group replaced by an amino functionality. 2-Amino-2-deoxy-glucose is one of the most abundant amino sugars; it is a constituent of the polysaccharide chitin. It also appears in mammalian glycoproteins, linking the sugar chain to the protein. Monosaccharides may also be substituted with sulfates and phosphates. Furthermore, deoxy functions can often be present, and important examples of this class of monosaccharides are L-fucose and L-rhamnose.

1.3 Conformational properties of monosaccharides[7–10]

1.3.1 Ring shapes of pyranoses and furanoses

The concepts of conformational analysis are fundamental to a proper understanding of the relationship between the structure and properties of carbohydrates. Conformational analysis of monosaccharides is based on the assumption that the geometry of the pyranose ring is substantially the same as that of cyclohexane and that of furanoses is the same as that of cyclopentane. The ring oxygen of saccharides causes a slight change in molecular geometry, the carbon–oxygen bond being somewhat shorter than the carbon–carbon bond.

There are a number of recognised conformers for the pyranose ring[11, 12] there being two chairs ($^{1}C_{4}$, $^{4}C_{1}$), six boats ($^{1,4}B$, $B_{1,4}$, $^{2,5}B$, $B_{2,5}$, $^{o,3}B$, $B_{o,3}$), twelve half chairs ($^{o}H_{1}$, $^{1}H_{o}$, $^{1}H_{2}$, $^{2}H_{1}$, $^{2}H_{3}$, $^{3}H_{2}$, $^{4}H_{3}$, $^{3}H_{4}$, $^{4}H_{5}$, $^{5}H_{4}$, $^{5}H_{o}$, $^{o}H_{5}$) and six skews ($^{1}S_{5}$, $^{5}S_{1}$, $^{2}S_{o}$, $^{o}S_{2}$, $^{1}S_{3}$, $^{3}S_{1}$). To designate each form, the number(s) of the ring atom(s) lying above the plane of the pyranose ring is put as a superscript before the letter designating the conformational form and the number(s) of ring atoms lying below the plane is put after the letter as a subscript (Figure 1.6). The principal conformations of the furanose ring are the envelope (^{1}E, E_{1}, ^{2}E, E_{2}, ^{3}E,

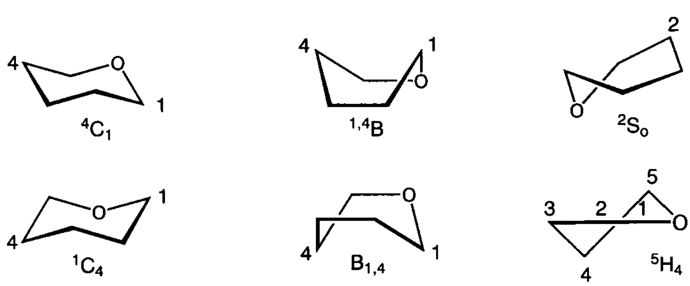


Figure 1.6 Conformers of pyranoses: chair (C), boat (B), skew (S) and half chair (H).

E_3, ^4E, E_4, ^4E, E_4), and the twist form ($^OT_1$, ^1T_o, $^1T_2$, $^2T_1$, $^2T_3$, $^3T_2$, $^3T_4$, $^4T_3$, ^4T_o, $^oT_4$), and they are designated in the same manner as the pyranoses (Figure 1.7).[13]

Most aldohexopyranoses exist in a chair form in which the hydroxymethyl group at C(5) assumes an equatorial position. All the β-D-hexopyranoses exist predominantly in the $^4C_1$ form since the alternative $^1C_4$ conformer involves a large unfavourable *syn*-diaxial interaction between the hydroxymethyl and anomeric group (Figure 1.8). Most of the α-D-hexopyranosides also adopt the $^4C_1$ conformation preferentially. Only α-idopyranoside and α-D-altropyranose show a tendency to exist in the $^1C_4$ conformation, and they coexist with the alternative $^4C_1$ conformations according to ^{1}H-NMR (hydrogen nuclear magnetic resonance) spectroscopy studies.

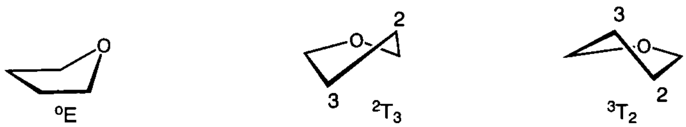


Figure 1.7 Conformers of furanoses: envelope (E) and twist (T).

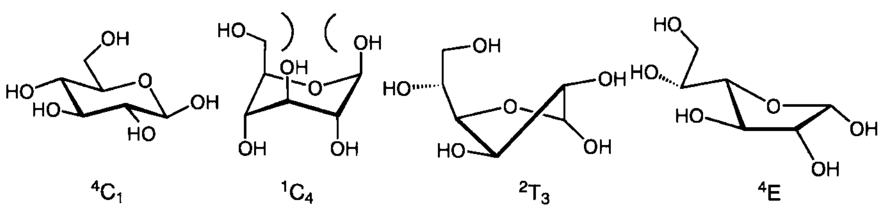


Figure 1.8 Some conformations of D-glucopyranose and furanose.

The conformational preferences of the aldopentoses, which have no hydroxymethyl group at C(5), are mainly governed by minimising steric repulsion between the hydroxyl groups. Thus, D-arabinopyranose favours the $^1C_4$ conformer, and α-D-lyxopyranoside and α-D-ribopyranoside are conformational mixtures and the other aldopentoses are predominantly in the $^1C_4$ form.

The preferred conformation of pyranoses in solution can be predicted by empirical approaches.[14] For example, free energies have been successfully estimated by summing quantitative free-energy terms for unfavourable interactions and accounting for the anomeric effects, which are individually depicted in Figure 1.9. The estimated free energies for both chair conformers can be calculated by summation of the various

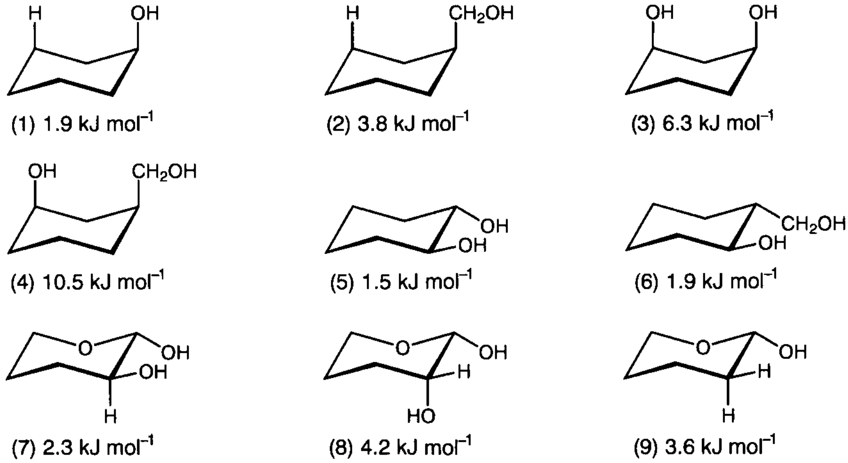
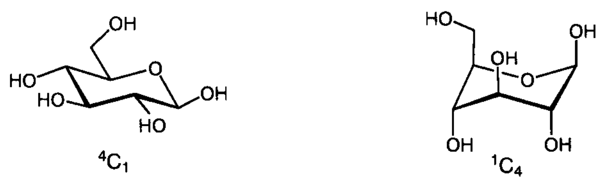


Figure 1.9 Estimated values for nonbonding interactions and anomeric effects in aqueous solution. Interactions (1)–(6) are nonbonding interactions, and interactions (7)–(9) arise from anomeric effects.

steric interactions and taking account of a possible absence of an anomeric affect. The predicted conformational preference was found to be in excellent agreement with experimental data. For example, it has been determined that the $^4C_1$ conformation of β-D-glucopyranose has a conformational energy of 8.7 kJ while that of the $^1C_4$ conformer is 33.6 kJ, which are in agreement with experimental data (Table 1.1). When

Table 1.1 Destabilising values for β-D-glucopyranose in $^4C_1$ and $^1C_4$ conformation



Gauche interactions	Free energy (kJ mol^{-1})	Axial–axial 1–3 interactions	Free energy (kJ mol^{-1})
O-1–O-2	1.5	O-1–O-3	6.3
O-2–O-3	1.5	O-2–O-4	6.3
O-3–O-4	1.5	C-6–O-1	10.5
O-4–O-6	1.9	C-6–O-3	10.5
Anomeric effect	2.3		
Total	8.7	Total	33.6

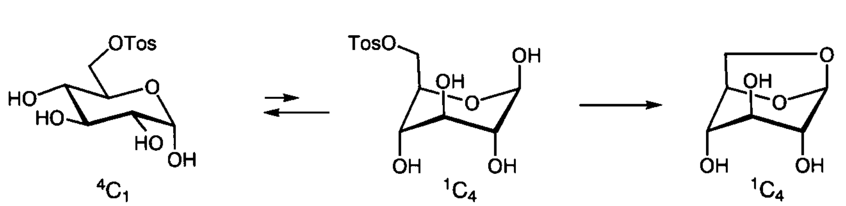
the free-energy difference between the two chair conformers is less than $3\,kJ\,mol^{-1}$, both conformers will be present in comparable amounts.

Computational methods have been used to predict the anomeric configuration and ring conformation of most aldopyranosides, and generally all are within reasonable agreement with experimental data.[15] Computational studies have also revealed other interesting properties of saccharides. For example, it has been proposed that D-glucose may undergo changes in its ring conformation with a rotation of 10° in the dihedral angles but surprisingly with virtually no changes in energy.[16]

In most cases, the boat and skew conformational isomers are significantly higher in energy and are therefore very sparsely populated conformational states. However, not all monosaccharides take on this conformational behaviour. For example, in solution D-alduronic acid exists as a mixture of a chair and skew conformer. An alduronic acid containing pentasaccharide, that is derived from heparin, has been singled out as having potent antithrombinic activity. It has been proposed that the skew conformation, which the alduronic unit actively adopts, accounts for the biological activity of the pentasaccharide.[17]

Most furanoses prefer the envelope conformation and it appears that a quasi-equatorial exocyclic side chain and a quasi-axial C(1)—O(1) bond (anomeric effect) are equally important stabilising factors (Figure 1.8).

It should be realised that minor conformational isomers may be important reaction intermediates. For example, treatment of 6-*O*-tosyl-D-glucopyranose with base results in the formation of a 1,6-anhydro derivative. The starting material exists mainly in the $^4C_1$ conformation. However, for reaction to occur the alternative $^1C_4$ conformation has to be adopted (Scheme 1.2). The introduction of protecting groups may alter the preferred conformation of saccharides.



Scheme 1.2 Formation of 1-6-anhydro-D-glucose.

1.3.2 *The anomeric effect*[18–25]

In general, the stability of a particular conformer can be explained solely by steric factors, and a basic rule for the conformational analysis of cyclohexane derivatives is that the equatorial position is the favoured orientation for a large substituent. The orientation of an electronegative substituent at the anomeric centre of a pyranoside, however, prefers an axial position. For example, in the case of α anomers with a D-gluco configuration, the tendency for axial orientation of the halogen atom is so strong that it is the only observed configuration both in solution and in the solid state. In aqueous solution, unsubstituted glucose exists as 36:64 mixture of the respective α and β anomer. The greater conformational stability of the β isomer with all its substituents in the equatorial orientation seems to be in accord with the conformational behaviour of substituted cyclohexanes. However, the *A*-value of the hydroxyl group in aqueous solution has been determined at $-1.25\,\mathrm{kcal\,mol^{-1}}$ and hence an α:β ratio of 11:89 is the predicted value.

The tendency of an electronegative substituent to adopt an axial orientation was first described by Edward[26] and named by Lemieux and Chü[27] 'the anomeric effect'. This orientational effect is observed in many other types of compounds that have the general feature of two heteroatoms linked to a tetrahedral centre; i.e. C—X—C—Y, in which X = N, O, S, and Y = Br, Cl, F, N, O or S, and is termed the generalised anomeric effect.[28,29]

Over the years, several models have been proposed to explain the anomeric effect, which has been the subject of considerable controversy. It has been proposed that the anomeric effect arises from a destabilising dipole–dipole or electron-pair–electron-pair-repulsion (Figure 1.10). These interactions are greatest in the β anomer, which therefore, is disfavoured. The repulsive dipole–dipole interactions will be reduced in solvents with high dielectric constants.[30] Indeed, the conformational

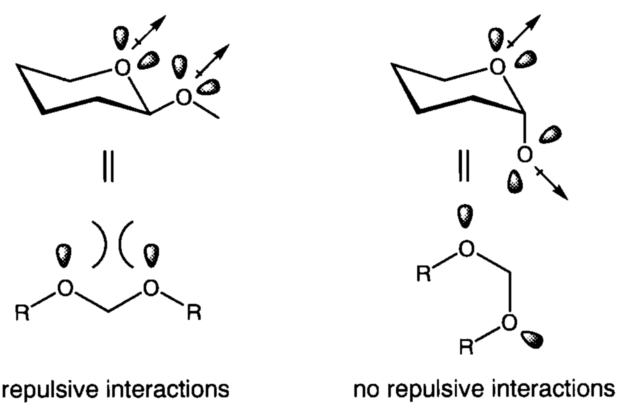
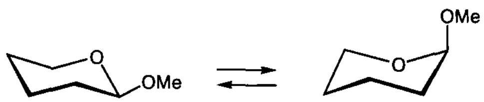


Figure 1.10 The anomeric effect: unfavourable dipole–dipole interactions in an equatorially substituted compound.

equilibrium of 2-methoxytetrahydropyran is strongly solvent-dependent, and the highest proportion of the axially substituted conformer is observed in tetrachloromethane and benzene, both solvents having very low dielectric constants (see Table 1.2).[31,32]

Table 1.2 Solvent dependence of the conformational equilibrium of 2-methoxytetrahydropyran



Solvent	Dielectric constant (ε)	Percentage axially substituted conformer
CCl_4	2.2	83
C_6H_{12}	2.3	82
CS_2	2.6	80
$CHCl_3$	4.7	71
$(CH_3)_2CO$	20.7	72
CH_3OH	32.6	69
CH_3CN	37.5	68
H_2O	78.5	52

Detailed examination of the geometry of compounds that experience an anomeric effect reveals that there are characteristic patterns of bond lengths and angles associated with particular conformations. For example, the C—Cl bond of chlorotetrahydropyran, which prefers the axial orientation, is significantly lengthened, and the adjacent C—O bond is shortened.[33] However, this effect is only observed in compounds with the favoured *gauche* conformation about the RO—C—X group. Thus, it is not seen in equatorially substituted compounds. Dipole–dipole interactions fail to account for the differences in bond length and bond angle observed between α and β anomers. To account for these effects, an alternative explanation for the anomeric effect has been proposed.[34] Thus, the axial conformer is stabilised by delocalisation of an electron pair of the oxygen atom to the periplanar C—X bond (e.g. X=Cl) antibonding orbital (Figure 1.11). This interaction, which is not present in the β anomer, explains the shortening of the C—O bond of the α anomer, which has some double bond character. The size of the alkoxy group has little effect on the anomeric preference. For example, in a solution of chloroform, 2-methoxytetrahydropyran (R = Me) and 2-*tert*-butoxytetrahydropyran (R = *t*-Bu) both adopt a chair conformation with the substituent mainly in the axial orientation.[35] On the other hand, the electron-withdrawing ability of the anomeric substituent has a marked

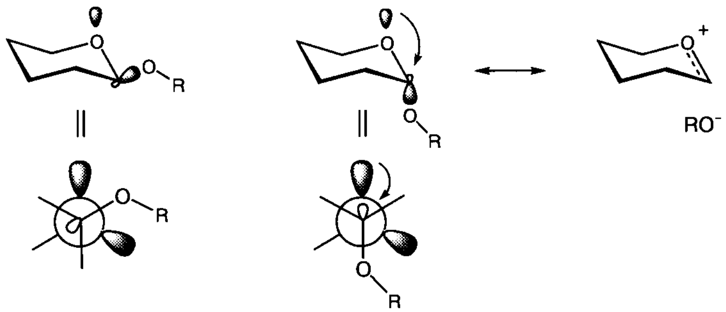


Figure 1.11 The anomeric effect: interaction of the endocyclic oxygen electron lone pair with the nonbonding orbital in an axially substituted compound.

effect on the axial preference[36] and, in general, a more electronegative anomeric substituent exhibits a stronger preference for an axial orientation. The partial transfer of electron density from a heteroatom to an antibonding σ-orbital is enhanced by the presence of a more electronegative anomeric substituent.

The term 'exoanomeric effect' was introduced to describe an orientational effect of the aglycon part.[31] In this case, the electron density of the lone pair of the exocyclic oxygen atom is transferred to the antibonding orbital of the endocyclic C—O bond (Figure 1.12). Essentially, this effect

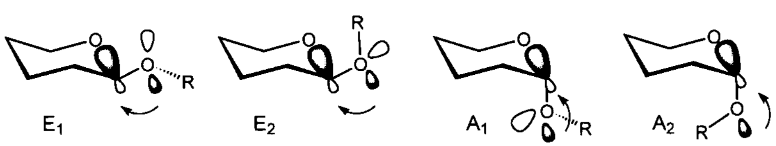
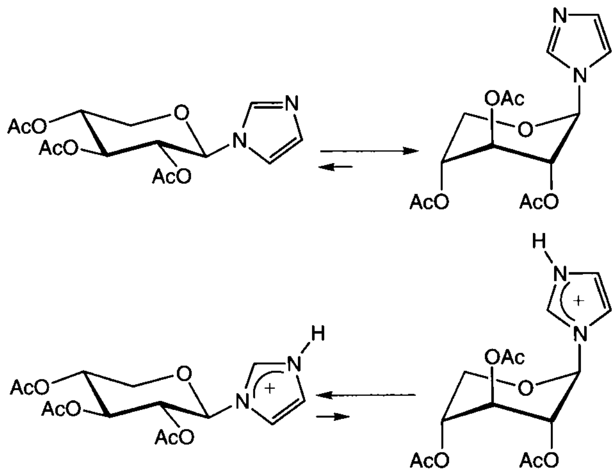


Figure 1.12 Conformations that are stabilised by the exoanomeric effect.

is maximised when the p orbital for an unshared pair of electrons is periplanar to the C(1)–ring-oxygen bond. As can be seen in Figure 1.12, the exoanomeric effect is present in the α as well as in the β anomer. Thus, the α anomer can be stabilised by two anomeric effects (both exo and endo) and the β anomer by only one (exo). Furthermore, two conformations (E_1 and E_2) for the equatorial substituted anomer can be identified that are stabilised by an exoanomeric effect. However, E_2 experiences unfavourable steric interactions between the aglycon and ring moiety and is approximately 0.6 kcal mol^{-1} higher in energy than the corresponding E_1 conformer. In the case of the axially substituted anomer also, two conformations are stabilised by an anomeric effect (A_1 and A_2) but A_2 is strongly disfavoured for steric reasons. In the case of the α anomer, the two anomeric effects compete for electron delocalisation towards the anomeric carbon. In the case of a β anomer this competition is absent and hence its exoanomeric effect is stronger.

Another remarkable anomeric effect has been observed which has been named the 'reverse anomeric effect'.[37] By protonation of the imidazole-substituted D-xylo derivative the equilibrium shifts from mainly axial form to mainly equatorial form (Scheme 1.3). There are no changes in the steric requirement between the two compounds and therefore only a stereoelectronic explanation can account for this anomaly. Lemieux has



Scheme 1.3 The reverse anomeric effect.

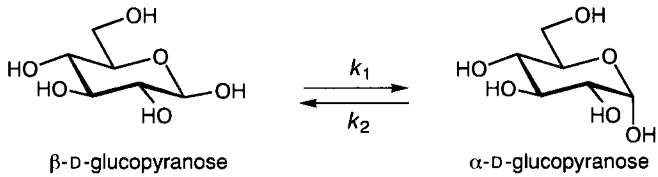
proposed that a strongly electronegative aglycon is unable to stabilise a glycosidic linkage because of the lack of lone-pair electrons. An alternative argument is that the anomeric effect for such a protonated compound is reversed because dipole–dipole interactions no longer reinforce the stereoelectronic preference.

The conformational effects arising from the endoanomeric effect are for furanoses much less profound and as a result relatively little research has been performed in this area. The puckering of the furanose ring of an α and a β anomer usually adjusts the anomeric substituent in a quasi-axial orientation and hence both anomers experience a similar stereoelectronic effect. On the other hand, the conformational preference of the exocyclic C—O bond is controlled by the exoanomeric effect in the usual way.

1.3.3 *The equilibrium composition of monosaccharides in solution*[38, 14b]

In solution, the α and β forms of D-glucose have a characteristic optical rotation that changes with time until a constant value is reached. This change in optical rotation is called mutarotation and is indicative of an anomeric equilibration occurring in solution.

For some monosaccharides, the rate of mutarotation ($K = k_1 + k_2$) is found to obey a simple first-order rate law in which $-d[\alpha]/dt = k_1[\alpha] - k_2[\beta]$ (Scheme 1.4). Glucose, mannose, lyxose and xylose exhibit



Scheme 1.4 Mutarotation of glucose.

this behaviour. The equilibrium mixture consists predominantly of the α and β pyranoses, when mutarotation can be described by this equation whether measured starting from the α or β anomer. Other sugars such as arabinose, ribose, galactose and talose show a much more complex mutarotation consisting of a fast change of optical rotation followed by a slow change. The fast change in optical rotation is attributed to a pyranose–furanose equilibration, and the slow part to anomerisation.

In general, a six-membered pyranose form is preferred over a five-membered furanose form because of the lower ring strain, and these cyclic forms are very much favoured over the acyclic aldehyde or ketone forms. As can be seen in Table 1.3, at equilibrium, the anomeric ratios of pyranoses differ considerably between aldoses. These observations are a direct consequence of differences in anomeric and steric effects between monosaccharides. The amount of the pyranose and furanose present in aqueous solution varies considerably for the different monosaccharides. Some sugars, such as D-glucose, have undetectable amounts of furanose according ^{1}H-NMR spectroscopic measurements whereas others, such as D-altrose, have 30% furanose content under identical conditions.

The main steric interactions in a five-membered ring are between 1,2-*cis* substituents. For example, D-glucofuranose experiences an unfavourable interaction between the 3-hydroxyl group and the carbon side chain at C(4), which explains its small quantity in solution. On the other hand, this steric interaction is absent in galactofuranose, and, at equilibrium, the latter isomer is present in significant quantity (Figure 1.13).

Table 1.3 Composition of some aldoses at equilibrium in aqueous solution

	Pyranose (%)			Furanose (%)		
Aldose	α	β	total	α	β	total
Glucose	38	62	100	0.1	0.2	0.3
Mannose	65.5	34.5	100	–	–	–
Gulose	0.1	78	78	<0.1	22	22
Idose	39	36	75	11	14	25
Galactose	29	64	93	3	4	7
Talose	40	29	69	20	11	31
Ribose	21	59	80	6	14	20
Xylose	36.5	63	99.5	–	–	<0.5
Lyxose	70	28	98	1.5	0.5	2
Altrose	27	43	70	17	13	30

3-Deoxy-D-glucose which also lacks this unfavourable steric interaction has 28% of the furanose form in aqueous solution.

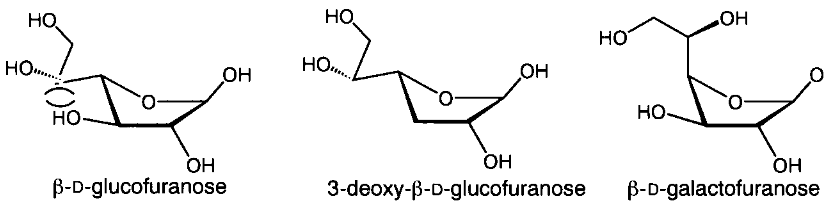


Figure 1.13 Conformations of β-D-glucofuranose, 3-deoxy-β-D-glucofuranose and β-D-galactofuranose.

The orientation of a C(2) substituent has a remarkable effect on the anomeric equilibrium. In general, an axial alkoxy group at C(2) increases and an equatorial alkoxy group decreases the anomeric effect. For example, in aqueous solution, D-mannose contains at equilibrium as much as 65.5% of the α anomer whereas only 38% of this form is present for D-glucose. Reeves argued[39] that for D-mannose the β anomer is destabilised by the proximity of the endocyclic oxygen and the C(1) and C(2) oxygen atoms, resulting in unfavourable dipole–dipole interactions (Figure 1.14). This effect, which was named the Δ2 effect, has also been explained in stereoelectronic terms. It has been proposed[40] that the anomeric effect for α-D-mannose is significantly stronger because of lowering of the antibonding orbital of the C(1)—O(1) bond as a result of secondary orbital overlap between the antibonding orbitals of C(1)—O(1) and C(2)—O(2).

The presence of particular substituents and the nature of the solvent appear to have an effect on the equilibrium composition of particular monosaccharides. As already discussed, the anomeric effect is stronger in