Carbohydrates: Occurrence, Structures and Chemistry

FRIEDER W. LICHTENTHALER, Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Darmstadt, Germany

1. Introduction

Terrestrial biomass constitutes a multifaceted conglomeration of low and high molecular mass products, exemplified by sugars, hydroxy and amino acids, lipids, and biopolymers such as cellulose, hemicelluloses, chitin, starch, lignin and proteins. By far the most abundant group of these organic products and materials, in fact about two thirds of the annually renewable biomass, are carbohydrates, i.e., a single class of natural products. As the term 'carbohydrate' (German '*Kohlenhydrate*'; French '*hydrates de carbone*') implies, they were originally considered to consist solely of carbon and water in a 1:1 ratio, in recognition of the fact that the empirical composition of monosaccharides can be expressed as $C_n(H_2O)_n$. Today, however, the term is used generically in a much wider sense, not only comprising polysaccharides, oligosaccharides, and monosaccharides, but substances derived thereof by reduction of the carbonyl group (alditols), by oxidation of one or more terminal groups to carboxylic acids, or by replacement of one or more hydroxyl group (s) by a hydrogen atom, an amino group, a thiol group, or similar heteroatomic groups. A similarly broad meaning applies to the word 'sugar', which is often used as a synonym for 'monosaccharide', but may also be applied to simple compounds containing more than one monosaccharide unit. Indeed, in everyday usage 'sugar' signifies table sugar, which is sucrose (German '*Saccharose*'; French '*sucrose*' or '*saccharose*'), a disaccharide composed of the two monosaccharides D-glucose and D-fructose.

Carbohydrates appear at an early stage in the conversion of carbon dioxide into organic compounds by plants, which build up carbohydrates from carbon dioxide and water by photosynthesis. Animals have no way of synthesizing carbohydrates from carbon dioxide and rely on plants for their supply. The carbohydrates are then converted into other organic materials by a variety of biosynthetic pathways.

Carbohydrates serve as sources (sugars) and stores of energy (starch and glycogen); they also form a major portion of the supporting tissue of

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plants (cellulose) and of some animals (chitin in crustacea and insects); they play a basic role as part of the nucleic acids DNA and RNA. Other carbohydrates are found as components of a variety of natural products, such as antibiotics, bacterial cell walls, blood group substances, glycolipids, and glycoproteins, the latter, due to their multifaceted carbohydrate-based recognition phenomena, forming the basis of glycobiology.

At the turn of the millenium, a large collection of books on carbohydrate chemistry and biochemistry have appeared, ranging from comparatively brief introductions [1–3] to more elaborate monographs [4–7] and *multivolume* comprehensive treatises [8, 9]. They are recommended as more profound sources of information.

2. Monosaccharides

The generic term 'monosaccharide' denotes a single sugar unit without glycosidic connection to other such units. Chemically, monosaccharides are either polyhydroxyaldehydes or *aldoses* (e.g., glucose) or polyhydroxyketones or *ketoses* (e.g., fructose), the ending 'ose' being the suffix to denote a sugar. Monosaccharides are classified according to the number of carbon atoms they contain, i.e., hexoses and ketohexoses (or hexuloses) of the general formula $C_6H_{12}O_6$ or pentoses and pentuloses ($C_5H_{10}O_5$). Subdivisions are made according to functional groups which may also be present, for example, aminohexoses ($C_6H_{13}O_5N$), deoxyhexoses ($C_6H_{12}O_5$), and hexuronic acids ($C_6H_{10}O_7$). Monosaccharides with fewer (trioses, tetroses) or more carbon atoms (heptoses, octoses, etc.) are rare.

A large variety of monosaccharides occur in nature [10], the most common being D-*Glucose* (→ Glucose and Glucose-Containing Syrups) [50-99-7], also known as dextrose, blood sugar, or grape sugar ('*Traubenzucker*' in German), is a pentahydroxyhexanal, hence belonging to the class of aldohexoses (see Section 2.1). Glucose can be considered the parent compound of the monosaccharide family, because it is not only the most abundant monosaccharide in nature but also the one most extensively studied. It occurs as such in many fruits and plants, in concentrations of 0.08 – 0.1 % in human blood, and constitutes the basic building unit of starch, cellulose, and glycogen. Other ubiquitous aldohexoses are D-*mannose* [3458-28-4], occurring naturally mainly in polysaccharides ('mannans', e.g., from ivory nut) and D-*galactose* [59-23-4], a frequent constituent of oligosaccharides, notably lactose and raffinose, and of primary cell wall polysaccharides (pectins, galactans, arabinogalactans). A corresponding isomeric 2-ketohexose is D-*fructose* [57-48-7] (→ Fructose), the sweetest natural sugar, which occurs in many fruits and in honey, and, glycosidically linked, in sucrose and the polysaccharide inulin (→ Inulin) a reserve carbohydrate for many plants (chicory, Jerusalem artichoke). Other important natural sugars are the aldopentose D-*ribose* [50-69-1], which constitutes a building block of the ribonucleic acids, L-*arabinose*, widely distributed in bacterial polysaccharides, gums and pectic materials, and D-*xylose* [58-86-6], of widespread occurrence in pentosans ('xylans') that accumulate as agricultural wastes (cottonseed hulls, corn cobs).

2.1. Structure and Configuration

D-Glucose, the most abundant monosaccharide, has the molecular formula $C_6H_{12}O_6$ as shown by elemental analysis and molecular mass determination. As evidenced from ensuing reactions (see below) this is consistent with a six-carbon, straight-chain pentahydroxyaldehyde of the following structural formula, an aldohexose in carbohydrate notation (Fig. 1).

This structure contains four asymmetric centers, thus $2^4 = 16$ stereoisomers exist, which can be grouped into eight pairs of enantiomers, and classified as D- and L-sugars. In the D-sugars, the highest numbered asymmetric hydroxyl

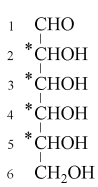


Figure 1. Structural formula of aldohexoses, of which [due to the four chiral centers (marked by *)] 16 stereoisomers are possible

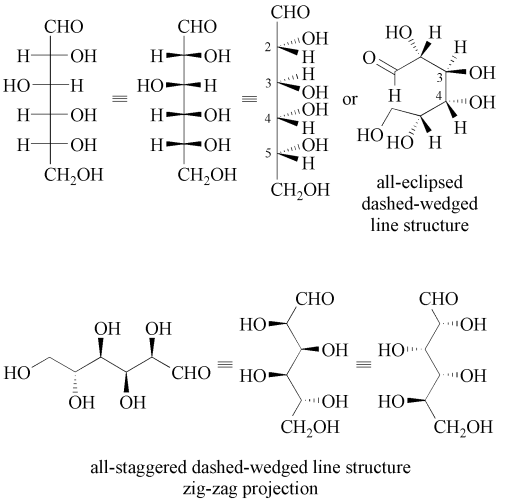


Figure 2. Configurational representations of the linear (acyclic) form of D-glucose: Traditional Fischer projection formula (top left) and its transformation into the more realistic dashed-wedged line depictions with the six-carbon chain in zigzag arrangement.

group (C-5 in glucose) has the same configuration as the asymmetric center in D-glyceraldehyde and, likewise, all L-sugars are configurationally derived from L-glyceraldehyde. A convenient way to show configurational relationships was introduced by EMIL FISCHER in 1891 [11, 12], now termed Fischer projection formula (Fig. 2), as it — literally — projects tetrahedral space relationships into a plane. The resulting formulas are simple to write and easy to visualize, yet they require the setting up of conventions: The carbon chain of a sugar is oriented vertically and to the rear with the aldehyde group at the top; hydrogen atoms and hydroxyl groups at the asymmetric carbon atoms stand out in front. The resulting three-dimensional model is then imagined to be flattened and the groups are laid on the plane of the paper. If the lower-most asymmetric center (C-5 in glucose) has the hydroxyl group to the right, it is considered to have the D-configuration. FISCHER's decision to place the hydroxyl group of natural glucose to the right, hence D-glucose, was purely arbitrary, yet proved to be a fortunate one, since much later, in 1951, it was proven by special X-ray structural analysis [13] that he had made the right choice.

The D-aldose family tree is shown in Figure 3, comprising five of the most important monosaccharides, the aldopentoses D-ribose and D-xylose, and the hexoses D-glucose, D-mannose, and D-galactose, each having the hydroxyl group at the highest-numbered stereocenter (at the bottom) pointing to the right. Likewise, all L-aldoses are configurationally derived from L-glyceraldehyde, entailing a family tree with the lowest hydroxyl group to the left; the respective projection formulas being, in essence, mirror images to those in Figure 3.

A similar system is used to build up the series of ketohexoses or hexuloses, i.e., monosaccharides with a keto group at C-2, which therefore contain one asymmetric carbon atom less (Fig. 4).

2.2. Ring Forms of Sugars: Cyclic Hemiacetals

In the solid state and in solution monosaccharides exist in a cyclic hemiacetal form, ring closure corresponding to reaction between the aldehyde group and either the C-4-OH or C-5-OH. Cyclization involving O-4 results in a five-membered ring structurally related to furan and therefore designated as a *furanose*, whilst hemiacetal formation with O-5 gives rise to an essentially strain-free, hence sterically more favored, six-membered ring, a derivative of pyran, hence termed a *pyranose*. Either ring formation generates a new asymmetric carbon atom at C-1, the anomeric center, thereby giving rise to diastereomeric hemiacetals which are called and labeled α and β. For visualization of the cyclic hemiacetal forms of sugars, HAWORTH, in 1928 [14], introduced his projection formula, in which the rings are derived from the open-chain form and drawn as lying perpendicular to the paper with the ring oxygen away from the viewer. To facilitate this mode of viewing, the front part is usually accentuated by wedges as shown in Figure 5 for the β-anomers of pyranose and furanose forms of D-glucose. The projections devised by MILLS in 1954 [15], corresponding to those customary for terpenes and steroids, are also very useful for revealing the stereochemistry of sugars in their cyclic hemiacetal forms: the ring is placed in the plane of the paper with solid or broken wedge-shaped lines to show the orientation of substituents (i.e., OH and CH_2OH groups).

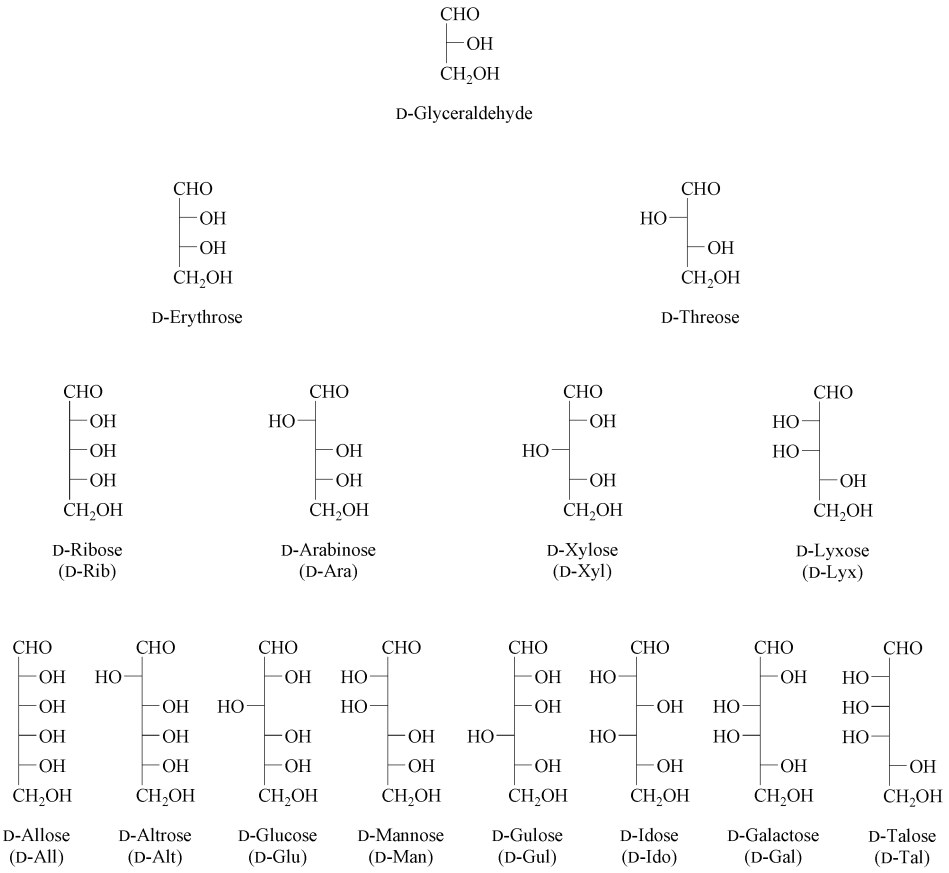


Figure 3. The D-aldose family tree (up to aldohexoses) in their acyclic forms: Common names and Fischer projection formulas, with secondary hydrogen atoms omitted for clarity

2.3. Conformation of Pyranoses and Furanoses

The concepts of conformation are fundamental to a proper understanding of the structure–property relationships of carbohydrates, most notably of the regio- and stereoselectivities of their reactions. The conformational analysis of monosaccharides is based on the assumption that the geometry of the pyranose ring is essentially the same as that of cyclohexane and, analogously, that of furanoses the same as that of cyclopentane — a realistic view, since a ring oxygen causes only a slight change in molecular geometry. Hence, the rhombus-shaped Haworth formulas which imply a planar ring, and the equally flat dashed-wedged line configurational depictions by Mills (Fig. 5) are inadequate to represent the actual three-dimensional shape of the rings and the steric orientation of the ring substituents (OH and CH_2OH groups). For the six-membered pyranose ring a number of recognized conformers exist [16]: two chairs ($^1C_4$, $^4C_1$), six boats (e.g., $^{1,4}B$ and $B_{1,4}$ in Fig. 6), six skews and twelve half-chairs (e.g., $^oS_2$ and $^5H_4$ forms).

Although there are exceptions, most aldohexoses adopt the chair conformation that places the bulky hydroxymethyl group at the C-5 terminus in the equatorial position. Hence, β-D-hexopyranosides are predominantly in the $^4C_1$ chair conformation, since each of the alternative forms outlined in Figure 6, most notably the $^1C_4$ chair, are energetically less favored. For glucose, this preference means that, in the α-form, four of the five substituents are

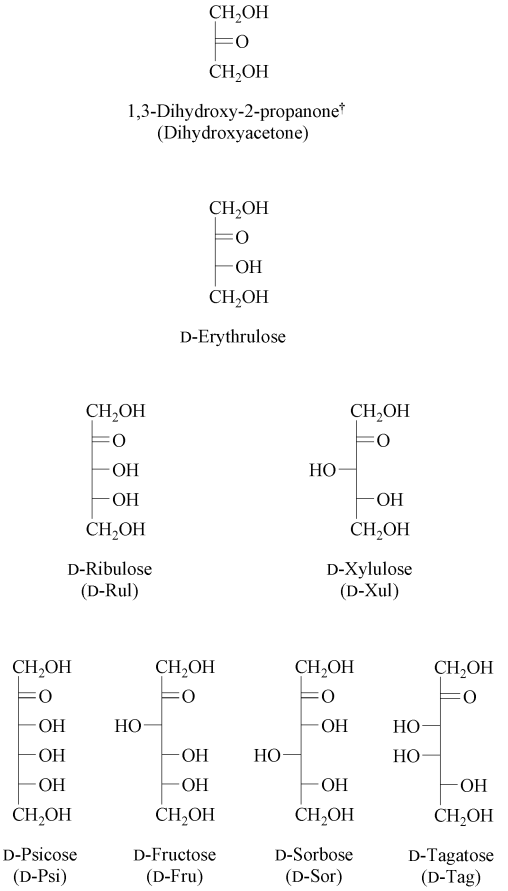


Figure 4. The D-ketohexose (or D-hexulose) family tree: Trivial names, systematic designation (in brackets) and Fischer projection formulas
† Not regarded as being a sugar, due to absence of an asymmetric carbon atom.

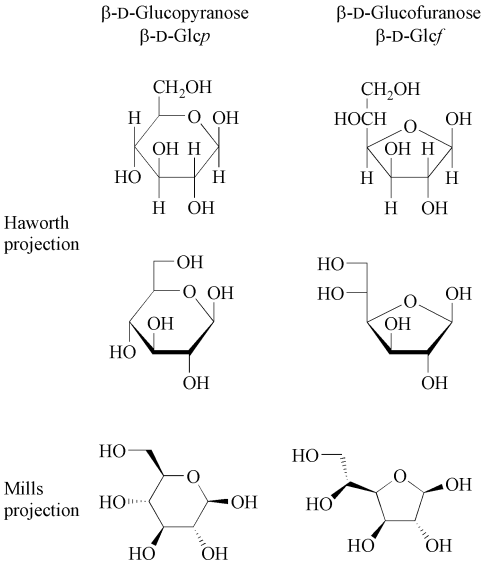


Figure 5. Haworth and Mills projection formulas for the β-anomers of D-glucopyranose and D-glucofuranose (in the formula at the center and at the bottom, the carbon and C-hydrogen atoms are omitted for clarity)

equatorial, and one is forced to lie axial; in the β-form, all substituents are equatorial (Fig. 7). This situation is unique for glucose; the other seven D-aldohexoses contain one or more axial substituents.

The hexulose counterpart to the conformational forms of D-glucose is the D-fructose isomerization scheme depicted in Figure 8. Whilst the crystalline product is the β-D-fructopyranose in the $^2C_5$ chair conformation as evidenced by X-ray analysis [17], on dissolution in water, equilibration is essentially instantaneous to yield a mixture mainly containing the β-*p*-form (73 % at 25 °C, the only sweet one in fact), together with the β-*f*- (20 %), α-*f*- (5 %) and α-*p*-forms (2 %) [18]. The acyclic form through which equilibration occurs is present only to a minute extent.

The principal conformations of the furanose ring are the *envelope* (*E*) — one atom lying above or below a plane formed by the other four ring atoms — or the *twist* (*T*) arrangement, in which three ring atoms are in a plane and the other two above and below, respectively. As energy differences between the various *E* and *T*

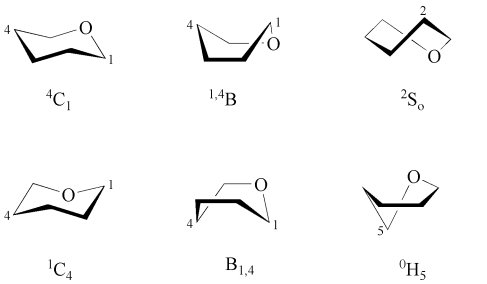


Figure 6. Conformational forms of pyranose rings: chair (*C*), boat (*B*), skew (*S*) and half-chair (*H*).
To designate each form, the ring atom numeral lying above the plane of reference appears as a superscript preceding the letter, those below the plane are written as subscripts and follow the letter

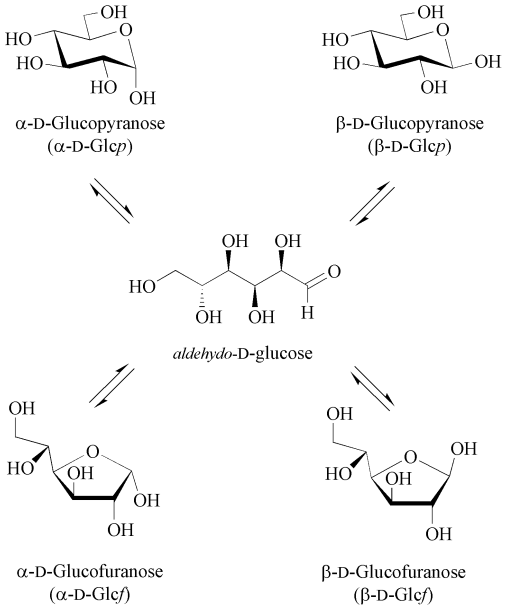


Figure 7. Cyclic hemiacetal forms of D-glucose in configurational representation. In solution, these forms rapidly interconvert through the energetically unfavorable acyclic form; in water at 25 °C the two pyranoid forms are nearly exclusively adopted, the equilibrium mixture amounting to 62 % of the β-*p* and 38 % of the α-*p* anomers. From water, D-glucose crystallizes in the α-pyranose form
The six-membered (pyranose) ring is denoted by the symbol *p* after the three-letter symbol for the monosaccharide (for example, Glc*p*), the five-membered (furanose) ring correspondingly is signated by an *f* (e.g., Glc*f*).

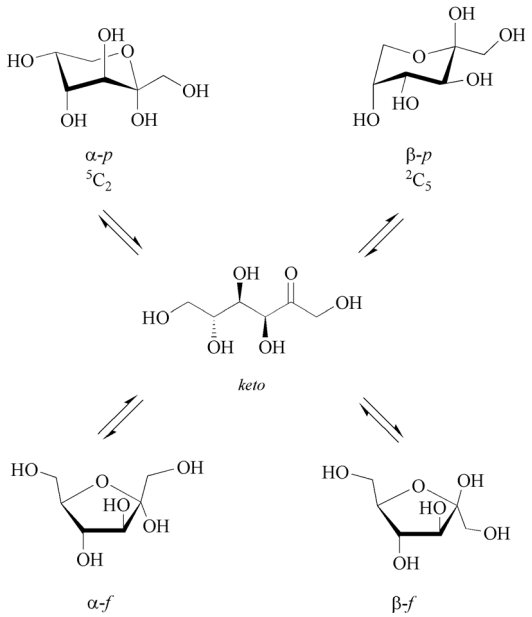


Figure 8. Forms of D-fructose in solution. In water, the major conformers are the β-pyranose (β-*p*, 73 % at 25 °C) and β-furanose (β-*f*, 20 %) forms [18]. On crystallization from water, D-fructose adopts the $^2C_5$ chair conformation in the crystal lattice as evidenced by X-ray analysis [17]

conformations are small, the form actually adopted depends on the type of ring substitution (hexoses, hexuloses, pentoses), their configuration, their solvation and the type of intra- or intermolecular hydrogen bonding present. Accordingly, the exact conformation of an individual furanose is usually not known — except for the crystalline state when an X-ray structural analysis is available. Thus, the planar Haworth and Mills projection formulas are the preferred way of drawing furanose forms (Fig. 9).

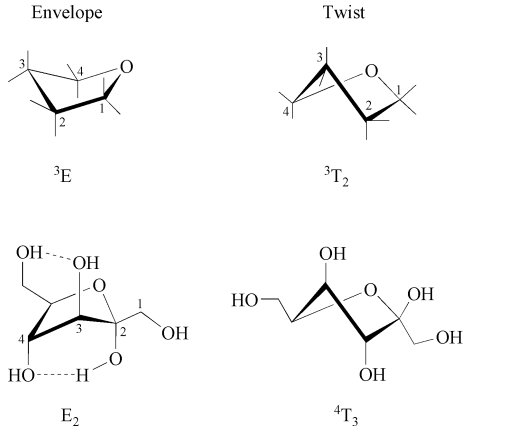


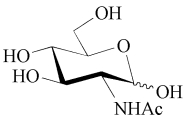
Figure 9. The envelope conformation (top left) is the ^3E form as defined by the C-3 atom lying above the plane formed by the other ring atoms. The defined plane for the twist form (top right) is the triangle given by C-1, C-4, and O-4, entailing the conformational description $^3T_2$. In aprotic solvents (dimethyl sulfoxide) D-fructose populates the E_2 envelope conformation to a substantial extent [18], whilst in crystalline sucrose, the β-D-fructofuranose portion adopts the $^4T_3$ twist form [19, 20] (bottom entries)

2.4. Structural Variations of Monosaccharides

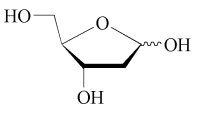
Sugars may possess functionalities other than hydroxyl groups. Amino sugars are aldoses, which have a hydroxyl group replaced by an

amino functionality, e.g., D-*glucosamine* (2-amino-2-deoxy-D-glucose), which is one of the most abundant sugars. In its *N*-acetylated form (*N*-acetyl-D-glucosamine), it is a constituent of the polysaccharide chitin (→ Chitin and Chitosan), that forms the hard shells of crustaceans and other anthropods, but also appears in mammalian glycoproteins and links the sugar chain to the protein. Monosaccharides lacking a hydroxyl group at the terminal C-6, i.e., 6-deoxy-sugars, are likewise of wide occurrence, for example, L-*rhamnose* (6-deoxy-D-mannose) is found in plant and bacterial polysaccharides whereas L-*fucose* (6-deoxy-D-galactose) is present in combined form in animals, plants, and microorganisms. 2-Deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) is the exceedingly important sugar component of DNA, various mono-, di- and trideoxy sugars are constituents of many antibiotics, bacterial polysaccharides, and cardiac glycosides.

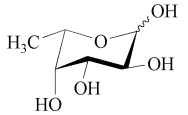
The uronic acids are aldoses that contain a carboxylic acid chain terminating function, and occur in nature as important constituents of many polysaccharides. The D-*gluco* compound, D-*glucuronic acid*, was first isolated from urine (hence the name), in which it occurs in the form of glycosides and glycosyl esters of toxic substances that the body detoxifies in this way.



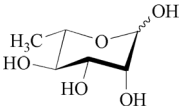
N-Acetyl-D-glucosamine
2-acetamido-2-deoxy-D-glucopyranose
(D-GlcNA*cp*)



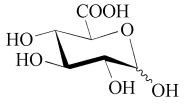
2-Deoxy-D-ribose
2-deoxy-D-*erythro*-pentafuranose (D-dRib*f*)



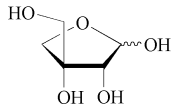
L-Fucose
6-deoxy-L-galactopyranose
(L-Fuc*p*)



L-Rhamnose
6-deoxy-L-mannopyranose
(L-Rha*p*)



D-Glucuronic acid
(D-GlcA*p*)



D-Apiose
3-*C*-hydroxymethyl-D-*glycero*-tetrose (D-Api*f*)

Branched-chain sugars, i.e., saccharides with a nonlinear carbon chain, are comparatively uncommon, the more widely occurring being D-*apiose* (3-*C*-hydroxymethyl-D-*glycero*-tetrose), abundant in polysaccharides of parsley and duckweed [21], and D-*hamamelose* (2-*C*-hydroxymethyl-D-ribose), a component of the bark of witchhazel [22].

3. Oligosaccharides

Oligosaccharides are compounds in which monosaccharide units are joined by glycosidic linkages, i.e., simple polymers containing between two and ten monosaccharide residues. Accordingly, there are disaccharides — a disaccharide composed of two hexopyranoses can have 5120 distinguishable isomeric forms — trisaccharides, tetrasaccharides, etc. They may be further subdivided into homo- (consisting of only one type of sugar) and hetero-oligosaccharides, and into those that are reducing (presence of a free hemiacetal group) or nonreducing. A comprehensive listing of the di-, tri-, and higher oligosaccharides known up to 1990 is available [23].

3.1. Common Disaccharides

3.1.1. Sucrose

Sucrose, affectionately called "the royal carbohydrate" [24], is a nonreducing disaccharide because its component sugars, D-glucose and D-fructose, are glycosidically linked through their anomeric carbon atoms: Sucrose is a-β-D-fructofuranosyl α-D-glucopyranoside (see Fig. 10). It is widely distributed throughout the plant kingdom, is the main carbohydrate reserve and energy source and an indispensable dietary material for humans (→ Sugar). For centuries, sucrose has been the world's most plentiful produced organic compound of low molecular mass, the present (2008) annual production from sugar-cane and sugar beet being an impressive 169×10^6 t [25]. Its chemistry is fairly well developed [26].

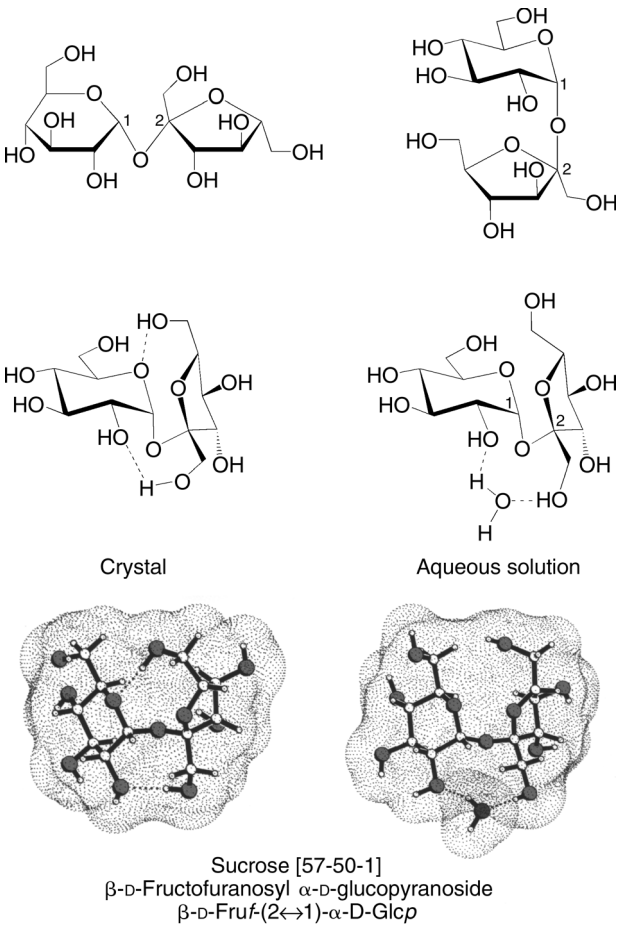
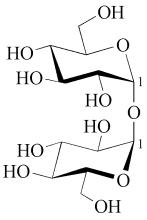


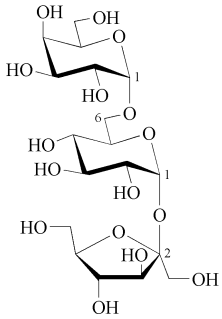
Figure 10. Common structural representations of sucrose (top entries), the molecular geometry realized in the crystal featuring two intramolecular hydrogen bonds between the glucose and fructose portion [19, 20] (bottom left), and the sterically similar disposition of the two sugar units towards each other in aqueous solution form, caused by hydrogen bonding through a 'water bridge' [27]. The bottom entries show the solvent-accessible surfaces (dotted areas) of the crystal form (left) and the form adopted in water [27] (right), clearly demonstrating that sucrose has an unusually compact overall shape, more so than any other disaccharide

3.1.2. *α,α*-Trehalose and Raffinose

α,α-Trehalose, a nonreducing D-glucosyl D-glucoside, occurs extensively in the lower species of the plant kingdom (fungi, young mushrooms, yeasts, lichens, and algae). In bakers' yeast it accounts for as much as 15 % of the dry mass, in the metabolic cycle of insects it circulates like glucose does in the mammalian cycle. Similarly nonreducing, due to being a galactosylated sucrose, is the trisaccharide *raffinose*, distributed almost as widely in the plant kingdom as sucrose, yet in lower concentration (e.g., less than 0.05 % in sugar beet).



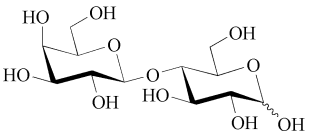
α,α-Trehalose [99-20-7]
α-D-glucopyranosyl
α-D-glucopyranoside
(α-D-Glc*p*[1↔1]
α-D-Glc*p*)



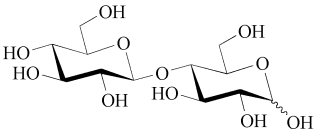
Raffinose [512-69-6]
α-D-galactopyranosyl-
(1→6)-sucrose
(α-D-Gal*p*-(1→6)-α-D-
Glc*p*(1↔2)-β-D-Fru*f*)

3.1.3. Lactose, Cellobiose, and Maltose

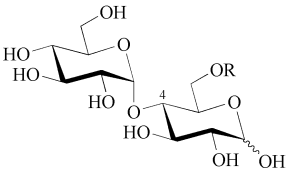
There are only very few naturally occurring oligosaccharides with a free anomeric hydroxyl group, which therefore possess reducing properties. The most important example is *lactose* (milk sugar, → Lactose and Derivatives), an ingredient of the milk of mammals (up to 5 % in cows). As it is produced on an industrial scale, from whey, it represents the only large-scale available sugar derived from animal rather than plant sources. Uses include human food, pharmaceuticals, and animal feeds. The reducing gluco-disaccharides *cellobiose* and *maltose* (malt sugar) are chemical or enzymatic hydrolysis products of the polysaccharides cellulose and starch, respectively, and, hence are not regarded as native oligosaccharides.



Lactose [63-42-3]
β-D-galactopyranosyl-(1→4)-D-glucopyranose
(β-D-Gal*p*-[1→4]-D-Glc*p*)



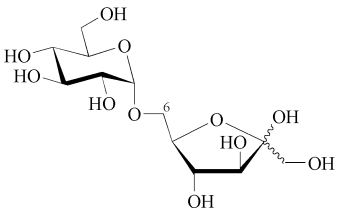
Cellobiose [528-50-7]
β-D-glucopyranosyl-(1→4)-D-glucopyranose
(β-D-Glc*p*-(1→4)-D-Glc*p*)



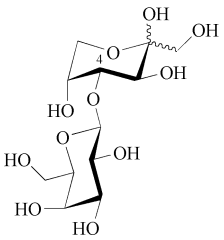
Maltose [69-79-4]
α-D-glucopyranosyl-(1→4)-D-glucopyranose
(α-D-Glc*p*-(1→4)-D-Glc*p*)

3.1.4. Isomaltulose and Lactulose

Isomaltulose (palatinose, → Sugar Alcohols, Section 5.1) and lactulose are both produced in fairly large amounts from sucrose and lactose, respectively, and constitute 6-*O*-glucosyl- and 4-*O*-galactosyl-fructoses. The sucrose → isomaltulose transformation, industrially realized presently (2009) at an estimated 8×10^4 t/a-scale, is effected by a *Protaminobacter rubrum*-induced glucosyl shift from the anomeric fructosyl oxygen to its O-6 position, taking place in a mostly intramolecular fashion via a closed-shell intermediate [28], whilst the generation of lactulose from lactose, presently running at a 12×10^3 t/a level, comprises a base-promoted C-1 → C-2 carbonyl shift. Most of the isomaltulose produced is subsequently hydrogenated to isomalt (→ Sugar Alcohols, Section 5.2), a low-calorie sweetener with the same taste profile as sucrose. Lactulose (→ Lactose and Derivatives, Section 2.1) has medical and pharmaceutical applications, mainly for treating intestinal disorders.



Isomaltulose [13718-94-0]
α-D-glucopyranosyl-(1→6)-D-fructofuranose
(α-D-Glc*p*-(1→6)-D-Fru*f*)



Lactulose [4618-18-2]
β-D-galactopyranosyl-(1→4)-D-fructopyranose
(D-Gal*p*-β(1→4)-D-Fru*f*)

3.1.5. Other Heterooligosaccharides

Heterooligosaccharides of considerably higher complexity occur in large variety in plants, animals and microorganisms where they are covalently bound to proteins ('glycoproteins')

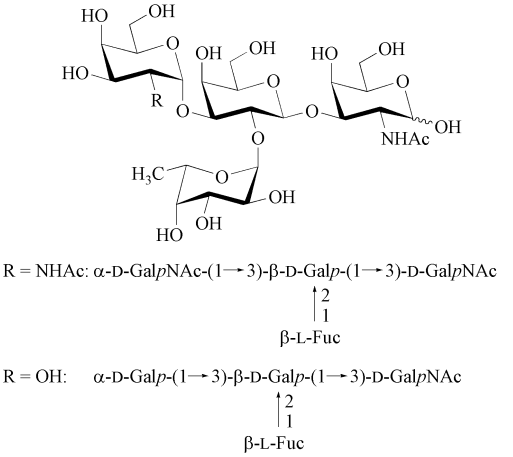


Figure 11. Human blood groups determinants: Differentiation between type A (R = NHAc) and B (R = OH) is effected by relatively simple changes within a branched tetrasaccharide linked to lipid components on the surface of red blood cells

and lipids ('glycolipids') or other hydrophobic entities, and, as such, are implicated in a range of key biological processes: cell-cell recognition, fertilization, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organization into specific tissues, viral and bacterial infection and tumor cell metastasis [29–31]. Red blood cells, for example, carry carbohydrate antigens which determine blood group types in humans: type A people have the tetrasaccharide in Figure 11 with R = NHAc (i.e., a GalNAc residue) as a key antigen linked by lipid components to the surfaces of red blood cells; in type B blood, the tetrasaccharide determinant is exceedingly similar — formal replacement of NHAc by OH, i.e., GalNAc by Gal — yet on mixing with type A blood leads to clumping and precipitation [32].

All *N*-glycoproteins (*N*-glycans) share the peptide-linked pentasaccharide fragment in Figure 12, consisting of three mannose units in a branched arrangement and two GlcNAc residues, of which the terminal one is *N*-glycosidically linked to an asparagine moiety of the protein. Branching out from this uniform core region are monosaccharides and oligosaccharide chains of high structural diversity leading to multiple types of branched and unbranched glycoproteins [33].

3.2. Cyclodextrins (→ Cyclodextrins)

Although discovered more than 100 years ago, the cyclic glucooligosaccharides termed cyclodextrins (based on dextrose, which is an old name for glucose) remained laboratory curiosities until the 1970s when they began to be used commercially [34]. Their large-scale production is based upon the degradation of starch by enzymes elaborated by *Bacillus macerans* ('CGTases'), involving excision and reconnection of single turns from the helical α-(1→4)-glucan (amylose) chain (cf. Fig. 13) to provide cyclic α-(1→4)-linked glucooligosaccharides with six, seven and eight glucose units. They are named α-, β- and γ-cyclodextrin, respectively.

Cyclodextrins are truncated cones with well-defined cavities. All the secondary hydroxyl groups are located at the wider rim of the cone leaving the primary CH_2OH groups to protrude from the narrower opening. The respective

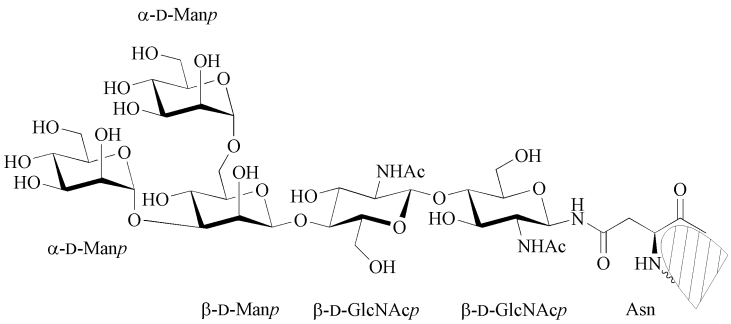


Figure 12. Central core region common to all *N*-glycoproteins is a pentasaccharide, *N*-glycosidically linked to the carbamido nitrogen of an asparagine moiety (Asn) within the peptide chain

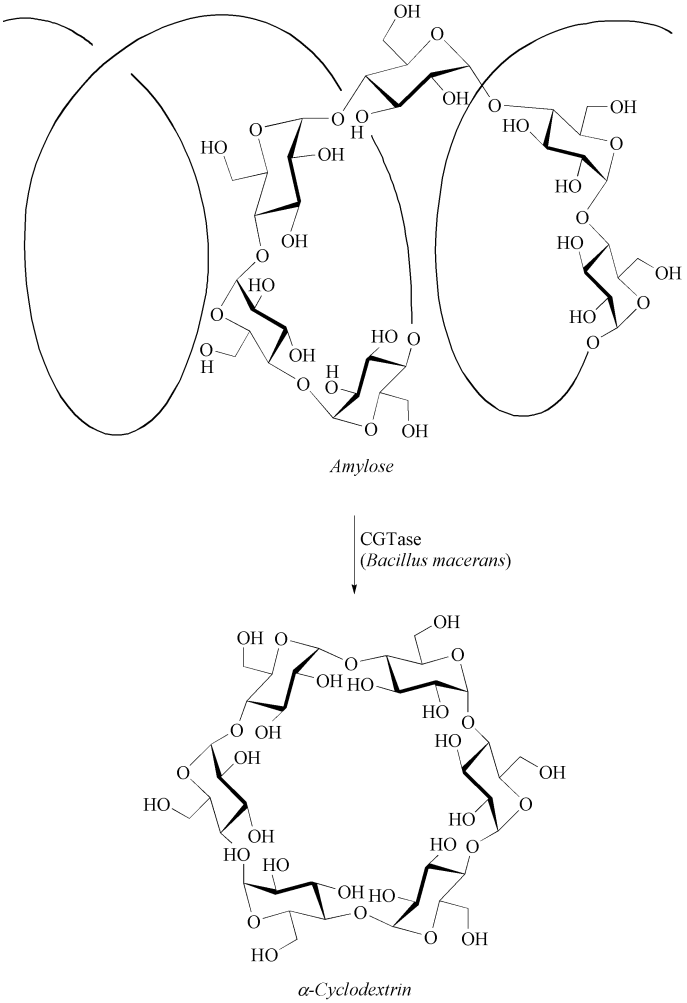


Figure 13. Sketch representation of a left-handed, single-stranded helix of V_H-amylose (top), and of α-cyclodextrin (bottom), which de facto represents a single turn of the amylose helix excised and re-connected by *Bacillus macerans*-derived enzymes (CGTases). The close analogy allows V_H-amylose to be considered as a tubular analogue of α-cyclodextrin.

cavities, as exemplified by that of α-cyclodextrin with its six glucose units (Fig. 14 [35, 36]), are distinctly hydrophobic in character, and show an amazing propensity to form stable complexes with a large variety of equally hydrophobic, sterically fitting guest molecules by incorporating them into their cavities [34, 35], thereby changing the physical and chemical properties of the included guest. The features and properties of the resulting cyclodextrin inclusion compounds has led to the exploitation of cyclodextrins for a wide variety of purposes: as drug carriers [37, 38], as stationary phases for the separation of enantiomers [39, 40], as building blocks for supramolecular structures [41], and as enzyme models [42].

4. Polysaccharides

The bulk of the annually renewable carbohydrate-biomass are polysaccharides (glycans), such as cellulose, hemicelluloses, chitin, starch, and inulin. Invariably composed of

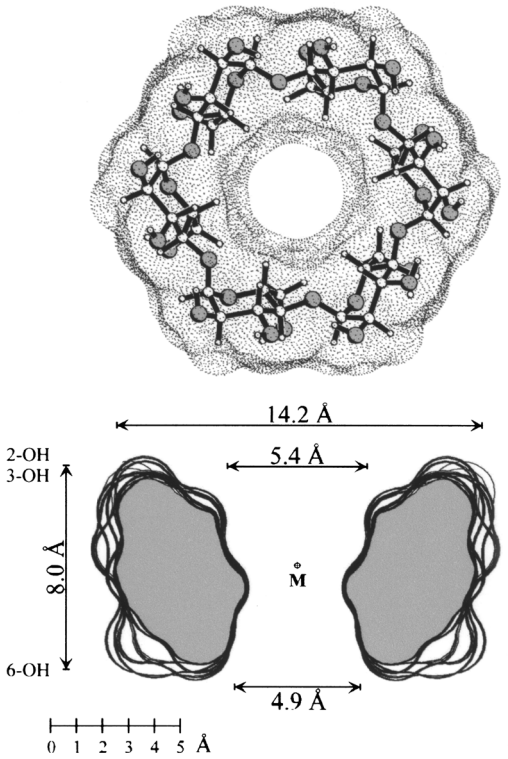


Figure 14. Top: Ball-and-stick model representations of the X-ray-derived solid-state structure of α-cyclodextrin, together with its solvent-accessible surface, shown as a dotted pattern
Bottom: Cross section contour of a plane perpendicular to the macrocycle's mean plane with approximate molecular dimensions [35, 36]

monosaccharide units, they have high molecular masses and, hence, differ significantly in their physical properties. The majority of naturally occurring polysaccharides contain 80 – 100 units, although a few are made up of considerably more.

4.1. Cellulose (→ Cellulose)

Cellulose [9004-34-6] is an unbranched glucan composed of β-(1→4)-linked D-glucopyranosyl units (see Fig. 15) with an average molecular mass equivalent to about 5000 units. It is the most abundant organic material found in the plant kingdom, forming the principal constituent of the cell walls of higher plants and providing them with their structural strength. Cotton wool is almost pure cellulose, but in wood, the other chief source of the polymer, cellulose is found in close association with other polysaccharides (mainly hemicelluloses) and lignin. X-ray analysis and electron microscopy indicate that these long chains lie side by side in bundles,

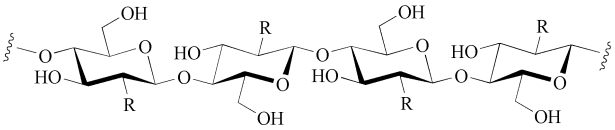


Figure 15. Structural representations of segments of cellulose (R = OH), chitin (R = NHAc), and chitosan (R = NH_2)

held together by a multiplicity of hydrogen bonds between the numerous neighboring OH groups. These bundles are twisted together to form rope-like structures, which themselves are grouped to form the fibers that can be seen. In wood (→ Wood, Chap. 1) these cellulose "ropes" are embedded in lignin to give a structure that has been likened to reinforced concrete.

4.2. Chitin (→ Chitin and Chitosan)

Chitin is a polysaccharide composed of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranosyl residues (cf. Fig. 15), of which about one out of every six is not acetylated. Chitin is the major organic component of the exoskeleton (shells) of insects, crabs, lobsters, etc. and, hence, an abundant byproduct of the fishing industries.

Chitosan, a related water-soluble polysaccharide in which the vast majority of residues is not acetylated (i.e., a β-(1→4)-linked chain of 2-amino-2-deoxy-D-glucose residues), can be obtained from chitin by deacetylation in concentrated sodium hydroxide solution.

4.3. Starches (→ Starch)

The principal food-reserve polysaccharides in the plant kingdom are starches. They form the major source of carbohydrates in the human diet and are therefore of great economic importance, being isolated on an industrial scale from many sources. The two components, amylose and amylopectin, vary in relative amounts among the different sources; from less than 2 % of amylose in waxy maize to about 80 % of amylose in amylomaize (both corn starches), but the majority of starches contain between 15 and 35 % amylose.

4.3.1. Amylose

Amylose [9005-82-7] is made up of long chains, each containing 100 or more α-(1→4)-linked glucopyranosyl units which, due to the kink in every α-glycosidic linkage, tend to coil to helical segments with six glucose units forming one turn (see sketch in Fig. 13). Amylose is the fraction of starch that gives the intense blue color with iodine; this color arises because iodine molecules become trapped within the hydrophobic channel of the helical segments of the polysaccharide (Fig. 16).

An illustration of a left-handed, single stranded helix of V_H-amylose forms the top sketch of Figure 16, whereas a more detailed representation of its molecular geometry, based on X-ray diffraction data [43] and calculation of the solvent-accessible contact surfaces [44], is indicated by dots with ball-and-stick models superimposed and presented as the central diagram within the same figure. The channel generated by the helical arrangement of the α-D-glucose residues, of dimensions corresponding to those of the cavity of α-cyclodextrin, is clearly apparent. The outside surface area of V_H-type amylose is uniformly hydrophilic (in conformity with its solubility in water) whereas the central channel is distinctly hydrophobic — making it predestined to incorporate equally hydrophobic guests such as iodine or fatty acids [44]. Thus, in the case of iodine a linear polyiodide chain becomes embedded into this channel (see bottom diagram of Fig. 16), producing an intensely blue-colored starch-iodine complex [44].

4.3.2. Amylopectin

Amylopectin [9037-22-3] is also an α-(1→4)-glucan, yet the molecule is branched via *O*-6 at about every 25 units. The molecular size of amylopectin is of the order of 10^6 D-glucose residues, making it one of the largest naturally occurring molecules. The secondary structure is characterized by several hundred linear chains of about 20 – 25 glucose units each, which are connected in a variety of arrangements to give clusters for which the tassel-on-a-string model (see Fig. 17) is proposed. With iodine, amylopectin produces only a dull-red color, indicating that the short linear chain portions cannot coil effectively to provide the helices required for formation of inclusion complexes.

4.4. Dextrans (→ Dextran)

Dextrans are linear water-soluble α-(1→6)-glucans with only occasional branches via

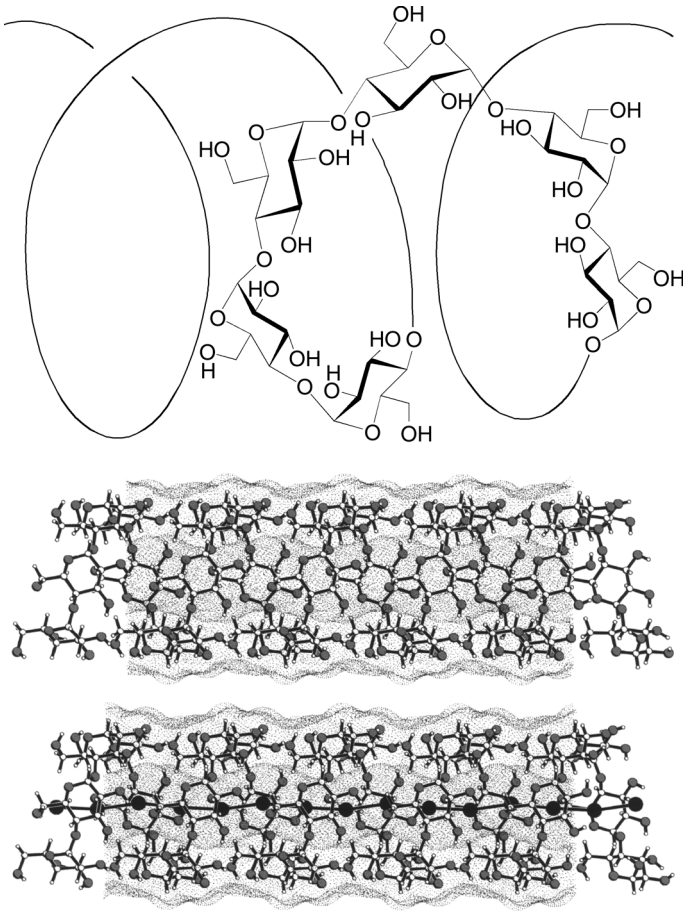


Figure 16. Top: single stranded helix of V_H-amylose; Center: ball-and-stick model of the architecture of the V_H-amylose helical array; Bottom: the complexation of iodine within the central channel of the helical array [43, 44]

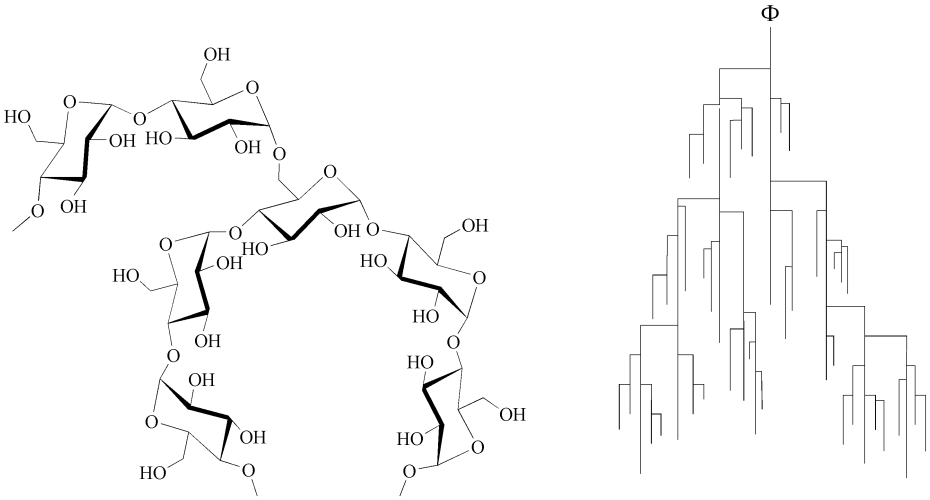


Figure 17. Schematic representation of a section of amylopectin with an $\alpha(1\rightarrow6)$-branch of a helical chain of $\alpha(1\rightarrow4)$-glucopyranosyl residues (left), with the tassel-on-string model of its higher level structure (ϕ = reducing end)

O-2, O-3 or O-4. They are generated from sucrose by a large number of organisms, of which *Leuconostoc mesenteroides* is used to produce the slightly branched commercial dextran, used clinically as a plasma volume expander.

4.5. Inulin(→ Inulin)

Inulin is a polysaccharide composed of $\beta(1\rightarrow2)$-linked D-fructofuranose units with varying chain length of about 15 – 30 units. It is present to the extent of 30 % or more in various plants such as dahlias or Jerusalem artichokes where it replaces starch either partially or completely as the food storage carbohydrate [45, 46]. The structure of inulin is unique in leaving no 'reducing end', as this is glycosidically blocked by an α-D-glucopyranose residue — a sucrose unit in fact (Fig. 18).

Commercial inulins, e.g., those isolated from chicory, have a degree of polymerization far below that found in other polysaccharides, their molecular sizes ranging from around 5 to 30 units [44].

4.6. Other Polysaccharides (→ Polysaccharides)

A plethora of other homo- and heteropolysaccharides are found in nature, most notably

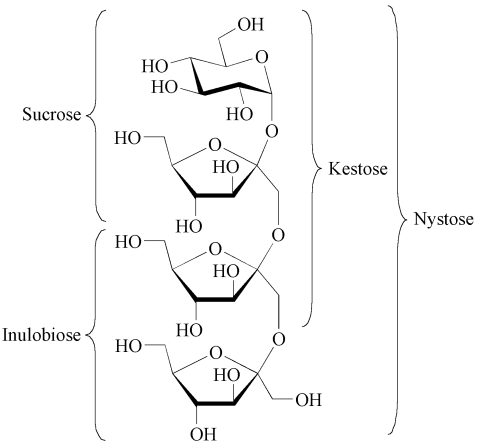


Figure 18. Nystose fragment of inulin, showing sub-fragments corresponding to sucrose, inulobiose and 1-kestose [44]

D-xylans (hemicelluloses with linear chains of β-(1→4)-D-xylopyranosyl units), *pectins* (principal constituent D-galacturonic acid), plant gums (building blocks D-galactose, L-arabinose, L-rhamnose) and various algal and microbial polysaccharides with, in part, unusual sugar units: L-guluronic and D-mannuronic acids in alginates, glucuronic acid and pyruvate acetals in agar, sulfated galactosyl residues in carrageenans, or ribitol phosphates in *teichoic acids*. Excellent accounts on this subject have been given [47, 48].

5. Nomenclature

According to common practice, trivial names are used for monosaccharides and for many naturally occurring oligosaccharides. With the development of carbohydrate chemistry, however, and ever-increasing numbers of newly defined compounds, it has become necessary to introduce a semi-systematic nomenclature which has been approved by the joint commission of IUPAC (International Union of Pure and Applied Chemistry) and IUB (International Union of Biochemistry) [49]. This nomenclature is based on the classical names for monosaccharides which appear, written in italics, as a "configurational prefix". For example, D-*xylo*, L-*arabino* and D-*gluco* refer to the distribution of asymmetric carbon atoms along a carbon chain of any length, designating the configuration of the corresponding monosaccharide.

Monosaccharides with an aldehydic carbonyl or potential aldehydic carbonyl group are called aldoses; those with a ketonic or potential ketonic carbonyl group, ketoses, with the chain length given by the root, such as pentose, hexose, or heptose and pentulose, hexulose, etc. In ketoses the position of the keto group is indicated by the position number. D-Fructose is systematically named D-*arabino*-2-hexulose.

Replacement of a hydroxyl group by hydrogen is indicated by the prefix deoxy, for example, L-rhamnose is a 6-deoxy-L-aldohexose of *manno*-configuration. Replacement of a hydroxyl group by any other substituent is formally regarded as taking place via the deoxysugar. Thus, a sugar with an amino group instead of hydroxyl is called an aminodeoxysugar. Formation of ether groups, most

commonly methyl, is indicated by adding '*O*-methyl-' to the front of the name preceded by the number of the carbon atom whose hydroxyl group has been etherified. Esters, for example, acetates are designated by adding either '*O*-acetyl-' before the name or 'acetate' after it, in each case again preceding the descriptor with the appropriate carbon number.

The ring size is indicated by a suffix: pyranose for six-membered rings, furanose for five-membered rings, and pyranulose for six-membered ketose rings. The six-membered cyclic hemiacetal of D-fructose is named D-*arabino*-2-hexopyranosulose. The symbol α or β for the anomeric configuration is always written together with the configurational symbol D or L (α-D, β-D, α-L, β-L).

Names of oligosaccharides are formed by combining the monosaccharide names, usually the trivial names. The nonreducing disaccharide sucrose is a β-D-fructofuranosyl α-D-glucopyranoside. The endings "yl" and "ide" describe the fructose part as the aglycone and the glucose part as the glycone in this "glycoside". It is thus clearly indicated that both sugars are glycosidically linked by their anomeric hydroxyl groups. In reducing oligosaccharides the reducing monosaccharide is the root, and all attached monosaccharide units are named as substituents. The disaccharide lactose is therefore named β-D-galactopyranosyl-(1→4)-D-glucopyranose. Position numbers and arrows indicate a β-configurated glycosidic bond between the anomeric hydroxyl group (carbon atom 1) of D-galactose (glyconic part) and the hydroxyl group at C-4 of D-glucose (aglyconic part).

For a description of more complex oligosaccharides an abbreviation system has come into use — as for oligopeptides and oligonucleotides — that is unambiguous and practical; thus, each monosaccharide is abbreviated by a three-letter symbol, comprising the first three letters of its trivial name, i.e.:

Glucose	Glc	Xylose	Xyl
Fructose	Fru	Arabinose	Ara
Galactose	Gal	Ribose	Rib
Mannose	Man	Deoxyribose	dRib
Fucose	Fuc	Glucosamine	GlcN
Rhamnose	Rha	*N*-Acetylglucosamine	GlcNAc

The anomeric configuration and D- or L-affiliation is written before the three-letter acronym, the ring size (*p* for pyranose, *f* for furanose) is added to the end, followed by the intersaccharidic linkage position in the case of oligosaccharides. Sucrose (see Fig. 10), accordingly, is β-D-Fru*f*-(2→1)-α-D-Glc*p*, lactose β-D-Gal*p*-(1→4)-D-Glc*p*.

6. General Reactions

6.1. Hydrolysis

The hydrolysis of disaccharides such as sucrose and lactose, or polysaccharides like starch and cellulosic materials to their free component sugars is of great importance not only in the food and fermentation industries, but increasingly so in the chemical industry as well toward the generation of bulk chemicals from polysaccharidic waste materials (→ Carbohydrates as Organic Raw Materials). This release of the component sugars from di-, oligo- or polysaccharides can be effected by enzymes called glycosidases or chemically by acid treatment.

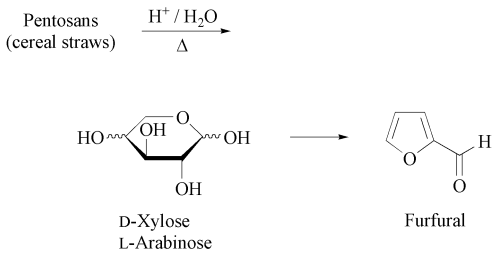
Enzymatic hydrolysis proceeds with high specificity towards both the sugar and the configuration at the anomeric center. Maltase, an α-D-glucosidase obtainable from barley malt, catalyzes the hydrolysis of α-linked di-, oligo- and polysaccharides (sucrose, maltose, starch, dextrans), whereas the almond emulsin-derived enzyme is a β-glucosidase cleaving only β-linked glycosides.

Acid-induced hydrolysis of glycosides requires comparatively harsh conditions, standard techniques requiring 1 M sulfuric acid at 100 °C for 4 h for hexose-containing polysaccharides and 0.25 M H_2SO_4 at 70 °C for hemicellulose pentosans [50, 51]. The acid hydrolysis of starch, for example, is performed industrially on a 10^6 t/a basis, the resulting D-glucose being used in the liquid form (corn syrup) as a sweetener (→ Glucose and Glucose-Containing Syrups, Chap. 4).

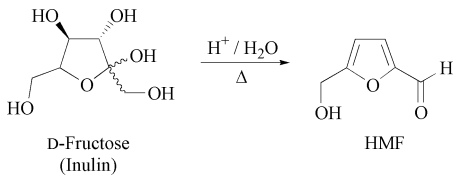
6.2. Dehydration

Under the rigid acidic conditions required for polysaccharide hydrolysis to the constituent

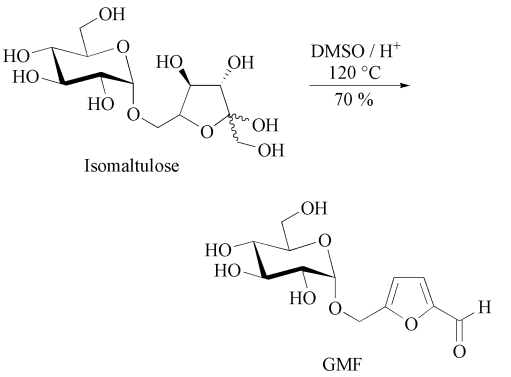
sugars, their partial degradation can usually not be avoided, as strong acid induces elimination of water in various ways. When selecting special conditions though, these dehydrations can be crafted into generating furfural (2-furaldehyde) from the hemicellulose pentosans contained in agricultural and forestry wastes, the pentoses initially formed then being dehydrated. This process is industrially realized on a 2×10^5 t/a level [52] (→ Furfural and Derivatives), thus furfural is one of the very few biomass-derived large-volume organic chemicals.



Another key biomass-derived chemical of high industrial potential is 5-hydroxymethylfurfural (HMF) readily accessible from fructose or inulin hydrolysates by acid-induced elimination of three moles of water [53]. Developments towards its production from polysaccharides contained in agricultural and forestry waste materials appears to be well advanced [54] (→ Carbohydrates as Organic Raw Materials).



When using nonaqueous conditions (e.g., DMSO as the solvent and a strongly acidic resin) the fructose part of disaccharides such as isomaltulose can similarly be converted into the respective, glucosylated HMF-derivative (GMF) without cleaving the acid-sensitive glycosidic linkage [55].



The trisaccharide *raffinose*, a storage carbohydrate in many plants, can be cleaved enzymatically with α-galactosidase into sucrose and galactose. This reaction is used in the beet sugar industry to increase the yield of sucrose, as well as to improve the digestibility of food from leguminous plants. Raffinose can also be fermented by bakers' yeast to form melibiose (α-D-Gal*p*-(1→6)-D-Glc*p*).

6.3. Isomerization

Under basic conditions aldoses isomerize to their C-2 epimers and the corresponding ketoses. Specific conditions may be applied for the preparation of particular products. In 0.035 % aqueous sodium hydroxide at 35 °C for 100 h, for example, any one of the three sugars D-glucose, D-fructose, or D-mannose is converted into an equilibrium mixture containing D-glucose (57 %), D-fructose (28 %), and D-mannose (3 %). This interconversion is known as the *Lobry de Bruyn – van Ekenstein rearrangement* [56], which occurs by enolization of either sugar to the 1,2-enediolate — the mechanism being best visualized in the Fischer projection formulae (Fig. 19). In favorable cases alkali-promoted stereoisomerizations can be of preparative use, especially when the starting sugar is relatively abundant and when structural features minimize competing reactions. Thus, lactulose can be satisfactorily made by the epimerization of lactose (→ Lactose and Derivatives), or maltulose from maltose [57, 58], using either sodium hydroxide alone or with borate or aluminate as coreagents.

Alternatively, C-2-epimerization without ketose involvement can be induced by use of

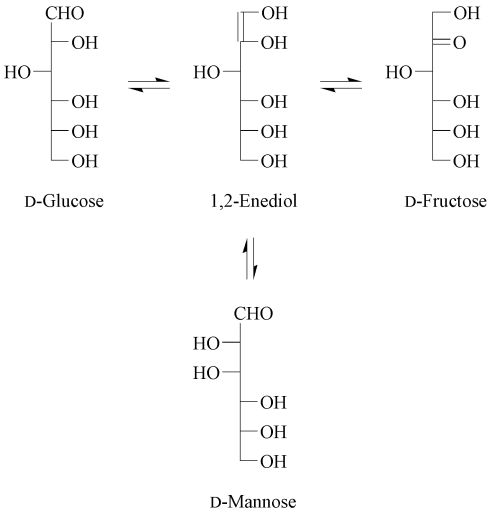


Figure 19. Lobry de Bruyn-van Ekenstein rearrangement

molybdate under mildly acidic conditions. This remarkable transformation (*Bílik reaction*) [59] involves a C-1/C-2 interchange within the carbon skeleton.

6.4. Decomposition

Exposure of carbohydrates to high temperatures leads to decomposition (dehydration) with darkening (caramelization). This can be used to produce a caramel color (e.g., that of cola beverages). Thermal decomposition in the presence of amino acids (*Maillard reaction* [60]) is responsible for many color- and flavor-forming reactions, such as in the baking of bread and roasting of meat or coffee. The highly complex Maillard reaction, elicited during cooking or the preservation of food, involves condensations, Amadori-type rearrangements of glycosylamine intermediates, and degradations. The dark-colored products formed are responsible for the nonenzymic browning observed with various foodstuffs.

7. Reactions at the Carbonyl Group

In solution, reducing sugars establish an equilibrium between their pyranoid and furanoid hemiacetal forms via the open-chain carbonyl species. Although the latter is present only to a very minor extent, equilibration between the different forms is fast, so that reducing sugars undergo the typical carbonyl reactions with *O*-, *N*-, *S*-, and *C*-nucleophiles.

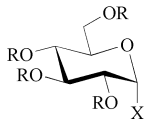
7.1. Glycosides

With alcohols in the presence of acid catalysts reducing sugars give the respective full acetals, called glycosides (Fischer glycosidation) [61]. Depending on the distribution of furanoid and pyranoid tautomeric forms in the reaction mixture, not only glycosides with different ring sizes, i.e., glycopyranosides and glycofuranosides, can result, but also the corresponding α- and β-anomers. Thus, when D-glucose is heated with methanol in the presence of anhydrous hydrogen chloride, pure crystalline methyl α-D-glucopyranoside can be isolated in 90 % yield, whilst the same reaction with D-galactose yields a mixture of the two furanoid and pyranoid methyl galactosides, from which the methyl α-D-galactopyranoside can be obtained in crystalline form but in only 41 % yield.

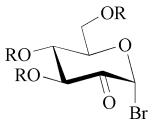
Although the Fischer glycosidation presents one of the easiest means for preparing glycosides, the synthesis of more complex members of this series, particularly the construction of the biologically important heterooligosaccharides widely distributed in nature, requires the use of more sophisticated methodologies. These preparative techniques generally involve the coupling of suitably OH-group protected glycosyl donors (i.e., glycosides with an anomeric leaving group) with an alcohol component — usually a mono-, di-, or oligosaccharide in which the hydroxyls carry protecting groups [62] except for the one to be glycosylated ('the glycosyl acceptor'). Effective glycosyl donors, derived from D-glucose, are listed in Table 1. They represent the presently most suitable donors for achieving glycosidic bond-forming reactions with high stereocontrol: glycosyl bromides [63], and iodides [64], 2-oxoglycosyl bromides [65–67], anomeric phosphates [68] and trichloroacetimidates [69], thioglycosides [70], glycosyl sulfoxides [71], and 1,2-anhydrides [72], some of these methodologies being amenable to combinatorial and solid phase synthesis [73].

For further details on this subject, presently under intense further exploration, some recent

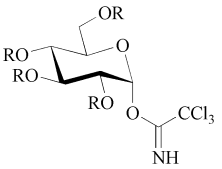
Table 1. Established glycosyl donors for the stereoselective synthesis of oligosaccharides



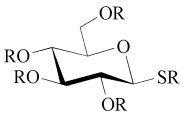
Glycosyl halides, X = Cl, Br



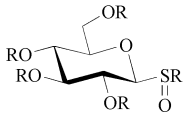
Ulosyl bromides



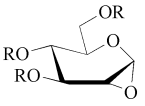
Glycosyl trichloroacetimidates



Thioglycosides



Glycosyl sulfoxides
(R = acetyl, benzoyl, benzyl)

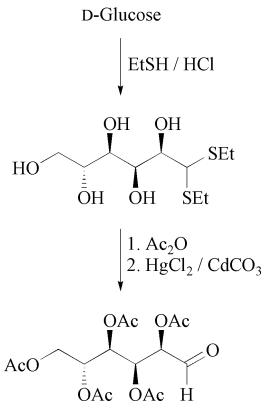


1,2-Anhydro-sugars

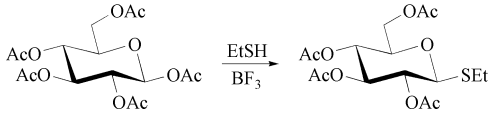
general treatments [30, 74–76, 67, 77, 78] are recommended.

7.2. Thioacetals and Thioglycosides

Sugars react rapidly with alkanethiols in the presence of acid catalysts at room temperature to give acyclic dialkyl dithioacetals as the main products [79], and therefore the reaction is markedly different from the Fischer glycosidation. These open-chain compounds can be used to prepare monosaccharide derivatives with a free carbonyl group, such as 2,3,4,5,6-penta-*O*-acetyl-D-glucose:

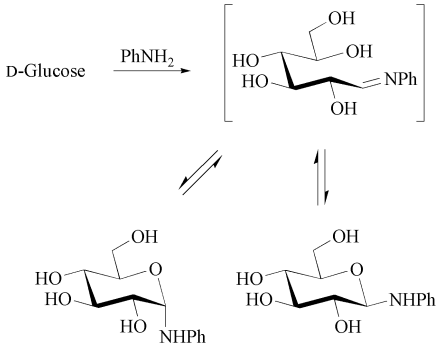


1-Thioglycosides, established glycosyl donors in oligosaccharide syntheses (upon activation with methyl trifluoromethanesulfonate or other promoters) [70], have to be prepared indirectly, e.g., from peracylated pyranoses (or their 1-halides) by exposure to thiols in the presence of BF_3 etherate or zinc chloride:



7.3. Glycosylamines, Hydrazones, and Osazones

Aldoses condense with ammonia and with primary and secondary amines upon loss of water — reactions that are analogous to the Fischer glycosidation. The initial condensation products appear to be the open-chain aldimines, which then cyclize to the *glycosylamines* — also called *N*-glycosides. The pyranose forms of the products are preferentially adopted as these are thermodynamically more stable. Accordingly, D-glucose reacts with aniline in methanol to give the α- and β-*N*-glucopyranosides:



Acids also catalyze a transformation called the *Amadori rearrangement* [80] which often accompanies attempts to prepare glycosylamines from aldoses and amines. This reaction is related to the *Lobry de Bruyn – van Ekenstein* reaction of aldoses and involves the rearrangement of *N*-alkylamino-D-glucopyranosides into 1-alkylamino-1-deoxy-D-fructoses (Fig. 20).

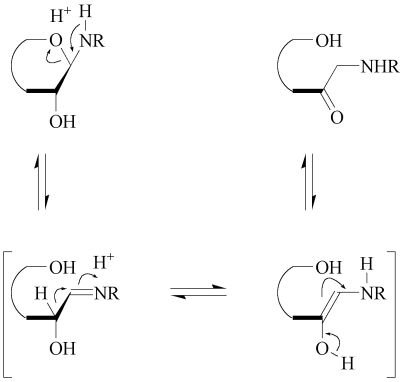
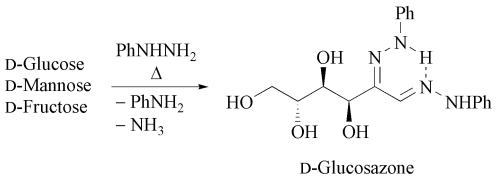


Figure 20. Amadori rearrangement of glycosyl amines induced by acid catalysis: D-Glucopyranosylamine is converted into a 1-alkylamino-D-fructose [79]

Glycosylamine derivatives are probably involved in the complex Maillard reaction [60], whereby sugars, amines, and amino acids (proteins) condense, rearrange, and degrade during cooking or the preservation of food. Hydrazones and osazones result when aldoses or ketoses are reacted with hydrazine or arylhydrazines, the product depending on the conditions used [81]. With hydrazine acetate in highly acidic medium in the cold, hydrazones are formed, which initially adopt the acyclic structure, but tautomerize in aqueous solution to the cyclic glycosylhydrazine forms. However, when free sugars are treated with an excess of phenylhydrazine, the reaction proceeds further to give — in a formal oxidation of the vicinal C-2-OH group — the highly crystalline, water-insoluble phenylosazones that contain two phenylhydrazine residues per molecule, with a third phenylhydrazine molecule being converted into aniline and ammonia. As C-2 of a sugar is involved in this process, D-glucose, D-mannose, and D-fructose yield the same product:



D-Glucosazone

This result played a fundamental role in EMIL FISCHER's elucidation of the configurational interrelationships of the sugars, eventually leading [11, 12] to the sugar family trees depicted in Figures 3 and 4.

7.4. Chain Extension

The carbonyl group offers excellent opportunities for extension of the sugar chains and the formation of 'higher' sugars. However, only a few carbon nucleophiles can be applied directly to the free sugars, i.e., without protection of the hydroxyl groups. The classical methods comprise the addition of cyanide ion (*Kiliani – Fischer extension*) [82] and of nitromethane under suitable alkaline conditions [83]. In either case, the cyano and nitromethylene group newly introduced can be converted into an aldehyde functionality by hydrolysis of the diastereomeric cyanohydrins to aldonic acids, lactonization and subsequent reduction, or by applying the *Nef reaction* to the nitroalditols; thus, providing methods for the ascent of the sugar series. For example, the rare sugar D-allose can be readily prepared from D-ribose [84] (Fig. 21), whereas the nitromethane addition approach allows the acquisition of the equally scarce hexoses L-glucose and L-mannose from L-arabinose [85] (Fig. 22).

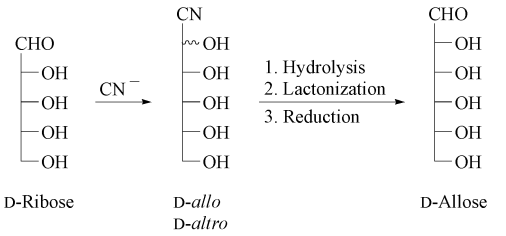


Figure 21. The Kiliani – Fischer cyanohydrin synthesis with D-ribose: the approximate 1:1 mixture of the 2-epimeric D-*allo*- and D-*altro*-cyanohydrins can be separated at the aldonic acid stage, subsequent reduction of the D-allonic acid in the form of its 1,4-lactone then providing D-allose (34 % overall yield)

A special case of chain extension by nitromethane is the cyclization of sugar-derived dialdehydes — readily and quantitatively obtained from anomerically blocked glycopyranosides or furanosides by periodate oxidation — to give 3-nitrosugars [86, 87]. As exemplified for methyl β-D-glucopyranoside (Fig. 23), a mixture of 3-nitrohexosides is primarily obtained

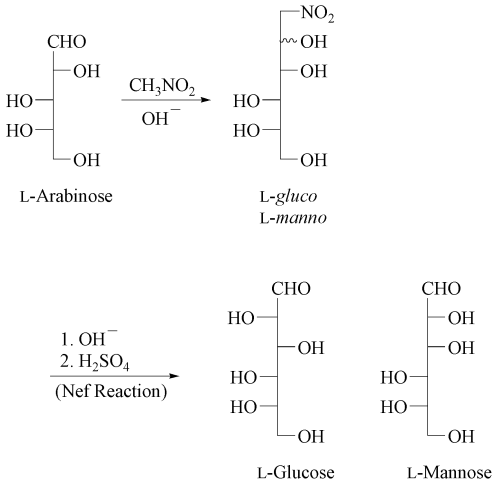


Figure 22. Nitromethane addition to L-arabinose in alkaline medium generates a mixture of the 2-epimeric L-nitroalditols (of L-*gluco* and L-*manno* configuration) which, upon separation, are subjected to the Nef reaction [83]

from which the major product, the D-*gluco* isomer crystallizes out. Subsequent catalytic hydrogenation then provides the 3-amino-3-deoxy-D-glucoside [88].

This nitromethane cyclization sequence can be extended to nitroalkanes (e.g., nitroethane or even nitroacetate [89]), thus providing a ready access — upon hydrogenation of the nitro group — to 3-methyl- or 3–carboxy-branched 3-aminosugars.

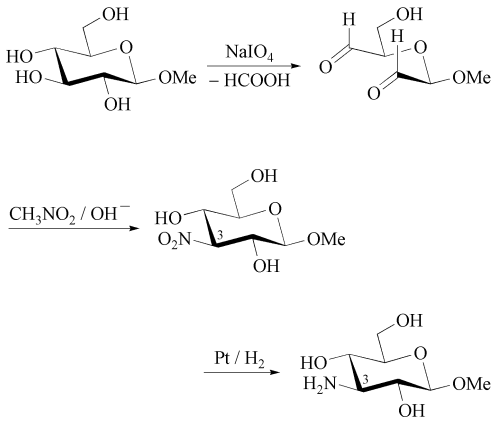
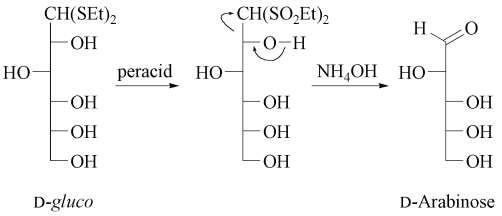


Figure 23. Conversion of methyl β-D-glucoside into its 3-amino-3-deoxy derivative via the dialdehyde – nitromethane cyclization approach [86]

7.5. Chain Degradation

The removal of a terminal carbon atom from a sugar or sugar derivative to leave an aldehyde group is realizable in a variety of ways, but the yields are often poor. The most practical approach involves conversion of an aldose into the corresponding dialkyl dithioacetal (mercaptal) by reaction with an alkanethiol, then oxidation to the bissulfone with a peracid. Treatment of the bissulfone with dilute ammonia causes expulsion of the stabilized bis(ethylsulfonyl)methyl carbanion and gives the aldose with one carbon atom less. This three-step protocol smoothly converts D-glucose, for example, into D-arabinose [90]:



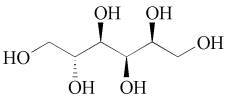
7.6. Reductions to Alditols

Aldoses and ketoses can readily be reduced to alditols (Table 2) with the generation of a new alcoholic group from the carbonyl functions. The names of the reduced products are derived from the respective aldoses by replacing the 'ose' suffix with 'itol'. Thus, reduction of D-glucose gives D-glucitol. Originally, sodium amalgam was the reducing agent most commonly used for these reductions, but now it has been superseded by others, particularly sodium borohydride in aqueous solution or, for alkali-sensitive sugars, by sodium cyanoborohydride in acetic acid. High pressure hydrogenation of aldoses and ketoses over rare metal catalysts, especially nickel is used for the commercial preparation of alditols (→ Sugar Alcohols).

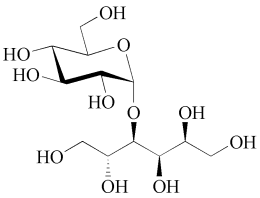
7.6.1. D-Glucitol

D-Glucitol [50-70-4] (→ Sugar Alcohols, Chap. 3), common name sorbitol, produced at

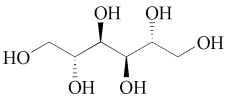
Table 2. Low-caloric, noncariogenic sugar alcohol sweeteners, obtained by catalytic hydrogenation of the parent aldoses. Recommended nomenclature [49] for sorbitol is D-glucitol (hence D-Glc-ol). Being a meso compound, xylitol requires no D- or L-prefix



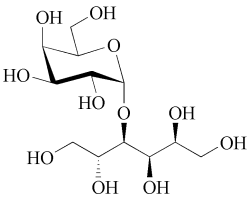
D-Glucitol
(sorbitol)
(D-Glc-ol)



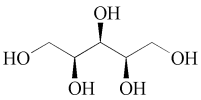
Maltitol
(α-D-Glc-(1→4)-D-Glc-ol)



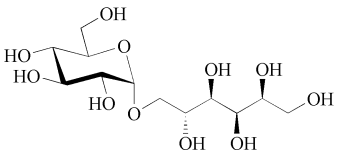
D-Mannitol
(D-Man-ol)



Lactitol
(α-D-Gal-(1→4)-D-Glc-ol)



Xylitol
(Xyl-ol)



Isomalt
(α-D-Glc-(1→6)-D-Glc-ol
(α-D-Glc-(1→4)-D-Man-ol)

a level of 9×10^5 t/a worldwide, has a sweet taste and is used in foods for diabetics [91, 92]. It is also the synthetic precursor for ascorbic acid (vitamin C), with about 20 % of the annual production sorbitol going to this use. Sorbitol is used as a humectant in cosmetic and pharmaceutical formulations and in foods. It is also applied as an alcoholic component in the preparation of rigid polyurethane foams. Fatty acid esters of monoanhydrosorbitol (1,4-sorbitan) are widely used as emulsifiers and nonionic surfactants. The mono- and dinitrate esters of 1,4:3,6-dianhydrosorbitol (isosorbide [652-67-5]) are coronary vasodilators.

7.6.2. D-Mannitol

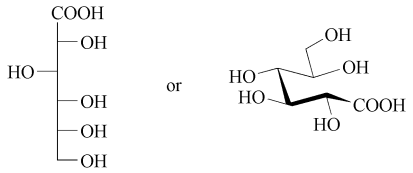
D-Mannitol [87-78-5] (→ Sugar Alcohols, Chap. 4), is prepared by hydrogenation of the fructose portion of invert sugar [91–93], which yields a mixture of mannitol and sorbitol. In contrast to sorbitol, mannitol is not hygroscopic; world production in 2007 was approximately 3×10^4 t. Mannitol is used in the manufacture of dry electrolytic condensers and synthetic resins; in the pharmaceutical industry as a diluent for solids and liquids and in the preparation of the vasodilator mannitol hexanitrate; in the food industry as an anticaking and free-flow agent, and as a lubricant, stabilizer, and nutritive sweetener.

7.6.3. Other Sugar Alcohols

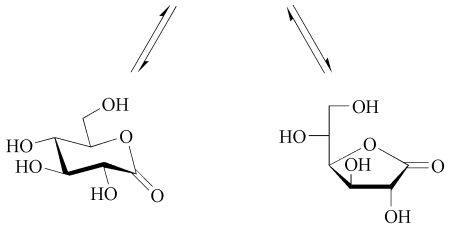
Other sugar alcohols, mostly used as sweeteners, are *xylitol*, obtained by catalytic hydrogenation of D-xylose, which in turn is acquired from wood xylans or maize cobs by acid hydrolysis, and a series of disaccharide alcohols, each manufactured analogously from the respective parent disaccharide: *maltitol* (from partially hydrolyzed starch syrup; Lycasin [93] contains a high proportion of this sugar alcohol), *lactitol* and, most notably, *isomalt*, which due to its mild, pleasant sweetness, ready crystallizability and excellent thermal stability appears presently the most prevalent. Isomalt, also called "palatinit", consists of an approximate 1:1 mixture of α-D-glucosyl-(1→6)-D-sorbitol and α-D-glucosyl-(1→1)-D-mannitol (see Table 2). The latter forms a dihydrate, the two water molecules being attached to the mannitol portion in a hydrogen-bonded water bridge [94]. Isomalt is produced from sucrose through *Protaminobacter rubrum*-induced isomerization to isomaltulose ('palatinose') and subsequent catalytic high-pressure hydrogenation (→ Sugar Alcohols, Section 5.2).

7.7. Oxidation [95, 96]

Controlled stoichiometric oxidations of carbohydrates to yield glyconic acids or their derivatives are limited to aldoses. Such oxidations can be carried out almost quantitatively either enzymatically by dehydrogenases or oxidases, or chemically with bromine or iodine in buffered solution. Under these conditions, D-glucose — through its pyranose form prevailing in solution — is directly converted into the 1,5-lactone of D-gluconic acid (i.e., the internal ester rather than the free acid), which on addition of base is converted into the salt (in open-chain form). However, by crystallization from aqueous solution it is possible to obtain the free acid or the 1,4-lactone. For different aldonic acids the amounts of each form present at equilibrium vary with structure and with the pH of the solution; in contrast to the free sugars, the five-membered ring lactones are relatively favored.

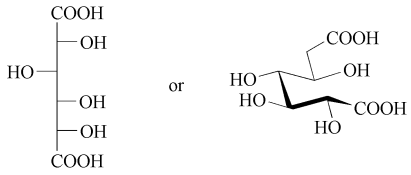


D-Gluconic Acid

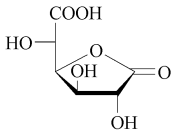


1,5-Lactone 1,4-Lactone

Strong nitric acid appears to be one of the few oxidants that is able to oxidize the terminal primary hydroxyl group of aldoses but leave the secondary hydroxyl groups unchanged. D-Glucose treated with this reagent gives D-*glucaric acid* [97], its name being derived by replacing the ending 'ose' in the sugar by 'aric acid'. Aldaric acids can form mono- or dilactones, in the case of D-glucaric acid, the well crystallizing form is the furanoid 1,4-lactone:



D-Glucaric Acid



D-Glucaric Acid 1,4-Lactone

Under the influence of very strong oxidizing agents such as potassium dichromate or permanganate, sugars suffer oxidative degradation. Hence, these oxidants have no preparative value.

8. Reactions at the Hydroxyl Groups

8.1. Ethers

The most simple compounds of this type are *methyl ethers* which occur in a range of natural carbohydrates. Methyl ethers belong to the most stable *O*-substituted sugar derivatives, such that per-*O*-methylated hexoses can even be distilled. Traditionally, the labeling of free OH- groups in polysaccharides is effected by methylation, structural analysis being then based on the *O*-methyl sugars obtained on hydrolysis. Methyl ethers are conveniently prepared using methyl bromide, iodide, or sulfate in polar aprotic solvents such as dimethylformamide or dimethyl sulfoxide. Agents for deprotonation of the hydroxyl group and for binding the mineral acids liberated include alkali hydroxides or hydrides and barium or silver oxide. With high molecular mass carbohydrates, quantitative deprotonation is best carried out with sodium or potassium methylsulfinyl methanide (the conjugate base of dimethyl sulfoxide) [98].

Benzyl ethers are amongst the most commonly used protecting groups in carbohydrate

chemistry [99] as the *O*-benzyl moiety is easily removed by hydrogenolysis (Pd/C, H_2) to yield the respective alcohol and toluene [62]. For the preparation of these ethers, traditional methods involve such reagents as benzyl halides in combination with sodium hydroxide, sodium hydride, or silver oxide.

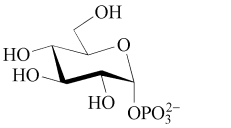
Triphenylmethyl (trityl) ethers are used mainly for the temporary substitution of primary hydroxyl groups and are usually prepared using trityl chloride in pyridine. Trityl ethers are readily cleaved under mildly acidic conditions; for example, with acetic acid or boron trifluoride in methanol.

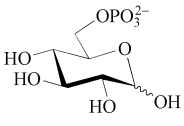
Trimethylsilyl ethers, although extremely sensitive both to base- and acid-catalyzed hydrolysis, are often used in analytical and preparative carbohydrate chemistry. The per-*O*-trimethylsilylated monosaccharides and small oligosaccharides are relatively volatile, highly lipophilic, and thermostable, and therefore, ideal derivatives for gas chromatographic analysis. The trimethylsilyl ethers are rapidly formed in pyridine solution by using a mixture of hexamethyldisilazane and trimethylchlorosilane as reagents [100].

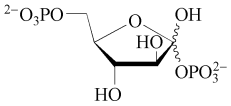
Cellulose ethers (→ Cellulose Ethers) are generally manufactured by the Williamson synthesis: namely the reaction of sodium cellulose (prepared by treating cellulose with 20 to > 50 % sodium hydroxide) with an organic halide such as chloromethane or sodium monochloroacetate. The latter reagent produces sodium carboxymethyl cellulose (NaCMC), which is widely used, for example, as a thickening agent in foods. Worldwide production of NaCMC is in the range of several hundred thousand tons per year.

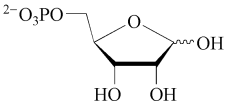
8.2. Esters of Inorganic Acids

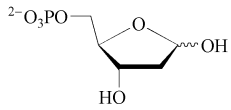
Phosphoric acid esters of sugars play vital roles in such fundamental processes as the biosynthesis and metabolism of sugars and, hence, are present in every organism; the most important esters being D-glucose 1-phosphate [59-56-3], D-glucose 6-phosphate [56-73-5], and D-fructose 1,6-diphosphate [488-69-7]. In addition, phosphates of D-ribose and its 2-deoxy derivative form fundamental components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), and also of various coenzymes (→ Nucleic Acids).

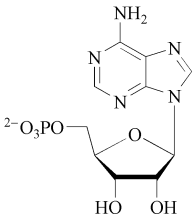

α-D-Glucose-1-phosphate


D-Glucose-6-phosphate


D-Fructose-1,6-diphosphate


D-Ribose-5-phosphate


2-Deoxy-D-ribose-5-phosphate

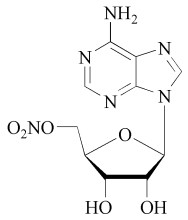

Adenosine-5-phosphate (AMP)

Both chemical and enzymic methods are available for the synthesis of specific phosphates. Chemically, anomeric phosphate esters are usually prepared either from glycosyl halides or other glycosyl donors by reaction with silver dibenzyl phosphate, whilst phosphorylation of nonanomeric hydroxyl groups is effected with specifically blocked sugar derivatives and diphenyl or dibenzyl phosphorochloridate [101]. Biochemically, phosphates are produced by the action of phosphatases on provided substrates [102].

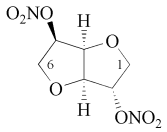
Sulfate Esters. Sulfate groups are present in many biologically important polysaccharides such as heparin and chondroitin sulfate. Sulfated monosaccharides can be prepared from suitable monosaccharide derivatives by reaction with chlorosulfuric acid in pyridine [103].

Nitrate esters of carbohydrates [104] are not found in nature, yet a large variety ranging from monoesters to peresters have been prepared; favorable conditions being cold nitric acid/acetic anhydride for nonanomeric hydroxyl groups, whilst anomeric nitrate esters are accessible via reactions of acyl glycosyl halides with silver nitrate. Sugar mono- and

dinitrates are stable crystalline compounds; examples are adenosine mononitrate (AMN), the nitrate analogue to AMP [105], and the dinitrate of 1,4:3,6-dianhydro-D-glucitol ('isosorbide dinitrate'). This last compound is in broad pharmaceutical use as a coronary vasodilator [106]:



Adenosine 5-nitrate (AMN)



Isosorbide dinitrate

More highly substituted derivatives are heat and shock sensitive, and include mannitol hexanitrate or nitrate esters of cellulose (nitrocellulose). These contain as many as three ONO_2 groups per glucose unit. The product with about 13 % nitrogen is the well-known guncotton (→ Cellulose Esters), whereas celluloid is nitrocellulose containing about 10 % nitrogen, plasticized with camphor. Celluloid is one of the oldest known plastics and was once the principal photographic and movie film, but has since been replaced by other films because of its high flammability.

8.3. Esters of Organic Acids

For the esterification of the hydroxyl group of free or partially otherwise blocked sugars, acyl halides or acid anhydrides are usually used; for example, acetic anhydride/sodium acetate or zinc chloride, or acetic anhydride/pyridine readily yield the respective *peracetates*.

Perbenzoylation can be effected with benzoyl chloride in pyridine or benzoyl cyanide in acetonitrile with triethylamine as the catalyst. However, the formation of tertiary hydroxyl groups, present in ketoses or branched-chain sugars, usually require the addition of 4-(dimethylamino)pyridine as a coreagent.

Whereas peracetates and perbenzoates of simple sugars are important intermediates for the preparation of the respective glycosyl halides and, hence, acylated glycals and hydroxyglycals (see Section 8.4), those of some polysaccharides are of industrial relevance. Acetate esters of cellulose are manufactured on a large scale, whereby the degree of acetylation determines their solubility and use: the triacetate (3.0-acetate) is soluble in chloroform, the 2.5-acetate in acetone, and the 0.7-acetate in water. These esters, as well as mixed cellulose acetate/propionate and acetate/butyrate are widely used in the production of lacquers, films, and plastics (→ Cellulose Esters).

Polysaccharide esters in which the carbohydrate portion is the acid component occur in the plant kingdom in fruits, roots, and leaves. For example, *pectins* are high molecular mass polygalacturonic acids joined by α-(1→4)-glycosidic links, in which some of the carboxylic acid groups are esterified with methanol (→ Polysaccharides). In the production of fruit juices the formation of methanol, which can be liberated through the action of pectinesterases, should be avoided. Pectins in which 55 – 80 % of the carboxyl groups are esterified are called high-methoxyl pectins (HM-pectins), and have the important property of gelling at very low concentrations ($\approx$ 0.5 %) in water in the presence of sugars and acid. Low-methoxyl (LM, $<$ 50 % of the carboxyl groups esterified) pectins form gels with divalent cations such as a Ca^{2+}; 0.5 % of a low-methoxyl pectin can bind 99.5 % of the water in the gel matrix. These pectins can be used as gelling agents in the production of jellies from fruit juices.

8.4. Acylated Glycosyl Halides

Per-*O*-acylated monosaccharides can be converted smoothly into glycosyl halides by dissolving them in cold solutions of the hydrogen halide in glacial acetic acid (acetates of acid-sensitive oligosaccharides may undergo cleavage of glycosidic bonds). Because of the dominance of the anomeric effect in the pyranosyl cases, the anomer with axial halide is substantially preferred. Accordingly, on acylation and subsequent HBr-treatment, usually performed as a one pot operation, D-glucose yields the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide ('acetobromoglucose', R = Ac in Fig. 24) or its benzoylated, pivaloylated (R = *tert*-BuCO) or benzylated (R = $C_6H_5CH_2$) analogues [63]. These halides are commonly used

directly for glycosylation reactions, which is the basis of the traditional Koenigs – Knorr procedure [107], or converted into more elaborate glycosyl donors.

Glycosyl halides are also of significance in terms of the use of monosaccharides as inexpensive enantiopure starting materials for the construction of complex, non carbohydrate natural products [108–110], which usually require the reduction of the number of chiral centers paired with the introduction of olefinic or carbonyl unsaturation. Treatment of glycosyl bromides with zinc/acetic acid [111] — or, preparatively more efficient by zinc/1-methylimidazole in ethyl acetate under reflux [112] — results in reductive elimination to give the glycal (this is illustrated in Figure 24 by the formation of tri-*O*-acetyl-D-glucal). Simple 1,2-elimination of hydrogen bromide using diethylamine in acetonitrile in the presence of tetrabutylammonium bromide or by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF [113, 114] yields the respective 2-hydroxyglycal esters. The D-glucose-derived benzoylated example in Figure 24 is an ester of the enol form of 1,5-anhydro-D-fructose, a naturally occurring ketosugar, which may be released from its tetrabenzoate by low-temperature deblocking with sodium methoxide/methanol [115].

Endowed with high crystallinity and shelf stability, the hydroxyglycal esters are of considerable preparative interest not only for the generation of a plethora of other unsaturated compounds, e.g., pyranoid enones [116] and enolones [109, 117], but also as precursors for the highly versatile 2-oxoglycosyl ('ulosyl') bromides, produced in high yields simply by exposure to *N*-bromosuccimide or bromine in the presence of ethanol [118, 119]. The utility of these ulosyl bromides as glycosyl donors in the straightforward synthesis of β-D-mannosides has been amply demonstrated [65–67, 118–120].

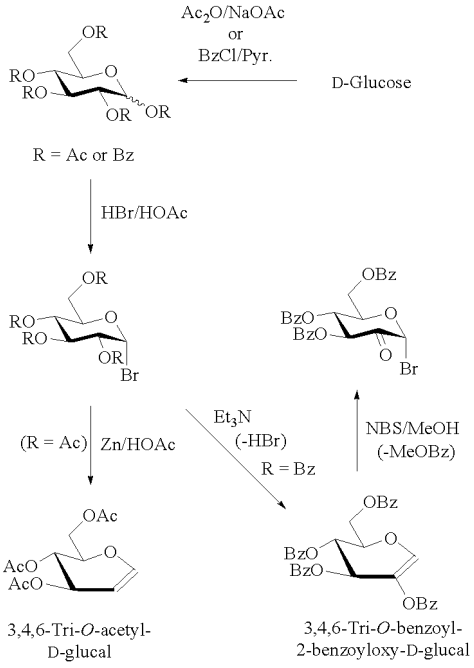
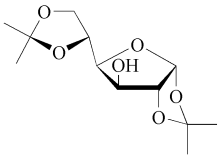


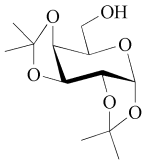
Figure 24. Formation of glycosyl and 2-oxoglycosyl ('ulosyl') bromides from peracylated monosaccharides, as exemplified for the D-glucose case, and their conversions into glucal and 2-hydroxyglucal esters

8.5. Acetals

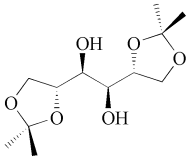
Acetals are generally derived from the reaction of an aldehyde or ketone — benzaldehyde and acetone being the most common — with a geometrically suitable diol grouping, of which there is a large variety in free sugars, glycosides, and alditols [121–123]. The reactions are normally carried out in the reagent aldehyde or ketone as solvent with an electrophilic catalyst (H_2SO_4 or $ZnCl_2$). Acetal formation under these conditions is thermodynamically controlled and usually very specific. Ketones such as acetone or cyclohexanone predominantly bridge vicinal diols to form five-membered cyclic products (1,3-dioxolanes) as exemplified by the di-*O*-isopropylidene derivatives of D-glucose ('diacetone-glucose'), D-galactose and D-mannitol:



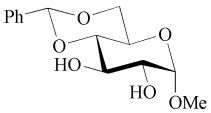
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose



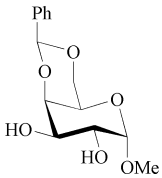
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose



1,2:5,6-Di-*O*-isopropylidene-D-mannitol



Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside

Aldehydes, however, show a distinct preference for 1,3-diols, as illustrated by the six-membered 4,6-*O*-benzylidene acetals of methyl D-glucoside and D-galactoside.

Introduction of cyclic acetal groups into sugars is simple and satisfactory in terms of yields. As cyclic acetals are stable towards alkali, the entire armory of organic reactions requiring basic conditions can be applied, and due to their ready removal with mild acid (e.g., 90 % aqueous trifluoroacetic acid at room temperature), they provide indispensable intermediates in preparative carbohydrate chemistry.

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