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Carbohydrates

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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 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.

In the last decade, 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.

D-*Glucose* (→ Glucose and Glucose-Containing Syrups, Chap. 2.) [*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, 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).

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

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 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 [10], [11], 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 OH group to the right, it is considered to have the D-configuration. FISCHER's decision to place the OH 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 [12] that he had made the right choice.

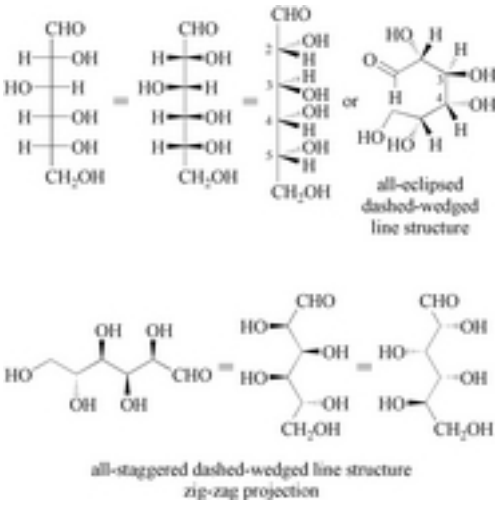


Figure 2. Configurational representations of the linear (acyclic) form of D-glucose: Traditional Fischer projection formula (top left) and its transformation into the more realistic dashed-wedged line depictions with the six-carbon chain in zigzag arrangement.

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 OH 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).

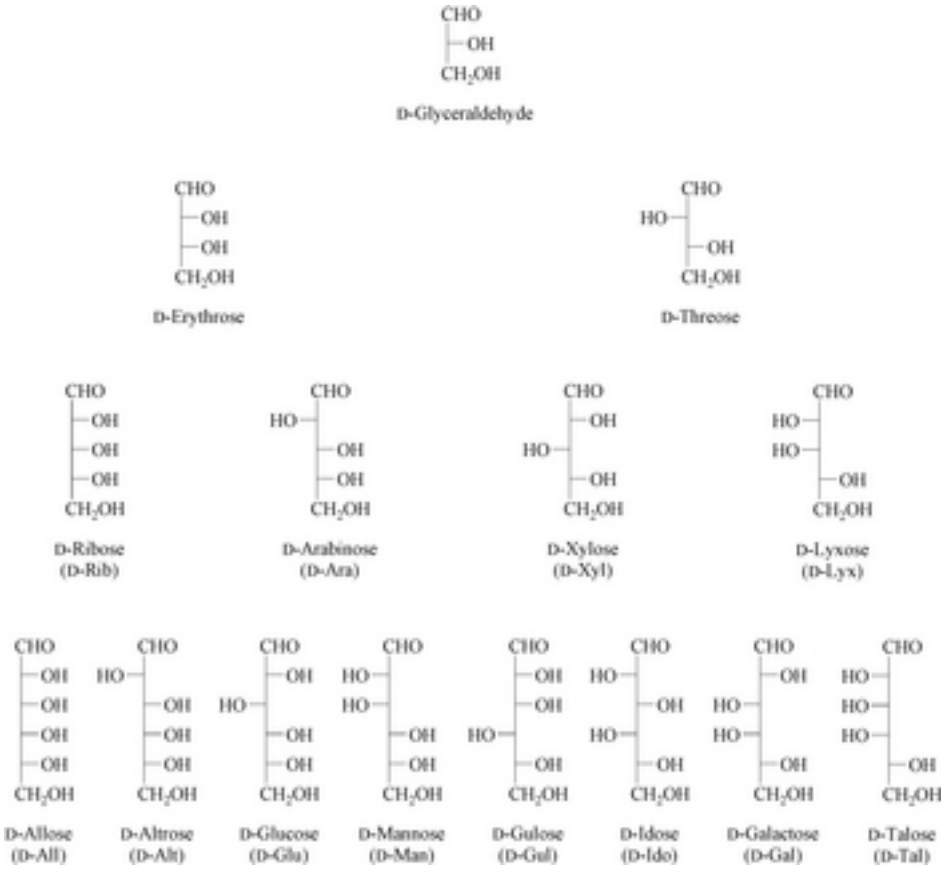


Figure 3. The D-aldose family tree (up to aldohexoses) in their acyclic forms: Common names and Fischer projection formulas, with secondary hydrogen atoms omitted for clarity.

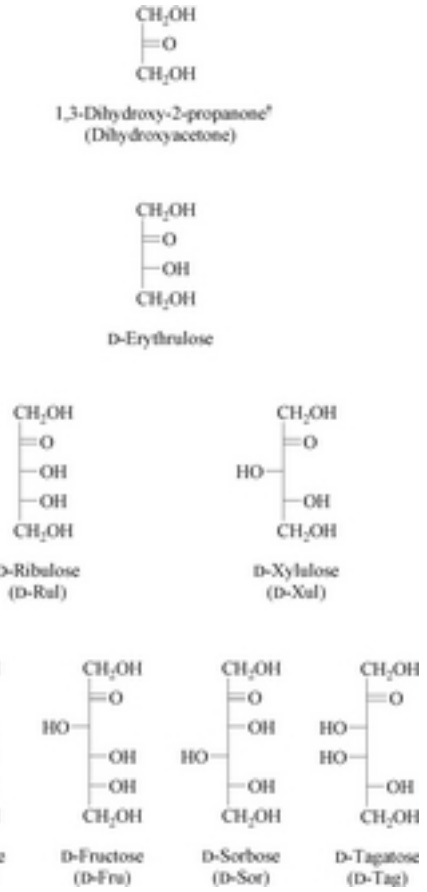


Figure 4. The D-ketohexose (or D-hexulose) family tree: Trivial names, systematic designation (in brackets) and Fischer projection formulas.
† Not regarded as being a sugar, due to absence of an asymmetric carbon atom.

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 [13], 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 [14], 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.

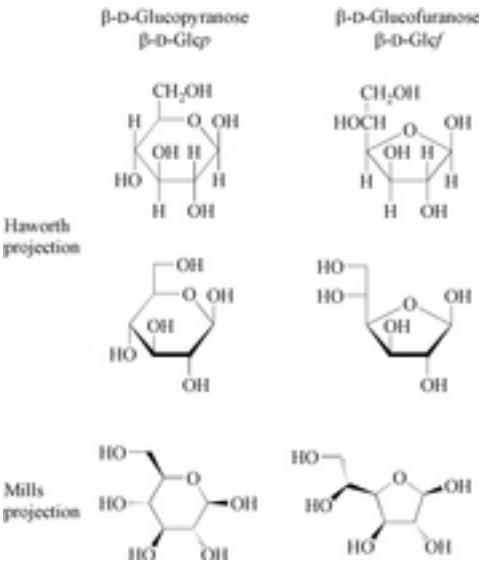


Figure 5. Haworth and Mills projection formulas for the β-anomers of D-glucopyranose and D-glucofuranose (in the formula at the center and at the bottom, the carbon and C-hydrogen atoms are omitted for clarity).

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 [15]: 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., $^{o}S_2$ and $^5H_4$ forms).

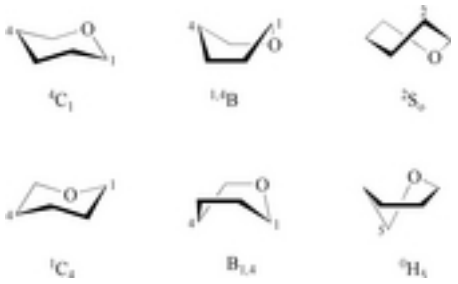


Figure 6. Conformational forms of pyranose rings: chair (*C*), boat (*B*), skew (*S*) and half-chair (*H*).
To designate each form, the ring atom numeral lying above the plane of reference appears as a superscript preceding the letter, those below the plane are written as subscripts and follow the letter.

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 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.

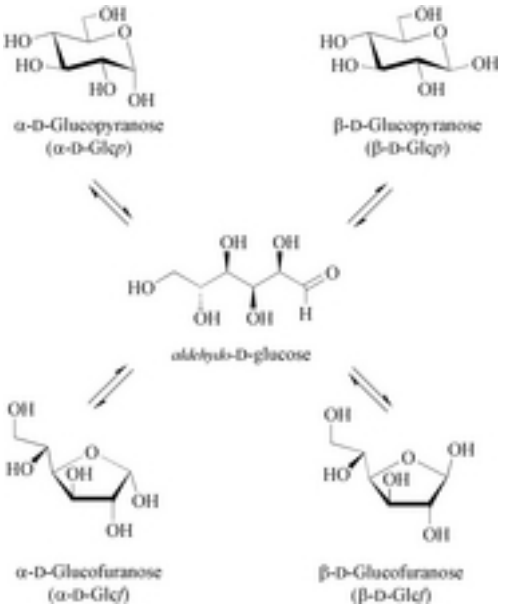


Figure 7. Cyclic hemiacetal forms of D-glucose in configurational representation. In solution, these forms rapidly interconvert through the energetically unfavorable acyclic form; in water at 25 °C the two pyranoid forms are nearly exclusively adopted, the equilibrium mixture amounting to 62 % of the 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*).

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 [16], 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 %) [17]. The acyclic form through which equilibration occurs is present to a minute extent only.

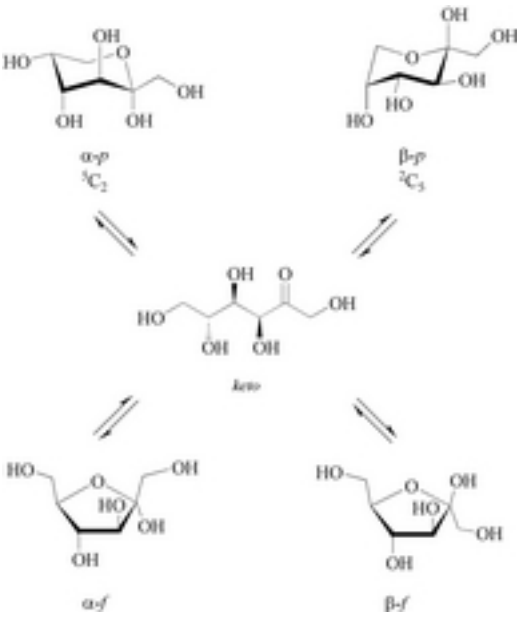


Figure 8. Forms of D-fructose in solution. In water, the major conformers are the β-pyranose (β-*p*, 73 % at 25 °C) and β-furanose (β-*f*, 20 %) forms [17]. On crystallization from water, D-fructose adopts the $^2C_5$ chair conformation in the crystal lattice as evidenced by X-ray analysis [16].

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* 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).

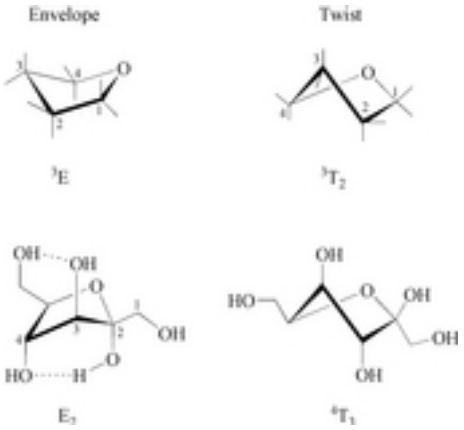
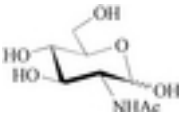


Figure 9. The envelope conformation (top left) is the ^3E form as defined by the C-3 atom lying above the plane formed by the other ring atoms. The defined plane for the twist form (top right) is the triangle given by C-1, C-4, and O-4, entailing the conformational description $^3T_2$. In aprotic solvents (dimethylsulfoxide) D-fructose populates the E_2 envelope conformation to a substantial extent [17], whilst in crystalline sucrose, the β-D-fructofuranose portion adopts the $^4T_3$ twist form [18], [19] (bottom entries).

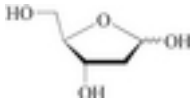
2.4. Structural Variations of Monosaccharides

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. 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.

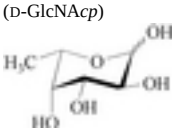
The uronic acids are aldoses that contain a carboxylic acid chain terminating function, and occur in nature as important constituents of many polysaccharides. The D-gluco compound, D-*glucuronic acid*, was first isolated from urine (hence the name), in which it occurs as glycosides and glycosyl esters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



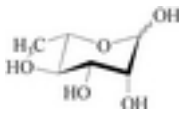
N-Acetyl-D-glucosamine
2-acetamido-2-deoxy-D-glucopyranose
(D-GlcNA*cp*)



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

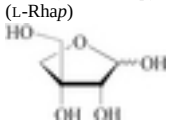


L-Fucose
6-deoxy-L-galactopyranose
(L-Fuc*p*)



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 non-linear carbon chain, are comparatively uncommon, the more widely occurring being D-*apiose* (3-C-hydroxymethyl-D-*glycero*-tetrose), richly present in polysaccharides of parsley and duckweed [20], and D-*hamamelose* (2-C-hydroxymethyl-D-ribose), a component of the bark of witchhazel [21].

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 non-reducing. A comprehensive listing of the di-, tri-, and higher oligosaccharides known by 1990 is available [22].

3.1. Common Disaccharides

Sucrose, affectionately called "the royal carbohydrate" [23], is a non-reducing 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 annual production from sugar-cane and sugar beet being an impressive 130×10^6 t [24].

α,α-Trehalose, a non-reducing D-glucosyl D-glucoside occurs extensively in the lower species of the plant kingdom (fungi, young mushrooms, yeasts, lichens, and algae). In baker's 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 beets).

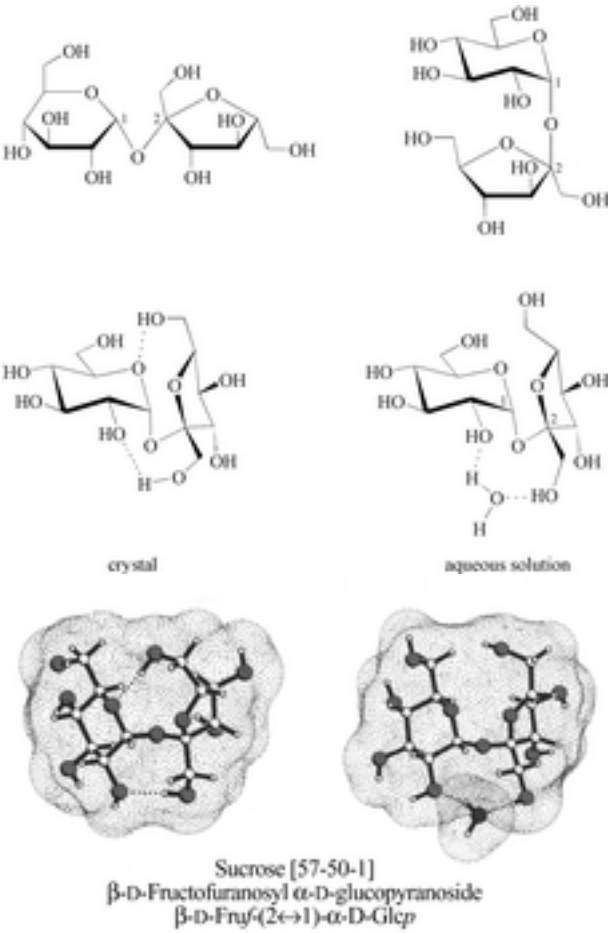
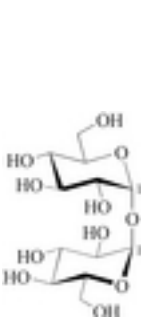
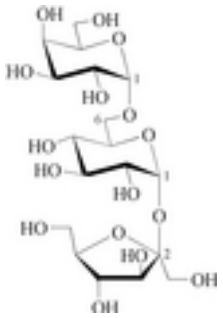


Figure 10. Common structural representations of sucrose (top entries), the molecular geometry realized in the crystal featuring two intramolecular hydrogen bonds between the glucose and fructose portion [18], [19] (bottom left), and the sterically similar disposition of the two sugar units towards each other in aqueous solution form, caused by hydrogen bonding through a 'water bridge' [25]. The bottom entries show the solvent-accessible surfaces (dotted areas) of the crystal form (left) and the form adopted in water [25] (right), clearly demonstrating that sucrose has an unusually compact overall shape, more so than any other disaccharide.



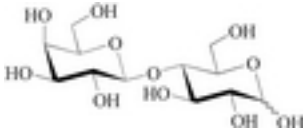
α,α-Trehalose [*99-20-7*]
α-D-Glucopyranosyl
α-D-glucopyranoside
(α-D-Glc*p*[1↔1]α-D-Glc*p*)



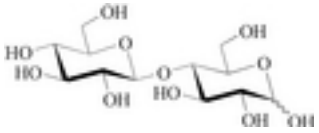
Raffinose [*512-69-6*]
α-D-Galactopyranosyl-(1→6)-
sucrose
(α-D-Gal*p*-(1→6)-α-D-
Glc*p*(1↔2)-β-D-Fru*f*)

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 reduc-

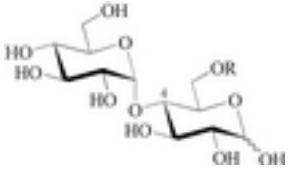
ing gluco-disaccharides *cellobiose* and *maltose* (malt sugar) are chemical or enzymatic hydrolysis products of the polysaccharides cellulose and starch, respectively, and, hence are not regarded as native oligosaccharides.



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

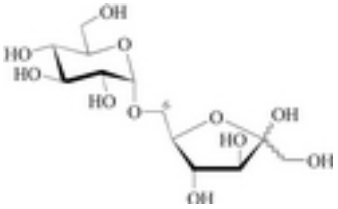


Cellobiose [*528-50-7*]
β-D-Glucopyranosyl-(1→4)-D-glucopyranose
(β-D-Glc*p*-(1→4)-D-Glc*p*)

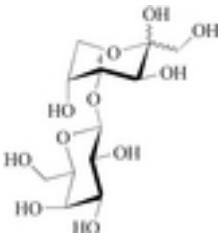


Maltose [*69-79-4*]
α-D-Glucopyranosyl-(1→4)-D-glucopyranose
(α-D-Glc*p*-(1→4)-D-Glc*p*)

Isomaltulose (palatinose, → Sugar Alcohols, Chap. 5.1.) and *lactulose*, both produced in fairly large amounts from sucrose and lactose, respectively, are 6-*O*-glucosyl- and 4-*O*-galactosyl-fructoses. The sucrose → isomaltulose transformation, industrially realized at a 40 000 t/a-scale [26], is effected by a *Protaminobacter rubrum*-induced glucosyl shift from the anomeric fructosyl oxygen to its *O*-6, taking place in mostly intramolecular fashion via a closed-shell intermediate [27], whilst the generation of lactulose from lactose, presently running at a 12 000 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, Chap. 5.2.), a low-calorie sweetener with the same taste profile as sucrose, lactulose (→ Lactose and Derivatives, Chap. 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-Glcp-(1→6)-D-Fru*f*)



Lactulose [*4618-18-2*]
β-D-Galactopyranosyl-(1→4)-D-fructopyranose
(D-Galp-β(1→4)-D-Fru*f*)

Other Heterooligosaccharides. Heterooligosaccharides of considerably higher complexity occur in large variety in plants, animals and microorganisms where they are covalently bound to proteins ('glycoproteins') and lipids ('glycolipids') or other hydrophobic entities, and, as such, are implemented 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 [28–30]. 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 [31].

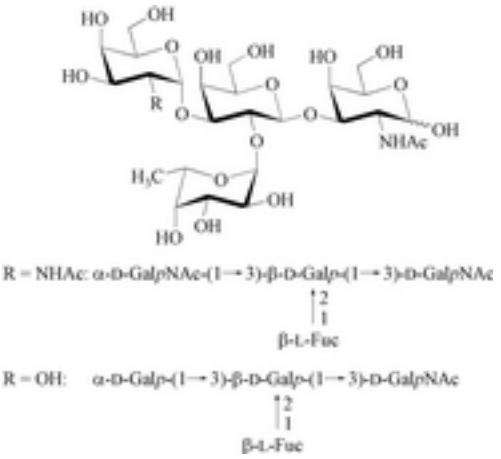


Figure 11. Human blood groups determinants: Differentiation between type A (R = NHAc) and B (R = OH) is effected by relatively simple changes within a branched tetrasaccharide linked to lipid components on the surface of red blood cells.

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 [32].

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 started to be used commercially [33]. 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 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 cavities, as exemplified by that of α-cyclodextrin with its six glucose units (Fig. 14, [34], [35]), 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 [33], [34], 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 [36], [37], as stationary phases for the separation of enantiomers [38], [39], as building blocks for supramolecular structures [40], and as enzyme models [41].

4. Polysaccharides

The bulk of the annually renewable carbohydrate-biomass are polysaccharides (glycans), such as cellulose, hemicelluloses, chitin, starch, and inulin. Invariably composed of 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, with a few though made up of considerably more.

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

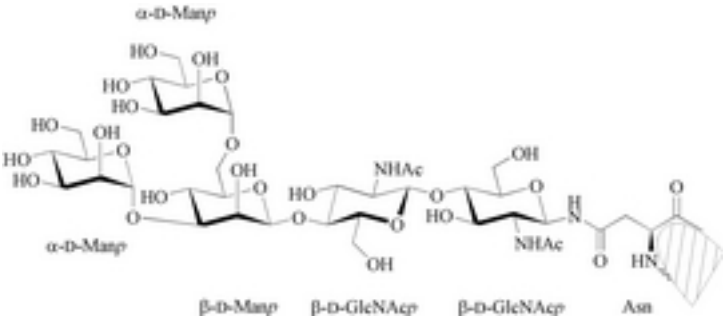


Figure 12. Central core region common to all *N*-glycoproteins is a pentasaccharide, *N*-glycosidically linked to the carbamido nitrogen of an asparagine moiety (Asn) within the peptide chain

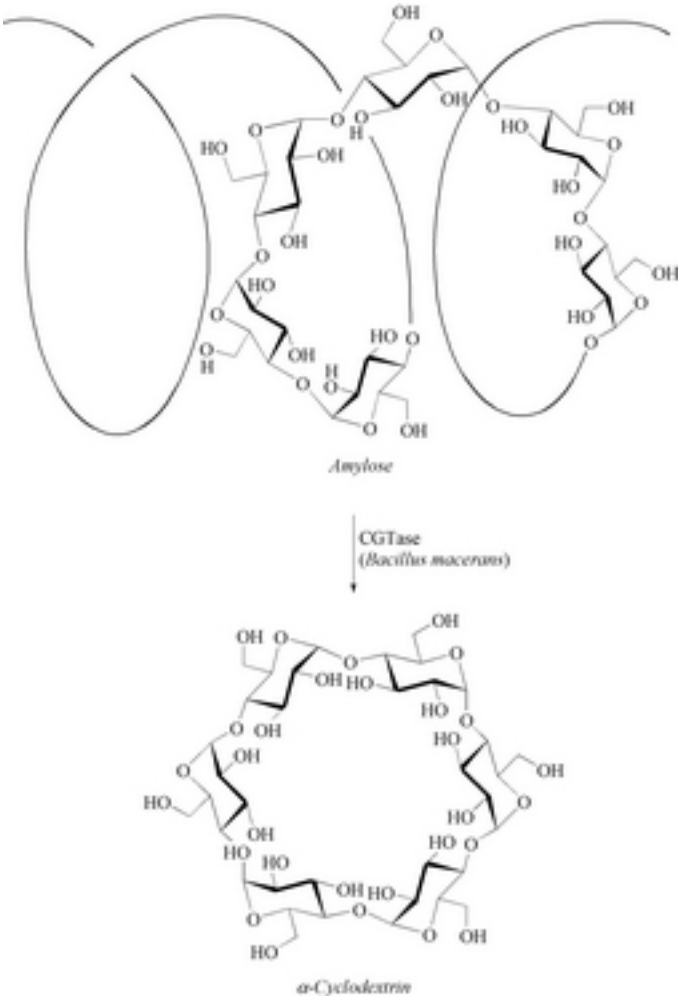


Figure 13. Sketch representation of a left-handed, single-stranded helix of V_H-amylose (top), and of α-cyclodextrin (bottom), which de facto represents a single turn of the amylose helix excised and re-connected by *Bacillus macerans*-derived enzymes (CGTases). The close analogy allows to consider V_H-amylose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

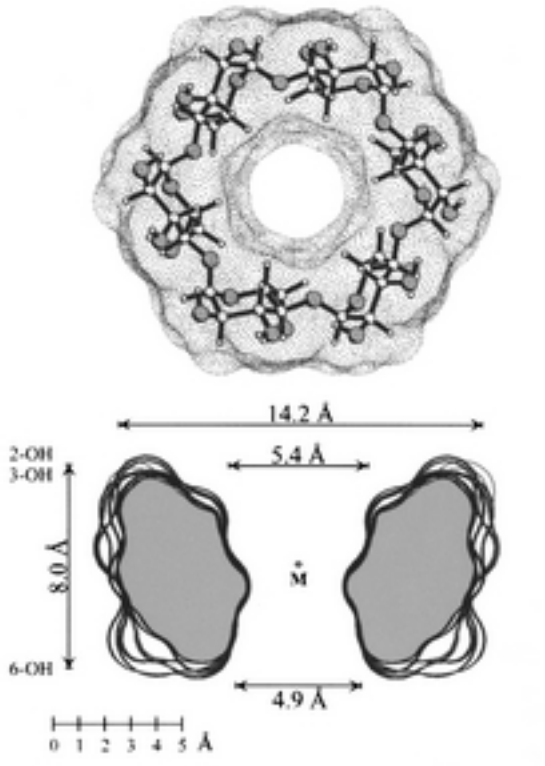


Figure 14. Top: Ball-and-stick model representations of the X-ray-derived solid-state structure of α-cyclodextrin, together with its solvent-accessible surface, shown as a dotted pattern.
Bottom: Cross section contour of a plane perpendicular to the macrocycle's mean plane with approximate molecular dimensions [34], [35].

that these long chains lie side by side in bundles, 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.

Chitin (→ Chitin and Chitosan) 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.

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 amount 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.

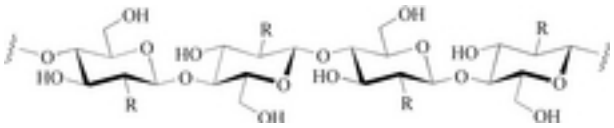


Figure 15. Structural representations of segments of cellulose (R = OH), chitin (R = NHAc), and chitosan ($R = NH_2$).

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, which has its cause in the trapping of iodine molecules within the hydrophobic channel of the helical segments of the polysaccharide (Fig. 16).

Amylopectin [*9037-22-3*] is also an α-(1→4)-glucan, yet there is a branch point via *O*-6 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 occuring molecules. The secondary structure is characterized by a 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) has been proposed. With iodine, amylopectin produces only a dull-red color, indicating that the short linear chain portions cannot coil effectively to the helices required for formation of inclusion complexes.

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

Inulin is a polysaccharide composed of β(1→2)-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 dahlia or Jerusalem artichoke where it replaces starch either partially or completely as the food storage carbohydrate [44], [45]. 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).

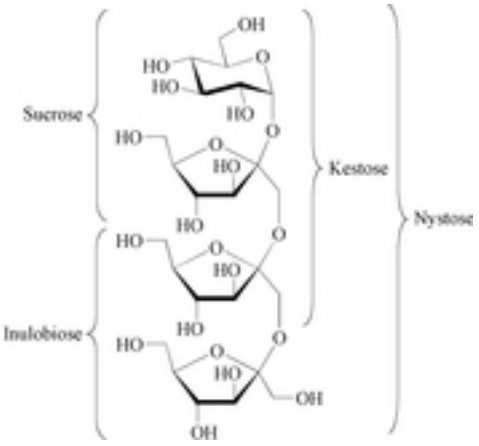


Figure 18. Nystose fragment of inulin, showing subfragments corresponding to sucrose, inulobiose and 1-kestose. Commercial inulins, e.g., those isolated from chicory, have a degree of polymerization far below that found in other polysaccharides, their molecular sizes ranging from around 5 to 30 units [43].

Other Polysaccharides (→ Polysaccharides). A plethora of other homo- and heteropolysaccharides are abound in nature, most notably 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 [46], [47].

5. Nomenclature

According to common practice, trivial names are used for monosaccharides and for many nat-

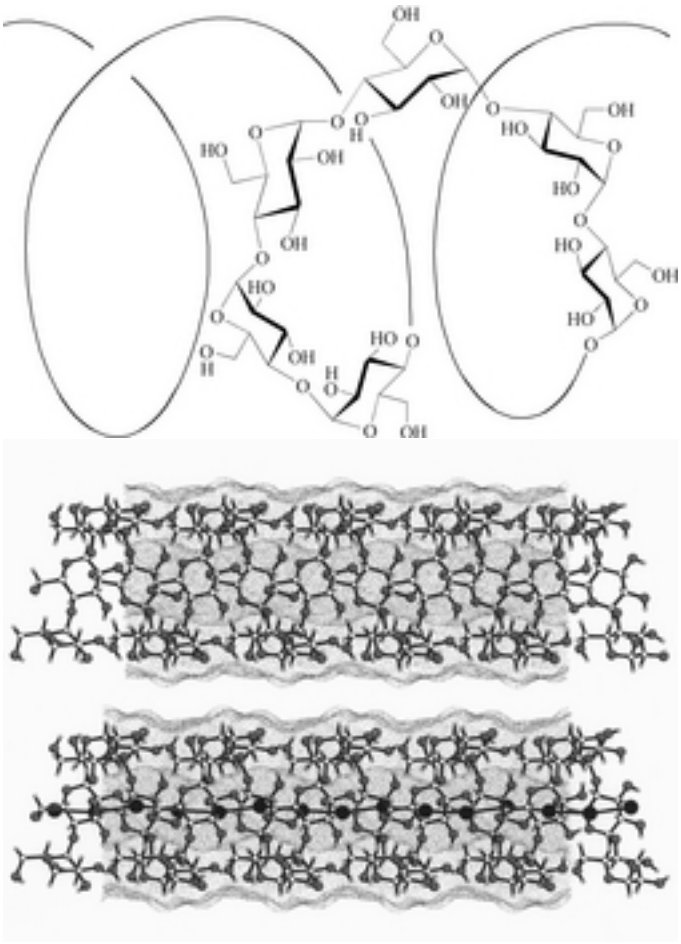


Figure 16. Sketch illustration of a left-handed, single stranded helix of V_H-amylose (top) and more detailed representation of its molecular geometry based on X-ray diffraction data [42] and calculation of the solvent-accessible contact surfaces [43], indicated by dots with ball-and-stick models superimposed.
Center: 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 center channel is as distinctly hydrophobic – predestined to incorporate equally hydrophobic guests such as iodine or fatty acids [43].
Bottom: A linear polyiodide chain embedded into the channel, corresponding to the intense blue starch-iodine complex [43].

urally occurring oligosaccharides. With the development of carbohydrate chemistry, however, and ever-increasing numbers of newly defined compounds, it has become necessary to introduce a semisystematic nomenclature which has been approved by the joint commission of IUPAC (International Union of Pure and Applied Chemistry) and IUB (International Union of Biochemistry) [48]. 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*, 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

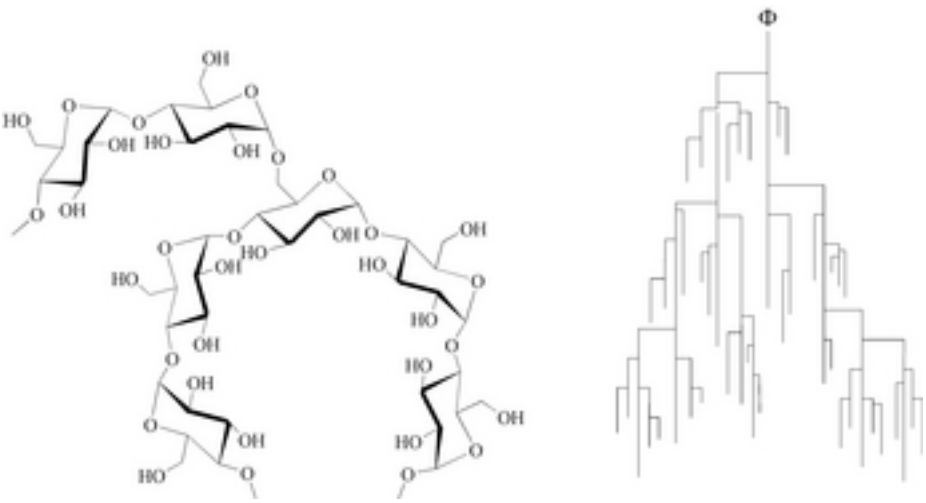


Figure 17. Schematic representation of a section of amylopectin with an $\alpha(1\rightarrow6)$-branch of a helical chain of $\alpha(1\rightarrow4)$-glucopyranosyl residues (left), with the tassel-on-string model of its higher level structure (ϕ = reducing end)

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, e.g., L-rhamnose is a 6-deoxy-L-aldohexose of *manno*-configuration. Replacement of a hydroxyl group by any other substituent is formally regarded as going via the deoxysugar. Thus a sugar with an amino group instead of OH is called an amino-deoxysugar. 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 shown by adding either '*O*-acetyl-' before the name or 'acetate' after it, in each case again preceding it 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-hexopyranulose. 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 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 carbon atom 4 of D-glucose (aglyconic part).

For description of more complex oligosaccharides an abbreviation system has come into use - as for oligopeptides and oligonucleotides - that is unambiguous and practical: 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 (Fig. 10), accordingly, is β-D-Fru*f*-(2→1)-α-D-Glc*p*, lactose β-D-Gal*p*-(1→4)-D-Glc*p*.

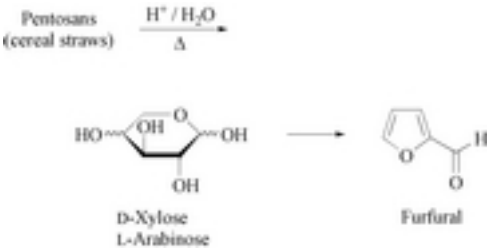
6. General Reactions

6.1. Hydrolysis

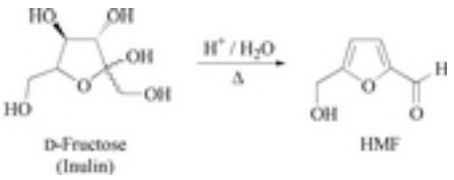
The hydrolysis of disaccharides such as sucrose and lactose, or polysaccharides like starch and cellulosic materials to their free component sugars is of great importance in the food and fermentation industries. It can be effected by enzymes called glycosidases or by acid treatment.

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, catalyses 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.

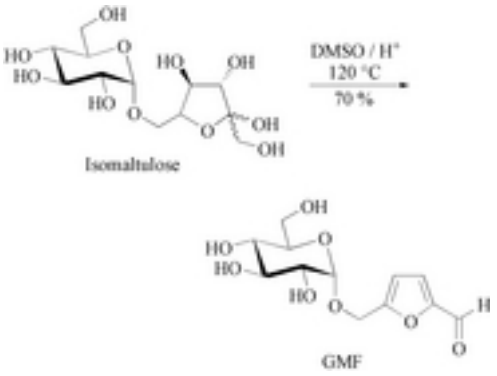
Acid-induced hydrolysis of glycosides requires comparatively harsh conditions, standards being 1 M sulfuric acid at 100 °C for 4 h for hexose-containing polysaccharides and 0.25 M H_2SO_4 at 70 °C for pentosans. Partial degradation of the resulting monosaccharides can usually not be avoided whatever conditions are used [49], [50]. Thus, aside from enzymatic hydrolysis, acid hydrolysis of *starch* is industrially performed on a 10^6 t/a basis, the resulting D-glucose being used in liquid form (corn syrup) as a sweetener (→ Glucose- and Glucose-Containing Syrups, Chap. 4.). Another significant industrial product, in fact the only large-volume organic chemical prepared from carbohydrate sources (∼ 200 000 t/a), is furfural (2-furaldehyde) [51], [52]. The technical process involves exposure of agricultural or forestry wastes to aqueous acid and fairly high temperatures, the *pentosans* first being hydrolyzed to pentoses, then undergoing cyclodehydration (→ Furan and Derivatives, Chap. 3.).



Similarly accessible by acid-induced elimination of three moles of water from *fructose* or *inulin hydrolysates* is 5-hydroxymethylfurfural (HMF) [26], [53].



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 [54].



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 fer-

mented by baker's yeast to form melibiose (α-D-Gal*p*-(1→6)-D-Glc*p*).

6.2. 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, either of the three following sugars 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* [55], 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 epimerization of lactose (→ Lactose and Derivatives, Chap. 2.1.2.), or maltulose from maltose [56], [57], using either sodium hydroxide alone or with borate or aluminate as coreagents.

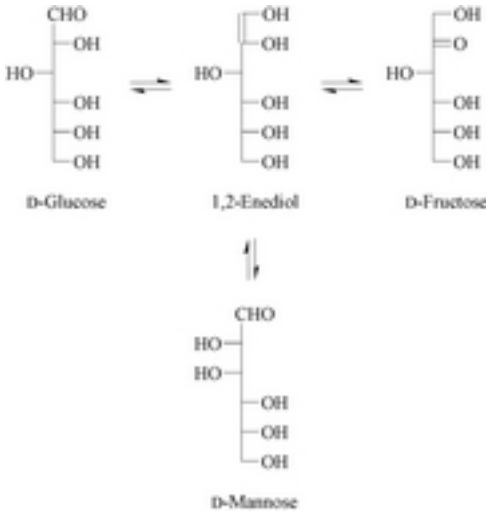


Figure 19. Lobry de Bruyn – van Ekenstein rearrangement

Alternatively, C-2-epimerization without ketose involvement can be induced by use of molybdate under mildly acidic conditions. This remarkable transformation (*Bilik reaction*) [58] involves a C-1 / C-2 interchange within the carbon skeleton.

6.3. Decomposition

Exposure of carbohydrates to high temperatures leads to decomposition (dehydration) with darkening (caramelization). This can be used to produce the caramel color, e.g., the color of cola beverages. Thermal decomposition in the presence of amino acids (*Maillard reaction* [59]) is responsible for many color- and flavor-forming reactions, such as in 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.

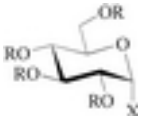
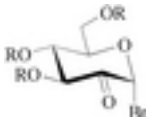
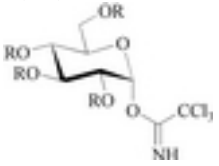
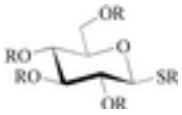
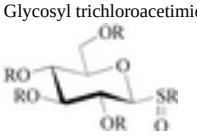
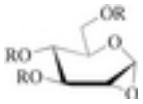
7.1. Glycosides

With alcohols in the presence of acid catalysts reducing sugars give the respective full acetals, called glycosides (Fischer glycosidation) [60]. 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 α- and β-anomers of each. 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 in 41 % yield only.

Although the Fischer glycosidation presents one of the easiest means for preparing glycosides, 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 [61] 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 chlorides and bromides [62], 2-oxoglycosyl bromides [63], [64], anomeric phosphates [65] and trichloracetimidates [66], thioglycosides [67], glycosyl sulfoxides [68], and 1,2-anhydrides [69], some of these methodologies being amenable to combinatorial and solid phase synthesis [70].

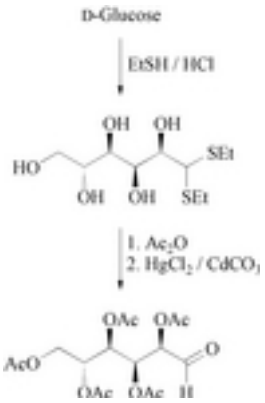
Table 1. Established glycosyl donors for the stereoselective synthesis of oligosaccharides

	
Glycosyl halides, X = Cl, Br	Ulosyl bromides
	
Glycosyl trichloroacetimidates	Thioglycosides
	
Glycosyl sulfoxides (R = acetyl, benzoyl, benzyl)	1,2-Anhydro-sugars

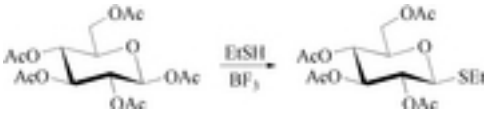
For further details on this subject, presently under intense further exploration, some recent general treatments [29], [71–73] are recommended.

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 [74], 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:

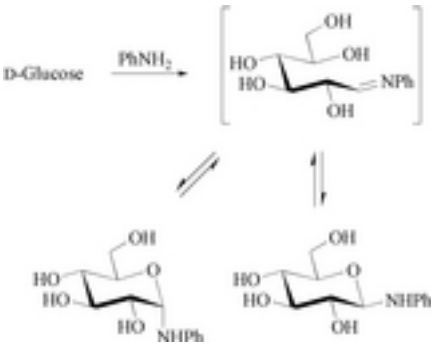


1-Thioglycosides, established glycosyl donors in oligosaccharide syntheses (upon activation with methyl trifluoromethanesulfonate or other promoters), have to be prepared indirectly, e.g., from peracylated pyranoses (or their 1-halides) by exposure to thiols in the presence of BF_3 etherate or zinc chloride:



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, Thereby, the pyranose forms are preferentially adopted as these are thermodynamically more stable. Accordingly, D-glucose reacts with aniline in methanol to the α- and β-*N*-glucopyranosides:



Acids also catalyze a transformation called the *Amadori rearrangement* [75] 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 involving the rearrangement of *N*-alkylamino-D-glucopyranosides into 1-alkylamino-1-deoxy-D-fructoses (Fig. 20).

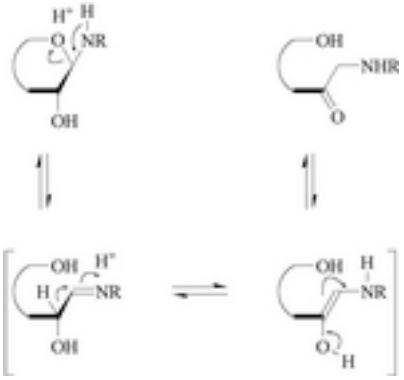
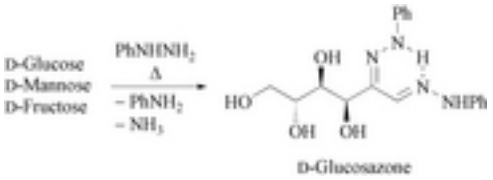


Figure 20. Amadori rearrangement of glycosyl amines induced by acid catalysis: D-Glucopyranosylamine is converted into 1-alkylamino-D-fructose [74]

Glycosylamine derivatives are probably involved in the complex Maillard reaction [59], 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 [76]. 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 ex-

cess of phenylhydrazine, the reaction proceeds further to give – in a formal oxidation of the vicinal 2-OH – the highly crystalline, water-insoluble phenylosazones which 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:



This result played a fundamental role in Emil Fischer's elucidation of the configurational interrelationships of the sugars, eventually leading [10], [11] 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 OH groups. The classical methods comprise the addition of cyanide ion (*Kiliani – Fischer extension*) [77] and of nitromethane under suitable alkaline conditions [78]. 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 ascent of the sugar series. For example, the rare sugar D-allose can be readily prepared from D-ribose [79] (Fig. 21), whereas the nitromethane addition approach allows the acquisition of the equally scarce hexoses L-glucose and L-mannose from L-arabinose [80] (Fig. 22).

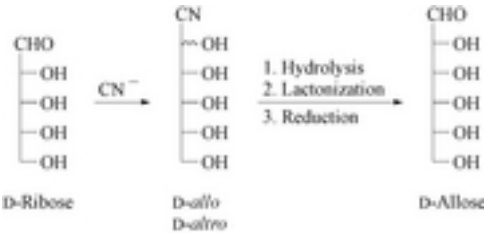


Figure 21. The Kiliani – Fischer cyanohydrin synthesis with D-ribose: the approximate 1:1 mixture of the 2-epimeric D-*allo*- and D-*altro*-cyanohydrins can be separated at the aldonic acid stage, subsequent reduction of the D-allonic acid in the form of its 1,4-lactone then providing D-allose (34 %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

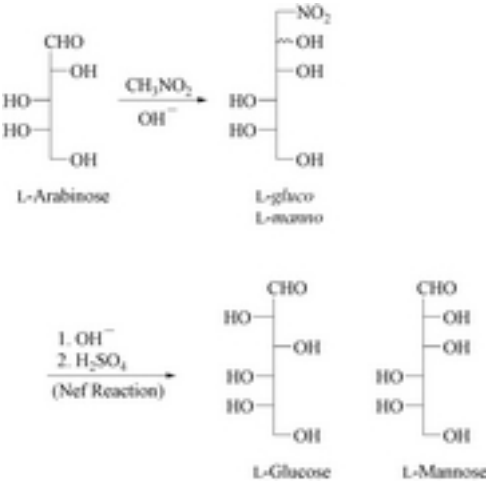


Figure 22. Nitromethane addition to L-arabinose in alkaline medium generates a mixture of the 2-epimeric L-nitroalditols (of L-*gluco* and L-*manno* configuration) which upon separation are subjected to the Nef reaction [78]

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 [81], [82]. As exemplified for methyl β-D-glucopyranoside (Fig. 23), a mixture of 3-nitrohexosides is primarily obtained from which the major product, the D-*gluco* isomer crystallizes. Subsequent catalytic hydrogenation then provides the 3-amino-3-deoxy-D-glucoside [83].

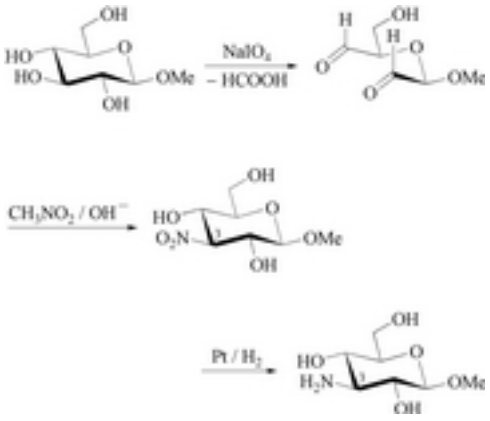
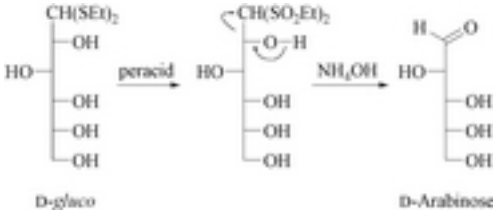


Figure 23. Conversion of methyl β-D-glucoside into its 3-amino-3-deoxy-derivative via the dialdehyde-nitromethane cyclization approach [81]

This nitromethane cyclization sequence can be extended to nitroalkanes, e.g., nitroethane or even nitroacetate [84], thus providing a ready access – upon hydrogenation of the nitro group – to 3-methyl- or 3–carboxy-branched 3-aminosugars.

7.5. Chain Degradation

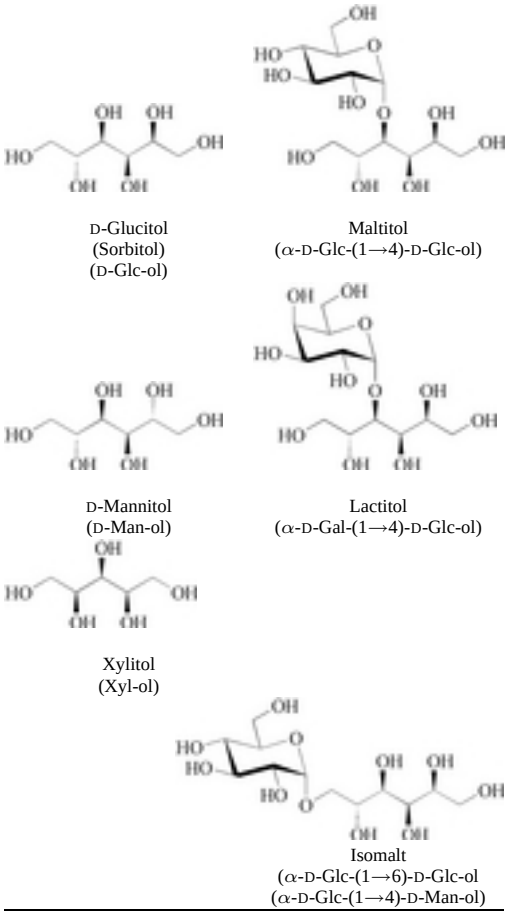
The removal of a terminal carbon atom from a sugar or sugar derivative to leave an aldehyde group is realizable in a variety of ways but the yields are often poor. The most practical approach involves conversion of an aldose to the corresponding dialkyl dithioacetal (mercaptal) by reaction with an alkanethiol, then oxidation to the bis-sulfone with a peracid. Treatment of the bis-sulfone 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 [85]:



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, their names being derived from the respective aldose 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 $NaBH_3CN$ 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).

Table 2. Low-caloric, non-cariogenic sugar alcohol sweeteners, obtained by catalytic hydrogenation of the parent aldoses. Recommended nomenclature [48] 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)

D-Glucitol [*50-70-4*] (→ Sugar Alcohols, Chap. 3.), common name sorbitol, produced at a level of 900 000 t/a worldwide, has a sweet taste and is used in foods for diabetics [86], [87]. 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 non-ionic surfactants. The mono- and dinitrate esters of 1,4 : 3,6-dianhydrosorbitol (isosorbide [*652-67-5*]) are coronary vasodilators.

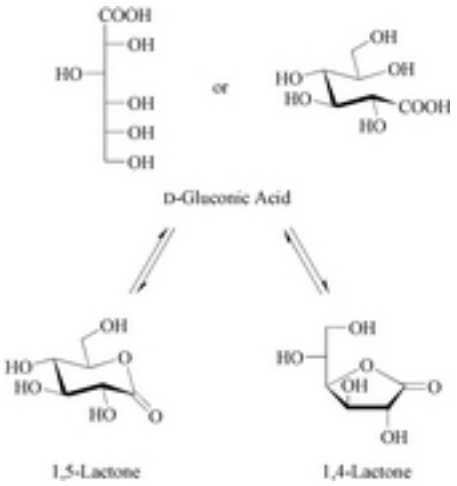
D-Mannitol [*87-78-5*] (→ Sugar Alcohols, Chap. 4.), is prepared by hydrogenation of the fructose portion of invert sugar [86], [88], which yields a mixture of mannitol and sorbitol. In contrast to sorbitol, mannitol is not hygroscopic; world production in 2000 was approximately 30 000 t. Mannitol is 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.

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 [88] contains a high proportion thereof), *lactitol* and, most notably, *isomalt*, which due to its mild, pleasant sweetness, ready crystallizability and excellent thermal stability appears presently the most prevailing. 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 21). The latter forms a dihydrate, the two water molecules being attached to the mannitol portion in a hydrogen-bonded water bridge [89]. Isomalt is produced from sucrose through *Protaminobacter rubrum*-induced isomerization to isomaltulose ('palatinose') and subsequent catalytic high-pressure hydrogenation (→ Sugar Alcohols, Chap. 5.2.).

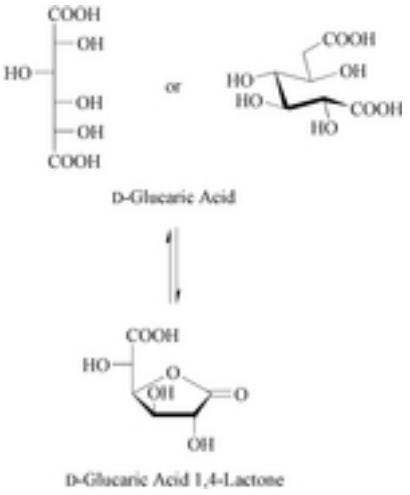
7.7. Oxidation

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 to 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 pH of the solution, in contrast to the free sugars, the five-membered ring lactones are relatively favored.



Strong nitric acid appears to be one of the few oxidants which is able to also 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* [90], 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:



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

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 esthers 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 from methyl bromide, iodide, or sulfate in polar aprotic solvents such as dimethylformamide or dimethylsulfoxide. 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) [91].

Benzyl ethers are amongst the most commonly used protecting groups in carbohydrate chemistry [92], as the *O*-benzyl moiety is easily removed by hydrogenolysis (Pd/C, H_2) to

yield the respective alcohol and toluene [61]. For the preparation of benzyl ethers, traditional methods involve such reagents as benzyl halides in combination with sodium hydroxide, sodium hydride, or silver oxide.

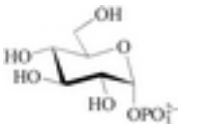
Triphenylmethyl (trityl) ethers are used mainly for the temporary substitution of primary hydroxyl groups and are usually prepared using trityl chloride in pyridine. Under mild acidic conditions, e.g., acetic acid or boron trifluoride in methanol, the trityl ethers are readily cleaved.

Trimethylsilyl ethers, although extremely sensitive both to base- and acid-catalyzed hydrolysis, are often used in analytical and preparative carbohydrate chemistry. The pertrimethylsilyl ethers of 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 by using a mixture of hexamethyldisilazane and trimethylchlorosilane [93].

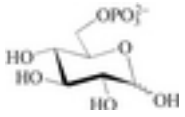
Cellulose ethers (→ Cellulose Ethers) are generally manufactured by the Williamson synthesis: reaction of sodium cellulose (prepared by treating cellulose with 20 to >50 % sodium hydroxide) with an organic halide such as chloromethane or sodium monochloroacetate. The latter reagent produces sodium carboxymethyl 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

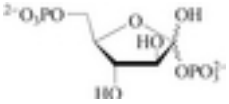
Phosphoric acid esters of sugars play vital roles in such fundamental processes as the biosynthesis and metabolism of sugars and, hence, are present in every organism, the most important esters being D-glucose 1-phosphate [*59-56-3*], D-glucose 6-phosphate [*56-73-5*], and D-fructose 1,6-diphosphate [*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 of various coenzymes (→ Nucleic Acids).



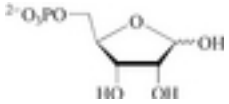
α-D-Glucose-1-phosphate



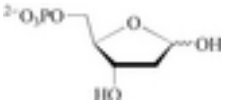
D-Glucose-6-phosphate



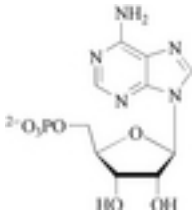
D-Fructose-1,6-diphosphate



D-Ribose-5-phosphate



2-Deoxy-D-ribose-5-phosphate



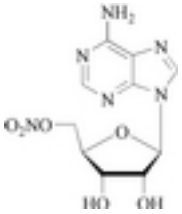
Adenosine-5-phosphate (AMP)

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 [94]. Biochemically, phosphates are produced by the action of phosphatases on provided substrates [95].

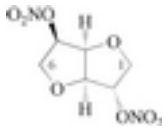
Sulfate Esters. Sulfate groups are present in many biologically important polysaccharides, such as heparin and chondroitin sulfate. Sulfated monosaccharides can be prepared from suitable monosaccharide derivatives by reaction with chlorosulfuric acid in pyridine [96].

Nitrate esters of carbohydrates [97] 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 OH groups, whilst anomeric nitrate esters are accessible via reaction of acyl glycosyl halides with silver nitrate. Sugar mono- and dinitrates are stable crystalline compounds, such as, e.g., adenosine

mononitrate (AMN), the nitrate analog to AMP [98], and the dinitrate of 1,4:3,6-dianhydro-D-glucitol ('isosorbide dinitrate'), which is in broad pharmaceutical use as a coronary vasodilator [99]:



Adenosine 5-nitrate (AMN)



Isosorbide dinitrate

More highly substituted derivatives are heat and shock sensitive, such as, e.g., 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, Chap. 1.), whereas celluloid is nitrocellulose containing about 10 % nitrogen plasticized with camphor; it is one of the oldest known plastics. This plastic was once the principal photographic and movie film, but has 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, e.g., 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. Tertiary OH groups, present in ketoses or branched-chain sugars, usually require the addition of 4-(dimethylamino)pyridine.

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 the 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, Chap. 2.1.).

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, Chap. 3.). 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 [62]. These halides are commonly used directly for gly-

cosylation reactions, which is the basis of the traditional Koenigs-Knorr procedure [100], or converted into more elaborated glycosyl donors (see Table 1).

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 [101–103], which usually require the reduction of the number of chiral centers paired with the introduction of olefinic or carbonyl unsaturation. Treatment of glycosyl halides with zinc/acetic acid [104] – or, preparatively more efficient zinc/1-methylimidazole in ethyl acetate under reflux [105] – results in reductive elimination to give the glycal, in Figure 24 illustrated with 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 [106], [107] 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.

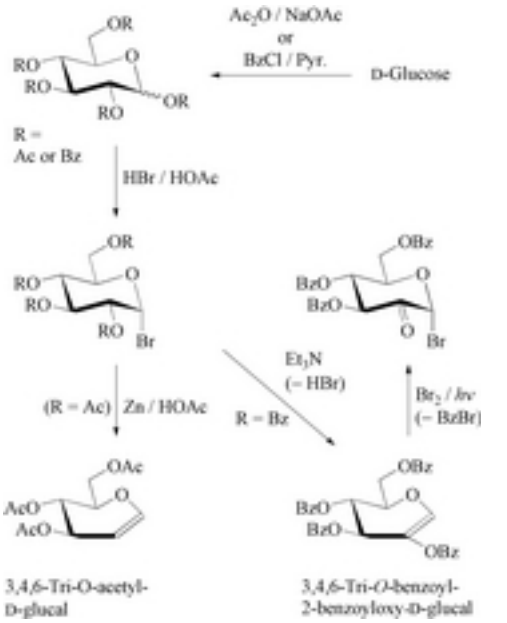
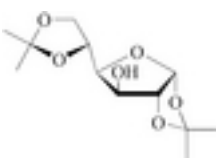


Figure 24. Formation of glycosyl and 2-oxoglycosyl ('ulosyl') bromides from peracylated monosaccharides, as exemplified for the D-glucose case, and their conversions into glucal and 2-hydroxyglucal esters

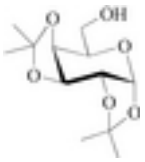
Endowed with high crystallinity and shelf stability, the hydroxyglycal esters are of considerable preparative interest not only for the generation of a plethora of other unsaturated compounds, e.g., pyranoid enones [108] and enolones [102], [109], but also as precursors for the highly versatile ulosyl bromides, produced in high yields simply by exposure to NBS or bromine in the presence of ethanol [110], [111]. The utility of these ulosyl bromides as glycosyl donors in the straightforward synthesis of β-D-mannosides has been amply demonstrated [62], [63], [112].

8.5. Acetals

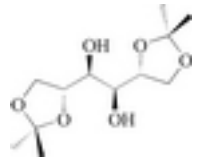
Acetals are generally derived from the reaction of an aldehyde or ketone – benzaldehyde and acetone being the most common – with a geometrically suitable diol grouping, of which there is a large variety in free sugars, glycosides, and alditols [113–115]. The reactions are normally carried out in the 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:



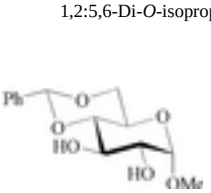
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose



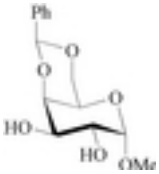
1,2:4,5-Di-*O*-isopropylidene-α-D-galactopyranose



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.

9. Carbohydrates as Organic Raw Materials

As our fossil raw materials are irrevocably decreasing – the end of cheap oil is realistically prognosticated for 2040 at the latest [116–118] – and as the pressure on our environment is building up, the progressive changeover of chemical industry to renewable feedstocks emerges as an inevitable necessity [118], [119].

The terrestrial biomass is considerably more complex than fossil raw materials, constituting a multifaceted accumulation of low and high molecular mass products. Carbohydrates, the most abundant of these materials, aside their traditional uses for food, lumber, paper and heat, are the major biofeedstocks to develop industrially and economically viable organic chemicals that are to replace those derived from petrochemical sources.

The bulk of the annually renewable carbohydrate-biomass consists of polysaccharides, yet their nonfood utilization is confined to textile, paper, and coating industries, either as such or in the form of simple esters and ethers. Organic commodity chemicals, however, are low molecular mass products; hence, they are more expediently acquired from low molecular mass carbohydrates than from polysaccharides. This in turn means that polysaccharides usually must be hydrolyzed before being further processed to organic commodity chemicals.

Table 3 lists the availability and bulk-quantity prices of the eight least expensive sugars – all well below €10/kg – as compared to some sugar-derived compounds and basic chemicals from petrochemical sources. The result is stunning, since the five cheapest sugars, some sugar-alcohols, and sugar-derived acids are not only cheaper than any other enantiopure product, such as hydroxy- or amino acids, but they compare favorably with basic organic bulk chemicals such as acetaldehyde or aniline. Actually, the first three of these sugars, sucrose, glucose, and lactose, are in the price range of some of the standard organic solvents.

Table 3. Annual production volume and prices of simple sugars, sugar-derived alcohols, and acids as compared to some petrochemically derived basic chemicals and solvents

	World production∗, t/a	Price ∗∗, €/kg
Sugars		
Sucrose	130 000 000	0.30
D-Glucose	5 000 000	0.60
Lactose	295 000	0.60
D-Fructose	60 000	1.00
Isomaltulose	50 000	2.00
Maltose	3000	3.00
D-Xylose	25 000	4.50
L-Sorbose	60 000	7.50
Sugar alcohols		
D-Sorbitol	900 000	1.80
D-Xylitol	30 000	5.00
D-Mannitol	50 000	8.00
Sugar-derived acids		
D-Gluconic acid	60 000	1.40
L-Lactic acid	> 100 000	1.75
Citric acid	500 000	2.50
L-Tartaric acid	35 000	6.00
Amino acids		
L-Lysine	40 000	5.50
L-Glutamic acid	500 000	7.00
Basic chemicals		
Aniline	1 300 000	0.95
Acetaldehyde	900 000	1.15
Adipic acid	1 500 000	1.70
Solvents		
Methanol	25 000 000	0.15
Toluene	6 500 000	0.25
Acetone	3 200 000	0.55

∗ Reliable data are only available for the world production of sucrose, the figure given referring to the crop cycle 2000/2001 [23]. All other data are average values based on estimates from producers and/or suppliers, as the production volume of many products is not publicly available.
∗∗ Prices given are those attainable in early 2002 for bulk delivery of crystalline material (where applicable) based on pricing information from sugar industry (sugars) and *The Chemical Market Reporter* **2002**, no. 2, 16 – 19 (acids, basic chemicals, and solvents). The listings are intended as a benchmark rather than as a basis for negotiations between producers and customers. Quotations for less pure products are, in part, sizably lower, e.g., for the commercial sweetener "high fructose syrup", which contains up to 95 % fructose, and, thus, may readily be used for large-scale preparative purposes.

Despite their large-scale accessibility, chemical industry, at present, utilizes these mono- and disaccharides only to a minor extent as feedstock for organic chemicals. This is amply documented by the fact that of the 100 major organic chemicals manufactured in the USA in 1995 [120], only seven were derived from biofeedstocks, and five of these – ethanol, sorbitol, citric acid, lysine, and glutamic acid – used carbohydrates as the raw material source. Intense efforts within the last decade to boost the production of organic chemicals from the sugars in Table 3 [121–127] have not basically changed this picture.

There are various reasons for that: at present, the use of fossil raw materials is more economic and the process technology for conversion of petrochemical raw materials into organic chemicals is exceedingly well developed and basically different from that required for transforming carbohydrates into products with industrial application profiles. This situation originates from the inherently different chemical structures of the two types of raw materials, of which the essence is manifested in their structure-based names.

Fossile Resources:	Renewable Resources:
HYDRO-CARBONS	CARBO-HYDRATES
C_nH_{2n+2}	$C_n(H_2O)_n$
oxygen-free,	overfunctionalized with
lacking functional groups	hydroxyl groups

Our fossil resources are *hydrocarbons*, distinctly hydrophobic, oxygen-free, and lacking functional groups, annually renewables are *carbohydrates*, overfunctionalized with hydroxyl groups and pronouncedly hydrophilic in nature. Needless to say, that the methods required for converting carbohydrates into viable industrial chemicals are diametrically opposed to those prevalent in petrochemical industry: microbial transformations or chemical processing with reduction of oxygen content and introduction of C=O and/or C=C unsaturation, or preferably both.

9.1. Microbial Synthesis

Microbial processing by direct fermentation of carbohydrates can be used to synthesize a large number of organic chemicals, yet only a few have clearly reached commodity status. They are *ethanol* (fermentation ethanol as distinguished from synthetic ethanol produced by hydration of ethylene), *citric acid* (from molasses by *Aspergillus niger*), *glutamic acid* and *lysine* (from glucose by *Brevibacterium lactofermentum* and others), and *gluconic acid* (from glucose by *Gluconobacter suboxydans*). Together, these chemicals have a sizable annual production (cf. Table 3), however, questions of how and when other microbially synthesized commodity chemicals will play a larger role in

the world's chemical markets remain to be answered.

By contrast, there is a broad range of specialty chemicals that are manufactured today by microbial conversion of carbohydrate feedstocks, usually products with molecular structures too complex for conventional chemical synthesis. Examples are antibiotics (penicillins, kanamycins, tetracyclins) and vitamin C, B_2 (riboflavin), and B_{12} (cyanocobalamin). The possibility, however, for production of further high-value-added specialty chemicals or pharmaceuticals from carbohydrates is almost unlimited as long as the appropriate organism and substrate are allowed to interact under suitable conditions [128].

9.2. Chemical Conversions

Presently, the dominant methods of converting carbohydrates to organic chemicals – be it bulk, intermediate or fine chemicals, pharmaceuticals, agrochemicals, high-value-added specialty chemicals, or simply enantiopure building blocks for organic synthesis – are chemical.

9.2.1. Furan Derivatives

Furfural appears to be the only large-volume chemical (200 000 t/a) produced from carbohydrate sources, usually agricultural and forestry wastes [51], [52] (→ Furan and Derivatives, Chap. 3.). Due to its ready accessibility, the ensuing chemistry of furfural is well developed, providing a host of highly versatile industrial chemicals by simple straightforward operations (Fig. 25): furfuryl alcohol and its tetrahydro derivative by hydrogenation of furfural, furfurylamine through reductive amination, furoic acid by oxidation, and furanacrylic acid (Perkin reaction) or furylidene ketones via aldol condensations. Furfural is also the key chemical for the commercial production of furan (through catalytic decarbonylation) and of tetrahydrofuran by hydrogenation, thereby providing a biomass-based alternative to its petrochemical production via dehydration of 1,4-butanediol. Further importance of these furanic chemicals results from their ring-cleavage chemistry, which has led to a variety of other established chemicals, e.g., levulinic acid (4-oxovaleric acid) and maleic anhydride [52], [129].

The bulk of the furfural produced is used as foundry sand linker in the refining of lubricating oil, and, together with furfurylalcohol and its tetrahydro derivative, enters into condensations with formaldehyde, phenol, acetone, or urea to yield a variety of resins of complex, ill-defined structures, yet excellent thermosetting properties, most notably high corrosion resistance, low fire hazard and extreme physical strength [52], [130].

5-(Hydroxymethyl)furfural (HMF). Like many petroleum-derived basic organic chemicals, e.g., adipic acid and hexamethylenediamine, 5-hydroxymethylfurfural (HMF) is a six-carbon commodity with high industrial potential, and, thus, has been termed "a key substance between carbohydrate chemistry and mineral oil-based industrial organic chemistry" [26]. It is readily accessible from fructose, or inulin hydrolysates by acid-induced elimination of three moles of water [53] and even a pilot-plant process has been developed [26].

Of high industrial potential as intermediate chemicals are the various HMF-derived products (Fig. 26), for which well worked-out, large scale-adaptable production protocols are available. Of these products, 2,5-bis(hydroxymethyl)furan, 5-hydroxymethyl-2-furoic acid, and the 2,5-dicarboxylic acid have extensively been exploited for the preparation of furanoic polyesters [136]. The diol has been reacted with various aliphatic and aromatic diacids; the ethyl ester of 5-hydroxymethylfuroic acid, upon polycondensation, gave a mixture of linear and cyclic products, whereas the furan diacid has been polyesterified with a series of aliphatic diols or bisphenols. Even an all-furanic polyester has been successfully prepared from its respective monomeric components [136].

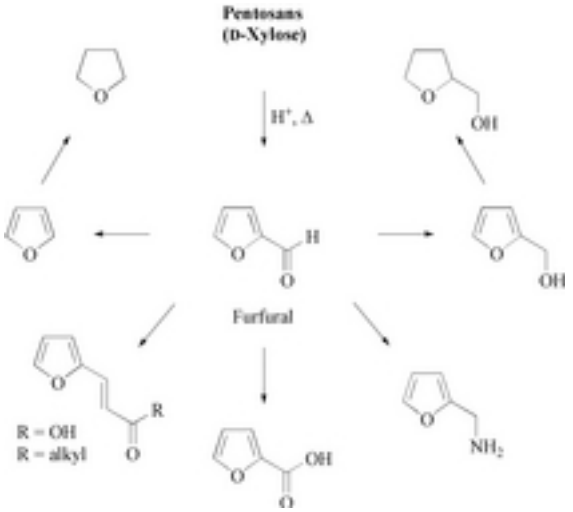


Figure 25. Versatile furanic commodity chemicals derived from pentosans in agricultural wastes (corn cobs, oat hulls, wood chips, bagasse)

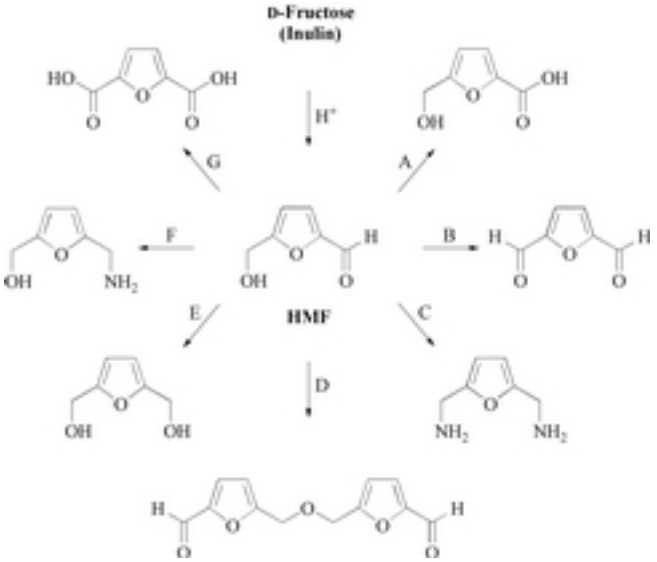
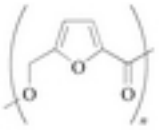
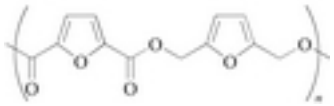


Figure 26. Versatile intermediate chemicals derived from hydroxymethylfurfural (HMF)

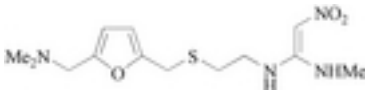
Key				
	A	Ag_2O, 100 °C, 75 % [130]	E	Pt, C / H_2, quant. [132]
	B	$BaMnO_4$, 93 % [130]	F	Ni/H_2, NH_3, 72 % [133]
	C	NH_2OH, then Ni/H_2, 33 %[130]	G	Pt, C / O_2, pH 7. 91 % [134]
	D	TsOH (H_2O↑), 89 %[131]		





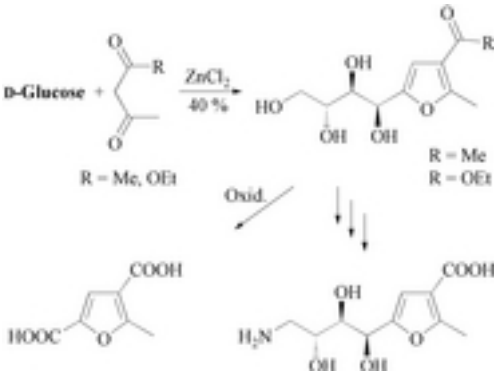
Another obvious outgrowth from the furan-2,5-dicarboxylic acid and the respective diamine was the generation of furanic polyamides, as they could potentially replace adipic or terephthalic acid, and, correspondingly, hexamethylenediamine or *p*-diaminobenzene in polyamides (see Section 9.2.5).

Despite this impressive array of useful HMF-derived intermediate chemicals, it is, as of now, not produced on an industrial scale. Obviously, the economic preconditions are not yet favorable enough. A recent assessment of the economics of HMF against competitive petrochemical raw materials [137] gives ample evidence thereof: prices of naphtha and ethylene are in the €150 – 400/t range, those of crude inulin or fructose (≈ €1000/t) give rise to an HMF-marketing price of at least €2500 per ton – too expensive at present for a bulk-scale industrial product. Accordingly, as long as the economic situation favors fossil raw materials, applications of HMF lie in high value-added products, such as pharmaceuticals or special niche materials. Prototype for this outlet is Ranitidine [138], an efficient antiulcer drug due to its potent oral inhibition of histamine-induced gastric acid secretion:



Ranitidine

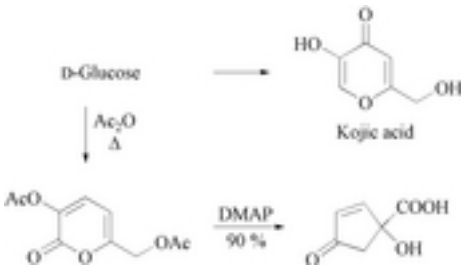
Furans with a Tetrahydroxybutyl Side Chain. Another simple, one-step entry from hexoses to more highly substituted furans involves their $ZnCl_2$-mediated reaction with 1,3-dicarbonyl compounds such as ethyl acetoacetate or 2,4-pentanedione. As only the first two sugar carbons contribute to the formation of the furan, a distinctly hydrophilic tetrahydroxylbutyl side chain is introduced into the heterocycle. D-Glucose, e.g., smoothly and efficiently provides furans with D-*arabino*-configuration in the polyol fragment [139], [140], which can be shortened oxidatively to the dicarboxylic acid or a variety of other furanic building blocks:



9.2.2. Pyrones and Dihydropyranones

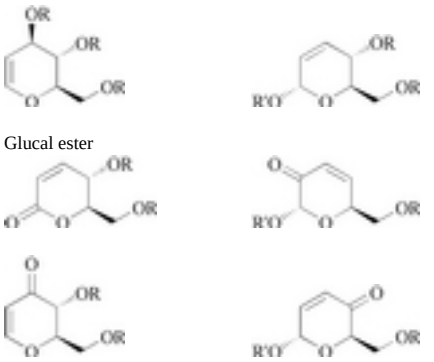
The bulk scale-accessible mono- and disaccharides listed in Table 3 are preferentially adopting the pyranose cyclohemiacetal forms, from which efficient reaction pathways lead to an unusually large variety of unsaturated pyranoid building blocks, such as pyrones, dihydropyrans, and dihydropyranones.

The γ-pyrone kojic acid is readily obtained from D-glucose either enzymatically by *Aspergillus oryzae* (growing on steamed rice) [141] or chemically via pyranoid 3,2-enolones [102], [109]. An isomeric α-pyrone is produced from D-glucose by oxidation to D-gluconic acid and acetylation (1 h, 80 °C, 90 %) [142]. Both, at present, are of little significance as starting materials for preparative purposes, despite a surprisingly effective route to cyclopentanoid products [143] which are surmised to have industrial potential.



Of higher interest, at least with respect to their extensive use for the total synthesis of non carbohydrate natural products [101], [102], are the bevy of enantiopure six-carbon building blocks of the dihydropyran and dihydropyranone type in Tables 4 and 5, all compounds depicted being readily accessible from D-glucose in no more than three to five straightforward steps [102], [144].

Table 4. Enantiopure six-carbon building blocks readily accessible in 3 – 5 straightforward steps from D-glucose via D-glucal ester as key intermediate (R = Ac, Bz) [107], [144] (R' = Me, Et)

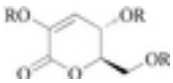


Glucal ester

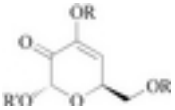
Table 5. Pyranoid building blocks from D-glucose via hydroxyglucal esters (R = Ac, Bz; R′ = Me, Et) [106] as key intermediates.

2-Hydroxyglucal ester

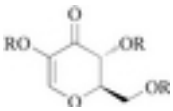
2,3-Enol esters [107]



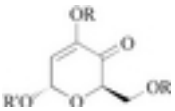
Enol lactones [148]



2,3-Enolones [146]



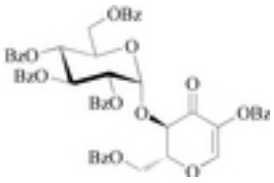
Ene-diolones [147]



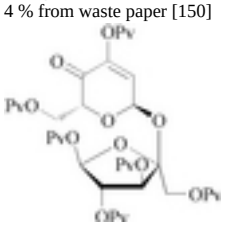
3,4-Enolones [148]

Some of these pyranoid building blocks are accessible even more directly, e.g., levoglucosenone, which has been used for the synthesis of a diverse variety of natural products [149]. Although the yield attainable from pyrolysis of waste paper [150] is low (3 – 4 %), relative large quantities can be amassed quickly. Similarly convenient are the preparations of the three glycosylated dihydropyranones requiring two, three, and four steps from maltose, sucrose, and lactose, respectively:

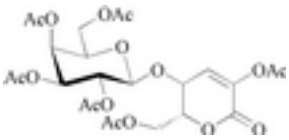
Levoglucosenone
4 % from waste paper [150]



58 % (2 steps)
from maltose [147]



38 % (3 steps)
from sucrose [27]



52 % (4 steps)
from lactose [145]

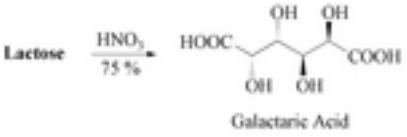
Ac = acetyl; Bz = benzoyl; Pv = pivalolyl

All of these pyranoid building blocks are enantiopure, and have a unique, highly diverse array of functional groups to which the huge arsenal of preparative organic methods can be applied directly, reflecting the extensive use of these building blocks in the total synthesis of non carbohydrate natural products in enantiopure form [101], [102], [149]. They have found little use, though, as high-value-added specialty chemicals. However, if suitable targets and appropriate preparative outlets can be found, particularly along pharmaceutical objectives towards biologically hopeful compound libraries via combinatorial techniques, these pyranoid building blocks are apt to become a plethora of attractive, industrially relevant specialty chemicals.

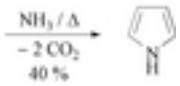
9.2.3. Sugar-Derived Unsaturated *N*-Heterocycles

Although transformation of sugars into trace amounts of *N*-heterocycles occurs extensively on exposure of foods to heat (Maillard reaction [59]), and despite the fact that various nitrogen heterocycles have been generated from saccharide derivatives [151], synthetic procedures meeting preparative standards are exceedingly scarce. Recent improvements of existing procedures and the development of new methodologies have led to the more ready access to various *N*-heterocycles from carbohydrates. Examples are imidazoles, pyrroles, pyrazoles, pyridines, and quinoxalines which due to their derivation from sugars have hydrophilic side chains.

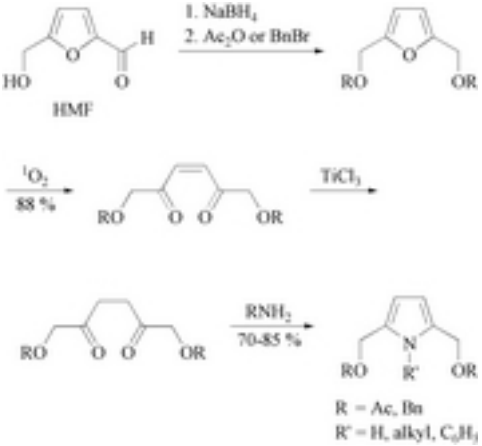
Pyrroles. The formation of pyrroles by heating a glycerol solution of the lactose-derived ammonium salt of galactaric acid [152] over a free flame [153] appears to be the production process from a carbohydrate source giving the highest yield (40 %). However, this process does not seem to be utilized industrially, neither in this nor in modified form.



Galactaric Acid

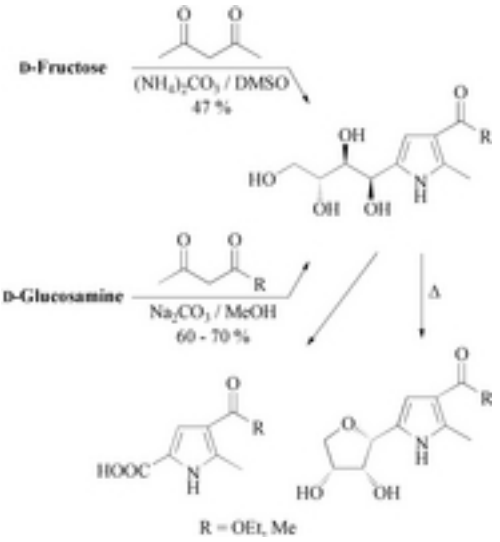


2,5-Disubstituted pyrroles are accessible from carbohydrate sources via HMF in a preparatively straightforward reaction sequence, involving photooxidative furan ring opening and cyclization of the saturated 2,5-diketones with ammonia or amines [154]:



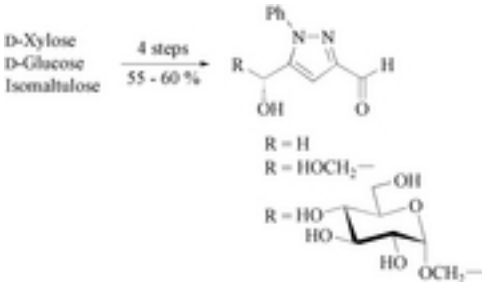
These reaction sequences can directly be transferred to GMF, leading to pyrroles carrying an additional glucosyl residue [154]. Pyrroles with an equally hydrophilic tetrahydroxybutyl substituent are available from D-glucosamine

by exposure to acetylactone or ethyl acetoacetate under mildly basic conditions [155] or in a one-pot reaction from D-fructose by heating with acetylacetone and ammonium carbonate in DMSO [156].



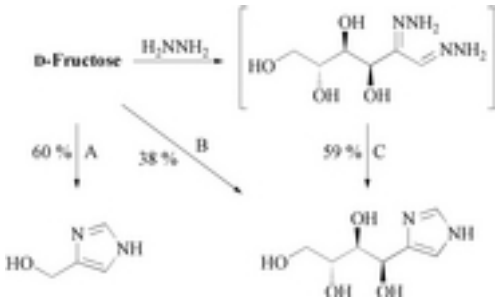
The hydroxylated side chain can, of course, be oxidatively shortened to give a variety of simple pyrrole building blocks, cyclized to a furanoid ring. These compounds may be considered as *C*-nucleosides [155].

Pyrazoles. An expeditious four-step approach to 1-phenylpyrazol-3-carboxaldehydes with a 5-hydroxymethyl, 5-dihydroxyethyl, or a 5-glucosyloxymethyl substituent has been elaborated starting from D-xylose [157], D-glucose, and isomaltulose [158], respectively.



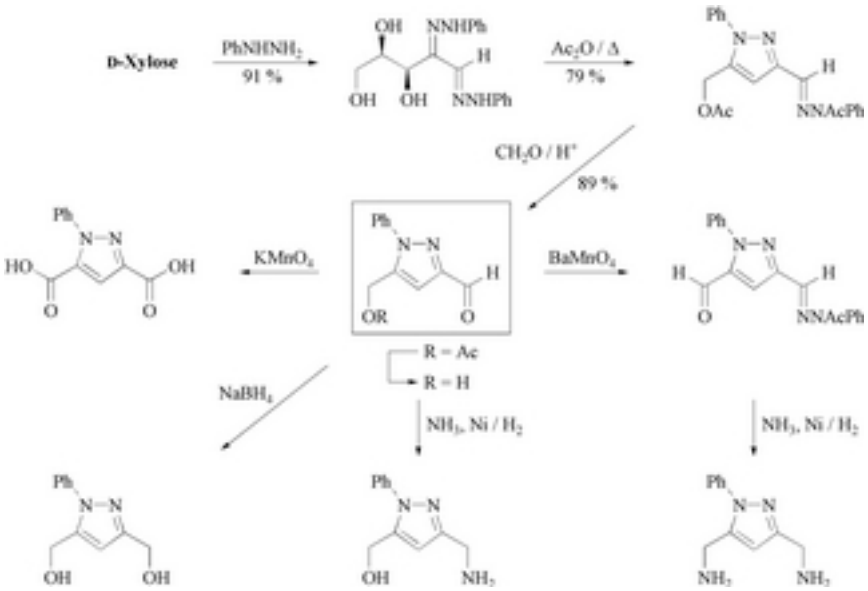
The osazone of D-xylose, nearly quantitatively formed on reaction with phenylhydrazine, straightforwardly cyclizes to the pyrazole upon addition to refluxing acetic anhydride. Subsequent removal of the *N*-acetylphenylhydrazone residue with formaldehyde/acetic acid and de-*O*-acetylation provides a pyrazole-aldehyde (57 % overall yield from D-xylose), a versatile heterocyclic building block, useful in the synthesis of pharmaceuticals or monomers for the production of polyamides and polyesters, e.g., in the form of its the diamino and diol derivatives [157]:

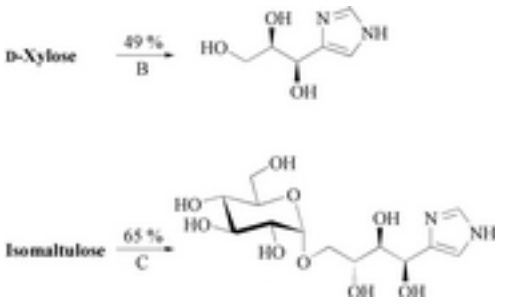
Imidazoles. Various imidazoles carrying hydrophilic substituents in the 4-position are readily accessible in one-pot procedures from the standard monosaccharides. Of those, the formation of 4-hydroxymethylimidazole by Cu(II)-promoted reaction of monosaccharides with formaldehyde and conc. ammonia [159] is rather unique, because obviously retroaldolization to glyceraldehyde and dihydroxyacetone is involved. The retroaldol fission can be partially suppressed when heating a monosaccharide, D-fructose for instance, with formamidinium acetate in liquid ammonia in a pressure vessel [160], or with formamidinium acetate in the presence of boric acid and hydrazine [161]. The latter reaction obviously proceeds via a boric acid complex of the bishydrazone of D-glucosone (2-ketoglucose).

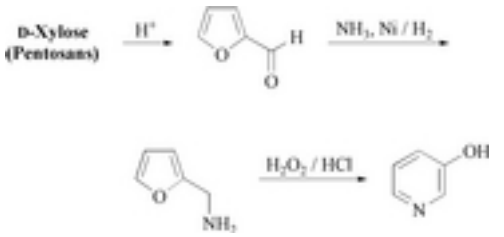


Conditions
A CH_2O, aq. NH_3, $CuCO3/Cu(OH)_2$, 2 h, 100 °C, [158]
B $HC(NH)NH_2 \cdot HOAc$/liq. NH_3, 15 h, 75 °C, [159]
C $N_2H_4/HC(NH)NH_2 \cdot HOAc$/aq. HOAc, H_3BO_3, 3 h reflux, [160]

These conditions can be readily applied to pentoses or disaccharides, as exemplified with D-xylose [160] and isomaltulose [161] in for one-pot procedures acceptable yields:



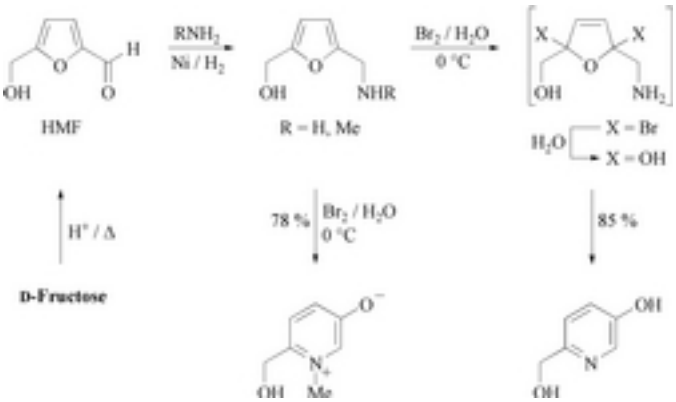


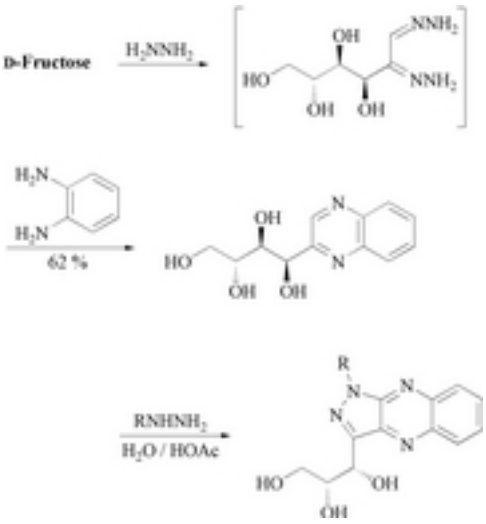


3-Pyridinols. The conversion of pentosans or pentoses into 3-pyridinol can be effected in a practical three-step sequence, involving acid-induced dehydration to furfural, reductive amination to furfurylamine, and subsequent oxidation wit hydrogen peroxide [134], [162], the last step conceivably proceeding through the stage of a 2,5-dihydroxy-2,5-dihydrofurfurylamine, which gives the pyridine nucleus via dehydration to a 5-aminopentenal intermediate and intramolecular aldimine formation. The pyridinol is an important intermediate in the preparation of herbicides and insecticides [163] as well as cholinergic drugs of the pyridostigmine type.

For the conversion of furfurylamines with oxidizable hydroxyl groups, e.g., those derived from fructose via HMF, the multistep process to the hydroxymethyl-pyridinol can be effected in a one-pot procedure simply by treatment with bromine in water-methanol at 0 °C [164]:

Quinoxalines. Useful one-pot procedures are also available for the conversion of various monosaccharides into tetrahydroxybutyl substituted quinoxalines, the preparatively most favorable conditions seem to be reaction of fructose with hydrazine, *o*-phenylenediamine and boric acid in dilute acetic acid with bubbling oxygen through the solution [165], the decisive intermediate being the bishydrazone of D-glucosone:





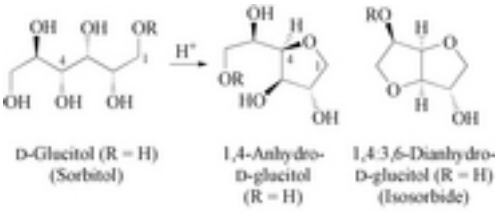
R = H (45 %) [166], R = Ph (90 %) [167]

On briefly refluxing the quinoxaline in aqueous acid with excess hydrazine or phenylhydrazine, a surprising oxidative cyclization takes place to form the trihydroxypropyl-substituted flavazols [166], [167].

9.2.4. Sugar-Based Surfactants

Utilization of cheap, bulk-scale accessible sugars as the hydrophilic component and fatty acids or fatty alcohol as the lipophilic part provides nonionic surfactants which are nontoxic, nonskin-irritating and fully biodegradable. The industrially relevant surfactants along this route are fatty acid esters of sorbitol and sucrose, fatty acid amides of 1-methylamino-1-deoxy-D-glucitol, and, most pronounced in terms of volume produced, fatty alcohol glucosides, the so-called alkyl polyglucosides (→ Surfactants, Chap. 7.4.; → Laundry Detergents, Chap. 3.1.2.6.).

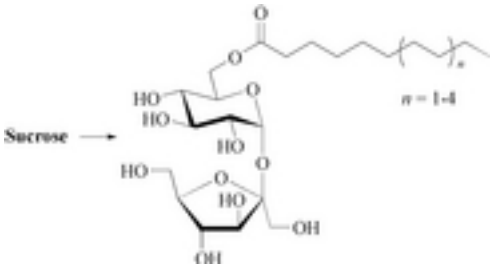
Fatty Acid Esters of Sorbitol (Sorbitan Esters). Sorbitol, well accessible by catalytic hydrogenation of D-glucose (see Table 3), readily undergoes dehydration to "sorbitan" which constitutes a mixture of sorbitol, its 1,4-anhydro and 1,4:3,6-dianhydro derivatives, the exact composition depending on the conditions employed, usually acid catalysis. Esterification of this mixture is generally carried out with fatty acids or their methyl esters at 200 – 250 °C with 0.1 N NaOH. Depending on the amount of fatty acids used, sorbitan monoester ('SMS', R = C_{16}/C_{18} acyl), di- or triester ("SMT") are formed:



SMS is dispersible in water and soluble in fats and oils and has low hydrophilic lipophilic balance (HLB) values, besides as a surfactant SMS finds use as an emulsifier in desserts [168].

Sucrose Fatty Acid Esters. Surfactants based on sucrose have gained limited accep-

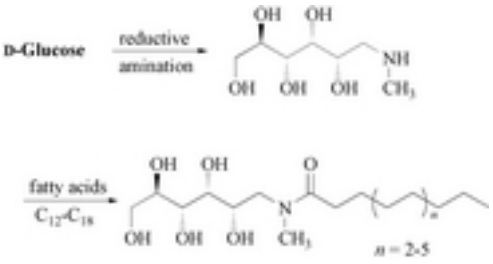
tance industrially due to the instability of its intersaccharidic bond, and its insolubility in conventional organic solvents. This requires the use of the rather toxic and expensive dimethylformamide or dimethylsulfoxide for effecting transesterification with fatty acid methyl esters and complete removal of the solvents. Alternately, transesterification of fats with sucrose without a solvent is also possible. In either case, the resulting sucrose monoester (if 1:1 molar ratios have been used in the esterification process) is not a defined product acylated exclusively at the primary glucose-6-OH, as indicated in the formula, but at the other primary and some of the secondary OH groups as well:



Sucrose fatty acid monoesters, presently produced at a 4000 t/a only, are mostly used in the food industry as emulsifiers and in cosmetic formulations because of their attractive physiological properties.

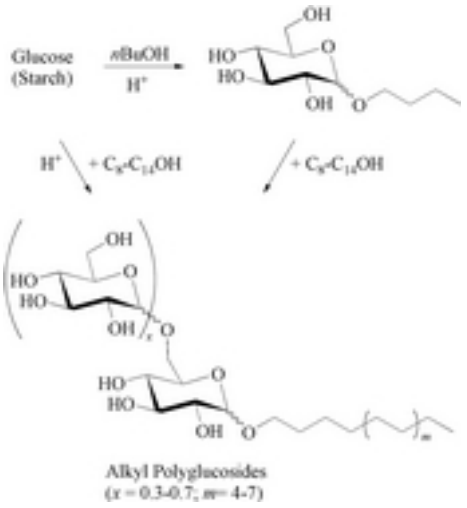
Whilst sucrose fatty acid mono- or diesters are biodegradable, fully or nearly completely esterified analogs (octa- or heptaesters) are not. The sucrose molecule is fully encased in a mantle of long-chain alkyl groups, so that enzymes have no way of binding to the sugar, which is a prerequisite for degradation. Thus, Olestra [169], a sucrose fatty acid hepta-/octaester, which has the consistency of an oil or a solid depending on the nature of fatty acid used, can be used as a noncaloric fat (‘fat-free fat’ [170]) in food applications including frying, due to its thermal stability.

***N*-Methyl-*N*-acyl-glucamides (NMGA).** Reductive amination of D-glucose with methylamine smoothly generates the respective aminoalditol, 1-methylamino-1-deoxy-D-glucitol, which on amidation with fatty acids gives the corresponding fatty acid amides, carrying a methyl group and a pentahydroxylated six-carbon chain at the amido nitrogen.



The NMGA’s possess highly advantageous ecological and toxicological properties which brought about their use as surfactants, cleansing agents and cosmetic applications [171], [172] (→ Laundry Detergents, Chap. 3.1.2.5.).

Alkylpolyglucosides (APG) [173]. Presently produced in two plants with a capacity of up to 40 000 t/a each, APG’s are by far the most important nonionic surfactants. Alkylpolyglucosides are fatty alcohol glucosides with an alcohol chain length normally between C_8 and C_{14}. Their industrial synthesis either comprises a direct acid-catalyzed Fischer glycosidation of glucose (in the form of a syrupy starch hydrolysate) or starch itself. The alternate process consists of two stages, the first being Fischer glycosidation with *n*-butanol to butyl glycosides which are subsequently subjected to acid-promoted transacetalization:

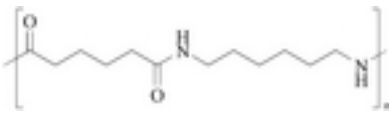


APG's are not skin-irritating, have good foaming properties, and are readily biodegradable, hence are widely used in manual dish-washing detergents and in formulations of shampoos, hair conditioners, and other personal care products.

9.2.5. Hydrophilic Monomers of Polyamides

Polyamide production worldwide amounted to about 5.8×10^6 t in 1998 [174]. More than 90 % of these polyamides are based on six-carbon monomers, i.e., caprolactam (nylon 6), and adipic acid/hexamethylenediamine (nylon 66).

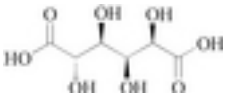
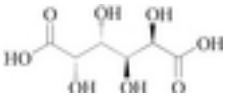
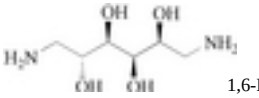
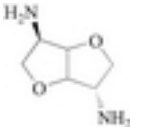
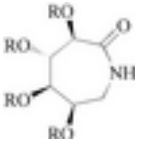
Nylon 6



Nylon 66

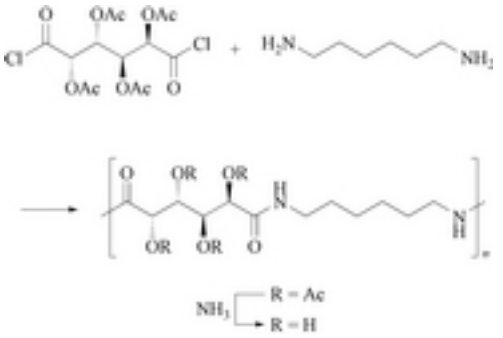
As six-carbon compounds in the form of hexoses are abundantly available in nature, substantial efforts have been made to derive monomers suitable for polyamidation from the bulk scale-accessible hexoses. This approach becomes particularly evident, when considering the large variety of amincarboxylic acids, dicarboxylic acids, and diamines (Table 6), that are accessible from the common six-carbon sugars [175], [176].

Table 6. Sugar-derived six-carbon building blocks suitable for polyamidation [175], [176]

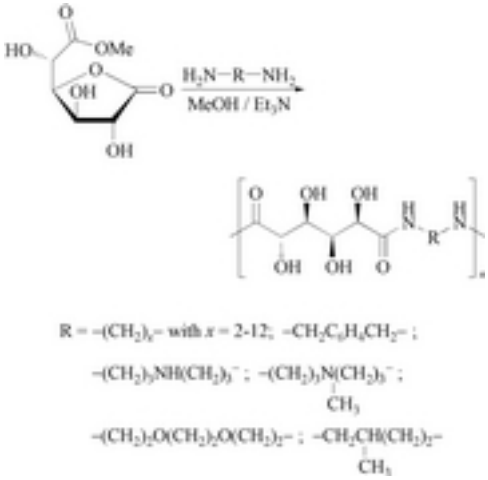
	D-Glucaric acid	(Glucose)
	D-Galactaric acid	(Lactose)
	Furan-2,5-dicarboxylic acid	(Fructose)
	1,6-Diamino-1,6-dideoxy-D-glucitol	(Glucose)
	2,5-Diamino-1,4:3,6-dianhydro-sorbitol	(Glucose)
	2,5-Bis(aminomethyl)furan	(Fructose)
	6-Amino-D-gluconic acid lactam (R = H, CH_3)	(Glucose)

Of the myriad of possible combinations of these sugar-derived monomers either with themselves or with the common, petrochemically derived diamines and dicarboxylic acids, an immense number have been realized. In the following only a few of the respective polyamides are exemplarily covered.

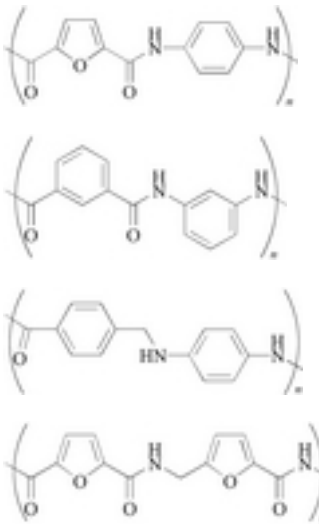
Solution or interfacial polycondensation of galactaric acid dichloride in its acetylated form with various aliphatic and aromatic diamines resulted in a series of polyamides [175], [177], the one resulting from 1,6-diaminohexane resembling a nylon-6,6 in which half of the hydrogens of the methylene chain have been substituted by acetoxy groups (R = Ac). These can be deacylated with aqueous ammonia to give the tetra-hydroxylated nylon 66:



In the case of D-glucaric acid, the use of its 3,6-lactone monomethyl ester proved advantageous to generate stereoregular polyglucaramides, effected with an impressive array of aliphatic and aromatic diamines [178]:



Sugar-based "quasi-aromatic" monomers for polyamides, i.e., the furan-2,5-dicarboxylic acid, appear particularly relevant as they embody the potential to replace petrochemically derived terephthalic or isophthalic acid in the present industrial products. Similar potential pertains to the furanic 1,6-diamine as a substitute for *p*-phenylenediamine. Indeed, a series of such furanic polyamides has been prepared [179] using the furan dicarboxylic acid and aliphatic as well as aromatic diamines. Of these, the polyamide resulting from condensation of furan-2,5-dicarboxylic acid with *p*-phenylenediamine, an analog of Nomex and Kevlar, has particularly promising decomposition and glass temperature parameters [180], distinctly better than those found for the all-furanic polyamide:



Nomex

Kevlar

In spite of the impressive array of highly useful products – with respect to their application profiles they compare on the market favorably with the well-known polyamides – none of these sugar-derived polyamides is, at present, produced on an industrial scale. The reasons are purely economic because the products derived from fossil raw materials are still cheaper by a factor of 5 on the average. Eventually though, with the end of cheap oil being prognosticated for 2040 at the latest [116], and the increasing pressure on the environment, this at present untoward situation for products from carbohydrate feedstocks will be changing.

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