Organic Synthesis with Carbohydrates

Geert-Jan Boons

and

Karl J. Hale

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GEERT-JAN BOONS
Complex Carbohydrates Research Center
Athens, Georgia
USA

KARL J. HALE
Department of Chemistry
University College London
UK

Sheffield
Academic Press

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Organic Synthesis with Carbohydrates

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Preface

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

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

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

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

Part B discusses enantioselective natural product synthesis from monosaccharides. Nowadays, most natural product syntheses are performed in an asymmetric manner. This development is due principally to the realisation

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

Geert-Jan Boons and Karl J. Hale

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1 Mono- and oligosaccharides: structure, configuration and conformation

G.-J. Boons

1.1 Introduction

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

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

In this chapter, the configurational, conformational and dynamic properties of mono- and oligosaccharides will be discussed and, in general, reference is made to reviews that cover these aspects. These

properties, as described in the discussion which follows, are not placed in a historical context.

1.2   Configuration of monosaccharides[5, 6]

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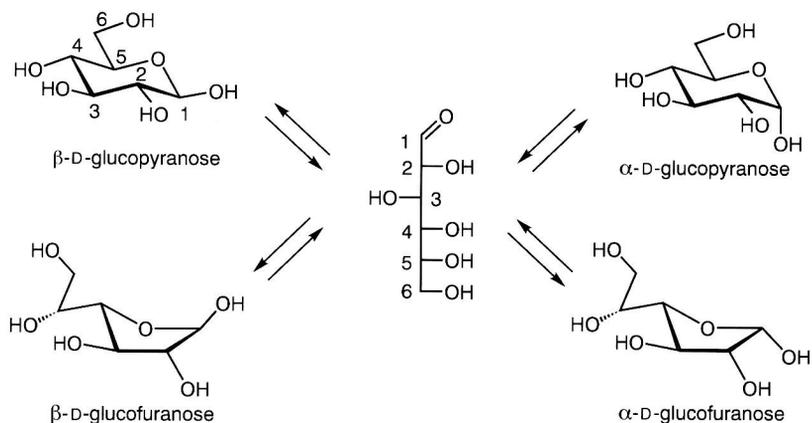
Scheme 1.1   Different forms of D-glucose.

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

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

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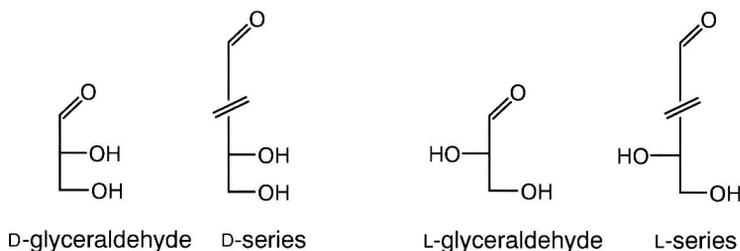

Figure 1.1 D and L sugars.

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

Haworth introduced his formula to give a more realistic picture of the cyclic forms of sugars. The rings are derived from the linear form and drawn as lying perpendicular to the paper with the ring oxygen away from the viewer and are observed obliquely from above. The chair conformation gives a much more accurate representation of the molecular shape of most saccharides and is the preferred way of drawing these compounds. It has to be noted that the Mills formula and zig-zag depiction are particularly useful for revealing the stereochemistry of the carbon centres of the sugars.
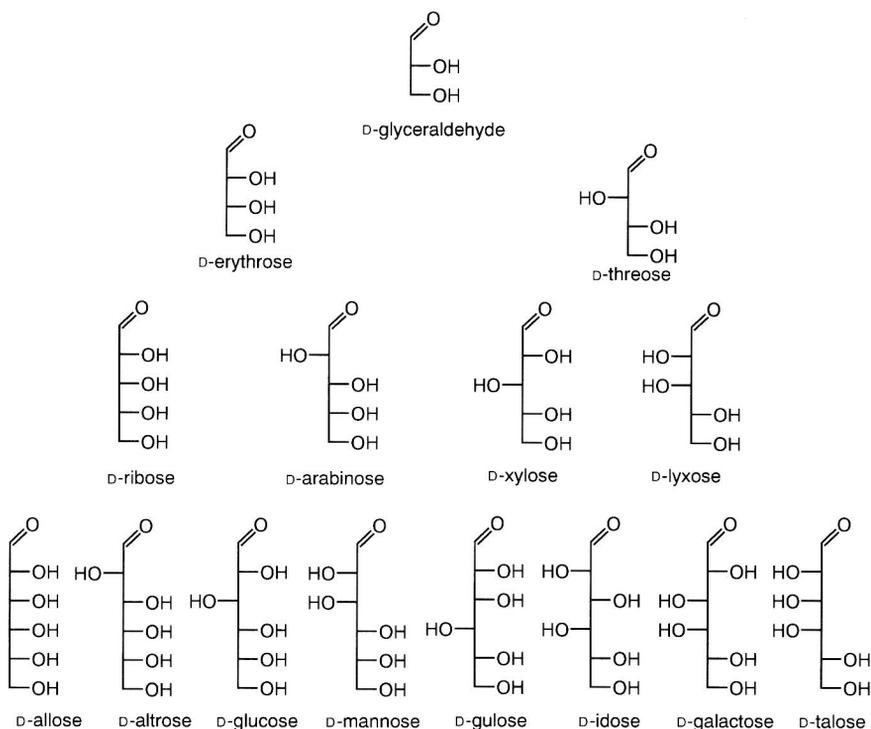
Figure 1.2   Acyclic forms of the D-aldoses.

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

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

As already mentioned, the ketoses are an important class of sugars. Ketoses or uloses are isomers of the aldoses but with the carbonyl group occurring at a secondary position. In principle, the keto group can be at each position of the sugar chain, but in naturally occurring ketoses the keto group, with a very few exceptions, is normally at the 2-position. D-Fructose is the most abundant ketose and adopts mainly the pyranose form.
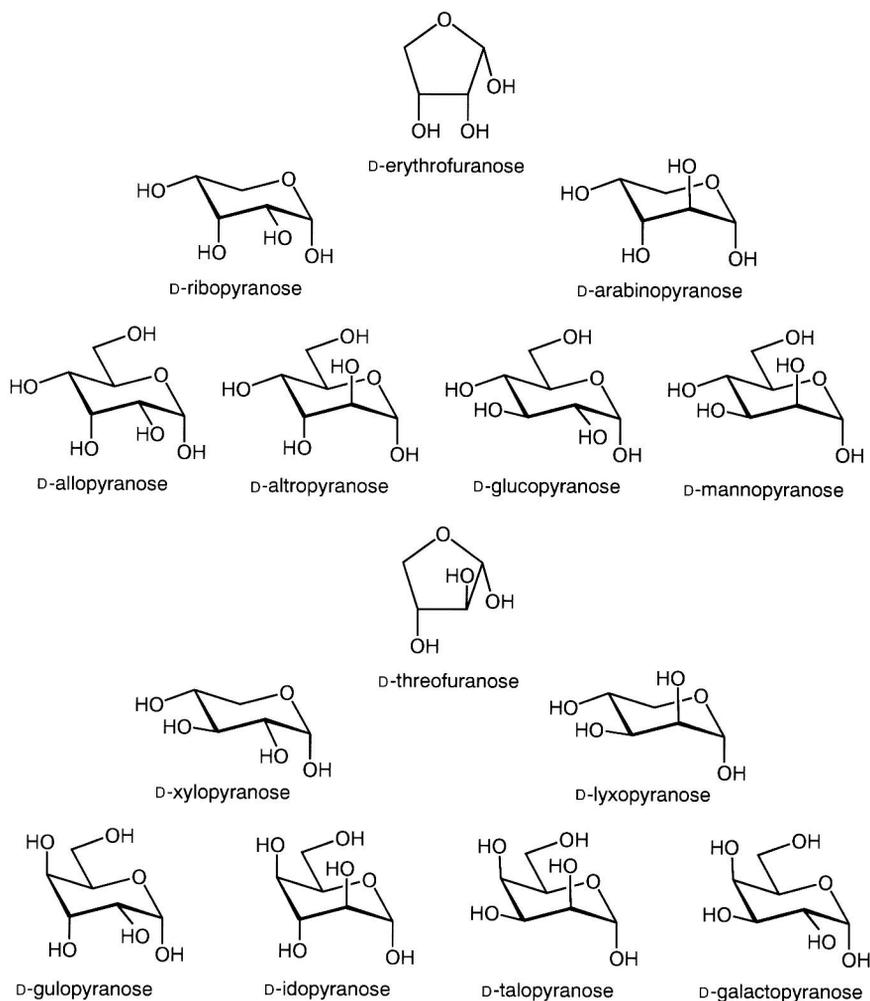
Figure 1.3 Cyclic forms of α-D-aldoses.

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