

CARBOHYDRATES

Structures, syntheses
and dynamics

Edited by Paul Finch



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Paul Finch

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Royal Holloway,
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E9960672



KLUWER ACADEMIC PUBLISHERS

DORDRECHT / BOSTON / LONDON

Library of Congress Catalog Card Number: 98-67965.

ISBN 0-7514-0235-4

Published by Kluwer Academic Publishers,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

Sold and distributed in North, Central and South America
by Kluwer Academic Publishers,
101 Philip Drive, Norwell, MA 02061, U.S.A.

In all other countries, sold and distributed
by Kluwer Academic Publishers,
P.O. Box 322, 3300 AH Dordrecht, The Netherlands.

Printed on acid-free paper

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Printed in Great Britain.

CARBOHYDRATES

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Preface

Longer ago than I enjoy remembering I found an annual frustration with the task of producing a concise and accessible reading list for students with more than a passing interest in carbohydrate chemistry. On some aspects good texts had been produced but were unavailable, on others concepts and knowledge had advanced considerably; in general there were considerable voids between the standard introduction in organic texts, and research-orientated reviews. Thus an invitation from Jon Walmsley of Blackie & Co actually took root and a project was initiated. The aim was to present authoritative overviews of the current status of some particular areas of structural and synthetic carbohydrate chemistry and which were perceived to be central to the subject. It is hoped thereby to underpin the steadily increasing perception and understanding of the roles of carbohydrates in nature.

Central to any consideration of carbohydrates is the monosaccharide unit; one testament to its enduring challenge and interest is the latest literature prediction of the anomeric ratio of glucose. Alfred French explains how the geometries of monosaccharides can be described and studied experimentally and theoretically. He makes clear how different geometries can be separated by relatively small differences in energy, and that in the condensed phase the influence of intermolecular interactions can be crucial. Whilst there is a steadily increasing body of experimental data, precise prediction remains extremely difficult. The structural theme is extended through oligo- and polysaccharides in chapters by John Brady and Serge Pérez and Milou Kouwijzer. John Brady summarises the experimental approaches to the determination of conformation at glycosidic linkages, and reviews the quantum and molecular mechanical methods for the calculation of conformational energies. Although convincing agreement between NMR-derived and modelled conformations is now a routine objective, Brady's careful analysis of the various limitations of calculations should caution against comfortable acceptance of a 'preferred' conformation. Serge Pérez and Milou Kouwijzer describe the methods for study of the geometry of extended carbohydrate chains. Repeat structural features give rise to ordered structures, especially in the condensed phase. However, the precise secondary and quaternary structure is not predictable from the repeat structure and linkage geometry, even for simple homopolysaccharides. In the hydrated state repeat structural features, especially if subject to interruptions, can lead to temporary or permanent gels. Pérez and Kouwijzer describe how

the properties of some hydrated systems can vary with such factors as concentration, salts and temperature. Although these are difficult systems to study and interpret, especially when mixtures of polysaccharides are taken, the incentive is the understanding of materials of real significance to nature and industry. Discerning intermolecular structural interactions is the central theme of the discussion by Louis Delbaere and Lata Prasad. The interactions between proteins and carbohydrates are the subject of intense contemporary study because of their key importance to the regulatory roles of carbohydrates. Despite their highly hydrophilic appearance, it seems that carbohydrates interact with proteins via non-polar as well as polar, including water-mediated, contacts. Ever since Fischer's proof of the structure of glucose, chemical synthesis has responded to the challenges posed by carbohydrate structure elucidation. Karl Hale and Dick Richardson present abundant evidence of the ingenuity and skill of modern synthetic organic chemistry applied to monosaccharides. Beyond the common examples, the variety of structures presented by nature is considerable, but it seems that none is beyond access. The construction of glycosidically-linked sugar units has been an enduring theme in synthetic carbohydrate chemistry; Stefan Oscarson, Horst Kunz, Birgit Löhr and Jörg Habermann set out the principles and procedures for these endeavours. Perhaps there will never be a universal solution to the problems of yields and anomeric selectivity – perhaps the seduction of libraries and 'combinatorial' mixtures will attenuate the incentive – but the structural specificity of nature and the value of a pure substance cannot be denied. As described by Manssur Yalpani, synthesis and degradation at the polymer level usually require an acceptance of 'fuzzy structures'; however, the scope and significance are great. The chemistry and consequences of one specific type of chemical modification of carbohydrates, namely the replacement of a hydroxyl substituent by a hemiester sulphate, are comprehensively described by Ruth Falshaw, Richard Furneaux and George Slim. Despite the notional chemical similarity of sulphate and phosphate, nature seems to have evolved generally different types of materials and roles for carbohydrates containing these anionic substituents. Although a mechanical/structural role for sulphate is preeminent, some more subtle functions are beginning to emerge.

I warmly thank the authors for their efforts in producing such informed and enlightening exposition on these topics in carbohydrate chemistry and I acknowledge the staff of Kluwer (née Blackie) for their patience and assistance.

Paul Finch
Egham
August 1998

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1 Monosaccharides: geometry and dynamics

ALFRED D. FRENCH and PAUL FINCH

1.1 Introduction

The geometries of sugars have long been recognized as determinants of their chemical and physical properties. For example, the 16 D-aldohexapyranoses do not differ in their empirical formula, $C_6H_{12}O_6$. Each aldohexapyranose has four hydroxyl groups and a hydroxymethyl group, yet, because of configurational differences at successive stereogenic carbon centres, each has distinct chemical reactivity and chromatographic behavior. Even the extents of their existence might seem to depend on the exact stereochemistry or chirality at each optical center. In the biosphere, D-glucose, mannose and galactose are nearly ubiquitous, while much less is seen of allose or gulose.

In 1971 Stoddart wrote a seminal book, *Stereochemistry of Carbohydrates* [1], that summarized much of the available knowledge. In the intervening quarter century, however, many advances have occurred. At that time, diffraction crystallography had solved a few structures but the 1970s and 1980s were especially fertile periods. Also, computer modeling was truly in its infancy. This chapter presents some of the new information as well as some of the basic ideas of carbohydrate geometry and dynamics. The reader is also referred to Eliel and Wilen's book, *Stereochemistry of Organic Compounds* [2], that covers many of the topics below in greater depth.

Monosaccharides are themselves important molecules. Just as important, however, is the role of monosaccharide moieties in oligosaccharides and polysaccharides. Substantial experience shows that the structural features of the polymer depend on the structural features of the monomeric building blocks as well as the geometries of the intermonomer linkages of the polymer. Therefore, the principles of monomeric geometry are essential to all carbohydrate chemistry.

1.1.1 How to describe preferred sugar structures

The preferred chemical forms of most monosaccharides and the majority of their derivatives are based on cyclic tetrahydropyran or tetrahydrofuran structures. In the solid state, and in glycosides, oligosaccharides and polysaccharides and other glycoconjugates, these cyclic structures are 'permanent'. In solutions of the 'free' sugars (aldoses, ketoses, some glycosylamines), the ring forms are in chemical equilibrium with, and connected via, the acyclic

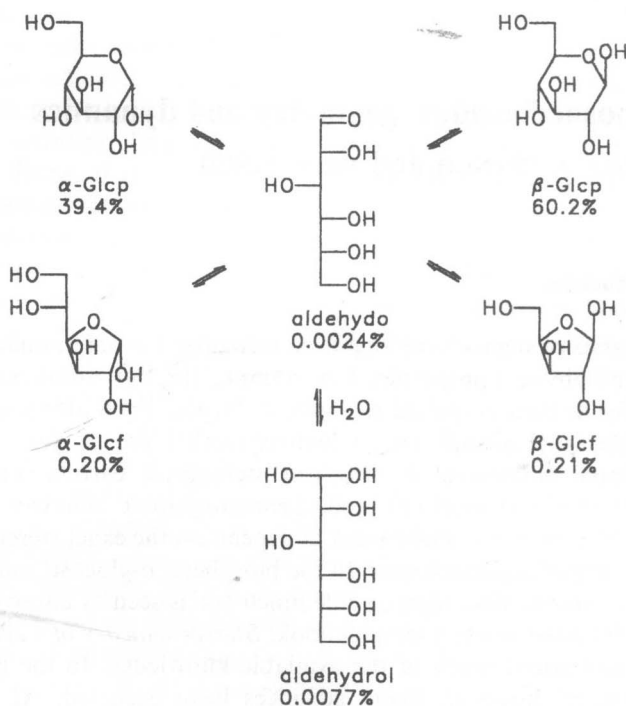


Figure 1.1 Structures of D-glucose forms at equilibrium in D_2O at $37^\circ C$, with percentages [113].

aldehyde or keto form which is structurally identical to the Fischer projection commonly used to present the stereochemical configurations of the monosaccharides. The proportion of the acyclic form, together with the hydrate, is generally small (less than 1%) for the common monosaccharides (Figure 1.1).

In some cases, the proportion of a carbonyl (e.g. pent-2-uloses, 15%–20%), or hydrate (e.g. dihydroxyacetone phosphate, 45%) may be much higher. Also, minor forms may be the relevant substrates for enzymes. In other cases, for example polyols and dithioacetals, the proportion of the acyclic form is necessarily 100%.

Within the approximation that variations of bond lengths and angles are unimportant, a complete description of a monosaccharide, for example in the crystalline, non-disordered solid state, requires choices among the following descriptors:

- number of carbon atoms (e.g. hexose, pentose);
- relative configuration at chiral centers, indicated by the sugar name prefix (e.g. *gluco-*, *ribo-*, *glycero-*);
- chirality (whether D or L);
- ring size (if any – furanose, pyranose, septanose);
- anomeric configuration (α or β);

information (if a ring, envelope, chair, etc. or, if planar, zig-zag or sickle); orientations of exocyclic groups (described by torsion angles for each substituent).

Crystalline molecules are sometimes disordered, that is, one or more of the atoms have fractional occupancies of different positions. At room temperature this disorder can be dynamic, in which case any given example of the atom in question occupies two different positions. Alternatively, the disorder can be statistical. In that situation, some of the atoms of a given type are more or less permanently in one position and some in another. Disorder is not uncommon for the location of the glycosidic oxygen atoms of reducing sugars. In that case, the percentages of both anomeric forms must be specified.

In solution the dynamic nature of sugar structures requires, at least in principle, description of the relative populations of the various forms. In particular, descriptions in terms of averages can be misleading. Presentation as an average can mask the dynamic nature of the molecule and the resulting average structure may in fact be virtually impossible on relevant time scales. A trivial but emphatic example is provided by fructose, which forms both five-membered and six-membered rings. There are no rings of 5.5 atoms. Not so obviously erroneous are results from computationally augmented experiments that determine torsion angles. If the values of a torsion angle have a bimodal distribution, then reporting it as unimodal hides the true nature of the system. It is true that a single ring form predominates for many of the important sugars, but this cannot be assumed in general.

1.1.2 Flexibility

Even when there is only one important configuration and ring conformation the atoms in molecules still exhibit positional variation. Thus, only one chair-shaped ring is important for glucose, but that chair undergoes substantial variations in shape. At any temperature above absolute zero there is continuous variation ('breathing') from thermal motion. Even in crystals at room temperature there is still considerable thermal motion. According to one school of thought, crystallization selects a subset of the range of structures existing in solution. This subset of the structures is elegantly presented by crystallographers as the ellipsoids of thermal motion that correspond to the half-probability (in this example) limits of nuclear positions, as shown in Figure 1.2, a plot [3] of β -L-arabinose [4].

The largest relative motions are typically the rotations about bonds that are described by changes in torsion angles. Motions that change the bond angles are typically much smaller because the forces required to bend a bond angle are much larger. Changes in bond length require even stronger forces for a noticeable motion.

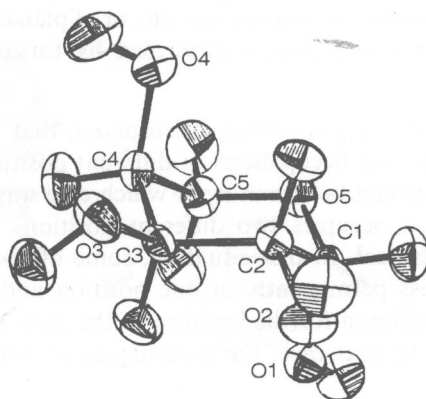


Figure 1.2 Oak Ridge thermal ellipsoid plot (ORTEP) [3] of β -L-arabinopyranose [4] at room temperature. The 50% probability ellipsoids are shown.

In solution, any bond for which the torsional barrier is 5 kcal/mol (*c.* 21 kJ/mol) or less, such as bonds to the exocyclic groups or within backbones of acyclic sugars, is considered to be ‘freely rotating’ at room temperature. The changes in the geometric details during such rotational motion are subtle but complex, because changes in these easily varied torsion angles lead to different bond lengths and bond angles. Bond angles can change by several degrees during changes in torsion angles while torsion-related bond-length stretching can amount to several picometres [5]. The changes in bond lengths and angles that are caused by changes in torsion angles result in part from changes in the atom–atom van der Waals repulsions. Another reason for the bond lengths and angles to change during torsional motions is that there are subtle shifts in the populations of the electrons as orbitals on adjacent atoms are given different relative orientations. Thus three types of flexibility of any molecule must be considered. The first is a degree of oscillation about a fixed ideal value, as in thermal motion, exemplified to a partial extent by the Oak Ridge thermal ellipsoid plots (ORTEPs). The second is a compensatory change in bond lengths and angles as a result of torsional movements. Third, there are many examples of well-populated multiple minima in torsion angle space, such as the two commonly found rotational orientations for O6 of glucopyranose (see section 1.6). For ring-forming molecules an additional type of flexibility is the concerted motion of all of the atoms, such as found in pseudorotation (section 1.4.4).

1.1.3 Prediction of structure

Because structure and behavior are so intertwined, much of carbohydrate chemistry has been devoted to the determination of geometries that characterize monosaccharides. If the observed molecular geometries of a range of

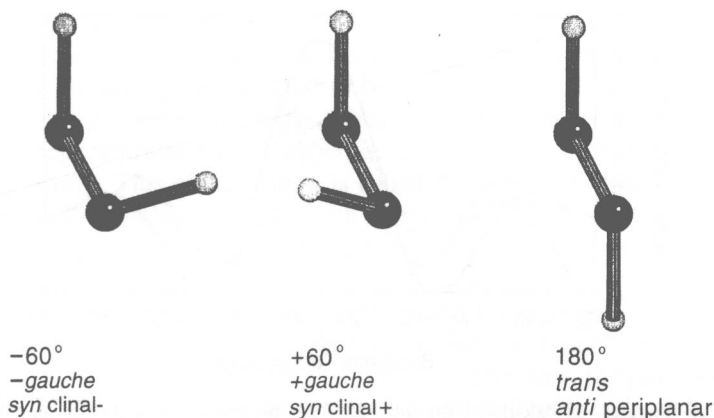


Figure 1.3 Various terms that define the torsion angle.

compounds can be predicted, then we can claim to understand the factors that govern their shapes. Thus, carbohydrate chemists have been driven to devise systems for predicting sugar ring shapes. These systems are based on important basic phenomena that must be understood.

The first principle governing sugar structures is that their sp^3 carbon atoms have tetrahedral bonding geometry, as proposed by van't Hoff [6] and Le Bel [7] in 1874, and later confirmed crystallographically in diamonds [8]. Second, it is well established that four-atom sequences of such carbon atoms, such as in *n*-butane, prefer to have a torsion angle (Figure 1.3) of about 180° , with secondary preferred values of $\pm 60^\circ$. Torsion angles with 180° values do not lead to ring formation. However, alternating $\pm 60^\circ$ torsions for a six-atom sequence lead to ring closure by averaging to 0° . Alternation avoids the high-energy conformation having eclipsed, 0° torsion angles that could also lead to ring formation for five-membered furanoid rings. Because one or more butane-like sequences often appear in monosaccharides, this is an important factor in determining the ring shape. The sp^3 oxygen atoms also have a tendency for nearly tetrahedral bond angles, and O—C—C and C—O—C sequences are thought to have threefold torsional preferences somewhat similar to those of butane (Figure 1.4).

This secondary preference of saturated C—C bonds for $\pm 60^\circ$ torsion angles gives substantial stability to chair forms of cyclohexane, the tetrahydropyran ring and many of the pyranose sugars. In 1939 the crystal structures of α -D-glucosamine hydrochloride and hydrobromide were solved, revealing 4C_1 chairs (the nomenclature indicates a chair form, with carbon atom 4 high and carbon atom 1 low when viewed in the standard viewing orientation; section 1.1.4) [9]. Variation in placement of substituents on these rings can either stabilize or destabilize that chair relative to the alternative chair or to the skew forms. Often, the preferred overall geometry of a