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Carbohydrates

Organic Chemistry
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Volume 7

Consultant Editor
D H Hey FRS
Volume Editor
G O Aspinall

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Carbohydrates

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Consultant Editor's Note

The ten volumes in Organic Chemistry in the Second Series of the biennial reviews in the International Review of Science follow logically from those of the First Series. No major omissions have come to light in the overall coverage of the First Series. The titles of the ten volumes therefore remain unchanged but there are three new Volume Editors. The volume on Structure Determination in Organic Chemistry has been taken over by Professor Lloyd M. Jackman of Pennsylvania State University, that on Alicyclic Compounds by Professor D. Ginsburg of Technion-Israel Institute of Technology, and that on Amino Acids, Peptides and Related Compounds by Professor H. N. Rydon of the University of Exeter. The international character of the Series is thus strengthened with four Volume Editors from the United Kingdom, two each from Canada and the U.S.A., and one each from Israel and Switzerland. An even wider pattern is shown for the authors, who now come from some sixteen countries. The reviews in the Second Series are mainly intended to cover work published in the years 1972 and 1973, although relevant results published in 1974 and 1975 are included in some cases, and earlier work is also covered where applicable.

It is my pleasure once again to thank all the Volume Editors for their helpful cooperation in this venture.

London

D. H. Hey

Preface

The second volume devoted to carbohydrates in the Organic Chemistry Section of the International Review of Science continues with the objective of publishing critical and well-documented articles with carefully selected rather than necessarily exhaustive lists of reference to the recent literature. Again a balance is maintained between those chapters dealing with the chemistry of monosaccharides and those dealing with carbohydrate polymers. Certain chapters extend the subject matter coverage of the first volume over the intervening two-year period, whilst other chapters review topics not previously covered in this series. The general chemistry of carbohydrates is again discussed in articles dealing with general carbohydrate synthesis, displacement, elimination and rearrangement reactions, and amino and nitro sugars. In addition, an article on sugar-containing antibiotics deals with a topic that both is of considerable biological importance and continues to provide much of the driving force for the development of new carbohydrate syntheses. The review on ^{13}C n.m.r. spectroscopy is of importance for applications both in monosaccharide chemistry and increasingly for structure determination of polysaccharides which have fairly regular 'repeating units'.

Topics of particular interest to biochemists are discussed in articles on membrane glycolipids (S. Hakomori), iduronic acid-containing glycosaminoglycans (U. Lindahl) and blood group substances and related glycoproteins (K. O. Lloyd). These articles are of importance in stressing the need for properly evaluated chemical data as a basis for understanding biological phenomena at a molecular level. Attention may be drawn to the forthcoming appearance of a volume on 'Biochemistry of Carbohydrates' in the Biochemistry Section of the International Review of Science. This should be regarded as a companion volume in which the editors (Dr. W. J. Whelan and I) have chosen topics for review which are mutually complementary rather than overlapping in content.

Ontario

G. O. Aspinall

Contents

1
Carbon-13 N.M.R. Spectroscopy of Carbohydrates

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1.1 INTRODUCTION

The proliferation of studies on the ^{13}C n.m.r. spectra of carbohydrates during the past four or five years attests to the current strong interest of chemists in exploring applications of this area of spectroscopy. It is now clear that ^{13}C n.m.r. is acquiring a status not only as a useful adjunct to ^{1}H n.m.r. spectroscopy, but one characterised by its own unique contributions.

Two comprehensive texts on ^{13}C n.m.r.[1,2] deal at some length with spectra of the carbohydrates, and recent reviews[3-5] cover the more current literature and include[5b] a detailed compilation of data. The intention of this article is to present a relatively broad description of the characteristics of these ^{13}C spectra, and to emphasise applications — demonstrated or potential — which yield information (or may do so) not readily attainable by other techniques.

1.2 CHEMICAL SHIFTS

1.2.1 General characteristics

Chemical shifts of the ^{13}C nuclei of carbohydrates and derivatives, aside from those of substituent groups that may be introduced, encompass most regions of the 200 p.p.m. range covered by organic compounds. It is common practice to obtain chemical shifts from proton-decoupled spectra*, in which the signal produced by a ^{13}C nucleus appears as a narrow singlet†. This simplified form of display, together with a resolution of 0.1 p.p.m. afforded by present instruments, usually ensures an overall excellent separation of resonance signals even with highly complex molecules or mixtures. Herein lies much of the power of ^{13}C n.m.r. spectroscopy.

* Normal irradiation of the sample at the ^{13}C resonance frequency is accompanied by an intense broadband irradiation at the appropriate ^{1}H frequency, thereby eliminating coupling between the ^{13}C and ^{1}H nuclei. In this process also, the signal intensity of a carbon bearing a proton is augmented by a factor of *ca.* 3 owing to nuclear Overhauser enhancement[1,2] and also by coalescence of the components of the split signal. This is an important gain, because of the low natural abundance (1.1%) and low sensitivity of ^{13}C nuclei.

† ^{13}C–^{13}C coupling causes no significant interference, because at the natural abundance level two ^{13}C nuclei rarely occur in the same molecule.

A good example of the signal separation that can be achieved with a complicated mixture of closely related compounds is illustrated in Figure 1.1 by the pulsed Fourier transform (FT)[1,2,6,7] spectrum of 3-*O*-methyl-D-psicose[8]: two pyranose and two furanose forms are in equilibrium (see Section 1.3), corresponding to 28 individual ^{13}C signals, each of which is

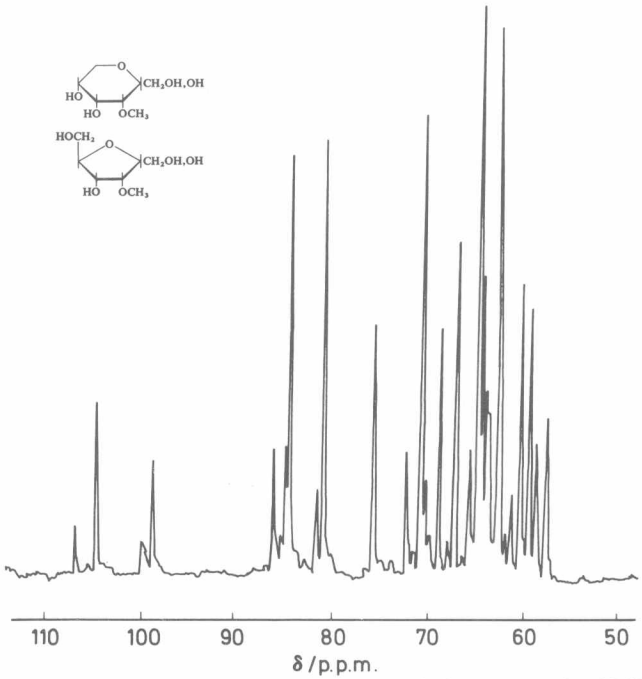


Figure 1.1 FT ^{13}C n.m.r. proton-decoupled spectrum (at 25.15 MHz) of 3-*O*-methyl D-psicose in D_2O at 30°C. Signals of the anomeric carbons (C-2) are displayed to low field of 95 p.p.m. Inset formulae represent the anomers of the pyranose and furanose forms (From Herve du Penhoat and Perlin[8], by courtesy of Elsevier)

detectable. In common with other FT ^{13}C spectra[1,2,7], quantitative aspects of this spectrum are not as generally satisfactory as those of protons. The peak areas are highly sensitive to the relaxation properties of the various ^{13}C nuclei and hence to the experimental pulsing procedure adopted, and vary also with the extent of Overhauser enhancement. Since spin–lattice relaxation is more efficient for a carbon that has an attached proton than for a non-protonated carbon, the small areas of the anomeric (C-2) signals in Figure 1.1 relative to those of the other carbons are a reflection of the fact that C-2 bears no hydrogen. Despite these limitations, however, the error in estimating the composition of a mixture will probably be $< \pm 5\%$ if comparisons of the integrated intensities are based on signals representing the same class of carbon (such as the four anomeric carbons in Figure 1.1).

Resonances of simple aldoses and ketoses[8-16] are distinguishable for the

most part in terms of anomeric, secondary and primary carbons: relative to tetramethylsilane (which is being widely adopted as a standard for ^{13}C as well as ^{1}H[1,2,5b]), these classes of nuclei usually resonate at 98 ± 6, 75 ± 5 and 65 ± 5 p.p.m., respectively. Variations within each class are associated with changes in configuration or ring size according to generally recognisable patterns, as described below (Sections 1.2.3 and 1.2.4).

1.2.2 Substituent effects

The effects on chemical shift owing to substituent groups or to other modifications of carbohydrates have as yet received limited systematic study. However, general experience with various classes of organic compounds shows a high degree of consistency in applying substituent effects to predict chemical shifts[1,2], and the same is therefore to be expected for carbohydrates. An outline of the data available on the main types of transformations within the sugar series* is given below; the impact on the carbon in question is usually accompanied by a much smaller one on neighbouring carbons, and it is noteworthy also that some of the effects (especially those of *O*-alkylation and *O*-acylation) are quite different from those of protons.

Most marked is the change observed when a carbinol group is converted into a carbonyl group (aldehyde, ketone or carboxyl), in which case the particular ^{13}C resonance is moved downfield into the region of 175–200 p.p.m.[1,2]. Uronic acid carboxyls, for example, produce signals at 176–180 p.p.m.[17,18].

Deoxy groups are characterised by an increase in shielding relative to the carbinol carbon of 25 p.p.m. (C-1 of 1,5-anhydro-D-glucitol) or 35–40 p.p.m. (C-2 and C-6 of 2-deoxy-D-glucose)[9,12].

A distinctive upfield shift is observed for aminodeoxy derivatives: C-2 of 2-acetamido-2-deoxyaldoses resonates 15–20 p.p.m. upfield of secondary carbinol signals[19]; the 2-deoxy-2-sulphamino group is associated with increased shielding of *ca.* 13 p.p.m.[17] and ^{13}C—NHMe by 10 p.p.m.[20].

For alkenes the chemical shift of an enolic carbon should be close to 145 p.p.m. (C-1 of 3,4,6-tri-*O*-acetyl-D-glucal resonates at 144.6 p.p.m.), and of other sp^2 carbons in the region of 100 p.p.m. [δ(C-2) of 3,4,6-tri-*O*-acetyl-D-glucal is 98.2 p.p.m.][21].

A deuterium atom markedly reduces the effective intensity of the signal of the ^{13}C nucleus to which it is attached (owing to splitting into a triplet, modified relaxation characteristics and loss of Overhauser enhancement), which essentially removes that signal from the spectrum[13,22]. In some instances an upfield shift of about 0.05 p.p.m. of signals produced by the β ^{13}C nuclei is observed[23]. These effects aid in the analysis of spectra.

O-Methylation to yield ethers usually induces deshielding of the α-C by 8–10 p.p.m.; adjacent carbons may show an increase in shielding of 0.5–1.0 p.p.m. or occasionally more[11,12]. However, it has been found[8] that C-2 of D-psicosides is deshielded by only 2–4 p.p.m. on methyl glycoside formation.

* Obviously, some of the functional groups listed are components of naturally-occurring carbohydrates; for convenience they are treated here as if a simple sugar is being chemically modified.

An anomeric phenyl or nitrophenyl group promotes deshielding of C-1 by 5–7 p.p.m.[24]. C-1 of 1,6-anhydrohexopyranoses is deshielded relative to the free sugar by 5–6 p.p.m.[18]. *O*-Tritylation has been found to produce an upfield shift of the C-6 signal of 1,2,3,4-tetra-*O*-acetyl-β-D-glucose or -D-mannose[25] by 1 p.p.m.

O-Acetylation to give esters has a relatively small, and diverse, effect[11] varying from deshielding by a few p.p.m. to increased shielding by a similar amount. An *O*-phosphate group promotes deshielding by 2–3 p.p.m.[26,27] and an *O*-sulphate deshielding by 6–7 p.p.m. (primary) or 8–10 p.p.m. (secondary)[17,28].

Strong deshielding of α carbons usually accompanies the formation of cyclic acetals. An *O*-isopropylidene group promotes a downfield displacement of 5–10 p.p.m. In *trans*-fused 4,6-*O*-benzylidene derivatives, C-4 is deshielded by *ca.* 10 p.p.m. and C-6 by *ca.* 7 p.p.m.; by contrast, C-5 shows an increased shielding of 11 p.p.m. and C-3 of 4 p.p.m.[29].

The formation of a glycosidic bond between two sugar residues causes deshielding both of the anomeric carbon and the other ^{13}C nucleus of the bond by 5–10 p.p.m.[17,30].

Lanthanide shift reagents have a relatively small impact on ^{13}C chemical shifts, especially compared with that on protons, but nevertheless are sufficiently large to offer substantial promise for use in spectral analysis[31,31a].

1.2.2.1 Chemical shifts of substituents

Chemical shifts of the carbons of a number of common substituents show small variations within each group, and as yet no consistent structural or stereochemical correlations with these differences have been detected. The approximate ranges of chemical shifts reported in the literature for some of these substituents are as follows: *O*-CH_3, 55–60 p.p.m.[5b,11,12,32]; *O*-$COCH_3$, 19–20 p.p.m. (CH_3) and 165–170 p.p.m. (C=O)[5b,31]; *N*-$COCH_3$, 22–24 p.p.m. (CH_3) and 175–177 p.p.m. (C=O)[19]; *O*-isopropylidene 26–30 p.p.m. (CH_3) and 128–135 p.p.m. (O—C—O)[5b]; *O*-benzylidene, 99–102 p.p.m. (O—C—O)[29].

1.2.3 Configurational and conformational effects on pyranoses

The proton-decoupled spectrum of α- and β-D-glucose (1) and (2) (Figure 1.2) illustrates a number of features of natural-abundance ^{13}C spectra of pyranoses[9-16]. Although a few of the signals overlap, the twelve resonance signals required for a mixture of two anomers are readily accounted for, and their relative intensities correspond to the expected α:β ratio of close to 2:3.

Carbons 1, 2, 3 and 5 of α-D-glucose all resonate 2.5–4.5 p.p.m. upfield of the corresponding nuclei of the β-anomer. That is, the carbon (C-1α) bearing the axial OH, carbons adjacent to it (C-2) and those involved in a *syn*-diaxial C—H,C—O interaction (C-3 and C-5) all show an increase in shielding; C-4 and C-6, which are more remote from the axial hydroxyl

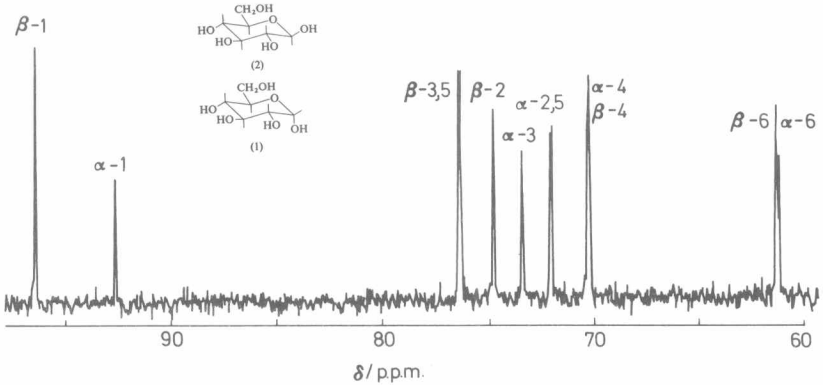


Figure 1.2 FT ^{13}C n.m.r. proton-decoupled spectrum (at 22.6 MHz) of α- and β-D-glucose in D_2O at 30°C

group, have the same chemical shifts as those of the β-anomer. It is convenient to describe the differences observed as α, β, γ or δ shielding effects[11,33]: an axial hydroxyl group is associated with a notable increase in shielding of the carbon to which it is bonded, and of the β and γ carbons, but usually not of the δ and more distant carbons. As a further example, the fact that the axial C-2—O bond of β-D-mannose introduces an additional orientational factor of this kind appears to be reflected in increased shielding (by an average of *ca.* 2.5 p.p.m.) of carbons 1–4 compared with β-D-glucose. Such shielding effects are described for α- and β-D-lyxose in Table 1.1.

An analogous relationship between chemical shift and orientation is observed for inositols[34], 2-hexuloses[8,16], 2-acetamido-2-deoxyhexoses[19], deoxynitro derivatives[35] and 4,6-*O*-benzylidene glycosides[29]. In all these instances, chemical shifts for the various members of the series can be interrelated with reasonable accuracy by taking account of the orientational differences expected, and adding or subtracting the appropriate shielding values (Table 1.1). Such data furnish a general reference base from which structural and stereochemical information may be derived when applied to other kinds of derivatives or higher molecular weight carbohydrates.

Although it seems reasonable to associate such shielding effects with steric interactions (see Section 1.2.4), the evidence for this is mainly circumstantial, and there are a number of inconsistencies. Thus, less shielding is observed for a *syn*-axial interaction between two OH groups than between an H and OH group, i.e. a shielding value of only 0–2 p.p.m.*, rather than 2.5–3 p.p.m., accounts for the chemical shifts observed[12,16,34], which is the reverse of the order of steric compressions. Among other examples[12,16] is the unexpectedly small impact on the shielding of C-4 and C-5 by axial C-4 of L-*arabino* isomers.

In comparing the chemical shifts of configurational isomers as above, one begins with the assumption that the basic architecture (bond angles, etc.)

* A value of 0 Hz is used (Table 1.1) for inositols (entry IV), and of 2.0 Hz for hexuloses (entries V and VI). More striking examples of this kind have been observed in the alicyclic series, in which some *syn*-axial OH,CH_3 orientations are associated with *deshielding*[36].

Table 1.1 ^{13}C Shielding differences between isomers

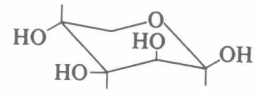
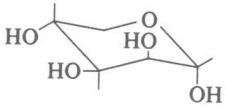
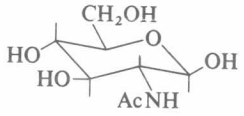
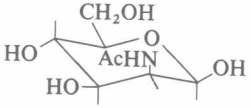
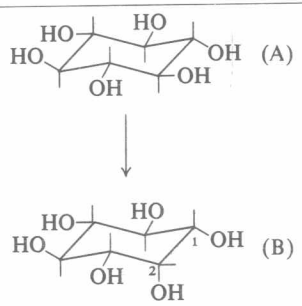
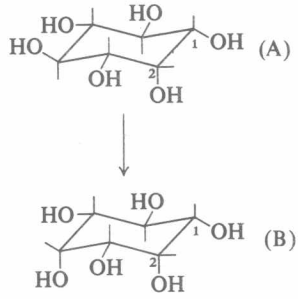
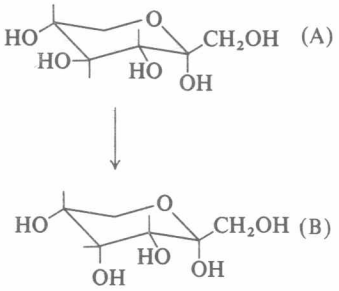
Inversion*		C	δA (expt.)	Relationship†	$\Delta\delta$	δB (calc.)	δB (expt.)
	 (A)						
		1	95.0	+ax. O, − O-1/O-2	+2.5, − 2.5	95.0	95.0
I		2	70.8	+adj. O-1, − O-2/O-1	+2.5, − 2.5	70.8	71.5
		3	73.7	+H/ /O-1	+2.5	71.2	71.1
	 (B)	4	67.6	—	0	67.6	68.5
		5	64.9	+H/ /O-1	+2.5	62.4	63.9
	 (A)	1	96.2	+adj. N-2	+2.5	93.7	94.3
		2	58.0	+ax. N	+2.5	55.5	55.3
		3	75.2	+adj. N-2	+2.5	72.7	73.2
II		4	71.2	+H/ /N-2	+2.5	68.7	67.8
		5	77.2	—	0	77.2	77.5
		6	62.0	—	0	62.0	61.7
	 (B)						

Table 1.1. *continued*

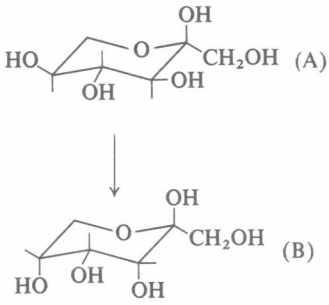
Inversion*	C	δA (expt.)	Relationship†	$\Delta\delta$	δB (calc.)	δB (expt.)
III  (A) → (B)	1	74.7	+adj. O-2	+2.0	72.7	73.4
	2	74.7	+ax. O	+2.0	72.7	73.2
	3	74.7	+adj. O-2	+2.0	72.7	73.4
	4	74.7	H/ /O-2	+2.0	72.7	72.1
	5	74.7	—	0	74.7	75.3
	6	74.7	H/ /O-2	+2.0	72.7	72.1
IV  (A) → (B)	1	73.4	—	0	73.4	72.7
	2	73.2	+O/ /O-4; −O/ /H-4	0, −2.0	75.2	75.5
	3	73.4	+adj. O-4	+2.0	71.4	71.1
	4	72.1	+ax. O, −H/ /O-2, +O/ /O-2	+2.0, −2.0, 0	72.1	75.5
	5	75.3	+adj. O-4	+2.0	73.3	72.7
	6	72.1	+H/ /O-4	+2.0	70.1	67.8

V



1	127.9‡	—	0	127.9	128.7
2	94.3	+O/ /O-4, −O/ /H-4	−0.5	93.8	94.6
3	121.1	+adj. 4	+2.5	123.6	127.3
4	117.7	+ax. O, +O/ /O-2, −H/ /O-2, +O/ /H-6	+4.5	122.2	127.8
5	122.3	+adj. 4	+2.5	124.8	123.9
6	130.0	+H/ /O-4	+2.5	132.5	13.15

VI



1	127.9‡	—	0	127.9	128.7
2	94.3	+adj. 3, −O/O-3	0	94.3	95.3
3	121.1	+ax. O, +O/ /O-5, −O/O-2	+2.0	123.1	122.5
4	117.7	+adj. 3, +adj. 5	+5.0	122.7	122.5
5	122.3	+ax. O, +O/ /O-3	+4.5	126.8	127.0
6	130.0	+adj. 5	+2.5	132.5	134.8

* Interconversion of A into B. I, β-D-lyxose [A], α-D-lyxose [B][12]; II, 2-acetamido-2-deoxy-β-D-glucose [A], 2-acetamido-2-deoxy-β-D-mannose [B][19]; III, *scyllo*-inositol [A], *myo*-inositol [B][34]; IV, *myo*-inositol [A], *opi*-inositol [B][34]; V, α-D-sorbose [A], α-D-psicose [B][8]; VI, α-L-sorbose [A], β-D-psicose [B][8]

† ax., axial substituent; adj., adjacent to axial substituent; H/ /O, *syn* diaxial H,O; O/O, *gauche* O,O; O/ /O, *syn* diaxial O,O; +, shielding; —, deshielding

‡ p.p.m. from CS_2

remains the same and that the only change is the inversion of configuration at a given centre. Hence, a substantial departure from the chemical shift pattern expected may be regarded as evidence of a significant change in stereochemistry. An example of this kind is found among the 2-hexuloses: by allowing for appropriate configurational and conformational factors, as discussed above, reasonably good agreement is found between observed and calculated ^{13}C chemical shifts for all members of the series, except α-D-psicopyranose[8] (see Table 1.1). Therefore, it appears justifiable to conclude that the conformation of α-D-psicopyranose differs significantly from the conformation of, e.g. α-D-sorbopyranose, which is the most conformationally stable of 2-hexuloses[37, 38].

Shielding differences between diastereomers may be conveniently compared by simply summing their individual chemical shifts, because the steric effects on chemical shift just discussed should be reflected in the 'overall' (or average) state of shielding of the ^{13}C nuclei in the molecule[12, 39]. This approach can be useful when a rigorous assignment of all of the individual resonances is particularly difficult. Since, as has been noted, an increase in ^{13}C shielding generally accompanies an increase in steric interaction, it is not surprising that 'total' ^{13}C chemical shifts of the pyranoses tend to

Table 1.2 A comparison of ^{13}C shielding and conformational stability among pyranoses

	$\Delta\Sigma\,^{13}C$* *chemical shifts*[8, 12, 18, 19]/p.p.m.	Δ (*free energy*)[37,38]/ kcal mol^{-1}
β-D-xylose	—	—
β-D-lyxose	14.1	0.8
α-D-ribose	19.0	1.5
β-D-glucose	—	—
β-D-galactose	5.4	0.5
α-D-glucose	14.1	0.4
α-D-sorbose	11.2	
α-D-mannose	13.4	0.5
α-D-tagatose	15.5	
α-D-galactose	22.0	0.8
β-D-fructose	21.0	
β-D-allose	15.3	0.9
β-D-psicose	28.6	1.6
2-acetamido-2-deoxy		
β-D-glucose	—	—
α-D-glucose	14.0	0.4†
β-D-galactose	8.5	0.5†
α-D-mannose	18.9	0.5†
1,6-anhydro-		
β-D-idose	—	—
β-D-altrose	5.5	0.6‡
β-D-gulose	13.3	0.8‡
β-D-galactose	16.8	3.3‡
β-D-glucose	3.1	5.4‡

* Sum of the chemical shifts (p.p.m.) of named compound *minus* the sum of the chemical shifts of the first compound of the group (a larger value corresponds to an *overall* stronger shielding of ^{13}C nuclei of the molecule, relative to the group of ^{13}C nuclei of the reference molecule)

† Free energy differences assumed to be comparable to those of the related aldoses

‡ Relative to energy of 1*C*(*D*) form in equilibrium[37]

vary as do their free energies[12]. Hence, the ^{13}C nuclei of β-D-xylose and β-D-glucose, which as a group are the least shielded among the aldoses, are also constituents of the most stable isomers within the series (Table 1.2). By contrast, relatively unstable isomers such as α-D-altropyranose and α-D-idopyranose contain the most shielded group of nuclei[12]. A similar relationship is found in the 2-hexulose series[8] and with 2-acetamido-2-deoxy-aldohexoses[19]. Furthermore, when 2-hexulopyranoses are compared with aldohexopyranoses of like free energies, the total ^{13}C chemical shifts also are found to be closely parallel in the two series[8] (Table 1.2). Data for 1,6-anhydrohexopyranoses show a similar overall trend, although the *gluco* isomer is strikingly atypical[18].

Variations in ^{13}C chemical shifts that occur on configurational inversion are largely mirrored by variations in proton chemical shifts: i.e. an increase in the shielding of carbon generally is accompanied by a decrease in the shielding of the appended proton. Many examples of such 'bond polarisation'[40,41] (see Section 1.2.5) are available from data on cyclohexanes[39-41] and carbohydrates[12,13], as illustrated for α- and β-D-glucose in Figure 1.3

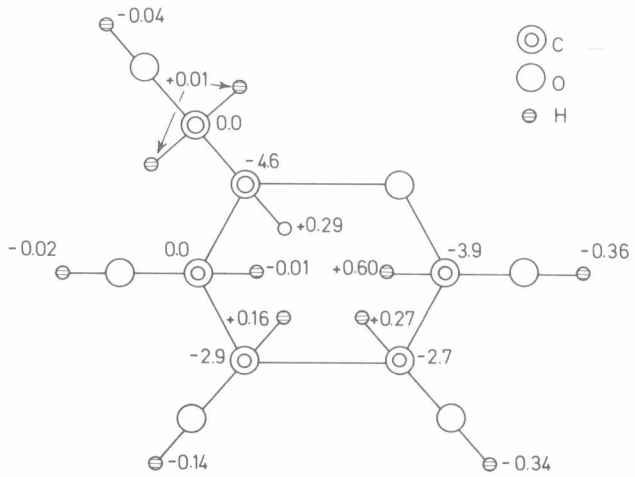


Figure 1.3 ^{13}C and ^{1}H chemical-shift differences ($\Delta\delta$) between α- and β-D-glucose, corresponding to the changes observed when the orientation of the anomeric hydroxy group (at C*) is altered from equatorial to axial (β to α); −, increased shielding; +, decreased shielding (From Koch and Perlin[13], by courtesy of Elsevier)

(hydroxyl proton data are included also). Since this type of feature appears so consistently in association with a steric perturbation, it may, in turn, serve as a reliable indication of the presence of a destabilising reaction within a molecule*.

* In this context, it should be especially interesting to examine the ^{1}H chemical shifts of compounds that exhibit apparently anomalous ^{13}C shielding (see footnote, p. 6).