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Note

An examination of ^{13}C- and ^{1}H-chemical shifts in relation to the conformational stabilities of D-glucopyranose disaccharides and polysaccharides

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N.m.r. chemical-shifts are influenced by steric interactions in a number of well recognized ways[1–3]. Effects attributable to substituents that are separated from a carbon or hydrogen atom by three bonds (γ-substitution effects) have proved to be particularly informative as stereochemical probes. For example, a methyl or hydroxyl group appears to promote increased shielding, by ~4–5 p.p.m., of a *gauche* methylene ^{13}C (γ-gauche effect[1]) and, simultaneously, a deshielding of ~0.3–0.4 p.p.m. of the protons of the methylene group. It has been proposed[1] that the steric interaction induces a polarization of the C–H bond. Although other interpretations may be advanced, experimental n.m.r. data for various classes of compounds are consistent[2,3] with a steric origin for this type of pattern of chemical-shift changes. Thus, for pyranoses[4,5] and cyclohexane derivatives[1,6], the isomer that incorporates a maximum of non-bonded interactions usually has the most strongly shielded ^{13}C-nuclei and least-shielded ^{1}H-nuclei, whereas, conversely, the most stable isomers exhibit the largest ^{13}C-chemical shifts and smaller ^{1}H-chemical shifts. In the present article, data for pyranose disaccharides are examined, to see if the introduction of a glycosidic bond influences this presumed relationship between conformational stability and chemical shift. Disaccharides of D-glucose have been chosen, because the most comprehensive set of ^{13}C and ^{1}H data is available[7–12] in this series. A comparison is also made between ^{13}C-n.m.r. characteristics of the bioses and those of structurally related D-glucans.

RESULTS AND DISCUSSION

Influence of the glucosidic linkage on ^{13}C- and ^{1}H-chemical shifts of individual residues of disaccharides. — In examining the chemical shifts of isomeric compounds, it is instructive to compare data not only for individual nuclei, but also those for the molecules in a broader sense. For the latter purpose, we have found it convenient to use the empirical parameter of the sum total[3–6] of ^{13}C- or ^{1}H-chemical shifts ($\Sigma\delta$) for all nuclei of a given molecule, or each unit of a disaccharide, in a manner

TABLE I

VARIATIONS IN THE ^{13}C- AND ^{1}H-CHEMICAL SHIFTS OF INDIVIDUAL UNITS OF D-GLUCOPYRANOSE DISACCHARIDES[a]

Linkage	*Configuration*[b]	*Reducing residue*				*Glycosyl group*			
		$\Sigma\delta\ ^{13}C$ *(in p.p.m.)*	Δ[c]	$\Sigma\delta\ ^{1}H$	Δ[d]	$\Sigma\delta\ ^{13}C$ *(in p.p.m.)*	Δ[c]	$\Sigma\delta\ ^{1}H$	Δ[d]
(1→2)	α,α	447.2	−0.1	28.03	0.48	451.2	3.9	27.42	−0.13
	α,β	463.4	2.5	26.37	0.19	452.7	5.4	27.72	+0.17
	β,α	457.4	10.1	27.92	0.37	467.9	7.0	26.06	−0.12
	β,β	466.5	5.6	—	—	466.7	5.8	—	—
(1→3)	α,α	449.8	2.5	—	—	452.6	5.3	—	—
	α,β	463.3	2.4	26.40	0.22	452.6	5.3	27.80	+0.25
	β,α	452.4	5.1	27.92	0.37	464.7	3.8	26.21	+0.03
	β,β	467.8	4.4	26.54	0.36	466.5	5.6	26.11	−0.07
(1→4)	α,α	453.4	6.1	—	—	456.8	9.5	—	—
	α,β	467.7	6.8	26.65	0.47	456.8	9.5	27.47	−0.08
	β,α	452.5	5.2	—	—	466.5	5.6	—	—
	β,β	466.5	5.6	26.58	0.40	466.5	5.6	25.94	−0.24
(1→6)	α,α	452.1	4.8	27.65	0.10	455.3	8.0	27.13	−0.42
	α,β	465.9	5.0	26.70	0.02	455.3	8.0	27.12	−0.43
	β,α	453.8	6.5	—	—	466.1	5.2	—	—
	β,β	467.2	6.3	26.61	0.43	466.1	5.2	25.87	−0.31

[a]Derived from chemical-shift data for ^{13}C in ref. 7, and for ^{1}H in ref. 12. [b]Configuration of the reducing residue is listed at the right, and of the D-glucosyl group, to the left. [c]Relative to $\Sigma\delta\ ^{13}C$ for α-D-glucopyranose (447.3) or β-D-glucopyranose (460.9). [d]Relative to $\Sigma\delta\ ^{1}H$ for α-D-glucopyranose (27.55) or β-D-glucopyranose (26.18).

already described for monosaccharides, as well as for alicyclic and other types of compounds. One feature of this approach is that it obviates the substantial problem of ensuring that assignments for all individual nuclei are correct.

As is well known[8], a comparison of the ^{13}C-chemical shifts of disaccharides with those of their constituent monosaccharides shows that carbon atoms engaged in bond formation become strongly deshielded (β-substituent effect), whereas adjacent carbon atoms may become slightly more shielded (γ-substituent effect). However, the results are far from uniform for all disaccharides. This may be seen (see Table I) from the apparent changes in chemical shift (Δ) for a molecule of α- or β-D-glucose when it is treated as the reducing component of a disaccharide. At one extreme, when α-D-glucopyranose is substituted at O-2 by a β-D-glucopyranosyl group, so as to constitute a β-(1→2) disaccharide, there appears to be a net increase (Δ) of 10.1 p.p.m. in the ^{13}C-chemical shifts ($\Sigma\delta$) of that residue, as compared with α-D-glucopyranose itself. By contrast, when the α-D-glucopyranose residue bears a 2-*O*-α-D-glucopyranosyl group [α-(1→2) isomer], it exhibits a negligible net difference

($\Delta = -0.1$) in ^{13}C-shielding relative to α-D-glucopyranose. Other values of Δ associated with reducing-end residues range from downfield shifts of 2.4 to 6.8 p.p.m.

A comparable examination of ^{13}C-chemical shifts for (nonreducing) end groups, in relation to those for the analogous anomer of D-glucopyranose, also produces a wide range of Δ values that may be ascribed to the formation of disaccharide structures. The data in Table I for the D-glucosyl groups of the isomeric disaccharides imply that the effect of the reducing residue on ^{13}C-shielding varies from 3.8 to 9.5 p.p.m. In this series, however, the isomers characterized by the largest and smallest values of Δ are β-(1→3) and α-(1→4), whereas, for the reducing-end residue, both extremes were represented by (1→2)-linked compounds.

Proton chemical shifts of the D-glucose disaccharides likewise demonstrate large differences in shielding characteristics (see Table I). Relative to α- or β-D-glucose, all reducing-end residues exhibit net downfield shifts (Δ), ranging from 0.47–0.48 p.p.m. for the α,β-(1→4) and α,α-(1→2) isomers, to 0.1 p.p.m. or less for α,α- and α,β-(1→6) isomers. In marked contrast, most of the nonreducing groups are characterized by a net *increase* in shielding relative to their D-glucose anomers, which is most pronounced for the α,β-(1→6) isomer.

In general, then, the co-occurrence of two D-glucopyranose units in the form of a disaccharide induces a net downfield displacement for the signals of the ^{13}C-nuclei of both the reducing residue and the nonreducing group. This observation is consistent with the operation of a β-substituent inductive-effect due to the C–O–C linkage, mentioned earlier. However, it appears that the influence of this linkage on shielding of the ^{1}H-nuclei bonded to the carbon atoms is partitioned in opposite directions between the reducing and nonreducing moieties of a disaccharide.

The source of these differences must include such stereochemical variables of the glycosidic linkage as bond length, bond angle, and rotamer population. Because each type of linkage may have a unique set of parameters (and, hence, shielding characteristics), the use of chemical-shift data for determining the structure of higher saccharides is necessarily complex. This fact limits the reliability of assignments made for linkage positions in oligo- and poly-saccharides on the basis of ^{13}C-chemical-shift data for model compounds and *average* shift-parameters associated with glycosidic bonding[13]. Nevertheless, the development of more-reliable methods[14] for the identification of ^{13}C-resonance signals promises to minimize the difficulty.

Chemical-shift differences (^{13}C and ^{1}H) between disaccharides. — Values of $\Sigma\delta$ for ^{13}C- and ^{1}H-nuclei of the intact disaccharides, representing the sums of chemical shifts for their individual units given in Table I, are characteristic of the anomeric configurations of the disaccharides. Hence, it is found (see Table II) that the total ^{13}C-chemical shifts increase progressively in the order $\alpha,\alpha < \alpha,\beta \simeq \beta,\alpha < \beta,\beta$ for all linkage positions. Although a less complete set of ^{1}H-chemical-shift data is available, the sequence of $\Sigma\delta$ values for protons is clearly the converse of that for carbon atoms (see Table II). In keeping with what has already been stated, these shielding differences are ascribed mainly to variations in stereochemical influences. As also pointed out earlier, destabilizing steric-interactions appear to induce upfield

TABLE II

COMPARISON OF $\Sigma\delta$ $^{13}C^{a}$ AND $\Sigma\delta$ $^{1}H^{b}$ (IN P.P.M.) FOR D-GLUCOPYRANOSE DISACCHARIDES ON THE BASIS OF LINKAGE[c]-POSITION

Parameter	*Linkage*						
	α,α	<	α,β	<	β,α	<	β,β
(1→2)-linked							
$\Sigma\delta$ ^{13}C	898.4		916.1		922.3		933.2
$\Sigma\delta$ ^{1}H	55.45		54.09		53.98		—
(1→3)-linked							
$\Sigma\delta$ ^{13}C	902.4		915.9		917.1		934.3
$\Sigma\delta$ ^{1}H	—		54.20		54.13		52.65
(1→4)-linked							
$\Sigma\delta$ ^{13}C	910.2		918.9		919.0		930.0
$\Sigma\delta$ ^{1}H	—		54.12		—		52.52
(1→6)-linked							
			β,α		α,β		
$\Sigma\delta$ ^{13}C	907.4		919.9		921.2		933.3
$\Sigma\delta$ ^{1}H	54.78		—		53.32		52.48

[a]Obtained from ^{13}C-chemical-shift data in ref. 7. [b]Obtained from ^{1}H-chemical-shift data in ref. 12 [c]Configuration of the reducing residue is listed to the right, and of the D-glucosyl group, to the left

shifts for ^{13}C-nuclei, and downfield shifts for the protons appended to them. Consequently, the chemical-shift differences between disaccharides, evident in the data of Table II, suggest that the β,β anomer in each series is the most stable conformationally, because it is characterized by the largest $\Sigma\delta$ value for ^{13}C, and the smallest value for ^{1}H. The α,α isomer should, accordingly, be the least stable of the group, whereas isomers possessing both an α- and a β-anomeric center would be expected to be of intermediate stability.

There are very few experimental data from other sources that may be used to check whether or not these proposals are valid. Nevertheless, it appears worthwhile to attempt some comparisons between the present observations and results from theoretical studies[15–21] on the conformations of D-glucopyranose disaccharides. For example, empirical force-field calculations[22] indicated that β-cellobiose is more stable than β-maltose, as it is characterized by a lower free-energy (the second minima are 14.24 kJ/mol (3.4 kcal/mol) *vs.* 25.54 kJ/mol (6.1 kcal/mol), as well as by greater conformational freedom (6 allowed conformations *vs.* 4). Consistent with this, it is found (see Table II) that the ^{13}C-nuclei of cellobiose are, on the average, less shielded than those of β-maltose, whereas its protons are more strongly shielded. Also, the fact that calculations for (1→2)-linked disaccharides[18] suggest that the α,α isomer (α-kojibiose) is less stable than the β,β compound (β-sophorose) is paralleled by their relative values of $\Sigma\delta$ ^{13}C, which are 898.4 and 933.2 p.p.m., respectively (see Table II).

TABLE III

COMPARISON OF $\Sigma\delta$ $^{13}C^{a}$ AND $\Sigma\delta$ $^{1}H^{b}$ (IN P.P.M.) FOR D-GLUCOPYRANOSE DISACCHARIDES ON THE BASIS OF LINKAGE[c] CONFIGURATION

Parameter	*Linkage*						
α,α	*(1→2)*	<	*(1→3)*	<	*(1→6)*	<	*(1→4)*
$\Sigma\delta$ ^{13}C	898.4		902.4		907.4		910.2
$\Sigma\delta$ ^{1}H	55.45		—		54.78		—
α,β	*(1→3)*	<	*(1→2)*	<	*(1→4)*	<	*(1→6)*
$\Sigma\delta$ ^{13}C	915.9		916.1		918.9		921.2
$\Sigma\delta$ ^{1}H	54.20		54.09		54.12		53.32
β,α	*(1→3)*	<	*(1→4)*	<	*(1→6)*	<	*(1→2)*
$\Sigma\delta$ ^{13}C	917.1		919.0		919.9		922.3
$\Sigma\delta$ ^{1}H	54.13		—		—		53.98
β,β	*(1→4)*	<	*(1→2)*	<	*(1→6)*	<	*(1→3)*
$\Sigma\delta$ ^{13}C	933.0		933.2		933.3		934.3
$\Sigma\delta$ ^{1}H	52.52		—		52.48		52.65

[a]Obtained from ^{13}C-chemical-shift data in ref. 7. [b]Obtained from ^{1}H-chemical-shift data in ref. 12. [c]Configuration of the reducing residue is listed to the right, and of the D-glucosyl group, to the left.

Comparing chemical shifts within series, based on a given configuration (see Table III), leads to the expectation that the β-(1→6)-linked disaccharide, namely, β-gentiobiose, should be more stable than the β-(1→4)-linked β-cellobiose, because their respective values of $\Sigma\delta$ ^{13}C are 933.3 *vs.* 933.0 p.p.m., and of $\Sigma\delta$ ^{1}H, are 52.48 and 52.52 p.p.m., respectively. Although these differences are small, both are in the correct order, relative to calculations[22] which indicated that β-gentiobiose is the more stable of these two isomers. Similarly, the ^{13}C-chemical-shift data are in accord with theoretical results[18] in suggesting that stability increases in the β,β series in the sequence β-sophorose (1→2) $\geqslant$ β-cellobiose (1→4) > β-laminarabiose (1→3).

There appears to be disagreement, however, between predicted stabilities and the chemical-shift data, in comparing α,α-linked disaccharides. That is, although calculations[17,18] suggested that the number of allowed conformations for the (1→2) isomer is slightly greater than for the (1→3) and (1→4) isomers, the $\Sigma\delta$ ^{13}C values are in the converse order (see Table III).

It is unclear as to which of these sets of data is the more reliable. If the chemical-shift measurements truly reflect conformational stability, their expression includes all possible influences on the conformation, including such important factors[16-18] as inter-residue hydrogen-bonding and solvation effects. In one theoretical study[18], allowance was made for the energy of inter-residue hydrogen-bonding and, indeed,

TABLE IV

SEQUENCE OF $\Sigma\delta$ ^{13}C VALUES (IN P.P.M.) FOR D-GLUCANS, IN RELATION TO THAT FOR STRUCTURALLY ANALOGOUS DISACCHARIDES

Linkage						
β-(1→3) >	*β-(1→6)* >	*β-(1→2)* >	*β-(1→4)* >	*α-(1→3)* >	*α-(1→4)* >	*α-(1→6)*
$\Sigma\delta$ ^{13}C						
475.0[a,b] (average)	471.2[b,c] (average)	469.6[d]	468.0[c,e] (average)	464.3[a]	461.1[a]	450.9[a]
Disaccharide type[f]						
β,β-(1→3) >	*β,β-(1→6)* >	*β,β-(1→2)* >	*β,β-(1→4)* >	*α,α-(1→4)* >	*α,α-(1→6)* >	*α,α-(1→3)*

[a]Ref. 9. [b]Ref. 23. [c]Ref. 7. [d]Ref. 24. [e]Ref. 25. [f]Sequence from Table II or III.

it was shown to make a substantial difference. However, although the conformations of α-linked disaccharides in water are known[17] to be affected more strongly by the solvent than those of β-linked anomers, specific solvent-effects were not included in the calculations[18], and consequently, the latter are less likely to be in accord with experimental observations in the α, than in the β, series.

As disaccharides are valuable (if not, as already mentioned, exact models) for the interpretation of n.m.r. spectra of polysaccharides[8–13], it is not surprising that some of the characteristics just described for glucobioses are also observed with D-glucans. This is shown in Table IV, for seven linear, uniformly linked types of glucan, by $\Sigma\delta$ ^{13}C values obtained from ^{13}C-chemical shifts reported from a variety of sources. It is found, in fact, that only the α-(1→3)-linked polymer is displaced from the sequence formed by the $\Sigma\delta$ ^{13}C values for the corresponding disaccharides.

Whether or not the present treatment of chemical-shift data constitutes a valid approach to an assessment of relative conformational stabilities among higher saccharides can be determined only as more-extensive theoretical and experimental data become available.

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