Intramolecular Hydrogen Bonding in 1′-Sucrose Derivatives Determined by SIMPLE ^{1}H NMR Spectroscopy

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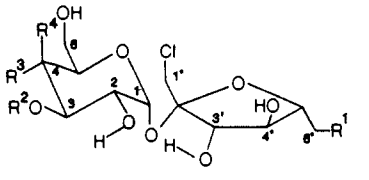
Abstract: Intramolecular hydrogen bonding in a series of 1′-sucrose derivatives having different numbers of hydroxyl groups has been investigated in Me_2SO-d_6 solution by SIMPLE ^{1}H NMR measurements, i.e., Secondary Isotope Multiplet NMR Spectroscopy of Partially Labeled Entities. Isotope effects, transmitted through intramolecular hydrogen bonds, are observed for the hydroxyl proton resonances; each separate hydrogen bond is manifested as a separate isotope shift. The existence of an intramolecular hydrogen bond in which OH3′ is the donor and OH2 is the acceptor hydroxyl group is revealed by isotope shift measurements of four 1′-chloro-1′-deoxysucrose derivatives: namely, 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-3-*O*-methyl-α-D-galactopyranoside (**1**); 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (**2**), 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl α-D-glucopyranoside (**3**), and 1-chloro-1-deoxy-β-D-fructofuranosyl α-D-glucopyranoside (**4**). It is found that the OH3′···O2 interresidue hydrogen bond in 1′-chloro-1′-deoxysucrose derivatives in solution is weaker than the analogous OH1′···O2 hydrogen bond in 3′-substituted sucrose derivatives. ^{1}H NMR measurements also show that the interresidue hydrogen bond stabilizes a weak hydrogen bond network between adjacent hydroxyl groups; the network extends to both sugar residues and the hydrogen bonds become progressively weaker at distances further from the relatively strong interresidue hydrogen bond, i.e., OH6·OH4···OH3···OH2····OH3′···OH4′. For this series of molecules it is also shown that the interresidue hydrogen bonds become stronger as the hydrogen-bonding network extends to more of the molecule, i.e., the process is cooperative.

Hydrogen bonding is an important interaction involved in determining the secondary structures of biomolecules such as proteins, nucleic acids, and carbohydrates. Evidence about the existence of hydrogen bonds in these systems comes from crystal structure determinations and, in particular, from neutron diffraction studies which provide the location of hydrogen atoms in the lattice. Hydrogen bonding in carbohydrate crystals has been studied extensively by Jeffrey and co-workers[1-6] and by Saenger and co-workers.[7,8] Many examples of hydrogen bonding in carbohydrate crystals occur as part of networks of intermolecular hydrogen bonds which may be chain-like[1-6] or circular.[7,8] Under these circumstances, it is found that bond distances are shorter (and hence hydrogen bonds presumed stronger) for hydroxyl groups involved in both donor and acceptor interactions compared to those where the hydroxyl group is a donor only (cooperative effect on hydrogen bonding). Quantum mechanical calculations[9,10] confirm that chain-like hydrogen bonds in the crystal structure are energetically favored above individual ones.

By comparison with crystallographic studies such detailed information about the strength and direction of hydrogen bonding is generally not available for molecules in solution, though a number of NMR methods have been used to provide information on the presence of both inter- and intramolecular hydrogen bonds, e.g., chemical shifts, solvent and temperature dependence of chemical shifts, solvent exchange studies, NOE effects, and magnitudes of appropriate spin coupling constants.[11] In an early study of intramolecular hydrogen bonding in solution Lemieux and Pavia[12] showed that hydrogen bonding of a strong acceptor such as Me_2SO to a hydroxyl group increased the ability of that hydroxyl to participate in intramolecular hydrogen bonding. Although NMR methods are used to indicate the presence of hydrogen bonding in carbohydrates, they are usually unable to discriminate between the donor and acceptor hydroxyl groups or to provide a basis for comparison of the relative strengths of hydrogen bonds in these molecules. This is particularly difficult in solvents like Me_2SO, which are strong hydrogen bond acceptors and where intermolecular (solvent) hydrogen bonding is predominant. On the other hand, recent ^{1}H NMR studies of carbohydrates in Me_2SO-d_6 solution (sucrose,[13-15] cyclodextrin,[16] and 3,3′,4′,6′-tetra-*O*-acetylsucrose (**5**)[17]) have shown that, for molecules with partially deuteriated hydroxyl groups observed under conditions of slow exchange, intramolecular hydrogen bonding between hydroxyl groups is manifested by isotopically shifted hydroxyl proton resonances. The phenomenon has been termed

Chart I



comp no	R^1	R^2	R^3	R^4	no. of OH groups
1	Cl	Me	H	Cl	4
2	Cl	H	H	Cl	5
3	Cl	H	OH	H	6
4	OH	H	OH	H	7

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Table I. ^{1}H NMR Chemical Shifts for Compounds **1**–**4**[a]

proton	compound 1	2	3	4
H-1	5.16	5.15	5.11	5.18
H-2	3.15[b]	3.59	3.18	3.16
H-3	3.15[b]	3.93	3.42	3.41
H-4	4.67	4.33	3.01	3.11
H-5	4.29	4.30	3.63	3.63
H-6a	3.51	3.48	3.63	3.52–3.60[b]
H-6b	3.47	3.44	3.41	3.52–3.60[b]
H-1′a	3.66	3.66	3.67	3.67
H-1′b	3.58	3.57	3.62	3.63
H-3′	4.03	4.02	4.05	4.01
H-4′	3.81	3.80	3.81	3.76
H-5′	3.74	3.74	3.73	3.52–3.60[b]
H-6′a	3.94	3.94	4.02	3.52–3.60[b]
H-6′b	3.75	3.74	3.73	3.48
OH-2	5.05	4.95	4.83	4.77
OH-3		5.22	4.75	4.76
OH-4			4.80	4.77
OH-6	4.94	4.88	4.49	4.38
OH-3′	5.16	5.17	5.17	4.94
OH-4′	5.57	5.55	5.52	5.30
OH-6′				4.45

[a] δ scale, relative to internal Me_2SO-d_5 at 2.49 ppm. [b] Due to overlap of signals, chemical shifts could not be determined accurately.

Table II. ^{1}H NMR Coupling Constants (Hz) for Compounds **1**–**4**[a]

coupling constant	compound 1	2	3	4
1,2	3.2[b]	3.7	3.7	3.7
2,3	8.5[b]	9.9	9.7	9.8
3,4	2.7	3.5	8.8	8.9
4,5	1.5	1.4	10.1	10.0
5,6a	5.9	6.0	2.0[b]	2.2
5,6b	6.6	6.5	5.4[b]	4.6
6a,6b	10.5[c]	10.7[c]	11.8[b,c]	*b*
1′a,1′b	12.2[c]	12.3[c]	12.3[c]	12.2[c]
3′,4′	8.3	8.5	8.4	8.6
4′,5′	8.1	7.9	8.0	7.8
5′,6′a	9.5	9.6	9.5	*b*
5′,6′b	2.7	2.7	2.8	4.8
6′a,6′b	13.2[c]	12.1[c]	12.1[c]	10.9[c]
2,OH2	6.0[b]	6.2	6.0	6.2
3,OH3		5.1	5.0	5.0
4,OH4			5.4	5.6
6a,OH6	4.6	4.8	4.5	5.2
6b,OH6	4.9	5.1	6.0	6.0
3′,OH3′	9.3	9.4	7.7	8.0
4′,OH4′	6.0	6.1	5.9	5.8
6′aOH6′				*b*
6′b,OH6′				*b*

[a] First-order analysis, $J \pm 0.1$ Hz. [b] Due to overlap of signals, couplings could not be determined accurately. [c] Magnitudes but not signs were determined.

Table III. Magnitudes and Signs of Isotope Effects ($\times 10^{-4}$ ppm)[a]

compound	aldose residue OH6	OH4	OH3	OH2	fructose residue OH1′	OH3′	OH4′	OH6′
1′-Chloro-1′-deoxysucrose Derivatives								
1				+30		+13		
2				+30		−13		
			b	12		+13	+9	
3	*b*	*b*	−13	+40		−21		
			+13	*b*		+21	+15	
4	*b*	*b*	−12	+46		−21		
			+12	*b*		+21	+10	*b*
						b		
3′-Substituted Sucrose Derivatives								
5[c]				+117	−30			
6[d]	*b*	*b*	−22	+125	−63			

[a] Estimated error in magnitude is $\pm 2 \times 10^{-4}$ ppm, except for those signals which exhibit additional small isotope effects manifested as line broadening where the estimated error is $\pm 3 \times 10^{-4}$ ppm. [b] Isotope effect (magnitude $\leq 8 \times 10^{-4}$ ppm) manifested as line broadening. [c] Reference 17. [d] Reference 20.

SIMPLE NMR because it entails the observation of Secondary Isotope Multiplets of Partially Labeled Entities.[18] From a combination of ^{1}H and ^{13}C NMR studies of hydrogen-bonding effects in cyclodextrin,[16,18] it was shown that the ^{1}H NMR observations in this molecule are consistent with the hypothesis that the hydroxyl group acting as donor exhibits a negative (to low frequency) isotope shift, when the acceptor hydroxyl group hydrogen atom is replaced by deuterium and, vice versa, for the hydroxyl group acting as hydrogen bond acceptor which exhibits an unusual positive (to high frequency) shift on replacement of the donor hydroxyl group hydrogen atom with the heavier isotope. A similar explanation was used to describe analogous ^{1}H NMR isotope shifts observed for sucrose[13-15] and 3,3′,4′,6′-tetra-*O*-acetylsucrose,[17] consistent with the existence of an interresidue hydrogen bond between OH1′ (donor, negative isotope shift) and OH2 (acceptor, positive isotope shift). Similar measurements of methyl maltoside in Me_2SO solution[19] revealed not only the presence of the OH2′/OH3 interresidue hydrogen bond in this molecule but also evidence for OH2′/OH3′ intraresidue hydrogen bonding. SIMPLE ^{1}H NMR measurements on 3′,6′-di-*O*-benzoylsucrose (**6**)[20] revealed the presence of a hydrogen bond network in which weak hydrogen-bonding interactions occur between all neighboring hydroxyl groups of the glucose residue; the network is stabilized by the relatively strong interresidue hydrogen bond between the OH1′ and the OH2 groups.

In contrast to the intramolecular hydrogen bond network observed in solution, neutron diffraction studies of sucrose[21] in the solid state show that most hydroxyl groups are involved in intermolecular hydrogen bonds either with water molecules or with hydroxyl groups on neighboring sucrose molecules; in addition, two intramolecular hydrogen bonds (OH1′ ··· O2 and OH6′ ··· O5) are observed for sucrose in the crystal.

In the present work, the hydrogen-bonding properties of four 1′-chloro-1′-deoxysucrose derivatives (Chart I) in Me_2SO-d_6 solution were studied by the SIMPLE ^{1}H NMR method: 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-3-*O*-methyl-α-D-galactopyranoside (**1**), 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (**2**), 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl α-D-glucopyranoside (**3**), and 1-chloro-1-deoxy-β-D-fructofuranosyl α-D-glucopyranoside (**4**). In order for comparisons between molecules to be most reliable, the structures of the compounds have the same substitution pattern at the 1′-position (i.e., they are all 1′-chloro-1′-deoxysucrose derivatives) and the same substituent (i.e., chlorine) at other appropriate positions. The series of molecules was designed to assess the effect on hydrogen bond strength in molecules with different numbers of hydroxyl groups that can take part in hydrogen bond interactions.

Experimental Section

Compounds **1** to **4** were synthesized at Tate & Lyle Group R & D with procedures described in the literature: **1**,[22] **2**,[23,24] **3**,[25,26] **4**.[25,26] The

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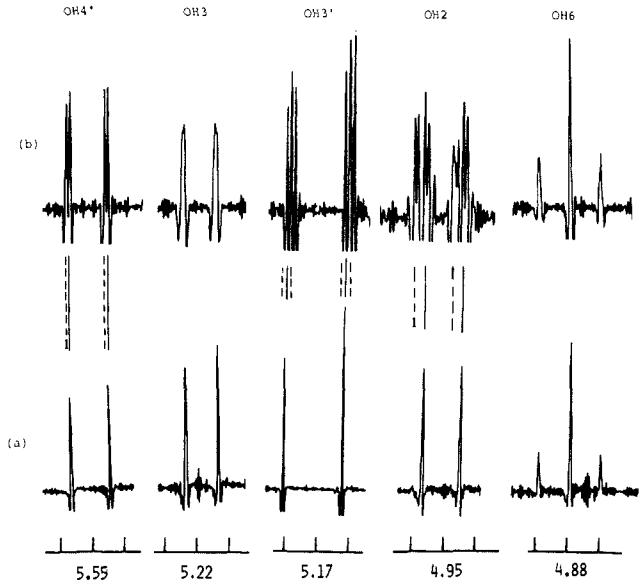

Figure 1. 500-MHz ^{1}H NMR spectrum of the hydroxyl proton resonances of 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (**2**) in Me_2SO-d_6 solution at OH:OD ratios of (a) 1:0 and (b) ca. 1:1. Isotope-shifted signals, including the appropriate coupling constants, are shown as dotted lines for hydroxyl groups with one (OH4′; H/D isotopomers) and two (OH3′, OH2) isotope effects. Two isotope effects on one signal give four resonances corresponding to the HH, HD, DH, and DD isotopomers, if the magnitudes of the isotope effects are significantly different. All four signals are observed for the OH2 group (eight lines if coupling is included), and both isotope effects are positive. If the two isotope effects have approximately equal magnitudes, only three resonance signals are observed as in OH3′ (six lines if coupling is included); in this case the isotope effects are of opposite signs.

samples were deuteriated and dried by lyophilizing from D_2O/acetone solutions (or D_2O solutions where solubility permitted) and then dissolved in dry Me_2SO-d_6 (sealed vials from Aldrich Chemical Co.). The OH:OD ratio was adjusted by adding appropriate amounts of protiated and deuteriated carbohydrate to the solvent. The extent of deuteriation was determined by comparison of the intensities of the H1 and residual OH signals.

Typically, 15 mg of material was used in 0.5 cm^3 of solution and 500-MHz ^{1}H NMR spectra (measured on a Bruker AM500 spectrometer) were calculated with resolution enhancement at good digital resolution (ca. 0.08 Hz point^{-1}). Assignment of signals was made by homonuclear decoupling or by 2D COSY NMR, where necessary. Chemical shifts of the fully protiated isotopomer (Table I) were measured with respect to the residual solvent signal and referenced with respect to Me_4Si (Me_4Si = Me_2SO-d_5 + 2.49 ppm). Coupling constants are summarized in Table II. The signs and magnitudes of isotope shifts (Table III) were determined by SIMPLE ^{1}H NMR measurements at different OH:OD ratios usually within the range 1:1 (where the number of isotope effects on each hydroxyl signal and their magnitudes are best determined) to 2:1 or 1:2 (where the signs of the isotope effects may be determined).

Results and Discussion

(1) The OH3′···O2 Interresidue Hydrogen Bond. The 500-MHz ^{1}H NMR spectrum of the hydroxyl proton resonances of **2** in Me_2SO-d_6 solution is shown in Figure 1a. The spectrum exhibits the expected doublets for the OH2 (6.2 Hz), OH3 (5.1), OH3′ (9.4), and OH4′ (6.1 Hz) signals due to vicinal coupling to the corresponding methine protons, and a pseudo-triplet for the OH6 signal (4.88 ppm, J_{av} = 4.9 Hz) due to coupling to the methylene protons. The SIMPLE ^{1}H NMR spectrum of **2** (OH:OD, ca 1:1) in Me_2SO-d_6 solution (Figure 1b) exhibits resolved isotopically shifted resonance signals for OH2, OH3′ and OH4′, and a small isotope effect for the OH3 signal which is manifested as line broadening. The OH4′ resonance exhibits one small positive isotope effect (+12 × 10^{-4} ppm), the OH3′ resonance exhibits two small isotope effects of opposite signs (±13 × 10^{-4} ppm), and

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Chart II

C3′-O-H···OH-C2

isotopomers		
	OH3′···OH2	i.e. HH
	OH3′···OD2	HD
	OD3′···OH2	DH
	OD3′···OD2	DD

the OH2 resonance exhibits two isotope effects, one relatively large effect that is positive (+30 × 10^{-4} ppm) and the other relatively small effect of magnitude 12 × 10^{-4} ppm whose sign was not determined unequivocally.

In this work it is shown that one of the two isotope effects observed for both the OH2 and OH3′ resonances is transmitted through an interresidue hydrogen bond between OH2 and OH3′ hydroxyl groups and that the direction of the hydrogen bond is predominantly OH3′ ··· O2 as shown in Chart II. Isotope effects on hydroxyl group protons are observed for those species in which D replaces H in the adjacent group, with the two-bond isotope effect being transmitted through the hydrogen bond. The two OH2 doublets correspond to the HH and HD isotopomers, and the relative intensities of the two signals equal the OH:OD ratio. Similarly the two OH3′ signals are observed for the HH and DH isotopomers.

Isotope effects observed for OH2 in compound **2** are caused by deuterium substitution of neighboring hydroxyl groups able to form hydrogen bonds to it, i.e., OH3 or OH3′. The fact that the same relatively large isotope effect (+30 × 10^{-4} ppm) is observed for OH2 of both compounds **1** and **2** (the former is the O3 derivative of compound **2**) indicates that the hydrogen bond is between OH2 and OH3′. The existence of this intramolecular hydrogen bond is supported by observation of the same hydrogen bond for compound **2** in the solid state by X-ray crystal structure determination.[22] The direction of the hydrogen bond is determined from the signs of the isotope effects by analogy with previous work on cyclodextrin.[16,18] It is likely that the positive isotope effect on OH2 is manifested by the acceptor group and that the negative isotope effect on OH3′ (see below) corresponds to the donor group, indicating that the direction of the interresidue hydrogen bond in **2** is predominantly OH3′···O2, as shown in Chart II. Measurements of analogous isotope effects in 1′-deoxy-1′-ethylsucrose (OH2, + 126 × 10^{-4} ppm; OH3′, −66 × 10^{-4} ppm) show unequivocally that the interresidue hydrogen bond is manifested by a positive isotope effect on OH2 (acceptor) and by a large negative isotope effect on OH3′ (donor), whereas the sign of the latter effect could not be deduced from the results for compound **2** because the magnitudes of the two isotope effects on OH3′ are similar and of opposite signs.

The involvement of OH3′ as the donor group of the intramolecular hydrogen bond is also manifested by the large vicinal coupling constant of 9.4 Hz which indicates a predominant (ca. 70%) conformation in which the O3′–H bond is anti to the H3′–C3′ bond using the J/θ Karplus relation modified by Fraser et al.[27] for H–C–O–H coupling systems. In this conformation the O3′–H bond projects in the correct direction for hydrogen bonding to O2, particularly with the fructofuranoside ring in the predominant $^4T_3$ conformation. The conformation of the fructofuranoside ring in 1′-sucrose derivatives is predominantly $^4T_3$ as shown by the large magnitudes of proton spin coupling constants ($J_{3'4'}$ ca. $J_{4'5'}$ ca. 7–9 Hz) observed for the compounds in this work (Table II), in sucrose[14] and in other β-D-fructofuranosides.[28] The $^4T_3$ conformation of the fructofuranoside ring is also observed in the crystal structure of compound **2**, consistent with the conformation proposed for the OH3′···O2 interresidue hydrogen bond formation.

No isotope effects are observed for the analogous hydroxyl signals of the constituent monomer residues, methyl α-D-glucopyranoside (i.e., OH2 and OH3) and methyl β-D-fructofuranoside

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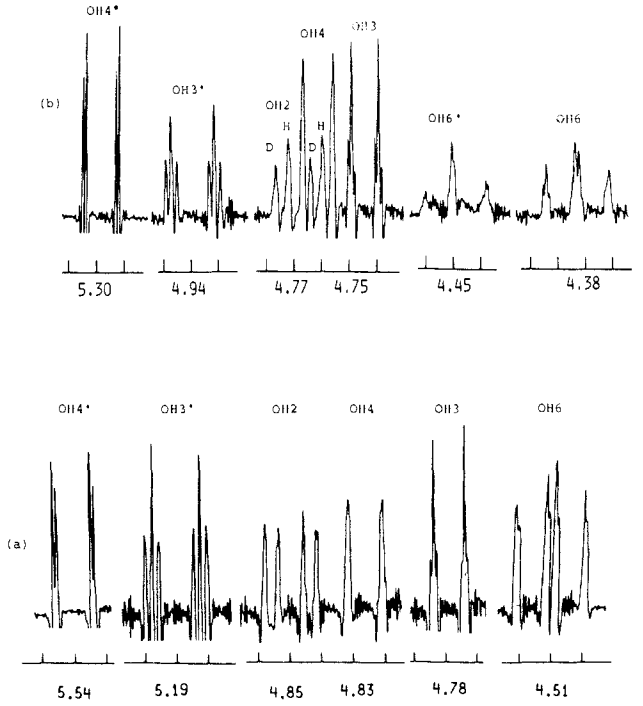


Figure 2. 500-MHz ^{1}H NMR spectra of the hydroxyl proton resonances of (a) 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl α-D-glucopyranoside (**3**) and (b) 1-chloro-1-deoxy-β-D-fructofuranosyl α-D-glucopyranoside (**4**) in Me_2SO-d_6 solution at a deuteriation ratio of OH:OD ca. 1:1.

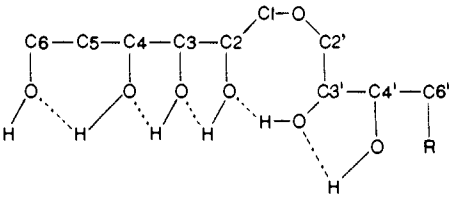
(i.e., OH3′ and OH4′), supporting the conclusion that the relatively large isotope effects observed for OH2 and OH3′ resonances result from the formation of an interresidue hydrogen bond. The extra isotope effects observed for OH2 and OH3′ and the small isotope effects observed for OH3 and OH4′ in compound **2** will be discussed in the next section.

The magnitudes of the isotope shifts may also provide information on the relative strengths of hydrogen bonds for molecules in solution, though it is recognized that the magnitudes depend not only on the intrinsic characteristics of the hydrogen bond but also on the relative populations of conformers appropriate to formation of a particular hydrogen bond, i.e., conformations of the glycosidic bonds, fructofuranoside rings, and exocyclic carbinol and hydroxyl groups. NMR isotope shifts have been observed previously between OH1′ and OH2 for 3,3′,4′,6′-tetra-*O*-acetylsucrose in Me_2SO-d_6 solution[20] consistent with the presence of the OH1′···O2 hydrogen bond. The magnitudes of the isotope shifts in this compound (OH1′ -30×10^{-4} ppm and OH2 $+117 \times 10^{-4}$ ppm) are significantly larger than the analogous isotope shifts (OH3′ -13×10^{-4} ppm and OH2 $+30 \times 10^{-4}$ ppm) found for compound **2** in this work, suggesting that the OH1′···O2 hydrogen bond in 3′-substituted sucrose derivatives is "stronger" than the OH3′···O2 hydrogen bond in 1′-chloro-1′-deoxysucrose derivatives.

(2) Intramolecular Hydrogen Bond Network. In compound **2**, apart from the isotope effects observed for OH2 and OH3′ which correspond to the interresidue hydrogen bond, additional isotope effects were observed for both signals as well as small isotope effects for both OH3 and OH4′. These observations may be rationalized by the presence of an intramolecular hydrogen bond network in both the glucose and fructose residues; the weak hydrogen bond network is stabilized by the relatively strong interresidue hydrogen bond (see below). The progressive participation of other hydroxyl groups in hydrogen bonding was studied in compounds **3** and **4** and compared to compound **2**.

The 500-MHz SIMPLE ^{1}H NMR spectrum of compound **3** (OH:OD, *ca.* 1:1) in Me_2SO-d_6 solution exhibits isotopically shifted resonances for all hydroxyl groups (Figure 2a), one isotope effect being observed for OH4′ ($+15 \times 10^{-4}$ ppm) and two isotope effects being observed for OH3′ ($\pm 21 \times 10^{-4}$ ppm), OH2 ($+40 \times 10^{-4}$ ppm and a small effect leading to line broadening), and

Chart III. Hydrogen Bond Network for Compound **3**



Isotope shifts	OH6	OH4	OH3	OH2	OH3′	OH4′
expected no	1	2	2	2	2	1
observed no	1[a]	1[a]	2	2	2	1
magnitude ($\times 10^{-4}$ ppm)					+21	+15
				+40	−21	
			+13	*b*		
	b	*b*	−13			

[a] Number of isotope effects could not be determined due to line broadening. [b] Isotope shift (magnitude $< 8 \times 10^{-4}$ ppm) manifested as line broadening.

OH3 ($\pm 13 \times 10^{-4}$ ppm). Small isotope shifts are also manifested as line-broadening on the OH4 and OH6 signals. The SIMPLE ^{1}H NMR spectrum of the hydroxyl signals of compound **4** in Me_2SO-d_6 solution at a deuteriation ratio of OH:OD ca. 0.6:0.4 (Figure 2b) exhibits isotopically shifted resonances for all hydroxyl groups in which the numbers, signs, and magnitudes (Table III) of the isotope effects are similar to those observed for compound **3**, except for an isotope effect on OH6′ (observed as line-broadening in **4**) which is not possible in compound 3 due to substitution in the 6′-position.

The number and magnitudes of isotope effects on each hydroxyl signal in compounds **2**–**4** may be rationalized in terms of an intramolecular hydrogen bond network extending to both the aldose and fructose residues and stabilized by the presence of the interresidue hydrogen bond. The relation between observed isotope effects and the hydrogen bond network will be discussed in detail for compound **3** and the hydrogen bond patterns derived by comparison for compounds **2** and **4**.

Observation of multiple isotope effects on one hydroxyl signal means that the hydroxyl group being observed interacts with more than one other hydroxyl group; each separate hydrogen bond is manifested as a separate isotope shift. The results for compound **3** are consistent with the limited hydrogen bond network shown in Chart III, in which the interresidue hydrogen bond stabilizes very weak hydrogen bonding for vicinal hydroxyl groups in the glucopyranoside and fructofuranoside rings. The magnitudes of isotope shifts linked horizontally in Chart III denote those hydroxyls linked by hydrogen bonds.

The relatively large positive isotope effect on OH2 (**3**, $+40 \times 10^{-4}$ ppm; **4**, $+46 \times 10^{-4}$ ppm) and the negative isotope effect on OH3′ (**3** and **4**, -21×10^{-4} ppm) correspond to the presence of the OH3′···O2 interresidue hydrogen bond in both compounds **3** and **4** as found in compound **2**. The second isotope effect on OH3′ ($+21 \times 10^{-4}$ ppm) and the small isotope shift on OH4′ (**3**, $+15 \times 10^{-4}$ ppm; **4**, $+10 \times 10^{-4}$ ppm) are consistent with a very weak hydrogen bond between OH4′ and OH3′ in the fructofuranoside residue. At first sight such a hydrogen bond appears unlikely because the OH3′ and OH4′ groups have a trans configuration in the fructofuranoside structure. However, as the fructofuranoside ring exists mainly in the $^4T_3$ conformation, the OH3′ and OH4′ groups are placed in a predominantly gauche conformation. In this conformation hydrogen bonding between the OH3′ and OH4′ groups is possible, particularly as the large vicinal coupling constant on OH3′ indicates a predominant anti conformation which facilitates OH3′ acting both as donor (to OH2) and as acceptor (from OH4′) for hydrogen bonding.

Isotope effects observed on hydroxyl signals of the glucose residue in compounds **3** and **4** correspond to a hydrogen bond chain from OH2 to OH3, OH3 to OH4, and OH4 to OH6, and the decrease in the magnitudes of the isotope effects corresponds to progressively weaker hydrogen bonding at distances further from the interresidue hydrogen bond. The hydrogen bonding in the

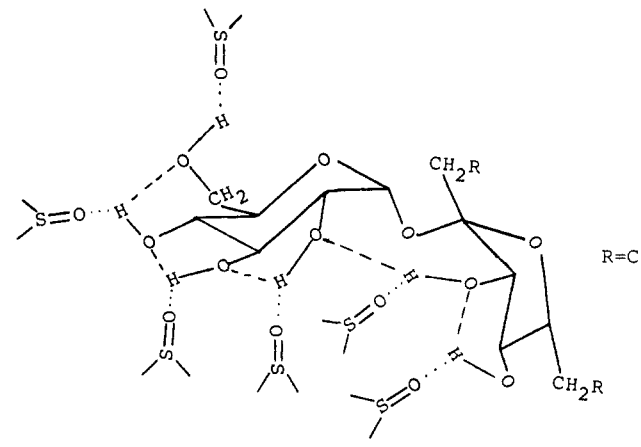
glucoside residue of compound **3** is extremely weak as shown by the small values of isotope effects which are just discernable for OH3 and only observed as line-broadening effects for OH4 and OH6. The hydrogen bond network observed for the glucose residue of 1′-sucrose derivatives in the present work is similar to that observed previously in 3′-sucrose derivatives.[20] Substitution of the glucose residue in the 4-position truncates the hydrogen bond network at OH3···OH2 as shown by the small isotope effects on these resonances in compound **2**.

The number, signs, and magnitudes of the isotope effects observed for each hydroxyl group in compound **4** (Table III) are similar to those observed for compound **3** showing a similar intramolecular hydrogen bond network in both compounds with similar "strengths" of analogous hydrogen bonds. In compound **4** there is an isotope shift on OH6′ (observed as line broadening) which is not possible in compounds **1–3** because the latter are substituted in 6′-position. One might expect the isotope effect to result from OH6′···OH4′ hydrogen bonding in the fructofuranoside ring, but there is no evidence of additional isotope shifts, even as line broadenings, on the OH4′ signal of compound **4**. In contrast there is a small isotope effect observed as line broadening on the OH3′ signals of compound **4** which can be seen in Figure 2 by comparison of the line widths of the OH3′ and OH4′ (narrow signals) for compound **4** or even by comparison of the line widths of the OH3′ signals for compound **3** (which is substituted in the 6′-position) and compound **4** (6′-position unsubstituted). Observation of such isotope shifts indicates the possibility of a very weak interaction between OH3′ and OH6′ which has recently been suggested by Perlin and co-workers[29] for D-fructofuranose in Me_2SO-d_6 solution, based only on hydroxyl group chemical shifts and their temperature dependence. Further evidence for and the implications of such hydrogen bonding in sucrose derivatives is being investigated.

(3) Cooperative Hydrogen Bonding. The present results confirm qualitatively one aspect of cooperative hydrogen bonding in carbohydrates, that hydroxyl groups for which the oxygen atom accepts a hydrogen bond will tend to occur more frequently and to form stronger hydrogen bonds than those where the oxygen atom is a donor only. The magnitudes of the isotope effects corresponding to the interresidue hydrogen bond are greater in compounds **3** and **4** (40–46 × 10^{-4} ppm) than in **1** and **2** (30 × 10^{-4} ppm), indicating that the interresidue hydrogen bond is stronger in the former compounds. At the same time, the hydrogen bond network is more extensive in compounds **3** and **4** than in compounds **1** and **2**, showing that, as more hydroxyl groups take part in the network, the strength of the interresidue hydrogen bond increases, i.e., the process is cooperative. The increase in strength of the hydrogen bonds in this series of molecules can also be seen in the hydrogen bond network. For example, the isotope effect on OH3′ resulting from OH3′···OH4′ interactions is smaller in compound **2** (+13 × 10^{-4} ppm) than in compounds **3** and **4** (+21 × 10^{-4} ppm) in line with the increasing strength of the interresidue hydrogen bond. Similar behavior is observed in 3′-substituted sucrose derivatives where the interresidue OH1′···O2 hydrogen bond is also stronger when it is part of a hydrogen bond network.[20] Indeed comparison of the magnitudes of isotope effects of 1′-chloro-1′-deoxysucrose derivatives with those for 3′-substituted derivatives (Table III) shows that the OH1′···O2 hydrogen bond is stronger than the OH3′···O2 hydrogen bond and that the stronger hydrogen bond stabilizes a stronger hydrogen bond network in the glucose residue.

For both the 1′- and 3′-sucrose derivatives it is found that the isotope effects on hydroxyl groups involved in the interresidue hydrogen bond have different magnitudes in which the positive isotope effect (corresponding to the acceptor) is larger than the negative isotope effect (donor); the magnitudes are in an appproximate 2(+ve):1(−ve) ratio. Similar behavior is found for pairs of hydroxyl groups involved in analogous hydrogen bonds in the network, though it is observed that the ratio of isotope effect magnitudes (i.e., +ve > −ve) and their relative signs (i.e., +ve, acceptor; −ve, donor) is not always found for such weak hydrogen bonds. The signs and magnitudes of isotope effects depend not only on the potential functions for the two interacting hydroxyl groups but also on the relative proportions of conformers necessary for the hydrogen bond to form. Little is known about the hydrogen bond potentials for the two hydroxyl groups in these molecules, but it is likely that the donor and acceptor group potentials will be different for nonsymmetrical hydrogen bonds leading to different magnitudes and, possibly, different signs of isotope effects. Some support for this hypothesis is given by NMR studies of primary isotope shifts for hydroxyl groups involved in strong hydrogen bonds where, depending on the shape of the potential function, it was shown (i) that both positive and negative isotope shifts are observed on going from a double potential minimum with low central barrier to a single minimum potential and (ii) that for weak hydrogen bonds the effect would be very small and tend toward zero because the double minimum potential function has a high central barrier and low anharmonicity at the potential minimum.[30]

Chart IV



Most hydroxyl groups of compounds **2–4** exhibit coupling constants in the range 4.8–6.0 Hz which are not too different from the free rotation value of about 5.3 Hz.[27] These observations show that the weak hydrogen bonds between vicinal hydroxyl groups of sucrose derivatives cause little change in the hydroxyl group conformations compared to the corresponding monomers, as judged by the similarity of analogous hydroxyl group coupling constants of methyl α-D-glucopyranoside[31] and methyl β-D-fructofuranoside[28] in Me_2SO-d_6 solution (except for OH3′ which is involved as the donor group in the relatively strong interresidue hydrogen bond). The inherent weakness of such hydrogen bonds may be due to the fact that the hydroxyl groups are unable to adopt the most favorable conformations for intramolecular hydrogen bonding because of the constraints of bond lengths, bond angles, and attachment of the hydroxyl groups to the relatively rigid pyranose ring. Nevertheless, hydrogen bonding does take place between vicinal hydroxyl groups in carbohydrates as shown by recent IR studies of monosaccharide derivatives in nonpolar solvents.[32,33] In the present work it is also likely that the solvent is involved in relatively strong hydrogen bonding to the hydroxyl groups as shown by near-IR measurements of glucose in polar solvents such as Me_2SO-d_6.[34] The importance of the role of the solvent in stabilizing cooperative hydrogen bonding between hydroxyl group resonances was recognized many years ago by Lemieux and Pavia[12] and called hydrogen bond conjugation. In the present work the solvent (Me_2SO-d_6) only acts as a hydrogen

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bond acceptor and its interaction with each hydroxyl group involved in the intramolecular hydrogen bonding network is envisaged in Chart IV, though it must be remembered that these molecules in solution are flexible and the hydrogen bonds resulting from time-averaged conformations and interactions are very weak. Support for the concept of three-center hydrogen bonds is given not only by previous solution studies[12] but also by detailed analysis of neutron-scattering results in carbohydrate crystals.[5,6] The major difference between solution- and solid-state studies is that for molecules in the solid state the hydrogen bond networks are intermolecular whereas in solution it has been shown in the present work that hydrogen bond networks are intramolecular.

Conclusions

Hydrogen bonding between hydroxyl groups in carbohydrates is conveniently studied by the SIMPLE ^{1}H NMR method (i.e., observation of Secondary Isotope Multiplet NMR of Partially Labeled Entities). In the present work we have shown that OH3′···O2 intramolecular hydrogen bonds occur for 1′-chloro-1′-deoxysucrose derivatives in Me_2SO-d_6 solution and that this hydrogen bond stabilizes cooperative hydrogen bonding in both the aldose (OH2···OH3···OH4···OH6) and fructose (OH3′···OH4′) residues, the extent of which depends on the substitution patterns in the two sugar residues. Assuming that the magnitudes of the isotope effects reflect the relative strengths of hydrogen bonds, it is shown that the strength of the hydrogen bonds in the aldose residue becomes progressively weaker at distances further from the relatively strong interresidue hydrogen bond. It is also shown that the strength of the interresidue hydrogen bond becomes stronger as the hydrogen bond network becomes more extensive, i.e., the process is cooperative.

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Oxygen-17 NMR Study of Bonding in Silicates: The d-Orbital Controversy

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Abstract: Bonding models for silicates are assessed in relation to the local environment of oxygen, as determined by analysis of the oxygen-17 nuclear quadrupole coupling constants (NQCC), using Townes–Dailey methods. The experimental NQCC of the silica polymorph low cristobalite is indicative of covalent charge transfer from the oxygen lone pairs to silicon and is consistent with Pauling's (d–p) π-bonding model. Bonding models for both hybridized and unhybridized oxygen which exclude lone pair charge transfer give poor agreement with the experimental results. The oxygen-17 NQCC of the bridging oxygen of diopside is shown to be in agreement with McDonald's (d–p) π-bonding hypothesis. Calcium coordination to the diopside bridging oxygen is consistent with calcium acting as a charge acceptor. The structural significance of the (d–p) π-bonding effect is discussed and related to the expected variation in the NQCC as a function of bridging bond angle. Trends in the NQCC of oxygen bonded to other elements are discussed and related to bond ionicities. The use of Pauling ionicities in conjunction with the Townes–Dailey model gives good agreement with the experimental NQCC results for a variety of well-defined oxide and silicate systems and further supports the (d–p) π-bonding hypothesis in silicates.

I. Introduction

The existence of delocalized π-bonding networks throughout silicate frameworks has been a topic of debate for a number of years. The two salient features of silicate silicon–oxygen bonds are (1) the large variability in bond length (1.55–1.80 Å) and (2) the large variability of the bond angle for the oxygen bridging the linked silicate tetrahedra (≈120–180°). In the 1950's Pauling[1,2] and Jaffe[3] used the concept of silicon-d oxygen-p π-bonding to account for bond lengths in TO_4^{n-} (T = Cl, S, P, Si) tetrahedra, which were considerably shorter than the single bond lengths predicted by Schomaker and Stevenson.[4] In 1961 Cruickshank[5] extended the treatment to a broad class of silicon, phosphorus, and sulfur compounds using valence bond formalism. He used group theory arguments to show that only the two E silicon d-orbitals ($3d_{x^2-y^2}$ and $3d_{z^2}$) are of suitable geometry to form strong π-bonds. For illustrative purposes we show in Figure 1 a schematic of the atomic orbitals involved. The large, diffuse, silicon d-orbitals are contracted by the positively charged silicon core, thereby facilitating overlap. Cruickshank attributed the variability in bridging-oxygen bond lengths to increased participation in (d–p) π-bonding of the "lone pair" sp^n orbital (in the Si–O–Si plane) as the bridging angle widens and the orbital gains p-character, thereby increasing the valence bond order and shortening the bond length. Cruickshank attributed the variability of the bridging bond angle to steric and Coulombic effects and not to (d–p) π-bonding. Others, however, have attached structural significance to the (d–p) π-bonding effect in regard to the bridging angle, and thereby rationalize, for instance, the increase in bridging angle from dimethyl ether (111°) to disiloxane (144°), or the planarity of trisilylamine.[6,7]

Over the years the topic has engendered lively debate. The nature of the silicon–oxygen bond has been extensively examined by semiempirical and ab initio methods.[8-37] While there is

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