Carbohydrate Research, 163 (1987) 269–274
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Comparison of intramolecular hydrogen-bonding conformations of sucrose-containing oligosaccharides in solution and the solid state

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(Received September 29th, 1986; accepted for publication, January 26th, 1987)

Many possibilities exist for hydrogen bonding in carbohydrates because of the prevalence of hydroxyl groups, which can act as both hydrogen-bond donors and acceptors, and ring oxygen atoms which can act as hydrogen-bond acceptors. In carbohydrate crystals, it has been shown by neutron and X-ray diffraction that extensive hydrogen bonding occurs usually in the form of long chains of intermolecular hydrogen bonds that involve not only the hydroxyl groups and ring oxygen atoms but also the water of crystallisation[1]. In a few molecules in the solid state, intramolecular hydrogen bonds have been observed between adjacent residues (*e.g.*, maltose[2] and sucrose[3]) and these sometimes persist in solution. For example, the intramolecular hydrogen bond between HO-2 and HO-3 groups on adjacent glucosyl residues in α-(1→4)-linked glucosides has been well documented for both the solid state[2] and solution[4–6], although other stable conformations have been proposed for methyl β-maltoside in solution based on a combination of nuclear Overhauser measurements and theoretical calculations[7]. In the light of our recent n.m.r. measurements on sucrose, which indicate a different hydrogen-bonding conformation in solution[8] from that found in the solid state[3], it is of interest to investigate the hydrogen-bonding properties of some other carbohydrates that contain the sucrose moiety [α-D-Glc*p*-(1↔2)-β-D-Fru*f*] and compare the solution behaviour with that of the solid state. In order to aid comparison of results from different molecules, the atom numbering of sucrose (**1**) is used for all structures containing the sucrose moiety.

The crystal structures of sucrose-containing oligosaccharides (Table I) show that the ring conformations of the glucopyranosyl ($^4C_1$) and fructofuranosyl ($^4T_3$) moieties are maintained in all structures[3,9–12], except for the five-membered ring in 1-kestose[13]. The magnitudes of the torsion angles of the inter-residue bonds reflect the relative disposition of the two rings. The crystal structure results for appropriate

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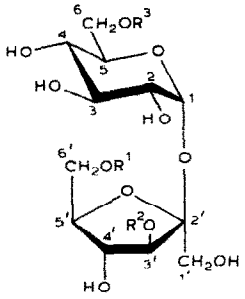
0008-6215/87/$ 03.50



	R^1	R^2	R^3
1 Sucrose	H	H	H
2 Raffinose	H	H	α-D-Gal
3 Stachyose	H	H	α-D-Gal-(1→6)-α-D-Gal
4 Melezitose	H	α-D-Glc	H
5 Planteose	α-D-Gal	H	H

ϕ and ψ conformational angles (Table I) indicate that the overall conformation of the sucrose moiety is similar in all structures (*e.g.*, $\phi \sim 99 \pm 10°$ and $\psi \sim -44 \pm 12°$), except for the ϕ bond in raffinose[9]. Although intermolecular hydrogen bonding is extensive in these crystals, in only two structures have intramolecular hydrogen bonds been reported. In sucrose, two intramolecular hydrogen bonds are found (HO-1′ · · · HO-2 and HO-6′ · · · O-5)[3], whereas in melezitose a bifurcated hydrogen bond occurs between HO-6′(Fru) and both O-5 and O-2 of the glucose residue, although the HO-6′ · · · O-2 component is very weak[11]. In view of the overall similarity of the conformations of the sucrose moiety in different crystal structures (except, of course, for raffinose), it is surprising that the inter-residue hydrogen bonding in sucrose, in particular the HO-1′ · · · O-2 hydrogen bond, is not found in more structures containing the sucrose moiety. In other structures, the HO-1′(Fru) group is involved in intermolecular hydrogen bonds to other molecules

TABLE I

CRYSTAL STRUCTURE CONFORMATIONS OF SUCROSE-CONTAINING OLIGOSACCHARIDES

Molecule[a]	*Sugar ring*		*Glycosidic bond*[b]		*Intramolecular H bonding*	*Ref.*
	Glcp	*Fruf*				
Sucrose	$^4C_1$	$^4T_3$	107.6	−44.4	Yes[d]	3
Raffinose	$^4C_1$	$^4T_3$	81.7	11.4[c]	None	9
Stachyose	$^4C_1$	$^4T_3$	109.6	−50.1	Not known	10
Melezitose	$^4C_1$	$^4T_3$	99.8	−30.7	Yes[e]	11
Planteose	$^4C_1$	$^4T_3$	108.2	−26.8	None	12
1-Kestose	$^4C_1$	E_4 or $^3T_4$	84.6	−65.8	None	13
Average			99 ±10	−44 ±12		

[a]Sucrose, α-D-Glc*p*-(1↔2)-β-D-Fru*f*; raffinose, α-D-Gal*p*-(1→6)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*; stachyose, α-D-Gal*p*-(1→6)-α-D-Gal*p*-(1→6)-α-D-Glc*p*-(1↔2)-β-D-Fru*f*; melezitose, α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(3←1)-α-D-Glc*p*; planteose, α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(6←1)-α-D-Gal*p*; 1-kestose, α-D-Glc*p*-(1↔2)-β-D-Fru*f*-(1←2)-β-D-Fru*f*. [b]Torsion angles ϕ (O-5–C-1–O-1–C-2′) and ψ (C-1–O-1–C-2′–O-2). [c]Omitted from average. [d]HO-6′ · · · O-5 and HO-6′ · · · O-2 hydrogen bonding. [e]HO-6′ · · O-5 and HO-6′ · · · O-2′ (weak) hydrogen bonding.

(*e.g.*, in raffinose[9]) or water (*e.g.*, in planteose[12]) in the crystal lattice. Perhaps the intramolecular hydrogen bond is not such a stabilising influence as one might expect for the conformation of sucrose-containing oligomers in the solid state and it is of interest to compare the behaviour of the same molecules in solution.

Using several n.m.r. criteria (δ, J, T_1, and n.O.e.) in conjunction with HSEA calculations, it was suggested by Bock and Lemieux[14] that the overall conformation of sucrose is approximately the same in $(CD_3)_2SO$ and D_2O solutions and that this conformation is similar to that observed in the solid state. From ^{1}H-n.m.r. measurements of partially deuterated hydroxyl groups of sucrose observed under conditions of slow exchange[15], the same workers found that the HO-1′ · · · HO-2 intramolecular hydrogen bond exists for sucrose in $(CD_3)_2SO$ solution and that this hydrogen bond appears to stabilise the same conformation of the molecule in solution as in the solid state. The conclusions of Bock and Lemieux[14,15] are supported by detailed analysis of ^{13}C-n.m.r. spin–lattice relaxation times of aqueous sucrose over a range of concentrations and temperatures where it was shown[16,17] that sucrose tumbles anisotropically in solution, that its conformation is independent of temperature and concentration, and that the data are consistent with the conformational model of sucrose in aqueous solution which is similar to the crystal conformation. On the other hand, recent SIMPLE n.m.r. isotope-shift measurements at higher field revealed[8] the presence of two intramolecular hydrogen-bond conformations for sucrose in $(CD_3)_2SO$ solution, in which HO-2 acts as acceptor for HO-1′ or HO-3′ of the fructofuranosyl residue. The two hydrogen-bond conformations exist in competitive equilibrium with the HO-1′ · · · O-2 hydrogen bond favoured over the HO-3′ · · · O-2 hydrogen bond in a ratio of ~2:1, assuming that the magnitudes of the isotope effects reflect the relative "strengths" of the hydrogen bonds. The HO-3′ · · · O-2 hydrogen bond has been observed previously in 1′-sucrose derivatives where substitution precludes formation of the HO-1′ · · · O-2 hydrogen bond[18].

Similar high-field ^{1}H-n.m.r. measurements have been made in this work on higher homologues of sucrose, *i.e.*, raffinose and stachyose. Despite the complexity of the spectra of each oligomer, the HO-2 and HO-1′ signals are observed with the same characteristics (δ and J) as in sucrose. The 500-MHz SIMPLE ^{1}H-n.m.r. spectra of raffinose (OH:OD ~1:1) and stachyose (OH:OD ~1:2) shown in Fig. 1 reveal two positive isotope effects for HO-2 and one negative isotope effect for HO-1′ similar to those observed for sucrose (Table II). Isotope effects on HO-3′ are not resolved but observed as line broadening of the SIMPLE n.m.r. spectrum compared to the spectrum of the normal protio form. These results may be interpreted in terms of the same competitive hydrogen-bond equilibrium occurring in raffinose and stachyose as it does for sucrose.

The intramolecular hydrogen-bond conformations of the sucrose moiety in these carbohydrate oligomers is different in the solid state and solution. Similar hydrogen-bond conformations are observed for sucrose, raffinose, and stachyose in solution, and the conformational equilibrium is quite different from any of the static

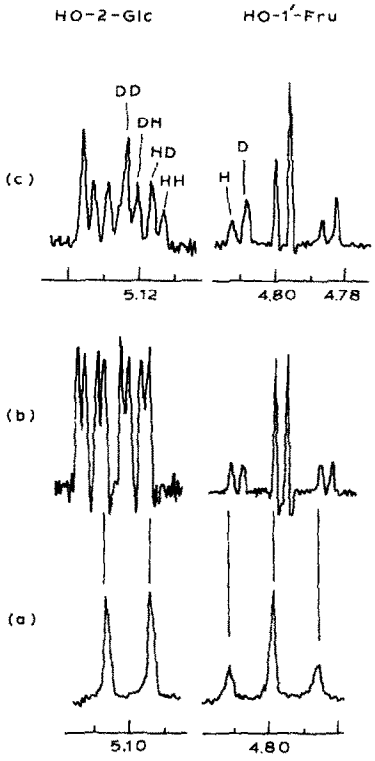


Fig. 1. 500-MHz SIMPLE ^{1}H-n.m.r. spectrum of the HO-2(Glc) and HO-1'(Fru) resonances of (a) raffinose (**2**; OH:OD, 1:0), (b) raffinose (**2**; OH:OD, ~1:1), and (c) stachyose (**3**; OH:OD, ~1:2), showing two positive isotope effects for HO-2 and one negative isotope effect for the HO-1' resonance. Chemical shifts are given with respect to Me_4Si by adding 2.5 p.p.m. to the residual $[^2H_5]Me_2SO$ proton signal.

TABLE II

INTRAMOLECULAR HYDROGEN-BONDING ISOTOPE EFFECTS ($\times 10^{-4}$ P.P.M.) IN SUCROSE-CONTAINING OLIGOSACCHARIDES[a]

Molecule	*HO-2(Glc) · · · HO-1'*		*HO-2(Glc) · · · HO-3'*	*Ref.*
Sucrose	+70	−43	+32	−22	8
Raffinose	+69	−41	+28	[b]	This work
Stachyose	+88	−53	+38	[b]	This work

[a]500-MHz ^{1}H-N.m.r. measurements for ~50mM solutions of partially deuterated carbohydrates (OH:OD ~1:1) in $(CD_3)_2SO$ at ambient temperatures. [b]Effect not resolved; observed as line broadening of HO-3' resonances of the SIMPLE n.m.r. spectrum compared to the spectrum of the normal protio-form.

conformations observed in the crystal. Previous work has suggested that the sweetness of sucrose might be related to the HO-1′ · · · O-2 intramolecular hydrogen-bond conformation found both in the solid state and in solution[14]. In view of the wide variation of hydrogen-bonding properties of the sucrose series of molecules in the solid state and the similarity of the intramolecular hydrogen-bond conformations of these molecules in solution, the sweetness of sucrose might be related to conformations of the molecule other than that observed in the solid state. One suggestion might be the HO-3′ · · · O-2 hydrogen-bond conformation which is present for the sucrose series of molecules in solution; this hydrogen-bond conformation also occurs in 1′-chloro-1′-deoxy derivatives of sucrose[18] which are noted for their enhanced sweetness compared to sucrose.

EXPERIMENTAL

Samples of raffinose and stachyose were obtained from the Sigma Chemical Co. and used without further purification. Hydroxyl groups were deuterated by lyophilising solutions of samples in D_2O. Solutions for n.m.r. were prepared by dissolving the deuterated sample (~0.05M) in $(CD_3)_2SO$ and adjusting the OH:OD ratio by addition of small aliquots of the normal sample or H_2O, as necessary. The OH:OD ratio was measured by comparison of the integrals of the residual OH signals with that of an undeuterated n.m.r. signal, such as H-1, and checked by measurement of the ratios of the HOH and HOD signals. 500-MHz ^{1}H-N.m.r. measurements of the partially deuterated samples at ambient temperature were made on a Bruker AM-500 spectrometer (N.I.M.R., London), and spectra were calculated with resolution enhancement using a data resolution of 0.1 Hz per point. Magnitudes of isotope effects are correct to $\pm 3 \times 10^{-4}$ p.p.m. Signs of isotope effects were determined from spectra of samples at OH:OD ratios other than 1:1, as shown for stachyose in Fig. 1(c) where OH:OD was ~1:2.

ACKNOWLEDGMENTS

We thank the S.E.R.C. for a post-doctoral research assistantship (to J.C.C.), and the M.R.C. for access to 500-MHz n.m.r. (N.I.M.R., London) and computing facilities (Birkbeck College).

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