

PHYSICAL CHEMISTRY OF AQUEOUS SOLUTIONS OF OLIGOSACCHARIDES *

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ABSTRACT

Many recent, and partly unpublished, thermodynamic data concerning the aqueous solutions of mono- and oligosaccharides (including cyclosaccharides) are critically reviewed, reference also being made to other physico-chemical properties. New hypotheses on the state of the water in the hydration shells of sugars are discussed in the light of interactions with a third component.

INTRODUCTION

Carbohydrates and their polymers have important biological functions, not only as sources of metabolic energy, as structural support of the cell walls of plants and bacteria and co-constituents of cartilages (proteoglycans), but also as the macromolecular basis of lubricants (synovial fluids and mucous gels), antiproteolytic preservatives (in glycoproteins) and antifreeze agents (some glycopeptides of Antarctic fishes). Their primary role in cell biology, however, is linked to the presence of sugar residues in the backbone of nucleic acids and in the membrane glycoconjugates which are responsible for cell recognition.

Polysaccharides, small carbohydrates and glycoconjugates have thus become the object of investigations concerning their chemistry (synthesis, derivatization and reactivity), biochemistry and technological applications.

Until a few years ago, however, the basic physical chemical properties of aqueous solutions of small carbohydrates in solution had been neglected, probably because their aqueous solutions were considered to be ideal. Many recent studies on aqueous solutions of organic molecules have emphasized the fact that the small deviations from ideality are an important addition to

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knowledge of the conformation dependent properties of biological molecules and biopolymers.

This report will mainly be limited to the equilibrium thermodynamics of dilute aqueous solutions of uncharged mono- and oligosaccharides and their derivatives, because of the decisive contributions provided by our laboratory in this field and because calorimetric techniques have played an important role. Three recent reviews by Cesáro [1], Franks [2] and Goldberg and Tewari [3], the first two partly based on our published and unpublished data, have covered the last subject partially. More recent work, however, has shown that the matter is one that requires continual reconsideration. Reviews on the conformational and spectroscopic properties are less recent and the more comprehensive are those by Angyal [4] and Altona and Haasnoot [5].

The oldest model for aqueous solutions of simple carbohydrates is the quasi-chemical model of Stokes and Robinson [6]. This attributes the non-ideality to a series of successive hydration reactions of a sugar S , assuming, for simplicity, the same equilibrium constant for each step



The number of considered equilibria is limited to the number of polar groups of the sugar or exceeds this number (second hydration shell). This rough model, recently reconsidered by Daldrup and Schönert [7], can explain the values of the osmotic and activity coefficients of aqueous solutions of glucose and sucrose, but cannot rationalize their volumetric and enthalpic properties.

Franks, Suggett and coworkers [8–12] later suggested that thermodynamic properties depend on a kind of specific hydration of sugars: they showed, refining the Kabayama–Patterson model [13], that the pyranose rings of monosaccharides (in the chair conformation) are compatible with a tridimite-like structure of ice [14]. In particular, the xylose and glucose β -anomers, characterized by having all their $-OH$ groups in equatorial positions, can organize a cage of water molecules that extends to the outer shell. Franks and Suggett introduced the important distinction between equatorial (structure-makers) and axial $-OH$ groups. Their subsequent spectroscopic, NMR and dielectric studies, however, do not lead to a further specification of the model. One of the main difficulties is the lack of reliable experimental data on enthalpies and free energies of hydration, owing to the thermal instability of these compounds towards vaporization.

Examination of the properties of dilute aqueous solutions of the sugars clearly reveals their main features: (a) solute–solute interactions are not favoured; (b) the non-ideal properties depend on the stereochemistry of the particular solute; and (c) excess Gibbs energies, enthalpies and entropies are qualitatively in agreement with the theory that sugars are largely hydrated and contribute to stabilizing the water structure. This is also supported by

the Raman studies of Walrafen [15] and by other spectroscopic and dielectric investigations reviewed by Suggett et al. [10–12] and by Franks [14].

THERMODYNAMICS OF DILUTE AQUEOUS SOLUTIONS OF MONOSACCHARIDES

Before discussing the thermodynamic properties, it is preferable to set out the expressions used by the researchers working in this field.

Using the so-called Lewis–Randall scale of molalities the excess properties J of unsymmetrical solutions of non-electrolytes can be defined as

$$J^E(\tilde{m}) = J(\tilde{m}) - J_1^0 - \sum m_x \bar{J}_x^0 - J^{ID} \quad (2)$$

where \tilde{m} is the total osmolality of the solution, m_x is the aquomolality of component x , J is the actual and J^{ID} the ideal property of the solution, J_1^0 is the molar property of the pure solvent and \bar{J}_x^0 is the limiting partial molar property of the solute x (standard state).

In what follows, the excess properties are reported in the form of virial expansions as a function of the solute molalities

$$J^E = \sum \sum j_{xy} m_x m_y + \sum \sum \sum j_{xyz} m_x m_y m_z + \dots \quad (3)$$

The data in the tables below will be discussed mainly on the basis of the pairwise virial coefficients (g_{xx} , g_{yy} , h_{xx} , h_{yy} , etc.). These have the most evident mechanical statistical significance, the higher order coefficients being much more difficult to interpret. The significance of the virial coefficients rests on the McMillan–Mayer [16] theory of solutions, as applied by Kauzmann et al. [17] and Friedman and Krishnan [18] to aqueous solutions of non-electrolytes. The McMillan–Mayer approach, however, was not conceived for treating these systems, which are characterized by the comparable intensity of all intermolecular interactions. These are in turn strongly orientation dependent in the presence of both polar solutes and solvents. For non-spherical but rigid solute molecules, for instance, the second virial coefficient of the Gibbs energy g_{xx} and of the enthalpy h_{xx} depend finally on the mean force potential $W(r, \phi_i)$ and on the pair correlation function $g(r, \phi_i)$, both being functions of the distance r between the centre of mass of the two solute molecules, and on a set of angles ϕ_i describing the reciprocal orientation of the solute molecules. To be introduced into statistical mechanical computations, however, both quantities must be submitted to averaging for all possible orientations of all solvent molecules. In other words, the virial coefficients will implicitly account not only for solute–solute interactions, but also for changes in solute–solvent and solvent–solvent interactions, with respect to the standard states. However, the use of the McMillan–Mayer notation is convenient as it gives a compact and unitary representation of the data.

TABLE 1
Values of the virial coefficients of the excess thermodynamic properties of monosaccharides in water at 298.15 K

	g_{xx}^a	h_{xx}^a	h_{xxx}^b	Ts_{xx}^a	α/β^c	Conformation ^d	Stereochemistry ^e
Aldopentoses							
D-arabinose	—	196(4) ^j	—	—	63/34	¹ C ₄	1E2E3E4A
L-arabinose	34(5) ^f	192(2) ^j	—	158(7)	34/63	⁴ C ₁	1E2E3E4A
D-ribose	{ 20(5) ^g 26(2) ^h	202(8) ^k	-6(5)	182(13)	20/56	⁴ C ₁	1E2E3A4E
D-lyxose	31(5) ^f	243(7) ^k	-11(4)	212(12)	71/29	⁴ C ₁	1E2A3E4E
D-xylose	56(7) ⁱ	332(9) ^l	—	276(13)	33/67	⁴ C ₁	1E2E3E4E
L-xylose	—	336(5) ^m	—	—	67/33	¹ C ₄	1E2E3E4E
Aldohexoses							
D-galactose	65(12) ^g	133(8) ^l	—	68(20)	27/73	⁴ C ₁	1E2E3E4A5E
D-mannose	43(8) ^f	207(14) ^l	-14(5)	164(22)	67/33	⁴ C ₁	1A2A3E4E5E
D-glucose	92 ⁿ	343(10) ^o	-13	251	33/64	⁴ C ₁	1E2E3E4E5E
D-allose	—	236(9) ^t	—	—	25/75	⁴ C ₁	1E2E3A4E5E
Ketohexoses							
D-fructose	83(11) ^f	264(18) ^l	-7(4)	181(25)	3/57	² C ₅	1E(2A)3E4E5A
L-sorbose	148(7) ^f	395(9) ^m	-16(4)	247(16)	PREV. β	² C ₅	1E(2A)3E4E5E
Deoxysugars							
2-deoxy-D-ribose	80(5) ^g	468(12) ^k	-21(8)	388(17)	PREV. β	⁴ C ₁	1E(2)3A4E
2-deoxy-D-galactose	58(6) ^g	442(22) ^k	-21(15)	384(28)	PREV. β	⁴ C ₁	1E(2)3E4A5E
2-deoxy-D-glucose	88(8) ^g	592(17) ^k	-36(12)	504(25)	PREV. β	⁴ C ₁	1E(2)3E4E5E
6-deoxy-D-galactose	—	669(8) ^c	—	—	PREV. α	⁴ C ₁	1E2E3E4A(5E)
6-deoxy-L-galactose	153(36) ^p	665(7) ^p	—	512(43)	PREV. α	¹ C ₄	1E2E3E4A(5E)
6-deoxy-L-mannose	162(34) ^p	685(32) ^p	-38(20)	523(66)	PREV. α	¹ C ₄	1E2A3E4E(5E)

^a Units, J kg mol⁻². ^b Units, J kg² mol⁻³. ^c Percentage ratio of pyranose anomers; when total percentage is lower than 100%, furanose forms are present. ^d Conformation of the predominant anomer. ^e Stereochemistry of the -OH group in the predominant conformer. The stereochemistry of other groups (-CH₂OH, -H, CH₃) is given in parentheses. ^f Unpublished data from the author's laboratory. ^g Ref. 20. ^h Ref. 22. ⁱ Ref. 23. ^j Ref. 24. ^k Ref. 25. ^l Ref. 26. ^m Ref. 27. ⁿ Ref. 6. ^o Ref. 28. ^p Ref. 29.

The numbers in parentheses are the 95% confidence limits. E stands for equatorial and A for axial.

TABLE 2

Values of the virial coefficients of the excess thermodynamic properties of methyl derivatives of monosaccharides in water at 298.15 K. Units as in Table 1

	g_{xx}	h_{xx}	h_{xxx}	TS_{xx}
α -Me-D-galactopyranoside	33(7) ^a	900(25) ^c	-42(14)	867(32)
α -Me-D-mannopyranoside	144(10) ^a	1206(14) ^c	-105(10)	1062(24)
α -Me-D-glucopyranoside	171(8) ^a	1097(39) ^c	-	926(47)
α -Me-D-xylopyranoside	114(16) ^a	1126(5) ^c	-38(3)	926(47)
β -Me-D-galactopyranoside	134(6) ^b	1081(28) ^d	-215(54)	948(34)
β -Me-D-glucopyranoside	82(11) ^b	1048(32) ^d	-64(32)	976(43)
β -Me-D-xylopyranoside	100(9) ^b	1098(12) ^d	-78(6)	998(21)

^a Ref. 30. ^b Unpublished data from the author's laboratory. ^c Ref. 31. ^d Ref. 32.

In Tables 1 and 2, all the known virial coefficients of the excess thermodynamic properties of aqueous solutions of the most commonly used monosaccharides, (including deoxysugars, whose crystalline structures have been partly resolved at our Department [19–21]) and of their 1-*O*-methyl derivatives are reported. The 95% confidence limits are given in parentheses.

Because of the positive values of all the g_{xx} coefficients, it can be assumed that the sugar–sugar interactions are prevented by the more favourable sugar–water interactions (at least in dilute solutions): the positive values of both the enthalpy and entropy coefficients can thus be attributed to partial retrogradation of the hydration with the concentration. In other words, on increasing the concentration the cosphere of each molecule will reduce, part of the water relaxing from the hydration shells (much extended at infinite dilution in the absence of competition with other solute molecules) to the less structured bulk water. The carbohydrates can then be regarded as structure-makers of the water, the structuring effect however being less than proportional to the molality or less effective on increasing the concentration. This hypothesis can explain the dependence of the excess properties on the stereochemistry of the solute, as they would result from changes in the solute hydration. This in turn depends on the reciprocal orientation of the polar groups on the solute molecule. Different correlations, however, determine the values of the Gibbs energies and enthalpies (Tables 3 and 4) and these subtle differences are not easy to rationalize. More evident is a general increase in the positive values of both g_{xx} and h_{xx} from monosaccharides to deoxy derivatives and to 1-*O*-methyl substitutes. Even in these cases, however, dependence on the stereochemistry of –OH and –OCH₃ groups can be detected (Table 5). The hypothesis that the labile orientation of the hydration water will affect the value of excess properties (mainly the enthalpy) of ternary solutions containing pairs of enantiomeric and isomeric carbohydrates is supported by the data in Table 6. A kind of chiral recognition seems to occur in the case of the D,L-arabinose and D,L-xylose

TABLE 3
Correlation between the excess Gibbs energy second virial coefficients and the stereochemistry of monosaccharides and deoxy derivatives

	g_{xx}	g_{xx}	g_{xx}	g_{xx}	g_{xx}			
3A	D-RIB	20(5)	D-ALL	—	2-deoxy-RIB	80(5)		
1A2A	D-LYX	31(5)	D-MAN	43(8)		L-RHAM	162(34)	
4A(5A)	L-ARA	34(5)	D-GAL	65(12)	D-FRUC	83(11)	L-FUCO	153(36)
—	D-XYL	56(7)	D-GLU	92	L-SORB	148(7)		
							2-deoxy-GLU	88(8)

Units as in Table 1.

TABLE 4
Correlation between the excess enthalpic second coefficients and the stereochemistry of monosaccharides and deoxy derivatives

A ^a	h_{xx}	h_{xx}	h_{xx}	h_{xx}						
4A(5A)	L-ARA	192(2)	D-GAL	133(8)	D-FRUC	264(18)	2-deoxy-GAL	442(22)	L-FUCO	665(7)
3A	D-RIB	196(4)	D-ALL	236(9)			2-deoxy-RIB	468(12)		
1A2A	D-LYX	332(9)	D-MAN	207(14)					L-RHAM	685(32)
	D-XYL	336(5)	D-GLU	343(10)	L-SORB	395(9)	2-deoxy-GLU	592(17)		

Units as in Table 1.

^a A; Positions of the axial —OH groups; the position 5A of fructose is equivalent to the 4A of other monosaccharides.

TABLE 5

Comparison between virial coefficients of excess Gibbs energies and enthalpies of α - and β -methyl derivatives of monosaccharides

	g_{xx}	h_{xx}		g_{xx}	h_{xx}
α Me-GALp	33(7)	900(25)	β Me-GALp	134(6)	1081(28)
α Me-MANp	144(10)	1206(10)			
α Me-GLUp	71(8)	1097(39)	β Me-GLUp	77(5)	1048(32)
α Me-XYLp	114(16)	1126(5)	β Me-XYLp	100(19)	1098(12)

Units as in Table 1.

TABLE 6

Chiral recognition between enantiomeric monosaccharides. Second virial coefficients of the excess enthalpies

	D-xylose	L-xylose	D-glucose
L-xylose(D)	332(9)	—	—
L-xylose(L)	317(6)	336(5)	—
D-glucose(G)	324(4) (337) ^a	329(4) (339) ^b	343(10)
	D-arabinose	L-arabinose	D-galactose
D-arabinose(D)	196(4)	—	—
L-arabinose(L)	213(8)	192(2)	—
D-galactose(G)	188(8) (164) ^a	191(9) (162) ^b	133(8) —
	D-fucose	L-fucose	
D-fucose	669(8) ^c	—	
L-fucose	664(12) ^c	665(7)	

Units as in Table 1.

^a Mean value, $\frac{1}{2}(h_{DD} + h_{GG})$. ^b Mean value, $\frac{1}{2}(h_{LL} + h_{GG})$. ^c Unpublished data from the author's laboratory; other data from ref. 24.

pairs; these are not the only such examples among dilute aqueous solutions of organic solutes, but it is not possible to generalize this effect to all the other pairs of enantiomeric sugars. In the case of 1-*O*- α - and 1-*O*- β -methyl derivatives, the ternary solutions show deviations from the average properties of the binary solutions (Table 7).

TABLE 7

Heterotactic interactions in aqueous solutions of α - and β -methylaldopyranoses

	$h_{\alpha\alpha}$ ^a	$h_{\alpha\alpha\alpha}$ ^b	$h_{\beta\beta}$ ^a	$h_{\beta\beta\beta}$ ^b	$h_{\alpha\beta}$ ^a	$(h_{\alpha\beta} - \bar{h})$ ^c
1-Me-GALp	900(25)	-42(14)	1081(28)	-215(54)	880(13)	-110
1-Me-GLUp	1097(39)	—	1048(32)	-64(32)	1026(14)	-46
1-Me-XYLp	1126(5)	-38(3)	1098(12)	-78(6)	1071(26)	-51

^a Units, J kg mol⁻². ^b Units, J kg² mol⁻³. ^c $\bar{h} = \frac{1}{2}(h_{\alpha\alpha} + h_{\beta\beta})$.

ARE MONOSACCHARIDES STRUCTURE-BREAKERS?

Many aspects are still unclear, however, and cannot be explained by a specific hydration model based solely on the distinction between equatorial and axial -OH groups. First of all, the values of the virial coefficients are relatively low in comparison with those of other, smaller, polar organic molecules, which is not to be expected in view of the large hydration of sugars. (If the solute-solvent and the solvent-solvent H-bonds are mainly responsible for the interactions, the energy differences seem not to arise from the nature of the latter but, rather, from their time-averaged number.) The concentration dependence of volumetric properties does not seem to be in agreement with a simple release of water from an ice-like to a more dense packing of molecules, i.e. that of bulk water. A third factor is incomplete enthalpy-entropy compensation at 298 K: this leads to a "structural temperature" for dilute aqueous solutions of sugars which is a few degrees lower than the actual one. This is in contrast to other evidence for the existence of the ability of sugars to enhance the water structure and form hydration cages. Limiting viscosities and activation energies for viscous flow of isomeric monosaccharides in water also show [33,34] some contradictory features that cannot be explained by the Suggett model. All these points strongly indicate that the theory that sugars (in the pyranosic chair conformation) are exclusively structure-makers of water must be reconsidered.

THERMODYNAMICS OF DILUTE TERNARY AQUEOUS SOLUTIONS CONTAINING A CARBOHYDRATE AND A CHAOTROPIC COSOLUTE

The theory that sugars can also be structure-breakers has been considered only for the furanose form of ribose (and fructose) [14]. Recent studies in our laboratory on the excess enthalpies of ternary aqueous solutions containing a sugar and an urea-like substance (urea, thiourea, biuret) [35-37] or a peptide [38] or an amino acid [39], have suggested that the properties of these solutions can be rationalized by the hypothesis that there is a release of water (less rich in interaction and richer in degrees of freedom than bulk water) from the cosphere of the sugars rather than from the cosphere of the chaotropic cosolutes. Evidence for this is the fact that all the h_{xx} coefficients are negative, but are also little sensitive to the size of the urea-like or polar amino acid cosolute (Table 8). On the other hand, their values depend on the number of sugar monomers, becoming about twice as large for disaccharides and three times as large for trisaccharides with respect to the monomers. This dissymmetry supports the view that water is released from the disordered part of the cosphere of the sugars, rather than that view based on the existence of an extended direct solute-solute interaction. Moreover, among the pentoses, D-ribose shows the most negative values of h_{xx} , in

TABLE 8

Values of the cross second virial coefficients h_{xy} of the excess enthalpy for aqueous solutions of oligosaccharides and chaotropic cosolutes at 298.15 K

	G^a	G_2^b	G_3^b	U^c	TU^d	BU
L-arabinose	-370(8)	-485(21)	-493(20)	-370(7)	-541(13)	-354(12) ^e
D-lyxose	-288(9)	-350(17)	-366(16)	-313(15)	-413(6)	-380(7) ^e
D-ribose	-414(8)	-578(24)	-625(7)	-370(5)	-560(16)	-515(6) ^e
D-xylose	-245(11)	-277(23)	-292(23)	-314(3)	-402(8)	-382(3) ^e
D-galactose				-397(6)		
D-mannose				-414(9)	-602(8)	
D-glucose				-377(7)	-466(19)	
2-deoxyglucose				-234(13)		
D-fructose				-405(9)	-507(16)	
sucrose				-596(6)	-978(31)	-1036(28) ^f
lactose				-646(6) ^f		
maltose				-692(28) ^f		
cellobiose				-688(17) ^f		
trehalose				-547(18) ^f		
melezitose				-846(26) ^f		
raffinose				-847(13) ^f		

Units, $J\ kg\ mol^{-2}$.

^a Glycine, ref. 38. ^b Glycylglycine and glycylglycylglycine, ref. 39. ^c Ref. 35. ^d Ref. 36. ^e Ref. 37. ^f Unpublished data from the author's laboratory.

agreement with the widely accepted idea that this sugar is a structure-breaker. These features of the behaviour of monosaccharides in solution are quite inexplicable on the basis of the preconceived idea that the axial -OH groups, the ring oxygen and all the perturbations induced by the conformational interconversions do not affect the thermodynamic properties. A simple inspection of molecular models suggests that other kinds of hydration can coexist with the hydration cage of the Suggett model. A more realistic discussion must also take into account (besides the prevailing structure-making ability of the monosaccharides) a less evident structure-breaking capability. The sugars would oscillate between two extreme hydration states: one giving preference to the hydration cage (essentially involving the equatorial -OH groups and more than one shell of water) and the other characterized by the hydration of the axial -OH groups and ring oxygens, which is not compatible with the orientation of water molecules in an ice-like structure. The substitution of -OH groups with hydrogens or -OCH₃ groups introduces a third kind of hydration, hydrophobic or "aperipheral" hydration, which is compatible with the hydration cage. These considerations can provide a partial answer to the contradictions mentioned earlier and give a fuller picture of the thermodynamic equilibrium properties.

Another contribution from our studies is the suggestion that the hydration cospheres of sugars and peptides are not compatible and that those

solutes do not interact favourably [38]. This is a possible explanation for the protective action of the saccharidic branched chains against the proteolytic attack of enzymes in the case of glycoproteins.

THERMODYNAMICS OF DILUTE AQUEOUS SOLUTIONS OF DI- AND TRISACCHARIDES AND CYCLODEXTRINS

The data for di- and trisaccharides and some cyclosaccharides are reported in Table 9. The discrepancies found in the literature are the subject of a study in progress at our laboratory. However, rationalization of the data is complicated by the freedom of rotation of the oligosaccharides around the glycosidic linkages. As a consequence they have a flexibility that makes a large number of conformations accessible; unfortunately the population distribution of these conformers is often not known. Models which try to correlate the enthalpic second virial coefficients with the capability of

TABLE 9

Virial coefficients of excess thermodynamic properties of oligosaccharides at 298.15 K

	g_{xx}	h_{xx}	Ts_{xx}
Disaccharides			
cellobiose	138 ^a	749(7) ^b 689(8) ^d	611
lactose	195(6) ^b	506(32) ^e 507 ^f 507(6) ^g	311(38)
maltose	100(6) ^b	488(3) ^b 571(27) ^h 439(22) ^g	388(9)
sucrose	205 ^c	577(6) ⁱ 596(17) ^g	372
trehalose	104(7) ^b	595(14) ^b 795(47) ^h	455(21)
Trisaccharides			
maltotriose	—	545(40) ^b	—
melezitose	—	607(27) ^b	—
raffinose	353 ^j	811(50) ^c	458
Cycloamiloses			
α -cyclodextrin	-1430 ^k	-3920(65) ⁿ	-2490
γ -cyclodextrin	-1480 ^k	—	—
2,6-dimethyl- β -cy.dex.	-16700 ^l	—	—
<i>myo</i> -inositol	-260 ^m	-800 ^p	-540

^a Ref. 40. ^b Unpublished data from the author's laboratory. ^c Ref. 41. ^d Ref. 42. ^e Ref. 26. ^f Ref. 43. ^g Ref. 33. ^h Ref. 44. ⁱ Ref. 28. ^j Ref. 45. ^k Ref. 46. ^l Ref. 47. ^m Ref. 48. ⁿ Ref. 49. ^p Ref. 50.

establishing hydrogen bonds with a tridimite-like structure of water surrounding the overall sugar molecule [44] are only partially satisfactory. Table 9 shows that the values of both the free energy and enthalpy coefficients seem to increase with increasing molecular weight (as for monosaccharides). However they seem to depend largely on the stereochemistry and distribution of the conformer populations. The abrupt change of sign of all the second coefficients of the excess properties is very remarkable, when the few cycloamyloses (cyclodextrins) studied are considered. The less insoluble are α CD (cyclohexaamylose), γ CD (cyclooctaamylose) and the derivative DM β CD (2,6-dimethylcycloheptaamylose). In Table 9, these data are compared with the values of the second virial coefficients of the cyclitol *myo*-inositol. This shows similar characteristics and similar differences with respect to linear homologues of lower molecular weight.

Rationalization of these values can be attempted by considering generally the accommodation of the overall solute molecule, namely a macrocycle, into the water. The accumulation of sets of nearest-neighbour polar groups, strongly orienting the hydration water (such as hydrogen bond formation sites), would generate competition for the molecules of the first shells of the solvent. These molecules are subjected to contradictory orientation effects, resulting in the disruption of the ice-like local structure of the water. Note, moreover, that on the outer surface of a cyclodextrine macro-ring, the -OH groups in positions 2 and 3 of each glucose ring can form hydrogen bonds with the -OH groups in positions 3' and 2'' of the preceding and following glucose rings respectively. Then only the -CH₂OH(6) and the -O-(5) groups of the ring are completely free to interact with water. However, both these groups can be structure-breakers. On the other hand, the hydration waters of the internal cavity of the cyclodextrins will be not removed unless a cosolute molecule replaces them. In this manner, the excess thermodynamic properties of cyclodextrins seem to resemble those of the chaotropic solutes of the urea family much more than those of the other saccharides! In the case of DM β CD, however, a solute-solute interaction may predominate because of the prevailing hydrophobic effect arising from the interaction between the -OCH₃(2) and/or -CH₂OCH₃(6) groups of two molecules.

DO SUGARS HAVE A HYDROPHOBIC CHARACTER?

Our recent calorimetric studies [51,52], concerning the interactions of sugars and alkanols in aqueous solutions, have shown that the hydrophobic properties of sugars, emphasized recently by Japanese authors [53,54] are often overestimated. The excess enthalpies of water-alkanol-sugar solutions can, in fact, be rationalized by assuming that they arise from retrogradation of the hydrophobic hydration of the alkanols, promoted by the competition for water of the more strongly hydrated sugars [51]. This is also not in

TABLE 10

Preliminary evaluation of the contributions to the h_{xy} enthalpic coefficients for monosaccharide-ethanol interactions

Equatorial C(H)OH (positions 1 (β), 2, 3, 4)	263
Axial C(H)OH (positions 1 (α), 2, 3, 4, 5)	191
Ring -O-	-255
Equatorial -CH ₂ OH (1, 6) (assumed)	0
Overall "pure" furanose form	1402

Units, J kg mol⁻².

contrast with reinforcing of the alkanol-alkanol hydrophobic interactions. Sugar-alkanol interactions, on the other hand, seem to be unfavourable. The conclusions of these studies shed new light on the formation in water of inclusion adducts between cyclodextrins (cycloamyloses) or other macrocyclic oligosaccharides and prevalingly hydrophobic organic molecules and ions. The formation of adducts is ruled by the minimization of cavitation energy and by the building-up of dipole-induced-dipole interactions in the dehydrated cavity of the macrocycle (these partially compensate for the dehydration of both the cavity and the hydrophobic residue of the cosolute) [49,55-58]. The thermodynamic parameters for the formation of α -cyclodextrin-alkanol adducts cannot be attributed to a "pure" hydrophobic effect [49,57].

A more quantitative analysis can be inferred from the sugar-alkanol studies to give a preliminary estimate of how the different, hydrated polar groups of the monosaccharides affect the enthalpic cross-interaction coefficient with ethanol. This estimate does not take into consideration the structure-making and structure-breaking ability of each group, since all the hydrophilic solutes destabilize the labile hydrophobic hydration cospheres in a comparable manner [51]. The values of these group contributions are reported in Table 10. They seem to indicate the existence of comparable effects on ethanol exerted by both structure-making and structure-breaking groups of the sugars.

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