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The Nature of the Cosolvent Effects of Sugars on the Aqueous Solubilities of Hydrocarbons

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Pentoses (D-arabinose, D-xylose, and D-ribose) and hexoses (D-glucose, D-galactose, and D-mannose) increased appreciably the aqueous solubilities of naphthalene and biphenyl, but all the sugars except ribose caused solubility depression of 1-octanol. Ribose increased most effectively the hydrocarbon solubilities while glucose showed the least effect. Deoxy sugars and methyl glycosides were more effective than the corresponding unsubstituted sugars. As to maltodextrins the solubility-increasing effect per glucose unit is cooperatively enhanced as the number of glucose residue increases. On the basis of these data, it was concluded that the cosolvent effects of the sugars are primarily brought about by their nonpolar interactions with hydrocarbons that occur at the structure-breaking sites of the sugar molecules.

We have previously reported that hexoses decreased to widely different extents the aqueous solubility of 1-octanol.[1] It was also shown that maltose, maltotriose and dextran, but not cellobiose and sucrose, caused solubility increases of 1-octanol and 1-heptanol particularly at high concentrations and that this effect was markedly enhanced as the temperature increased. These results apparently indicate that the cosolvent effects of sugars depend on the configurations of CH and OH groups in the monosaccharide molecules, the type of glycosidic linkages and the molecular size of the oligomers. Inspection of the relevant thermodynamic parameters suggested the presence of the hydrophobic interactions between the solute molecules and the hydrophobic surfaces[2,3] of sugars. We now report the effect of pentoses, hexoses, deoxy sugars, methyl glycosides and maltodextrins on the aqueous solubilities of 1-octanol, benzene, naphthalene and biphenyl, to look further into the nature of the cosolvent effect of sugars.

Experimental

Materials. Hexoses, pentoses and maltose of analytical reagent grade were purchased from Nakarai Chemical Ltd. (Kyoto, Japan) and were used as supplied. Maltotriose and maltopentaose (Nakarai Chemical Ltd.) and maltotetraose and maltohexaose (Seishin Pharm. Ltd., Chiba, Japan) were all analytical reagent grade. All other reagents used including benzene, naphthalene, biphenyl, 1-octanol, 1-butanol, and hexane were analytical reagent grade and were used as supplied.

Solubility Measurement of Aromatic Hydrocarbons and 1-Octanol. The solubilities of benzene, naphthalene, biphenyl and 1-octanol were measured in sugar solutions in the concentration range of 0—50%. As previously pointed out,[4] these aromatic hydrocarbons evaporated rapidly from their saturated aqueous solutions even in tightly closed vials with some air spaces. As a consequence, significantly lower apparent solubilities were often obtained from the solutions which stood for some time after separation from the excess hydrocarbons. This evaporation effect, which is the main source of error, could be practically eliminated by employing the following procedure: An appropriate amount (approximately 10 g) of a sugar solution plus an excess amount of a hydrocarbon was stirred for 6 h and gently shaken for another 18 h in a chamber thermostated within ±0.05°C. After removing a large part of the excess hydrocarbon using a transfer pipet, the mixture was allowed to stand without agitation for 6 h in the thermostated chamber. A portion of clear solution was taken up by a transfer pipet and immediately placed in a 15 ml vial containing a weighed amount of hexane with extreme care being taken not to touch the floating or sedimented residual hydrocarbon. The solubility measurements were made after extracting the solutes into hexane. Benzene, naphthalene and biphenyl were determined by spectrophotometry and 1-octanol by gas chromatography. The average percentage of deviation from the mean never exceeded 2%.

Results

The Cosolvent Effects of Monosaccharides. Figure 1 shows solubilities of 1-octanol, benzene, naphthalene and biphenyl in sugar solutions plotted against the sugar concentrations. The temperature dependence of the cosolvent effects of sugars is summarized in Table 1 for the aromatic hydrocarbons. The results obtained for 1-octanol were omitted here since the relevant data for this solute have been reported elsewhere.[1]

The Cosolvent Effects of Deoxy Sugars and Methyl Glycosides. To examine the effect of OH-H and OH-OCH_3 substitutions and the anomer effect, solubilities of the hydrocarbons were measured in the solutions of fucose, deoxy ribose and α- and β-methyl glycosides. The results are given in Table 2. It is clear that the substitution of one OH group with H and OCH_3 resulted in marked increase in the cosolvent effect, particularly for the large aromatic hydrocarbons. As to the methyl glycosides, β-anomers appear to be more effective than the α-

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anomers.

The Cosolvent Effects of Maltodextrins. To examine the effect of molecular size of maltodextrins on their cosolvent effects, solubility of naphthalene was measured in maltodextrin solutions of an identical glucose residue concentration (0.55 M†). Accordingly, the data given in Table 3 represent the cosolvent effect of glucose residue but not that of maltodextrin molecules. The results clearly show that the effect of glucose residue cooperatively increases as the degree of polymerization increases.

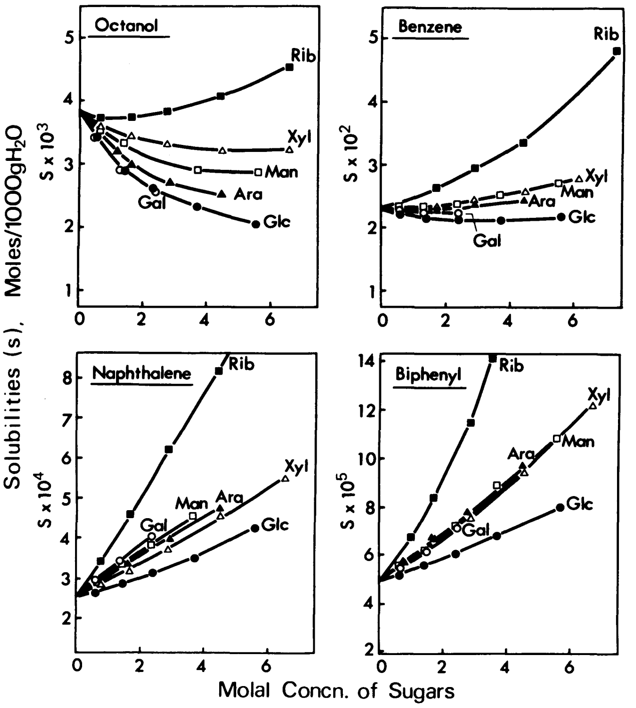

Fig. 1. Solubilities of 1-octanol, benzene, naphthalene, and biphenyl in sugar solutions at 25 °C.

Discussion

The Factors Determining the Cosolvent Effects of Sugars. The solubility plots of 1-octanol and benzene reveal that at low sugar concentrations the solubility-decreasing effect (the negative cosolvent effect) predominates but as the sugar concentration increases it is countervailed by the opposing effect (the positive cosolvent effect) resulting in leveling off or upward curvature of the solubility curves (Fig. 1). In solution of naphthalene and biphenyl the positive cosolvent effect prevails throughout the entire concentration range of sugars. We shall examine the nature of the cosolvent effects of sugars in the light of a current theory put forward by Roseman and Jencks.[5] According to their theory, the cosolvent effect or the transfer free energy of a nonpolar solute from water to a water-cosolvent mixture (ΔF_t) can be written as a sum of the free energy differences of the cavity formation (ΔF^{cav}), of the nonpolar solvent-solute interactions (ΔF^{int}_{np}), and of the polar interactions involving primarily solvent-solute hydrogen bonding (ΔF^{int}_{p}), in the two solvents. That is,

$$\Delta F_t = \Delta F^{cav} + \Delta F^{int}_{np} + \Delta F^{int}_{p}. \qquad (1)$$

On the basis of extensive data on the cosolvent effects, they concluded that ΔF_t is largely determined by the first two terms, $\Delta F^{cav}+\Delta F^{int}_{np}$, the last term ($\Delta F^{int}_{p}$) playing a minor role in solution of nonpolar solutes. The important part of their theory is that the primary effect of almost all organic cosolvents is to increase solubilities of nonpolar solutes by making ($\Delta F^{cav}+\Delta F^{int}_{np}$) more favorable. The relative

TABLE 1. EFFECT OF TEMPERATURE ON THE SOLUBILITIES (S)[a] OF AROMATIC HYDROCARBONS IN CONCENTRATED SUGAR SOLUTIONS

Sugar (mol kg^{-1} H$_2$O)	10 °C			25 °C		
	Benzene (S×10^2)	Naphthalene (S×10^4)	Biphenyl (S×10^5)	Benzene (S×10^2)	Naphthalene (S×10^4)	Biphenyl (S×10^5)
D-Glucose(4.5)	1.71	1.82	2.92	2.15	3.83	7.32
D-Galactose(2.0)	1.94	2.02	3.47	2.25	3.80	6.76
D-Mannose(4.7)	2.13	2.46	5.15	2.64	4.89	10.02
D-Arabinose(3.7)	1.96	2.34	4.84	2.42	4.43	8.91
D-Xylose(5.6)	2.21	2.79	5.97	2.70	5.10	10.83
D-Ribose(5.3)	2.94	4.62	10.43	3.69	9.33	20.76
H$_2$O	2.11	1.39	2.67	2.31	2.52	4.85

a) mol kg^{-1} H$_2$O.

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† 1 M=1 mol dm^{-3}.

magnitude of ΔF^{cav} and $\Delta F^{\mathrm{int}}_{\mathrm{np}}$, however, has not been evaluated. In the discussion that follows, the cosolvent effects of sugars will be examined in terms of ΔF^{cav} and $\Delta F^{\mathrm{int}}_{\mathrm{np}}$.

As previously noted,[1] the negative part of the cosolvent effect evident in the solubility plots of 1-octanol and benzene but obscured by the opposing effect in the plots of naphthalene and biphenyl may largely be attributed to the reduction of water activity caused by sugar hydration. One prominent feature of the solubility curves is their remarkable solute-dependence, *e.g.*, while the molar volumes of biphenyl and 1-octanol are comparable, their solubility curves are totally different. This indicates that $\Delta F^{\mathrm{int}}_{\mathrm{np}}$ rather than ΔF^{cav} predominates in the cosolvent effects of sugars. The decrement of the activity coefficients (see Eq. 5) of the solutes on transfer from water to sugar solutions increases in the order, 1-octanol<benzene<naphthalene<biphenyl, indicating that the nonpolar interactions of the hydrocarbons with the sugars are enhanced by the high polarizability and planarity of aromatic rings.[5] The effective nonpolar interactions through Van der Waals' forces can be achieved only when water molecules are excluded and the sugar and hydrocarbon molecules come close to each other. That is, for the effective interaction the water structure around the specific interaction sites of the sugar molecules, presumably the sites where CH density is relatively high, needs to be loose. This contention is consistent with the increased positive-cosolvent effect brought about by the OH-H and OH-OCH₃ substitutions (Table 2). The cooperative effect of glucose residues of maltodextrins (Table 3) may reflect that they form curved nonpolar surfaces, similar to the internal surfaces of the cyclodextrin cavities, that strongly interact with the hydrocarbons.[6]

Relative Magnitude of $\Delta F^{\mathrm{int}}_{\mathrm{np}}$ of Each Sugar. The foregoing evidence indicates that ΔF^{cav} is an important component of ΔF_{t} and a favorable ΔF^{cav} is prerequisite to the effective nonpolar interaction ($\Delta F^{\mathrm{int}}_{\mathrm{np}}$) but that the negativity of ΔF_{t} is largely attributed to the negativity of $\Delta F^{\mathrm{int}}_{\mathrm{np}}$. If the stoichiometric complex formations between the sugars (S) and biphenyl (B) are assumed, it is possible to estimate the relevant association constants. (Biphenyl was chosen because its ΔF_{t} values are all negative (Fig. 1)). Let us consider an equilibrium dialysis system in which an aqueous solution of sugar and biphenyl in dialysis bag permeable to water and biphenyl, but not to sugar, is in equilibrium with the external saturated aqueous solution of biphenyl. The equilibrium system can be described by

$$\mathrm{B} + \nu\mathrm{S} = \mathrm{BS}_{\nu}, \tag{2}$$

where ν is the average number of bound sugar molecules per biphenyl. Provided that ν does not fluctuate greatly,[7] the apparent association constant (K^{app}) can be written as

$$K^{\mathrm{app}} = \frac{[\mathrm{BS}_{\nu}]}{[\mathrm{B}][\mathrm{S}]^{\nu}}, \tag{3}$$

where [B], [S], and $[\mathrm{BS}_{\nu}]$ are the equilibrium molar concentrations. Since $[\mathrm{B}]=C^{\mathrm{o}}$ (the molar solubility of biphenyl in the external solvent water) and hence

TABLE 3. SOLUBILITIES (S) (mol kg^{-1} H_2O) OF NAPHTHALENE IN MALTODEXTRIN SOLUTIONS OF 0.55 M GLUCOSE RESIDUE CONCENTRATION AT 25 °C

Maltodextrin	S×10⁴	Maltodextrin	S×10⁴
D-Glucose	2.61	Maltotetraose	3.47
Maltose	3.05	Maltopentaose	3.59
Maltotriose	3.30	Maltohexaose	3.77
H_2O	2.58	—	—

TABLE 2. SOLUBILITIES (S)[a] OF 1-OCTANOL AND AROMATIC HYDROCARBONS IN SUGAR SOLUTIONS (1 mol kg^{-1}) AT 25 °C

Sugar	1-Octanol (S×10³)	Benzene (S×10²)	Naphthalene (S×10⁴)	Biphenyl (S×10⁵)
D-Glucose	2.89	2.08	2.81	5.33
α-Methyl D-glucoside	3.85	2.53	3.97	7.81
β-Methyl D-glucoside	3.63	2.88	4.24	7.98
D-Galactose	2.94	2.10	3.22	5.64
D-Fucose	nd	2.03	4.07	7.03
α-Methyl D-galactoside	3.66	2.41	4.42	7.88
β-Methyl D-galactoside	3.38	2.47	5.57	9.75
D-Ribose	3.61	2.32	3.78	6.59
2-Deoxy D-ribose	4.43	2.86	4.94	10.12
H_2O	3.83	2.25	2.60	4.94

a) mol kg^{-1} H_2O.

$[\mathrm{BS}_{\nu}]=C-C^{\circ}$ where C refers to the molar solubility of biphenyl in the sugar solution contained in the dialysis bag, Eq. 3 can be rewritten as

$$\frac{C^{\circ}}{C}=\frac{1}{1+K^{\mathrm{app}}[\mathrm{S}]^{\nu}}. \tag{4}$$

Assuming the activity coefficient of biphenyl in the saturated water solution to be unity,[8] the activity coefficient (f) in a sugar solution is given by

$$f=C^{\circ}/C. \tag{5}$$

Eq. 4 and Eq. 5 may be combined to yield

$$(1-f)/f=K^{\mathrm{app}}[\mathrm{S}]^{\nu}. \tag{6}$$

The term $(1-f)/f$ represents a relative decrement of the activity coefficient of biphenyl upon transfer from water to the sugar solutions. Since the concentration of the added sugar $[\mathrm{S_o}]$ is much greater than that of biphenyl (C°), $[\mathrm{S}]$ may be replaced by $[\mathrm{S_o}]$, and Eq. 6 can be rewritten as

$$\ln[f/(1-f)]=\ln(1/K^{\mathrm{app}})-\nu\ln[\mathrm{S_o}]. \tag{7}$$

Such an approach can only provide the rough estimates of the interaction parameters (K^{app} and ν), but these values are still quite informative.[9,10] Figure 2 shows the plots of $\ln[f/(1-f)]$ *vs.* $\ln[\mathrm{S_o}]$ for all the monosaccharides except glucose for which f is nearly 1 thereby yielding an infinite value of $f/(1-f)$. The values of K^{app} and ν evaluated from Fig. 2 are summarized in Table 4. The results show that each sugar forms 1 to 1 stoichiometric complex with biphenyl and the association constant increases in the order of glucose$\ll$galactose$<$mannose$<$xylose$<$arabinose$\ll$ribose. The difference in K^{app} may reflect the difference in the total surface area of CH group of sugars accessible to water molecule.[11] However, the cooperative enhancement of the positive cosolvent effect of glucose residues of maltodextrins, but not of cellobiose,[1] indicates the importance of the "CH-dense surface," a specific site of sugar molecule where the CH density is the highest, rather than the total CH-surface area.[6]

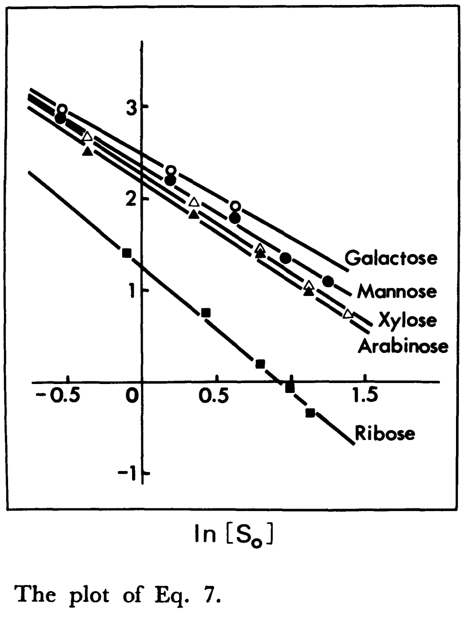

Fig. 2. The plot of Eq. 7.

The Specific Interaction Sites of the Sugar Molecules. The free energy for transfering one mole of the solutes (naphthalene and biphenyl) from pure water to the sugar solutions was calculated from Eq. 8 and summarized in Table 5.

$$\Delta F_{\mathrm{t}}=RT\ln f. \tag{8}$$

The temperature dependence of ΔF_{t} of the two solutes is negative indicating that their spontaneous transfer from water to the sugar solutions is endothermic and hence entropic in nature. These thermodynamic parameter changes may be interpreted in terms of the "structured water" hypothesis.[12–14] On the other hand, Howarth[15] showed by ^{13}C relaxation time measurements that water is unique in its ability to restrict the motion of hydrophobic part of solute molecules and that the motional restriction accounts for most part of the entropy change on solution.

TABLE 4. THE ASSOCIATION PARAMETERS PERTAINING TO THE SUGAR–BIPHENYL INTERACTIONS

Sugar	$\nu^{\mathrm{a)}}$	$K^{\mathrm{app}}\times 10^{\mathrm{b)}}$
D-Glucose	0	0
D-Galactose	0.94	0.82
D-Mannose	1.03	0.94
D-Xylose	1.10	1.00
D-Arabinose	1.05	1.13
D-Ribose	1.36	2.86

a) The average number of bound sugar molecules per biphenyl. b) The apparent association constant in mol^{-1} dm^{3}.

TABLE 5. TRANSFER FREE ENERGY$^{\mathrm{a)}}$ OF NAPHTHALENE AND BIPHENYL FROM WATER TO THE SUGAR SOLUTIONS

Sugar(mol dm^{-3})	Naphthalene		Biphenyl	
	10 °C	25 °C	10 °C	25 °C
D-Glucose(3.0)	81	−3	182	≈0
D-Galactose(1.6)	−92	−118	−29	−72
D-Mannose(3.0)	−76	−135	−124	−172
D-Arabinose(2.7)	−120	−152	−162	−178
D-Xylose(3.6)	−144	−157	−205	−215
D-Ribose(3.5)	−439	−526	−530	−612

a) cal mol^{-1}.

And according to Roseman and Jencks,[5] the presence of almost all organic cosolvents in water results in a decrease in the number density of hydrogen bonds. Accordingly, it is also possible to attribute the observed positive entropy of the transfer to the increased motional freedom in the sugar solutions relative to that in water. There will be a negative entropy contribution from the nonpolar sugar-aromatic hydrocarbon interaction, but its magnitude is expected to be relatively small. The water structure around the interaction sites of sugar molecules is presumably loose allowing easy access of the hydrocarbons.

It is generally accepted that sugars are structure maker[16–22] with a few exceptions, *e.g.* ribose,[20] and that the extent of hydration depends on the spatial orientations of the individual OH groups.[17,20,21] According to the "specific hydration model"[20] the spacing of equatorial OH groups in a pyranose ring is compatible with the ice-like structure of water thereby enhancing structure of surrounding water. However, ^{17}O NMR study could not distinguish between the hydration properties of glucose, galactose and mannose.[20] It seems that the solubility-increasing effect of the three hexoses as well as their significant differences in the effectivity are not readily explainable in terms of the "specific hydration model" alone. Furtheremore, the structure promoting effect of sugars has been questioned by several authors[23–25] and recently, Miyajima *et al.*[26,27] reported some notable hydration properties of mono- and oligosaccharides which are contrary to what would be expected from the "specific hydration model." Sugar molecules possess many CH groups which will not be compatibly caged in the preexisting network of water without causing serious entropy disadvantage. Recently, the direct evidence for the CH surface-sugar hydrophobicity correlation has been provided by Miyajima *et al.*[11] They showed that the CH and CH_2 surface area of sugars accessible to water molecule is closely correlated with their differential affinity for polystyrene gel.[6] On the basis of the proceeding arguments, we are inclined to conclude that the hydration shell around sugar molecule is quite loose at the vicinity of the "CH-dense surfaces" where the nonpolar sugar–hydrocarbon interactions occur through Van der Waals' forces.

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