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Relationship Between the Structure and the Properties of Carbohydrates in Aqueous Solutions:* Solute–Solvent Interactions and the Sweetness of D-Fructose, D-Glucose and Sucrose in Solution

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ABSTRACT

The solute–solvent interactions in aqueous solutions of sugars are known to result in a configurational and conformational equilibrium of the different isomers, a short range order of water molecules in the vicinity of the sugars (hydration) and a long range order of the bulk water (water structure). Sweet taste is based on the hydrogen bonding of an AH—B unit and the hydrophobic effect of a 'γ' center. As solute–solvent interactions in aqueous solutions of sugars have the same nature as glycophore–receptor interactions (hydrogen-bonding and hydrophobic hydration), an attempt is made to interpret the relative sweetness of D-fructose, D-glucose and sucrose in terms of their interactions with water.

INTRODUCTION

Since the hypothesis of Shallenberger & Acree (1967), it is usually accepted that the sweet-taste sensation requires the presence in the sweet compound of an AH—B unit (glycophore), where AH is a proton donor and B a proton acceptor in the hydrogen bonding established with the

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corresponding B—AH unit of the receptor site. A third component of the molecular theory of sweetness is a hydrophobic center in the sweet molecule (Deutsch & Hansch, 1966; Shallenberger & Lindley, 1977) called 'γ'. This parameter, 'γ', seems to act, when it is present, to amplify the sweet-taste sensation (Kier, 1972).

Observations like the identity of the saporous planar unit (AH—B, 'γ'), in D-glucose and β-D fructopyranose, in spite of the difference in their sweetness, raise some chirality problems. It has been observed that the anomers α and β-D glucopyranose are each sweeter than their mutarotated solution (Shallenberger, 1973) and this poses an intriguing question about which form (α or β) is the sweeter. Similarly, β-D fructopyranose is known to be about twice as sweet as sucrose but, after dissolution in water or thermal mutarotation, its sweetness is considerably reduced (Tsuzuki & Yamazaki, 1953). The chirality problems were recently studied by Shallenberger (1982), but, as far as we are aware, there has been no interpretation of the structure–sweetness relationship based on the rôle of water.

Although the mechanism of the chemoreception of the sweet taste is known to be linked to an ion (Na^+/K^+) transport across the proteic receptor membrane (Kobatake *et al.*, 1978), reports about the influence of the structure of the water in which the diffusion of Na^+ and K^+ takes place are scarce. We recently studied the solute–solvent interactions in aqueous solutions of D-fructose, D-glucose and sucrose using laser-Raman spectroscopy (Mathlouthi, 1980) and X-ray diffraction of the solutions (Mathlouthi, 1981). The influence of traces of the three sugars on the structure of liquid water (Mathlouthi & Luu, 1982) prompted us to propose, in this paper, an interpretation of the rôle of water structure in sweet taste reception.

The results of previous work (Shallenberger, 1978; Lindley & Birch, 1975; Hyvönen *et al.*, 1978) on the sweetness of the most common nutritive sugars could be interpreted in terms of water structure and water–sugar interactions. This is especially important as it appears that the participation of water is evoked in the term hydrophobic (Greek *hudor*, water; *phobos*, dread) which characterizes the center of repulsion of water molecules (or hydrophobicity) in the tripartite (AH—B,γ) glycophore. As we are interested in the behaviour of D-fructose, D-glucose and sucrose in water, all the physical properties of their solutions (viscosity, acidity, etc.) should be considered in order to support our hypothesis.

SOLUTE–SOLVENT INTERACTIONS IN AQUEOUS SOLUTIONS OF SUGARS

The interactions between water and each of the three sugars may be classified as follows: (a) the influence of water on the sugar structure shown by the configurational and conformational equilibria in aqueous solution; (b) the mutual weak energy interaction revealed by the specific hydration of each isomer and (c) the influence of the sugar on the 'water structure' demonstrated by the long range order of water molecules owing to more or less strong hydrogen bonds, depending on the arrangement in the space of the hydrophilic or hydrophobic groups in the periphery of the sugar ring.

(a) Configurational and conformational equilibria

The configurational and conformational equilibria obtained after dissolution of the sugar in water are essential in understanding the structure–sweetness correlation. β-D-fructopyranose, the only crystalline form of D-fructose, gives, at equilibrium in water at 20 °C, a proportion of 57 to 76 % of the β-D-pyranose isomer. The composition varies with the method of investigation. Doddrell & Allerhand (1971) using Fourier transform ^{13}C NMR, found the composition: 57 % β-pyranose, 37 % β-furanose, 9 % α-furanose and 3 % α-pyranose while Shallenberger (1973) indicated, by gas–liquid chromatography, a different composition (76 % β-D-fructopyranose, 20 % β-D-fructofuranose and 4 % of an unknown compound). These proportions depend also on the solvent. In pyridine, Funcke & Klemer (1976) give, at equilibrium, the percentages: 43 % β-pyranose, 35 % β-furanose, 15 % α-furanose, 5 % α-pyranose and 2 % of open chain. So, whatever the method of investigation or the solvent, the predominant constituent of the solution is the β-D-fructopyranose isomer. The mutarotation of D-glucose in water gives, at equilibrium, 62 % β-D-glucopyranose and 38 % α-D-glucopyranose (Isbell & Pigman, 1937). No detectable furanose or open chain forms are found. The percentage of the α-anomer varies with the solvent (37 % in water, 45 % in pyridine) (Franks, 1979). The disaccharides are capable of hydrophobic folding in water. This is the case for maltose (Neal & Goring, 1970) and probably also for the sucrose molecule in dilute solution (Mathlouthi, 1981). However, recent ^{13}C NMR studies of sucrose in mixtures of deuterated DMSO and heavy water indicated that intra-molecular hydrogen bonds are present in dilute solution (Bock & Lemieux, 1982). The influence of the solvent on the inter- and intramolecular hydrogen bonds of the solute was studied by Lemieux & Pavia (1969). They showed that each hydroxyl group engaged in a hydrogen bond to a proton acceptor provokes the strengthening of the hydrogen acceptor character of the oxygen atom. They also proposed the concept of conjugated hydrogen bonds which has also been developed by Jeffrey (1978).

(b) Hydration

The most numerous studies concerning solute–solvent interactions in aqueous solutions of carbohydrates dealt with hydration and used different techniques (Robinson & Stokes 1966; Garrod & Harrington, 1970; Tait *et al.*, 1972; Allen *et al.*, 1974; Akhumov, 1975; Harvey *et al.*, 1976; Suggett & Clark, 1976; Bociek & Franks, 1979). The results seem to depend on the technique of investigation. The hydration number (molecules of water in the first shell of hydration) varies from 2·7 (Suggett & Clark, 1976) to 11 (Harvey *et al.*, 1976) for D-glucose, and from 5 to 21 (Allen *et al.*, 1974) for sucrose. The association of a first layer of water molecules to the sugar hydroxyl groups should influence its properties. The hydration water is, for example, at the origin of the persistence of supersaturation in deeply frozen aqueous solutions of sugars (Franks, 1977). Moreover, the crystallization of sucrose is slowed because it needs a step of water–sugar dissociation before the sugar–sugar hydrogen bonding of the crystal (Van Hook, 1977). This hydration is specific for the conformation and configuration of the sugar (Lemieux & Pavia, 1969). One of the most characteristic types of hydration is that of β-D-glucopyranose. The fact that all the hydroxyl groups are equatorial facilitates a tridymite-like organization of water which seems to be very stable (Kabayama & Patterson, 1958). This organization of water could be evoked in order to explain the high solubility of β-D-glucopyranose. It is necessary to heat (up to 110 °C) a 95 % concentrated solution of D-glucose in order to dissociate water from the β-D-glucose and to allow it to crystallize (Newkirk, 1937). The hydration water probably competes with the AH—B unit of the bud in hydrogen bonding, and this should be taken into account in the interpretation of the sweet taste.

(c) Water structure

Ryazanov (1978) differentiates the short range order around the sugar molecule (hydration) from the long range order of the bulk water (water structure). The structure of water in aqueous electrolyte and non-electrolyte solutions was extensively studied recently (Franks, 1972–1982). Models have been proposed which may be classified in two categories—the 'continuum model' which describes water as having essentially a continuous network of hydrogen bonds on a long range scale

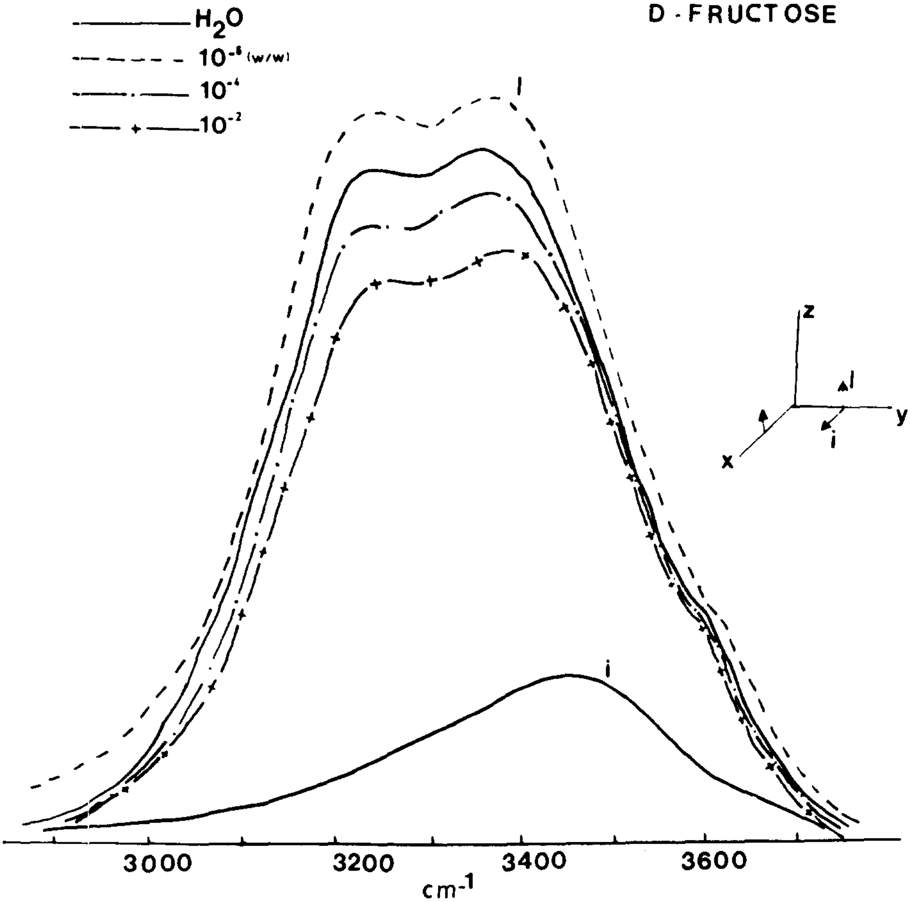


Fig. 1. Laser-Raman spectra of OH stretching of water in the presence of traces of D-fructose (10^{-6}–10^{-2} g/g).

with different states of distances and angles O—H···O (Horne, 1972) and the 'mixture model' which implies the existence of an equilibrium between different species that are distinguishable in an instantaneous picture (Nemethy, 1974). Recently, a semi-empirical method of deconvolution of the Raman bands of water stretching permitted Luu *et al.* (1982) to find at least five different species of association in water. Using the method of Luu *et al.* (1982), we found that traces (10^{-6} to 10^{-2} g/g) of D-fructose, D-glucose and sucrose modify the proportion of these species (Mathlouthi & Luu, 1982). The increase of the intensity of OH stretching vibration observed with 10^{-6} g/g D-fructose is due to the increase of the number of free water molecules (monomers) (Fig. 1).

The general behaviour of carbohydrates in aqueous solutions is influenced considerably by the nature of the solvent itself. Among the different methods used to investigate the interactions between sugars and water, infrared and Raman spectroscopies are able to detect OH-free groups and help in defining them as water structure promoters or breakers (Jackson & Symons, 1976).

VISCOSITY AND ACIDITY OF D-FRUCTOSE, D-GLUCOSE AND SUCROSE SOLUTIONS

The most common method in the study of the hydrodynamic behaviour of a molecule in dilute solution is the determination of the viscometric constants: $[\eta]$, the intrinsic viscosity and k', the Huggins constant, obtained from the equation:

$$\frac{\eta_{sp}}{c} = [\eta] + k'[\eta]^2 c + \cdots$$

where $sp = [(\eta - \eta_0)/\eta_0]$ is the specific viscosity, η and η_0 being, respectively, the viscosity of the solution and the solvent. c is the concentration in g dl^{-1}.

The intrinsic viscosity results from the shape of the molecule in solution, while the Huggins constant describes the interaction between the solute and the solvent (Mathlouthi, 1980). The viscometric results shown in Fig. 2 ($[\eta]$) and Fig. 3 (k') indicate a particular behaviour of D-fructose in dilute solution. The increase in viscosity of dilute ($c <$ 2 g dl^{-1}) D-fructose solutions is comparable with that observed in

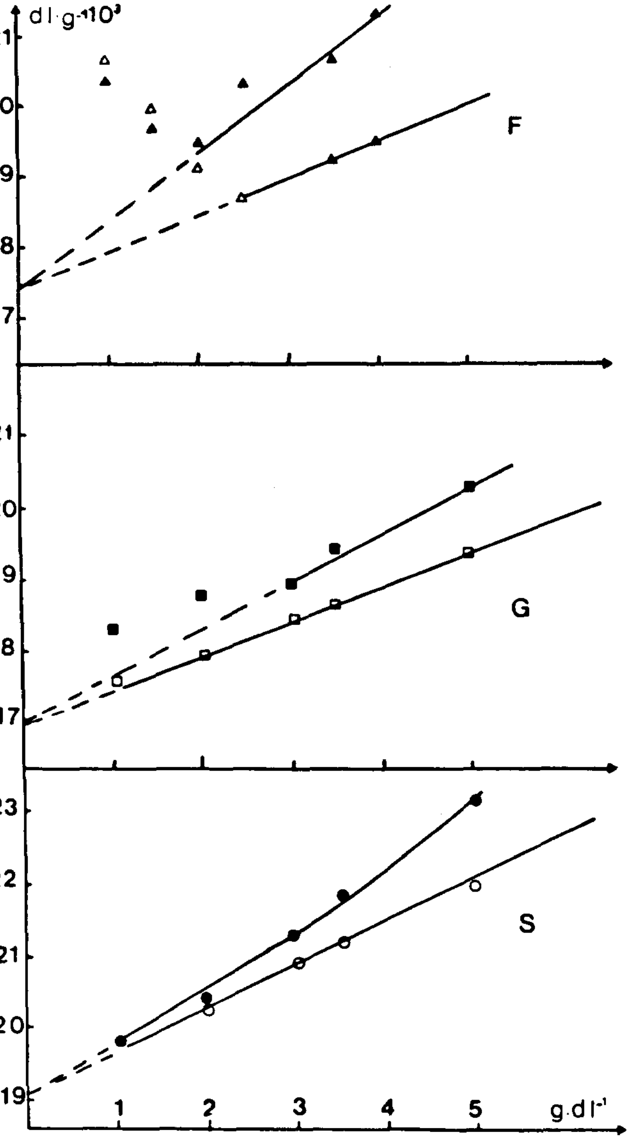


Fig. 2. Intrinsic viscosities of D-fructose (F), D-glucose (G) and sucrose (S) in water, 15 min (△, □, ○) and 24 h (▲, ■, ●) after dissolution.

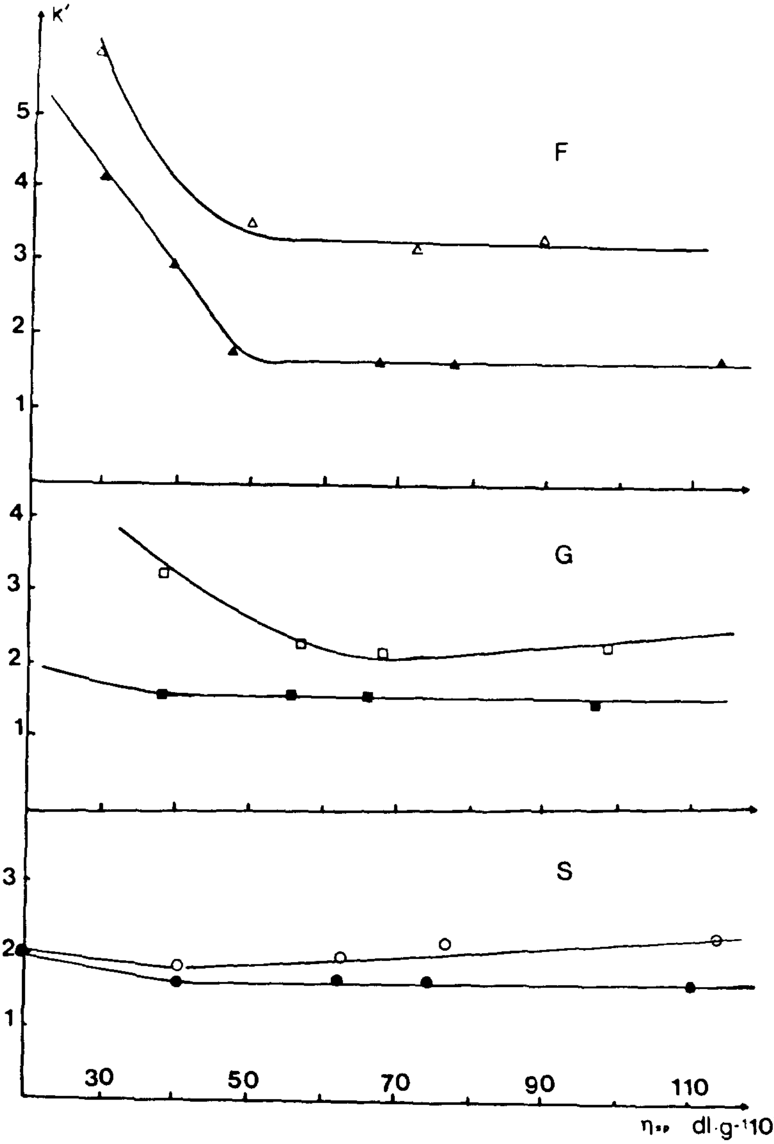


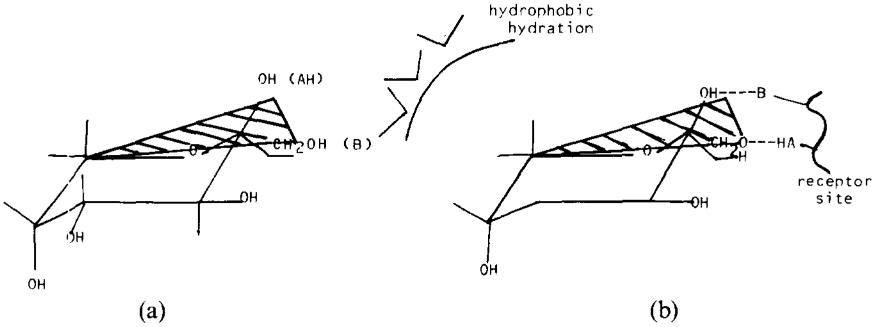
Fig. 3. Variation of Huggins constant k' in function of specific viscosity 15 min (△, □, ○) and 24 h (▲, ■, ●) after dissolution of D-fructose (F), D-glucose (G) and sucrose (S) in water.

polyelectrolyte solution (Bettelheim, 1970). Moreover, the acidity of D-fructose in aqueous solution is slightly greater than that of the other sugars ($pK = 12{\cdot}03$ for D-fructose, 12·28 for D-glucose) (Christensen *et al.*, 1970) and $pK_1 = 12{\cdot}18$; $pK_2 = 12{\cdot}69$ for sucrose (Palash & Kharin, 1966).

THE SWEET TASTE AND THE STRUCTURAL PROPERTIES OF D-FRUCTOSE, D-GLUCOSE AND SUCROSE IN AQUEOUS SOLUTIONS

(a) D-fructose

β-D-fructopyranose is known to be the sweetest natural sugar (Birch & Shallenberger, 1973). Its sweetness is about 1·8 times to twice that of sucrose and 2·5 times that of α-D-glucopyranose. Scheme 1 was proposed to show the tripartite saporous unit of β-D-fructopyranose (Shallenberger, 1978) (a):



Scheme 1. Representation of β-D-fructose mechanism of sweetness, (a) AH—B unit, (b) hydrogen bonds of AH with the receptor site and hydrophobic effect of γ.

The unit AH—B is common to all the sugars. What makes the sweetness of β-D-fructopyranose more intense is the methylene group of the carbon 6 specified as the hydrophobic–lipophilic 'γ' site. The effect of this group on water is a repulsion that strengthens the hydrogen bonds of the molecules in the bulk water which arrange themselves in a clathrate-like structure. Hence the molecules of water do not share the hydrogen bonds with the sugar on the receptor site (b). According to Samoilov (1978), the 'hydrophobic hydration' tends to inhibit translational motions of water molecules in solution, e.g. in the hydration of a hydrophobic radical (like a methyl group) in a complex molecule. Moreover, when the clathrate-like structure of water surrounds a molecule, it tends to enhance the ionic character of the charged radicals (Vinogradov & Linnell, 1971). This could be at the origin of the charge-transfer mechanism of the hydrogen bonding of the AH—B unit. According to this mechanism, proton donor (A—H) and proton acceptor (B) take part in hydrogen bonding as electron acceptor and electron donor, respectively, and the bonding energy may be interpreted as the stabilization energy caused by the resonance between two structures:

$$\text{A—H}\cdots\text{B} \rightleftharpoons \text{A}^-\cdots\text{H—B}^+$$

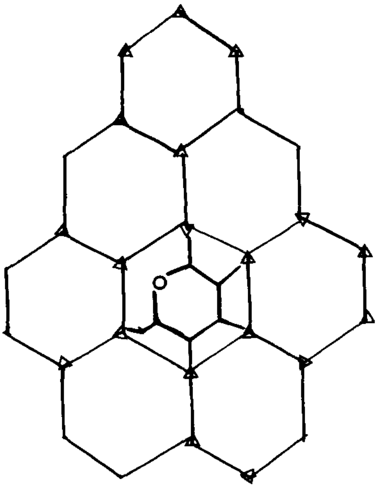
This supports the importance of the hydrophobic component 'γ' in the sweet taste. However, the impact time on the receptor site is short, as is the hydrophobic hydration. In the same short time as mutarotation takes place, the clathrate-like structure of water enters into equilibrium with the other forms of organization, particularly with the monomers. The free water thus liberated could facilitate the Na^+/K^+ transport across the membrane of the tongue. The more the water is dissociated, the more the permeability of the membrane to Na^+ is increased. This leads to a high value of the membrane potential (Sybesma, 1977) and could enhance the intensity of the sweetness. These conclusions agree with the polyelectrolyte behaviour of D-fructose in dilute solutions and with its relatively high acidity.

Moreover, the rôle of water structure in the biological properties of D-fructose solutions may be seen in other examples. The sugar is used in preventing and alleviating symptoms of alcoholic 'hangover' (Pawan, 1973). Its action is probably attributable to the water structure (Mathlouthi, 1980). It may be suggested that ethanol, which is capable of hydrophobic hydration, acts on the brain in a way close to that proposed by Pauling (1961) to explain the anesthesia phenomenon. D-fructose in aqueous solution could destabilize the clathrate-like structure of water induced by ethanol owing to the equilibrium established between free water molecules and clusters of molecules in the hydrophobic hydration shell of ethanol. The alcohol is then carried out into the blood and metabolized. This particular behaviour of D-fructose towards water is probably at the origin of its lack of utilization as a cryoprotector for the freezing of living cells. The water is not frozen but its mobility is high enough to provoke the migration of ions at low temperature. The isotonic equilibrium of the cryoprotected cell is then altered, which could be the reason why D-fructose is a bad cryoprotector.

In conclusion, it may be emphasized that D-fructose shows an ambivalent character towards water: a structure promoter effect due to its CH_2 group, especially in the β-D-pyranose isomer, and a structure breaker effect due to the other isomers in solution. The hydrophobic effect tends to enhance the charge-transfer character of the AH—B units and to prevent the sharing of hydrogen bonds of the sugar between the receptor site and water. The structure breaker effect is probably at the origin of the decrease of sweetness in the mutarotated solution but, by facilitating the Na^+/K^+ transport, it may extend the duration of the sweet taste sensation.

(b) D-glucose

The difference of sweetness between α-D-glucopyranose in the solid form and its mutarotated solution, on the one hand, and crystalline β-D-glucopyranose and its mutarotated solution, on the other (Shallenberger, 1973), could be interpreted in terms of solute–solvent interactions in the aqueous soluion of D-glucose. Both solid anomers are sweeter than the solution. The β anomer is even slightly sweeter than the α. The AH—B, 'γ' triangle of sweetness is similar to that of β-D-fructopyranose except that the γ center is an exocyclic CH_2OH group instead of the endocyclic CH_2 on the C-6 in β-D-fructopyranose (Shallenberger, 1982). The sweetness of the solid form is amplified by the hydrogen bonding of the crystal in which the hydroxymethyl participates and which leads to the increase of the hydrophobicity of CH_2. However, when the sugar is dissolved in water, the proton acceptor character of oxygen in the hydroxymethyl group is strengthened by the hydrogen bonding. This fact prevents the hydrophobic hydration which appears to play a major rôle in the case of β-D-fructopyranose. All the groups that have a strong hydrophobic effect (like halogens) should improve the sweetness when substituted on the CH_2OH groups. This is the case with the chloro (Hough & Phadnis, 1976) and the methyl (Lindley *et al.*, 1975) derivatives of sucrose. The lack of strong hydrophobicity in the D-glucose molecule, its lower acidity and the absence of the electrolyte character in the dilute solution diminish the charge transfer properties of the AH—B unit. In β-D-glucopyranose the good fitting between the equatorial disposition of hydroxyls and the tridymite structure of water (Kabayama & Petterson, 1958) prevents the



Scheme 2. Arrangement of water (Δ) in a tridymite-like structure around β-D-glucopyranose.

AH—B bonding to the receptor site, or at least weakens it (Scheme 2). As the β-configuration is stereochemically compatible with the water structure, it confers to the molecule in solution less sweetness than the α-configuration, or even more bitterness (Birch, 1976).

(c) Sucrose

The sweetness of sucrose is considered as a reference standard. This is due to its relative stability as no mutarotation problems are posed. The AH donor in the AH—B unit could be OH-3^g or OH-2^g, B being O-4^g or O-3^g. The γ unit is then the CH_2 group in C-1^f (Shallenberger, 1982). This group, as also CH_2OH of C-6^f, is engaged in the intramolecular hydrogen bonding revealed by the neutron diffraction analysis of the crystal (Brown & Levy, 1963). Because of the intramolecular hydrogen bonding, the hydrophobic character of CH_2 in the C-1-f and C-6-f hydroxymethyl groups is increased. On the other hand, the dilution or the heating of sucrose solution leads to a decrease of the sweetness. This could be explained by a rupture of the intramolecular hydrogen bonds. One could think that an increase of the mobility of water by increasing the temperature should improve the Na^+/K^+ transport and hence the sweet taste sensation, but the most important feature seems to be, in this case, as in β-D-fructopyranose, the hydrophobic character of the 'γ' center.

Similarly, the increase in sweetness with concentration could be linked to the hydrophobic folding of the molecule when the concentration is increased (Mathlouthi, 1981).

CONCLUSION

No systematic investigation of the rôle of water in sweetness has been undertaken in this work. We only wanted to compare our results on the solute–solvent interactions in aqueous D-fructose, D-glucose and sucrose solutions with the known properties of their sweet tastes. It appears that the rôle of the water structure is not negligible. One could establish a scale of sweetness of sugars based on their hydrophobic and hydrophilic interactions in solution. In a first approach, this classification could be based on the hydration properties of these molecules and their methylated, chlorinated, etc., derivatives in the crystalline state. Jeffrey (1969) gives a scale of hydration that could be used as a reference. It is seen, in his classification of organic hydrates, that carbohydrates are hydrophilic but alkyl groups, halogens, etc., are very strongly hydrated by hydrophobic clathration (Jeffrey, 1969). An investigation of water structure in aqueous solutions of model molecules by techniques like Laser-Raman spectroscopy could help in advancing the knowledge of the rôle of water in the sweet taste sensation.

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