Food Chemistry **21** (1986) 245–258

Structure/Activity Relationships in Sweetness*

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(Received: 21 February, 1986)

ABSTRACT

Although several classes of chemical compound may elicit a sweet response, the quality of sweetness appears to be dependent on molecular structure and, in particular, the temporal characteristics of the response bear a relationship to chemical class. Most of the recent chemical research on sweetness has centred on stereochemistry of the stimulus molecule but it is likely that the solution properties and thermodynamic behaviour of the molecule also play a part in the sweet response and must be considered as a clue to the mechanism of taste chemoreception. Intensity/time relationships in sweetness may be partly interpretable in terms of the kinetics of hydration of sweet molecules and the disturbance of water structure. This approach leads to an explanation of molecular accession to receptors and the sensory perception of binary mixtures.

INTRODUCTION

It is known that sugar molecules exist as hydrated structures in solution (Tait *et al.*, 1972; Franks *et al.*, 1972) and that their degree of hydration is governed by their intrinsic stereochemistry (Suggett *et al.*, 1976), equatorial hydroxyl groups being more easily hydrated than axial

* Paper presented at the symposium 'The Chemical Basis of Sensory Perception of Foods' held by the Royal Society of Chemistry on 18 October, 1985, at Savile Row, London, Great Britain.

hydroxyl groups. Hydrogen-bonding is responsible for hydration phenomena (Franks *et al.*, 1972) and the residence time of a proton participating in a hydrogen bond with a sugar hydroxyl is probably in the order of 10^{-10} s.

Hydrogen-bonding is also alleged to be the cause of sweetness in sugars and other molecules (Shallenberger & Acree, 1967) and much effort has been directed (Birch, 1976) toward explaining the varying sweetness of the sugars in terms of stereochemistry, which, in turn, governs the ways in which selected hydroxyl groups might hydrogen bond to receptors.

Little attention seems to have been paid to the manner in which *hydrated* sugar or sweetener molecules might interact with receptors and this is surprising, since hydrogen bonding is implicated in both solution phenomena and receptor binding. Presumably, sugar molecules exchange water molecules for receptors and thence cause triggering of the receptor ionophore system; in other words, one form of hydrogen bonding is substituted for another and this process is related to the solution thermodynamics of the sugar molecules.

This paper describes studies of apparent molar volumes and other solution properties of sugar and sweetener molecules in relation to some published sweetness data. It attempts to enlarge our understanding of sweetness chemistry by structural analogies between sweetener types and to seek further clues to the dynamics of taste chemoreception.

MATERIALS AND METHODS

Sugars and sweeteners used in this study were commercial and grade reagents (obtained from BDH Chemicals, Poole, Dorset, Great Britain, the Sigma Chemical Co., Poole, Dorset, Great Britain, and the Hoechst Co.). Water was twice glass-distilled.

Reducing sugar solutions were allowed 30 h in the refrigerator (5°C) after dissolution to reach mutarotational equilibrium.

Apparent molar volumes were determined with an Anton–Parr Precision Density Meter (DMA 60) and Density Measuring Cell (DMA 602) (Stanton Redcroft, London, Great Britain) equipped with an automatic sampler (SP2) and Anadex printer. Temperature control was achieved with a Hetofrig bath (Heto Birkerod, Denmark) coupled to the density measuring cell. The density meter was calibrated with air and

water and the method was as previously described (Birch & Catsoulis, 1985). All measurements were carried out at 20°C (±0·1°C).

Specific rotations were obtained with an Optical Activity Automatic Digital Polarimeter and spin–spin relaxation times (T_2 values) of water solutions were obtained with a Bruker Minispec Pulsed NMR Spectrometer at 20°C.

Surface tensions were determined with a Du Nouy Tensiometer (Cambridge Instrument Co., London, Great Britain) which is a torsion balance method in which a platinum loop is dipped into the liquid and the force (in millinewtons per metre) required to separate the loop from the surface is measured directly on a calibrated scale.

RESULTS AND DISCUSSION

The reason why apparent molar volume is important in taste chemoreception is that it provides information as to how sapid solutes interact with water. This interaction precedes and mediates interaction of the solute with receptors and we must imagine sweetness chemoreception as a process in which hydrated molecular species first accede to the receptor environment, then exchange their hydration water for receptors. The rate and extent of such an exchange is likely to be dependent on the nature of the hydrated species and its intrinsic stereochemistry; hence, different sugars exhibit different intensities and persistences of sweet response. Apparent molar volume (ϕ_V) is a direct measure of the displacement of water molecules, or disturbance of water structure, when one mole of a solute is dissolved in water. ϕ_V is therefore a measure of 'effective size' of a sugar molecule in solution, in relation to a water molecule, and ϕ_V values of sugars may be related to their degrees of hydration (Franks *et al.*, 1972; Tait *et al.*, 1972).

In taste chemoreception, it is important to compare molecular properties at several concentrations. This is the case because the relative sweetness of a molecule varies with concentration and a localised concentration of stimulus molecules, at or near the receptor site, may explain many persistence phenomena (Birch *et al.*, 1980; Munton & Birch, 1985). Apparent molar volume (ϕ_V) measurement, at different concentrations, raises a complication in that surface tension (a measure of molecular cohesion or compression) is likely to vary. If this occurs, the ϕ_V values obtained may not reflect the effective molecular size of

TABLE 1 (a)
Apparent Molar Volumes and Parachors of Monosaccharides

Sugar	*Concentration* (% *w/w*)	*Surface tension* (γ) (*dynes/cm*)	*Apparent molar volume* (ϕ_V) (cm^3/mol)	*Parachor* $[P] = \phi_V \gamma^{1/4}$
D-Xylose	5	64·5	93·05	264
D-Arabinose	3	71·5	91·33	266
L-Arabinose	3	71·4	91·82	267
D-Glucose	3	70·8	110·8	321
D-Galactose	3	71·0	109·0	317
D-Fructose	3	70·9	107·2	311
D-Xylose	10	59·9	95·11	264
D-Arabinose	10	70·7	92·16	267
L-Arabinose	10	70·5	92·30	268
D-Glucose	10	69·8	111·8	323
D-Galactose	12·0	68·2	110·7	318
D-Fructose	10	71·5	110·1	320
D-Xylose	30	52·2	96·09	258
D-Arabinose	30	70·0	92·58	268
L-Arabinose	30	69·5	91·80	265
D-Glucose	30	66·8	112·8	322
D-Galactose	30	60·2	111·7	311
D-Fructose	30	72·6	111·3	325

the sapid solute at the receptor. We have, therefore, calculated parachors ($[P] = \phi_V \gamma^{1/4}$) for all substances tested because the parachor is a measure of ϕ_V if the surface tension were to remain at unity.

Table 1(a) lists the ϕ_V and $[P]$ values of some monosaccharides between 3% and 30% (w/w).

Although the monosaccharides generally show an upward trend of ϕ_V with increasing concentration in accordance with previous observations (Birch & Catsoulis, 1985), the differences between sugars of similar molecular weight are very small. Moreover, despite opposite trends in surface tension values, the solution parachors $[P]$ show no significant differences between sugars of similar molecular weight. D-Fructose differs from the other monosaccharides in Table 1 in that it is the only substance to exhibit an increase in surface tension as the concentration increases. Accordingly, D-fructose also shows an increase in parachor. D-Fructose is an analogue of D-arabinose (Fig. 1) while D-galactose is an analogue of L-arabinose. D-Fructose is known to be

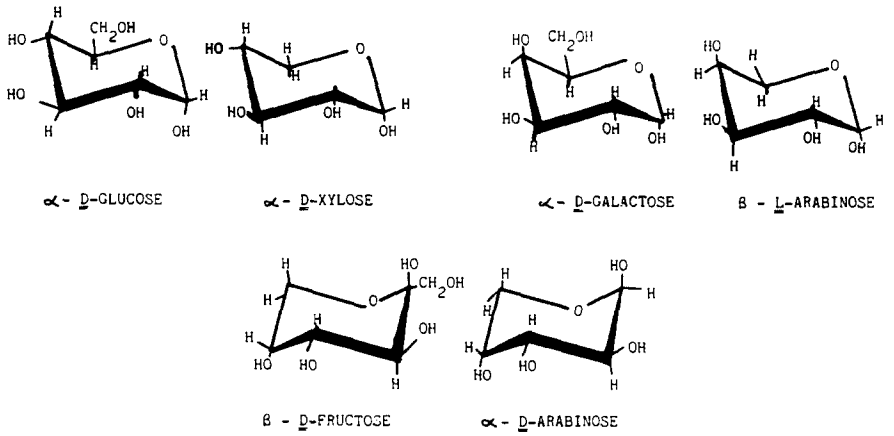

Fig. 1. Structural analogies between pyranoses.

distinctly sweeter than D-galactose, D- or L-arabinose (Birch & Catsoulis, 1985); hence, it appears that the primary alcohol group plays a key rôle in both the sweetness intensity of D-fructose and elevation of surface tension, as concentration increases. This presumably reflects some fundamental difference between fructose and other monosaccharides in its interaction with water, which might, in turn, affect the accession of fructose molecules to the sweet receptor.

Although the differences between the ϕ_V values of sugars of the same molecular weight are small, they are consistent. Thus, D-galactose has a smaller ϕ_V than D-glucose at all concentrations and L-arabinose has a smaller ϕ_V than does D-xylose. Consequently, the stereochemical

TABLE 1 (b)
Analogous ϕ_V Values of Conformationally Analogous Pairs of Sugars

Sugar	*Molecular weight*	*ϕ_V at 10% w/w (cm^3/mol)*	*Molecular weight hexose / Molecular weight pentose*	*ϕ_V hexose / ϕ_V pentose*
D-Xylose	150·1	95·11	} 1·20	} 1·18
D-Glucose	180·2	111·8		
L-Arabinose	150·1	92·30	} 1·20	} 1·20
D-Galactose	180·2	110·7		
D-Arabinose	150·1	92·16	} 1·20	} 1·20
D-Fructose	180·2	110·1		

analogies depicted in Fig. 1 are reflected in their apparent molar volumes (Table 1(b)).

Table 2 lists the ϕ_V values and parachors for sucrose, palatinose and raffinose at 3, 10 and 30% w/w. Sucrose is the only one of these three to elevate the surface tension of water and is also the most sweet (Birch & Catsoulis, 1985). Shifting the linkage between the glucose and fructose moieties of the disaccharide from 1→2 to 1→6 causes an increase (*ca.* 5%) in apparent molar volume (i.e. palatinose has a larger ϕ_V than sucrose) and this is consistent at all three concentrations.

TABLE 2
Apparent Molar Volumes and Parachors of Oligosaccharides

Sugar	*Concentration* (% *w/w*)	*Surface tension* (γ) (*dynes/cm*)	*Apparent molar volume* (ϕ_V) (cm^3/mol)	*Parachor* [*P*] $= \phi_V \gamma^{1/4}$
Sucrose	3	70·7	208·3	604
Palatinose	3	68·8	219·5	632
Raffinose[a]	3	68·8	299·1	862
Sucrose	10	71·8	210·5	613
Palatinose	10	64·0	219·7	622
Raffinose[a]	10	64·3	305·5	865
Sucrose	30	73·8	212·1	622
Palatinose	30	55·9	220·4	603
Raffinose[a]	30	59·5	307·7	855
Sucrose	6·5		210·0	
Galactosucrose	6·6		205·3	

[a] Relates to pentahydrate.

On the other hand, the sucrose parachor is greater than the palatinose parachor at 3% w/w while the opposite is the case at 30% w/w. This is due to the marked lowering of surface tension by palatinose. Table 2 also shows that galactosucrose has a smaller ϕ_V than sucrose. Galactosucrose (i.e. *O*-α-D-galactopyranosyl-(1→2)-β-D-fructofuranoside) is known to be devoid of sweetness (Birch, 1976; Lindley *et al.*, 1976) but the structural reason for this has never been fully explained. The axial configuration of OH-4 must be responsible for the loss of sweetness and this causes the apparent molar volume of galactose to be lower than that of glucose (equatorial configuration at OH-4).

Galactose exists as about 96% of the pyranose form and 4% of the furanose form at 20°C (Shallenberger & Birch, 1975) and it is therefore doubtful that the difference between ϕ_V values of glucose and galactose could be due to the furanose isomers. The intramolecular hydrogen bond between OH-4 and the ring oxygen atom is most likely the cause of the lower ϕ_V value of both galactose and galactosucrose.

Table 3 lists the apparent molar volumes, surface tensions and parachors of glycerol, xylitol and sorbitol. Only xylitol and sorbitol behave like D-fructose and sucrose is elevating both surface tension and

TABLE 3
Apparent Molar Volumes and Parachors of Polyols

Polyol	*Concentration* (% *w/w*)	*Surface tension* (γ) (*dynes/cm*)	*Apparent molar volume* (ϕ_V) (cm^3/mol)	*Parachor* [*P*] $= \phi_V \gamma^{1/4}$
Glycerol	3	66·2	70·55	201
Xylitol	3	71·2	100·6	292
Sorbitol	3	71·2	116·2	338
Glycerol	10	60·0	71·06	198
Xylitol	10	71·8	101·8	296
Sorbitol	10	71·7	118·8	346
Glycerol	32	54·0	71·14	193
Xylitol	30	74·5	102·8	302
Sorbitol	30	73·0	120·0	351

parachor as concentration is increased. It has previously been noted that both of these polyols have higher ϕ_V values than their parent sugars (Birch & Catsoulis, 1985) and this is a result of ring rupture and loss of the equatorial hydroxyl groups (particularly amenable to hydration) (Franks *et al.*, 1972).

Table 4 lists the apparent molar volumes, surface tensions and parachors of the two intense sweeteners, acesulpham-K and saccharin-Na. Notable in these results is the drop in ϕ_V of saccharin-Na as concentration is increased which, together with the drop in surface tension, causes a drop in parachor. On the other hand, acesulpham-K behaves like the sugars and polyols with a rising ϕ_V value (from 3-20% w/w) and a steady parachor.

Another way in which solute–water interactions may be observed is

TABLE 4
Apparent Molar Volumes and Parachors of Intense Sweeteners

Intense sweetener	*Concentration* (% *w/w*)	*Surface tension* (γ) (*dynes/cm*)	*Apparent molar volume* (ϕ_V) (*cm*^{3}*/mol*)	*Parachor* [*P*] $= \phi_V \gamma^{1/4}$
Acesulpham-K	3	70·1	106·0	307
Saccharin-Na	2·55	69·4	106·7	308
Acesulpham-K	10	67·0	107·6	308
Saccharin-Na	8·51	66·4	105·1	300
Acesulpham-K	20	63·5	109·4	309
Saccharin-Na	17·02	61·2	104·5	292

by pulsed NMR relaxation (T_2 values). This reflects loss of proton energy by spin–spin interaction and is evidently dependent on the disturbance of water structure by solute. Table 5 lists the T_2 values of glycerol, D-fructose, sucrose and palatinose which are seen to be inversely related to their ϕ_V values.

The changes in apparent molar volume and surface tension listed for all the substances in Tables 1–4 reflect changes in hydration characteristics associated with disturbance of water structure and cohesion between molecules. However, the *relationship* between apparent molar volume and surface tension for a particular sugar may be an issue of stereostructure of some significance for taste chemoreception. In Fig. 2 we have therefore illustrated the three-dimensional relationship between concentration, ϕ_V and surface tension (γ) for sucrose, fructose, galactose and glucose. The former two (sweeter) sugars show untwisted,

TABLE 5
Spin–Spin Relaxation Times (T_2 Values) of Glycerol, Fructose, Sucrose and Palatinose in 10% w/w Water Solution

Solute	ϕ_V	T_2 (*ms*)
Glycerol	71·06	1 619
D-Fructose	110·1	1 513
Sucrose	210·5	1 009
Palatinose	219·7	902

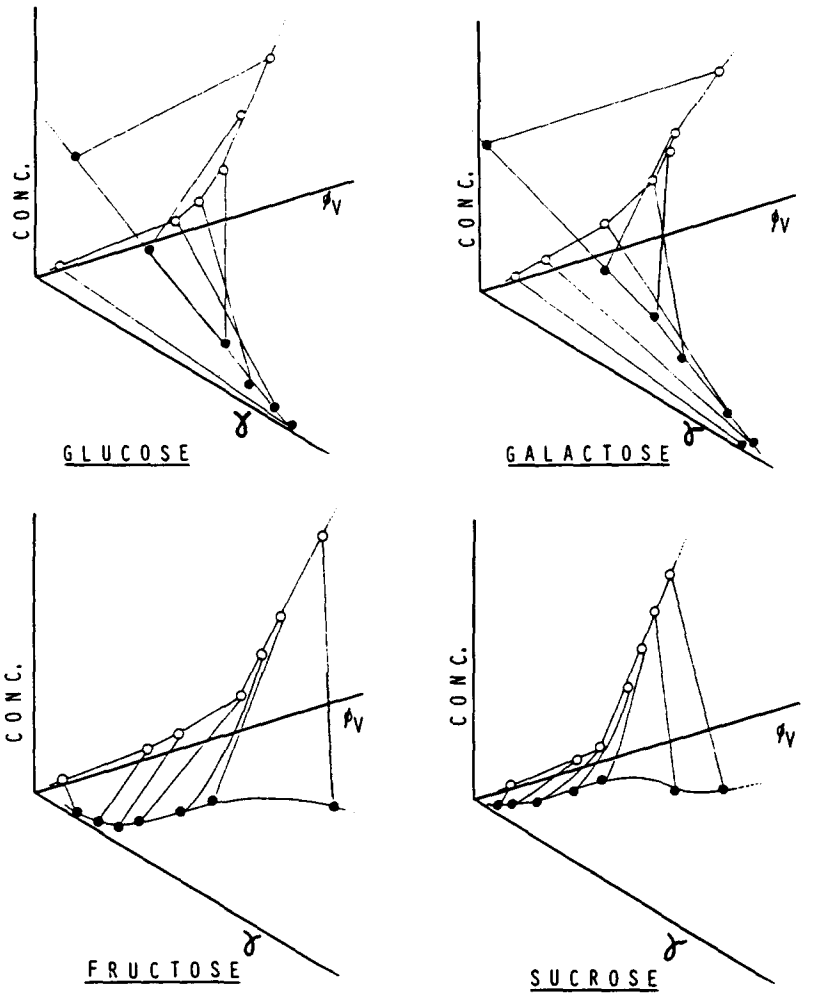

Fig. 2. Three-dimensionally connected 2-D plots of concentration against apparent molar volume (ϕ_V) (o) and surface tension (γ) (•) for glucose, galactose, fructose and sucrose.

somewhat similar, surfaces, whereas the latter two show markedly twisted surfaces. Clearly, the surfaces give much more information about solute–water interaction than do the simple two-dimensional graphs and this depiction of the data approaches the multidimensional procedures of Schiffmann *et al.* (1981) for sensory studies. These three-dimensional Figures emphasize the large differences in solution behaviour of different

molecules over similar concentration ranges. They illustrate solution changes which might affect accession rates to receptors.

The best way to compare the sweetness responses to different sugars is by the intensity–time technique. This method is especially valuable for assessing the persistence of response, which is a practical problem with many of the novel sweeteners. A device called a 'SMURF' (Birch & Munton, 1981) has been used for this purpose and has been developed by Pickering (1983; 1986). The device has been used to analyse the sweetness of a number of simple molecules and their binary mixtures (Munton & Birch, 1985). However, from the published results, although there are no simple relationships between ϕ_V and sweetness (intensity or persistence), there are clear relationships between chemical structure and persistence. Sucrose and D-fructose, for example, cause a significantly greater sweetness response than those substances that are structurally unrelated to D-fructose. Sucrose is sweeter in intensity than D-fructose on a molar basis but the opposite is probably true of persistence (Table 6). On a weight basis D-fructose is sweeter than sucrose and much more persistent. This is, in fact, a more appropriate basis on which to compare them at higher concentrations because the molarity of water should be the same for the sugars under test.

Munton & Birch's (1985) results were based on comparisons at threshold steps of concentration so they are of limited applicability to our current studies. However, Table 7 shows the superior sweetness intensity and persistence of sucrose and D-fructose in comparison with other molecules at slightly higher concentrations. Only xylitol approaches the sweetness intensity of sucrose but, like sorbitol, glucose and galactose, it falls far short in persistence.

When three-dimensional graphs of concentration, persistence and

TABLE 6
Intensity and Persistence of Sucrose and D-Fructose.
(Means of Thirty Results ± SEM)

	% *w/v*	*Intensity ('SMURF' units)*	*Persistence (s)*
Sucrose	2·3	30 (±1·97)	7·6 (±0·96)
	9·2	78 (±1·4)	15·5 (±1·8)
D-Fructose	2·0	33 (±2·3)	14·2 (±0·8)
	8·0	85 (±1·4)	30·9 (±1·3)

From Munton & Birch (1985).

TABLE 7
Intensity and Persistence of Sweet Molecules In Similar Range of Concentrations
(Means of Thirty Results ± SEM)

	% *w/v*	*Intensity ('SMURF' units)*	*Persistence (s)*
Sucrose	6·9	68 (±1·6)	13·1 (±1·3)
D-Fructose	6·0	75 (±1·49)	27·9 (±1·2)
Xylitol	7·65	69 (±1·4)	7·3 (±0·58)
Sorbitol	7·3	42 (±2·3)	8·2 (±0·78)
D-Glucose	7·5	37 (±2·1)	7·5 (±0·78)
D-Galactose	8·5	53 (±2·6)	10·0 (±1·1)

From Munton & Birch (1985).

intensity are constructed (Fig. 3), similarities are noted between the same pairs of structures as in Fig. 2. Glucose and galactose exhibit less flat and more skewed surfaces than the sweeter, and more persistent, pair, sucrose and fructose. The main point about these Figures is that they underline the fixed relationship between persistence and intensity for a fixed concentration of a particular sugar. Thus, for mixtures of sugars, the perceived intensity and persistence of sweetness response must be determined by segments of the surfaces depicted. Munton & Birch (1985) have used this approach to calculate the 'effective concentrations' of each substance in a binary mixture and the results have indicated that one substance in each mixture is absolutely dominant. This may mean that only one substance in any pair is able to accede to the receptor which could, for example, occur due to differences in hydration and hydrogen bond kinetics at the receptor. Munton and Birch observed that the dominant sugar in binary mixtures was always the least sweet (Table 8), even in mixtures where the sweeter sugar is in considerable excess. It is now clear (Tables 1 to 4) that the dominant sugar is the one with the smaller apparent molar volume. It is not, however, the smaller size of the dominant sugar which guarantees better receptor accession. If that were the case, greater differences would be expected between, for example, the sweetness of D-glucose and the sweetness of D-galactose. Rather, the low apparent molar volume of the dominant member of a pair (Table 8) indicates good compatibility with water structure and it is this which allows priority of receptor occupation.

The parachors which are listed in Tables 1 to 4 do not, in themselves,

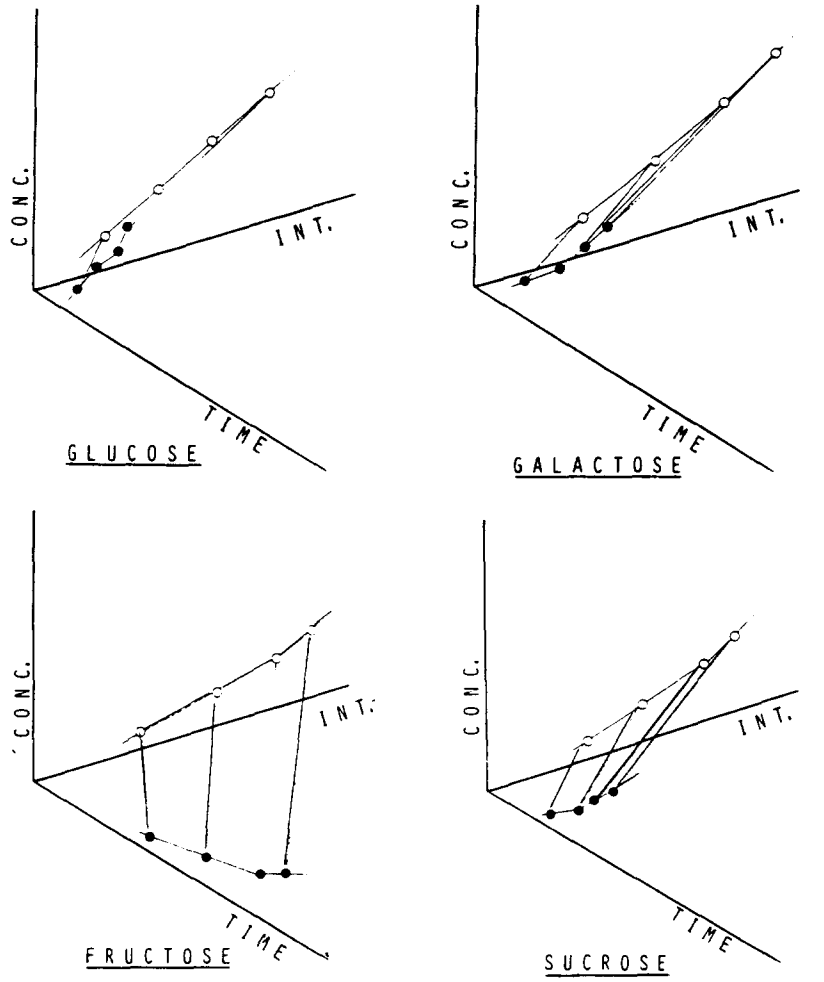

Fig. 3. Three-dimensionally connected 2-D plots of concentration against intensity (Int.) (o) and time (•) for glucose, galactose, fructose and sucrose.

show any correlation with sweetness, either intensity or persistence. Indeed, the parachors are very steady and generally show less or no more change with concentration than do the ϕ_V values. It is possibly worthy of note, however, that the increase in ϕ_V which occurs when sugars are hydrogenated (Tables 1 and 3) is exceeded by the increase in parachor (*cf.* glucose, sorbitol, xylose and xylitol), which may be a truer indication of the effective 'size' of the sweetener molecule at the receptor in relation to water. The parachor may therefore be useful for calculations

TABLE 8
Dominant Sugar (asterisked) in Binary Mixtures

Sucrose:	Sorbitol*
Sucrose:	Xylose*
Sucrose:	Galactose*
Glucose:	Galactose*

From Munton & Birch (1985).

of the displacement of water molecules around the receptor; in other words, calculations of volumes and flow rates of stimulus in relation to taste may need the inclusion of this variable.

Why do the differences in solution properties of the sweeteners not in themselves account for their marked taste differences? One answer to this would appear to be that the different solution properties of the sweeteners will probably affect the kinetics of exchange processes at the receptor but these are so fast that they make no difference to a normal pattern of taste response. Differences emerge only in mixtures when exchange rates may favour one component at the expense of another and thus allow preferential receptor occupation. This possibility may be significant in many food systems.

CONCLUSIONS

The solution parameters of simple sweet molecules show fine distinctions which are, in many cases, attributable to their structural differences. The major differences of intensity and time of the sweetness response between molecules do not appear to be simply related to solution properties. It seems more likely that intensity–time–concentration relationships are due to corresponding solution property–concentration relationships and this approach might lead to an understanding of the kinetics of taste chemoreception.

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