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Structural Functions of Taste in 5-Membered Ring Structures

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ABSTRACT

The taste properties of seventeen 5-membered cyclic molecules are examined in relation to their substituents, fused ring moieties and potential fused ring moieties due to intramolecular hydrogen bonding. Apparent molar volume measurements allow the effects of the different ring substituents to be quantified. The molecules possess taste (or olfactory) properties which can be explained by their compatibility with water structure.

INTRODUCTION

The taste properties of 5-membered ring structures have received less attention than 6-membered ring structures, probably because they are generally less common (and less stable) than 6-membered rings. 6-Membered ring structures have been investigated in detail for sweetness within the sugar series (Birch, 1976; Beets, 1978; Birch & Shamil, 1986), dihydrochalcones (Horowitz & Gentili, 1971), cyclamates (Spillane, 1983), peptides (van der Heijden *et al.*, 1985) and aspartame (Steginck & Filer, 1984). Likewise, 6-membered ring structures have been investigated for bitterness (Belitz *et al.*, 1983) in relation to receptor shape and by structure-activity relationships (Beets, 1978). Flavonoid molecules and their

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derivatives are well-known to contribute both bitterness and astringency (Horowitz & Gentili, 1971; Harborne, 1984).

By contrast, 5-membered ring structures have received only limited interest in the taste field. The exceptions are the sweetness and bitterness of the fructofuranose moiety of sucrose and certain 5-membered cyclic amino acids. Very recently the taste of some furan analogues has also been studied in flesh flies (Ohrui *et al.*, 1985; Shimada *et al.*, 1985). However, vast numbers of 5-membered cyclic structures contribute to olfactory response (Birch & Lindley, 1986). If there is only one chirally and spatially specific sweet receptor (Shallenberger & Acree, 1967; Shallenberger *et al.*, 1969), it is possible that this is commensurate only with the pyranose ring or closely related 6-membered structures. For example, the sweetest simple sugar known is β-D-fructopyranose which, upon dissolution in water, mutarotates and slowly loses about 30% of its sweetness. The mutarotation process is accompanied by the formation of about 30% fructopyranose, so this observation has been regarded as evidence that the fructofuranose form possesses no sweetness. On the other hand, Birch & Lee (1971) have reported the sweetness of a number of 1-deoxy furanose structures and this is evidence that the 5-membered rings are sweet, though the anomeric centre plays no part in the sweet response (Birch *et al.*, 1986).

The taste quality of a molecule depends on its ability to accede to a particular receptor prior to binding with it via an appropriate sapophore. It has recently been proposed (Birch & Catsoulis, 1985; Birch & Shamil, 1986; Shamil *et al.*, 1987) that the effective molecular size (i.e. apparent specific volume) in aqueous solution might play a fundamental role in accession efficiency of sapid molecules, and small ions or molecules might accede to deeper layers of the taste epithelium than larger ones. Using this approach, we now examine seventeen selected 5-membered cyclic structures in an attempt to see whether their taste properties (if any) are predictable from their structures and apparent specific volumes.

MATERIALS AND METHODS

Substances investigated in this work were reagent grade chemicals obtained from BDH Chemicals, Poole, Dorset, The Sigma Chemical Co., Poole, Dorset, Fluka AG, CH-9470 Buchs, Switzerland, or were synthetic products made in these laboratories. D-glucono-1,5-lactone and D-galactono-1,4-lactone were kind gifts from Tate and Lyle Ltd. Where possible, physical constants (e.g. melting point and optical rotation) were checked against literature reports.

The synthetic procedures for the following compounds are listed below: 2,5-anhydro-D-mannitol, 1,4:3,6-dianhydro-D-mannitol, 2,5-anhydro-D-glucitol, 1,5-anhydro-D-mannitol, 2,5-anhydro-1,6-dichloro-1,6-dideoxy-D-mannitol, 2,5-anhydro-1-chloro-1-deoxy-D-mannitol, and 2,5-anhydro-1,6-dideoxy-1,6-difluoro-D-mannitol.

2,5-Anhydro-D-mannitol

2,5-anhydro-D-mannitol was prepared in two steps from 2-amino-2-deoxy-D-glucose hydrochloride (glucosamine HCl). Glucosamine HCl was converted to 2,5-anhydro-D-mannose according to the procedure of Piper *et al.* (1983). The unstable aldehyde intermediate was reduced using sodium borohydride according to the method of Horton & Philips (1976) to afford syrupy 2,5-anhydro-D-mannitol. The syrup was purified on a dry packed silica gel flash column using 5/1/0·1 ethyl acetate–methanol–water. All 2,5-anhydro-D-mannitol was recrystallised several times from a minimum volume of absolute ethanol at reflux temperature prior to use. Analytical data were in accord with that of Horton & Philips (1976).

Dehydration of D-mannitol: preparation of 1,4:3,6-dianhydro-D-mannitol, 2,5-anhydro-D-glucitol and 1,5-anhydro-D-mannitol

D-mannitol was dehydrated according to the procedure of Fletcher (1963). The crude, syrupy product mixture was adsorbed onto silica gel using methanol, then purified on a dry packed silica gel flash column using 3/1/0·1 dichloromethane–ethanol–water. Early fractions contained 1,4:3,6-dianhydro-D-mannitol (isomannide), intermediate fractions contained 2,5-anhydro-D-glucitol and late fractions contained 1,5-anhydro-D-mannitol.

Semi-purified isomannide was re-chromatographed on a silica gel flash column using 10/1 dichloromethane–methanol and then recrystallised from a minimum volume of either ethyl acetate or methyl *tert*-butyl ether at reflux temperature. The melting range was in accord with Goodwin *et al.* (1980). Mass spectral analysis also supports the assigned structure. Semi-purified 2,5-anhydro-D-glucitol was re-chromatographed (silica gel/flash column) using 5/1/0·1 ethyl acetate–methanol–water. Although the compound is reported to be crystalline (Koerner *et al.*, 1977), it has remained as a syrup in our hands. The structure was confirmed by conversion into the crystalline 1,6-dibenzoate derivative which exhibited analytical data in accord with Koerner *et al.* (1977).

1,5-anhydro-D-mannitol-containing fractions were pooled, concentrated and seeded with authentic material. Analytical material used for these tests were obtained by repeated recrystallization from a minimum volume of

absolute ethanol at reflux temperature. The melting point was in accord with Fletcher (1963). The chromatographic mobility on TLC was also in accord with authentic 1,5-anhydro-D-mannitol from Sigma Chemical Company.

Chlorination of 2,5-anhydro-D-mannitol: 2,5-anhydro-1,6-dichloro-1,6-dideoxy-D-mannitol and 2,5-anhydro-1-chloro-1-deoxy-D-mannitol

2,5-anhydro-D-mannitol was treated with triphenyl phosphine (4 eq.) and carbon tetrachloride (2 eq.) in dry pyridine initially at 0°C then overnight at room temperature (Anisuzzaman & Whistler, 1978). After approximately 18 h, the crude reaction mixture was concentrated *in vacuo*, co-evaporated three or more times with toluene then purified on a dry packed silica gel flash column using 25/1 methylene chloride–methanol. Continued elution with higher concentrations of methanol in dichloromethane afforded variable quantities of the more-polar mono-chlorinated 2,5-anhydro-D-mannitol analogue. Treatment of 2,5-anhydro-D-mannitol with half the requisite quantity of carbon tetrachloride and triphenyl phosphine led to product mixtures containing approximately 30% of the mono-chlorinated species.

The dichloro compound was purified by recrystallization from a minimum volume of dichloromethane at reflux temperature. The observed melting point was in accord with the literature value. Mass spectral evidence was also in accord with the assigned structure.

The mono-chlorinated derivative of 2,5-anhydro-D-mannitol was purified by subsequent chromatographic separations in 20/1 methyl *tert*-butyl ether–methanol and 2/1 hexanes–acetone. So far, the only analytical data on this compound are provided by mass spectrometry.

2,5-Anhydro-1,6-dideoxy-1,6-difluoro-D-mannitol

2,5-anhydro-D-mannitol (1·02 g) was dissolved in pyridine (25 ml). Trityl chloride (3·63 g, 2·1 eq.) was added then stirred under argon overnight at room temperature. The solution was then cooled at 0°C and BzCl (1·58 ml, 2·2 eq.) and a trace of DMAP was added. After 4 h at room temperature, the reaction was quenched by addition of methanol then concentrated *in vacuo*. Excess pyridine was removed by co-evaporation with toluene. The solid residue was partitioned between ethyl acetate and water. The organic phase was then washed with 1N HCl, saturated aqueous sodium bicarbonate and brine then dried over Na_2SO_4 and concentrated.

The crude solid was dissolved in a mixture of ether (15 ml) and formic acid (15 ml). After 25 min, the solution was cooled at 0°C, neutralized by addition of water and solid $NaHCO_3$, and extracted into ether. The organic phase was washed with brine then dried using Na_2SO_4, concentrated and finally purified on a dry packed silica gel column (3/2 hexanes–acetone) to afford

pure 2,5-anhydro-3,4-dibenzoyl-D-mannitol (35·7% yield from 2,5-anhydro-D-mannitol).

2,5-anhydro-3,4-dibenzoyl-D-mannitol was fluorinated as follows: 768·6 mg of this dihydroxy compound was dissolved in dry dichloromethane (8 ml), cooled to 0°C under argon, treated with diethylaminosulfur trifluoride (0·6 ml, ~2·2 eq.) then heated at reflux temperature under argon overnight. The reaction was then cooled to 0°C and quenched with saturated aqueous sodium bicarbonate. The organic layer was separated, washed with brine, dried using Na_2SO_4, concentrated, then purified on a dry silica gel column using 5/1 hexanes–acetone (the yield was 61·1%).

Deprotection was carried out using 1% NaOH in methanol. The reaction was complete within 20 min. 1N HCl was added until the solution was neutralized (pH 6–8). The solution was concentrated *in vacuo*, taken up in ethanol twice and concentrated then taken up in ethyl acetate, filtered to remove inorganic salts, concentrated, then purified on a dry silica gel column using 1/1 hexanes–acetone (the yield was 94·8%). Analytical material was prepared by recrystallization from a minimum volume of diethyl ether at reflux temperature (m.pt. 80–80·5°C).

Water used for solution studies as well as taste work was 'Hyper Solv' water for HPLC from BDH Chemicals, Poole, Dorset. Reducing sugars were allowed 30 h in the refrigerator (5°C) after dissolution to reach mutarotational equilibrium. Measurements on D-glucono-1,5-lactone were made soon after dissolution due to its instability in water.

Apparent molar volumes ($^{\phi}V$) were determined in weight per weight solutions with an Anton-Parr Precision Density Meter (DMA 60) and Density Measuring Cell (DMA 602) (Stanton Redcroft, London) 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 by Birch & Catsoulis (1985). All measurements were carried out at 20°C (±0·1°C). Uncertainty in the density determinations was $\pm 3{\cdot}0 \times 10^{-6}$ g/cm^3.

Taste panel procedure

Ten previously-trained panellists were used for sensory evaluation. The concentration of each sample assessed was well above its recognition threshold. Panellists were asked to choose only one category from sweet, bitter, sour, combinations of any two of these or other tastes. No panellist ever chose the latter category and salt was adjudged absent in a preliminary trial. There was more than 60% agreement, between the panellists, on the taste of each sample.

TABLE 1
Apparent Specific Volumes and Tastes of 5- and 6-Membered Rings

Structure[a]	*Compound*	*m.wt.*	*Reps.*[b]	$^{\phi}V$[c]	$^{\phi}V/m.wt.$[d]	*Taste*
(a)	Tetrahydrofuran	72·10	3(3,5,10%)	75·61 ± 0·28	1·048 ± 0·004	None—volatile
(b)	Furfuryl alcohol	98·10	3 (3,5,10%)	83·89 ± 0·04	0·855 2 ± 0·004 8	None—volatile
(c)	Furfural	96·09	3(1,3,5%)	79·01 ± 0·05	0·822 2 ± 0·000 5	None—volatile
(d)	Furan-2-carboxylic acid	112·09	2(1,2%)	80·38 ± 0·61	0·717 1 ± 0·005 4	Unknown
(e)	Sautalon	128·12	1(3%)	119·0	0·928 8	Taste: faintly sweet with a bitter after-taste. Odour: spicy, curry-like
(f)	Linalool oxide	128·17	1(1%)	124·6	0·972 1	Tasteless—tactile. Odour: curry-like
(g)	L-Proline	115·13	3(3, 5,5,10%)	83·62 ± 0·05	0·726 3 ± 0·000 4	Sweet–bitter
(h)	2,5-Anhydro-D-mannitol	164·16	2(1·6,10%)	115·3 ± 0·05	0·702 1 ± 0·000 3	Sweet–bitter
(i)	2,5-Anhydro-1,6-dichloro-1,6-dideoxy-D-mannitol	201·04	1(3%)	134·2	0·667 5	Bitter
(j)	2,5-Anhydro-1-chloro-1-deoxy-D-mannitol	182·60	1(3%)	137·5	0·753 0	Bitter
(k)	2,5-Anhydro-1,6-dideoxy-1,6-difluoro-D-mannitol	168·14	1(1%)	116·3	0·691 7	Bitter

(l)	1,5-Anhydro-D-mannitol	164·16	1 (3%)	110·1	0·670 7	Sweet
(m)	2,5-Anhydro-D-glucitol	164·16	1 (3%)	117·1	0·713 3	Faintly sweet
(n)	1,4:3,6-Dianhydro-D-mannitol	143·14	1 (3%)	97·41	0·680 5	Sweet–bitter
(o)	L-Ascorbic acid	176·14	3 (3,5,10%)	106·6 ± 0·08	0·605 2 ± 0·000 5	Sour
(p)	D-Mannoheptulose	210·18	2 (3,5%)	127·6 ± 0·35	0·606 9 ± 0·001 7	Sweet
(q)	D-Galactono-1,4-lactone	178·14	3 (3,5,10%)	112·5 ± 0·37	0·631 5 ± 0·002 1	Sweet–bitter
(r)	D-Glucono-1,4-lactone	178·14	3 (3,5,10%)	114·1 ± 0·34	0·640 3 ± 0·001 9	Sweet–bitter
(s)	D-Glucono-1,5-lactone	178·14	3 (3,5,10%)	107·9 ± 0·17	0·605 5 ± 0·000 9	Sweet–sour
(t)	D-Glucuronic acid	194·14	1 (3%)	111·2	0·572 8	Sour
(u)	D-Glucurono-6,3-lactone	176·13	3 (3,5,10%)	103·0 ± 0·25	0·585 0 ± 0·001 4	Sweet–bitter
(v)	4,6-O-Propylidene-D-glucose	220·22	3 (2,4,8%)	155·9 ± 0·74	0·708 1 ± 0·003 4	Bitter
(w)	4,6-O-Ethylidene-D-glucose	206·19	3 (2,4,8%)	145·1 ± 0·43	0·703 7 ± 0·002 1	Bitter
(x)	4,6-O-Ethylidene-D-galactose	206·19	3 (4,6,10%)	138·7 ± 0·68	0·672 8 ± 0·003 3	Sweet–bitter
(y)	Creatinine	113·12	3 (3,5,8%)	83·95 ± 0·25	0·742 1 ± 0·002 3	Bitter

[a] Shown in Fig. 1.
[b] Reps. = Number of concentrations at which measurements replicated.
[c] ϕV = Apparent molar volume, measured in cm^3/mol.
[d] ϕV/m.wt. = Apparent specific volume, measured in cm^3/g.

RESULTS AND DISCUSSION

Figure 1 depicts the structures of the simple cyclic molecules under investigation and Table 1 lists their apparent molar and apparent specific volumes along with their taste properties where known. Apparent specific volumes range from 1·048 cm^3/g for tetrahydrofuran (very hydrophobic) down to 0·5728 cm^3/g for D-glucuronic acid (very hydrophilic) and the molecules vary in taste (if any) from 'none' to bitter to sweet to sour. In those cases where concentration effects have been investigated, very little change in apparent specific volume is noticeable. This contrasts sharply with six-membered sugar structures (Birch & Catsoulis, 1985) when increase of concentration leads to substantial elevation of apparent specific volume ($^{\phi}V$/m.wt.).

Tetrahydrofuran itself has such a high apparent specific volume that it is beyond the range of human taste perception (Shamil *et al.*, 1987); in other words, above about 0·93 cm^3/g. The apparent molar volume ($^{\phi}V$) of tetrahydrofuran is 75·87 cm^3/mol (at 3% conc.) whereas the corresponding value for tetrahydropyran is 91·00 cm^3/mol (Shamil, 1987). In other words the 5-membered ring skeleton is apparently smaller than the 6-membered ring skeleton and both are tasteless. However, substitution of polar functions around any ring skeleton depresses the apparent specific volume, the most hydrophilic structures probably having the lowest apparent specific volumes. Amino acids are more hydrophobic than sugars and other furan-substituted products and tend to have higher apparent specific volumes. L-proline, for example, has an apparent specific volume of 0·73 cm^3/g, which places it in the sweet–bitter region.

However, the apparent specific volume of 2,5-anhydro-D-mannitol (0·70 cm^3/g) is remarkably high for a simple hydrophilic furan analogue, and suggests some degree of intramolecular hydrogen-bonding to create a pseudo fused cyclic structure. In 2,5-anhydro-D-mannitol, there is likely to be long range intramolecular hydrogen-bonding (Speakman, 1974) between C_6OH—C_3OH and C_1OH—C_4OH. Evidence of this is provided by the much lower apparent specific volume of 2,5-anhydro-1,6-dichloro-1,6-dideoxy-D-mannitol, indicating lack of intramolecular hydrogen-bonding and an increase in the hydrogen-bonding with water. However, 2,5-anhydro-1-chloro-1-deoxy-D-mannitol has a much higher apparent specific volume than 2,5-anhydro-D-mannitol. This may be accounted for by the absence of dipole symmetry in the molecule, thus causing a considerable disturbance to water structure.

The taste of the mono-chlorinated analogue is bitter as predicted by its apparent specific volume (Shamil *et al.*, 1987). However, the taste of the dichlorinated analogue is also bitter even though its apparent specific

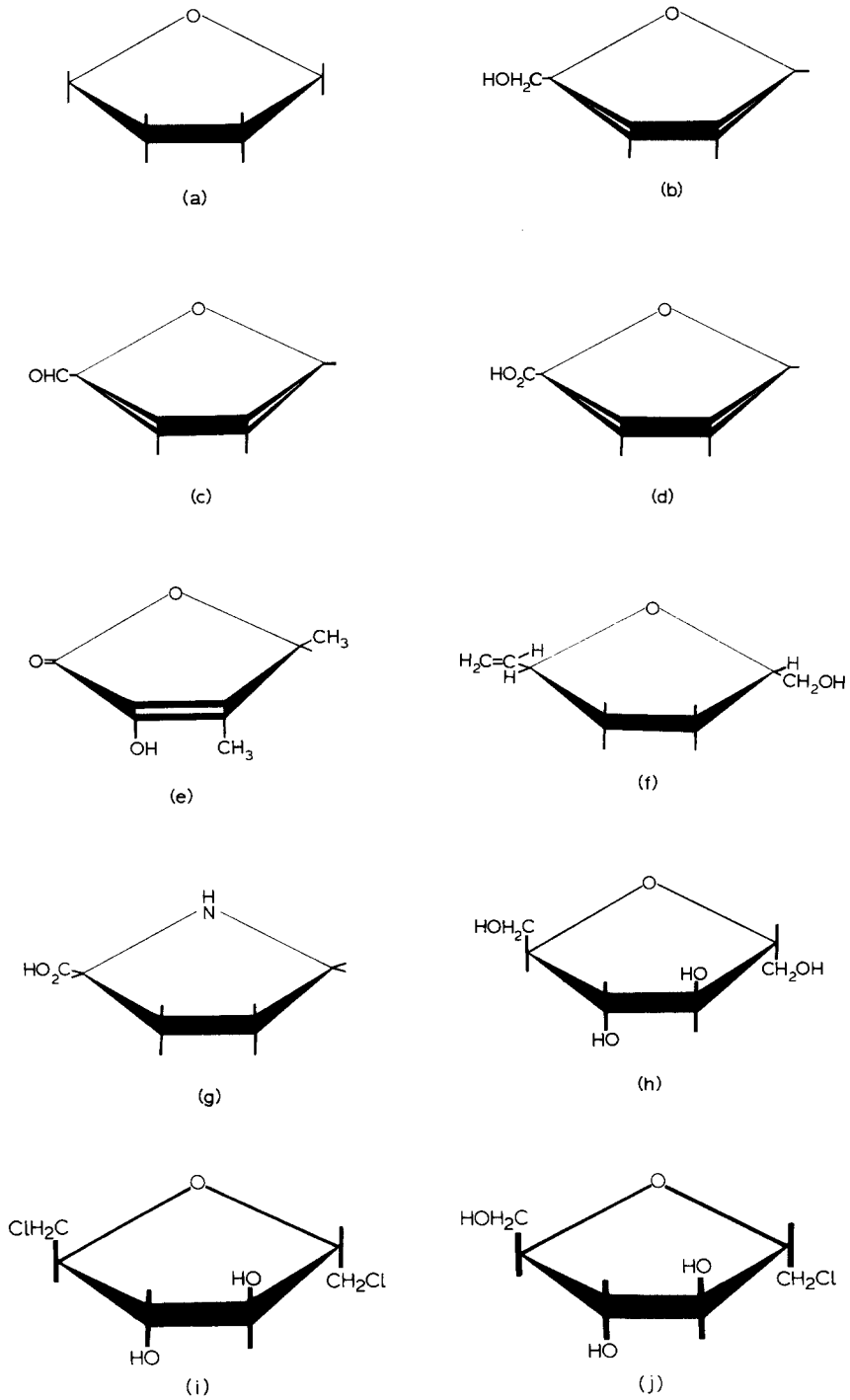
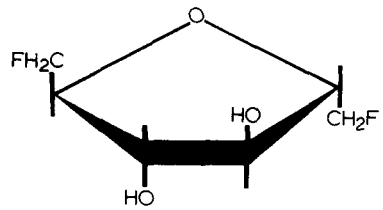


Fig. 1. Structures of the simple cyclic molecules listed in Table 1.



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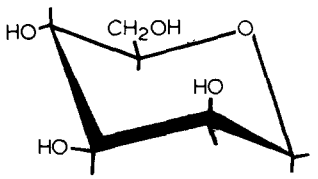
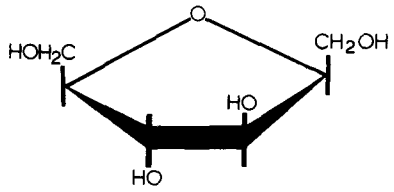


(l)



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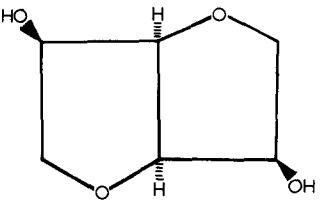

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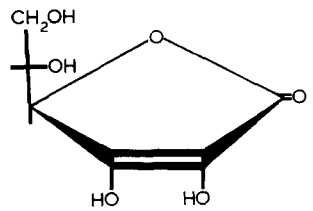

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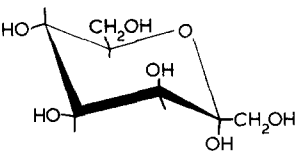

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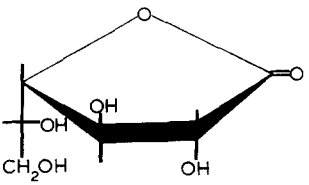

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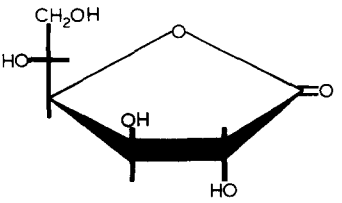
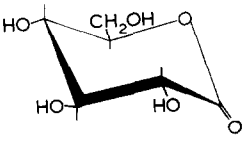


(r)



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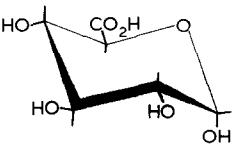

(t)

Fig. 1.—*contd.*

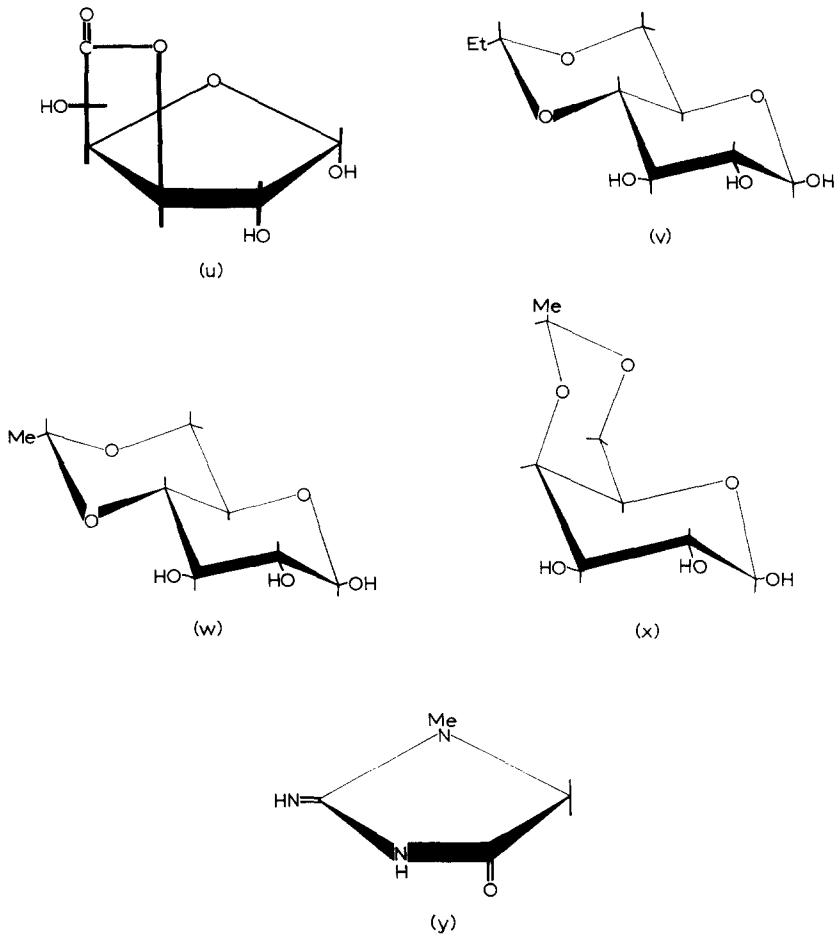

Fig. 1.—*contd.*

volume predicts sweet taste. The bitter taste may be a result of the high lipophilicity of the dichlorinated molecules creating a strong affinity for the bitter receptors. The latter being on the outermost region of the taste epithelium, therefore 'trap' the molecules and prevent them from acceding to the deeper sweet region.

The apparent specific volume of 2,5-anhydro-1,6-dideoxy-1,6-difluoro-D-mannitol is lower than that of 2,5-anhydro-D-mannitol but is higher than the dichlorinated analogue (Table 1). This may suggest some degree of intramolecular hydrogen-bonding in the molecule, resulting from the participation of the highly electronegative fluorine atoms.

Like 2,5-anhydro-D-mannitol, 2,5-anhydro-D-glucitol also has a very high apparent specific volume (0·71 cm^3/g) which indicates the formation of

a pseudo fused cyclic structure possibly due to intramolecular hydrogen-bonding between the two primary alcohol groups. For comparison, Table 1 includes some data on 1,4:3,6-dianhydro-D-mannitol and ethylidene compounds, which are true fused bicyclic structures. These have much higher apparent specific volumes than unicyclic structures of similar molecular weight (i.e. 4,6-O-ethylidene-D-glucose has a higher apparent specific volume than D-mannoheptulose), clearly illustrating the incompatibility of such fused rings with water structure.

The lactones are also of particular interest in Table 1. The aldono lactones (i.e. glucono and galactono) are simple structural analogues of the pyranoses and furanoses with >C=O replacing >CHOH of the anomeric centre. However, the urono-lactone, D-glucurono-6,3-lactone, is a true fused bicyclic structure, and its apparent specific volume is higher than that of the free acid (i.e. D-glucuronic acid). This again illustrates the effect of the fused cyclic substituent elevating the apparent specific volume.

$^{\phi}V$ values vary with hydrophilicity of the solute molecule but they really represent the disturbance (by the solute) of water structure. The effect of a substituent in a 5- or 6-membered ring skeleton depends upon three factors:

(1) the nature of the substituent;
(2) its interactions with the ring and/or other ring substituents;
(3) the interaction of the product with water structure.

The effect therefore depends on the nature of the environment which the substituent enters and Table 2 lists some effects of substituents on $^{\phi}V$ values in both polar and non-polar environments (Shamil, 1987). The CH_2OH function, for example, has a greater effect on $^{\phi}V$ in a polar environment whereas $—CH_3$ has a greater effect in a non-polar environment. The $^{\phi}V$ value of $—CH_3$ (22·57 cm^3/mol) is substantially greater than $—CH_2OH$ (8·04 cm^3/mol) in a non-polar environment, despite its having a lower molar mass.

Molecular weight may bear no relation to $^{\phi}V$ values because the critical factor is the interaction with, and disturbance of, water structure. Table 3 lists some comparisons of $^{\phi}V$ values for substances of similar molecular weight.

A large increase in $^{\phi}V$ value is observed in a molecule if it is substituted to create a fused bicyclic structure (Table 4(b)). This type of substitution, in particular, might prevent accession of the molecule to deeper layers of the taste epithelium (Shamil *et al.*, 1987) and therefore might affect receptor recruitment. The alkylidene compounds all have apparent specific volumes in the region 0·67–0·71 cm^3/g and comprise two fused 6-membered rings. D-glucurono-6,3-lactone, however, comprises two fused 5-membered rings and its apparent specific volume is only 0·5850 cm^3/g. Its taste is sweet in

TABLE 2

Quantitative Effects of Ring Substituents Obtained from Apparent Molar Volumes ($^{\phi}V$) of 5- and 6-Membered Rings in Polar and Non-Polar Environments[a]

Substituent	*Molar mass of substituent (m.m.)*	*Polar environment*		*Non-polar environment*	
		$^{\phi}m.V^{b}$ (cm^3/mol)	$^{\phi}m.V/m.$ (cm^3/g)	$^{\phi}V$ (cm^3/mol)	$^{\phi}m.V/m.$ (cm^3/g)
Carbonyl 'O'(C=O)	16·00	(−)2·50	(−)0·156 3	—	—
OH	17·01	0·50	0·029 4	—	—
CHO	29·02	—	—	3·14	0·108 2
CO_2H	45·02	17·40	0·386 5	4·51	0·100 2
CH_2OH					
H—C—OH	61·06	32·23	0·527 8	—	—
CH_2OH	31·03	17·00	0·547 9	8·04	0·259 1
CH_3	15·03	14·46	0·962 1	22·57	1·502

[a] Effects calculated from $^{\phi}V$ at 3% (w/w) concentrations.

[b] See Table 1 for definitions of these symbols.

Apparent molar volume of 5-membered ring skeleton = 75·87 cm^3/mol.

Apparent molar volume of 6-membered ring skeleton = 91·00 cm^3/mol.

TABLE 3

Comparison of Size of 5- and 6-Membered Rings of Similar Molecular Weight[a]

5-membered rings			*6-membered rings*		
Compound	$^{\phi}V^{b}$ (cm^3/mol)	$^{\phi}V/m.wt.^{b}$ (cm^3/g)	*Compound*	$^{\phi}V$ (cm^3/mol)	$^{\phi}V/m.wt.$ (cm^3/g)
2,5-Anhydro-D-mannitol (M.wt. = 164·16)	115·3	0·702 4	L-Fucose (M.wt. = 164·16)	106·3	0·647 5
			1,5-Anhydro-D-mannitol (M.wt. = 164·16)	110·1	0·670 7
D-Glucono-1,4-lactone (M.wt. = 178·14)	113·6	0·637 7	D-Glucono-1,5-lactone (M.wt. = 178·14)	107·8	0·605 1
			D-Glucose (M.wt. = 180·16)	110·8	0·615 0
D-Galactono-1,4-lactone (M.wt. = 178·14)	113·0	0·634 3	D-Galactose (M.wt. = 180·16)	109·0	0·605 0

[a] Values compared at 3% (w/w) concentrations with the exception of 2,5-anhydro-D-mannitol (1·6%, w/w).

[b] See Table 1 for definitions of these symbols.

TABLE 4
Comparison of Size of (a) Fused and (b) Pseudo Ring Moieties

(a)

Apparent molar volume of bicyclic fused structure (X) (cm^3/mol)	*Apparent molar volume of corresponding unicyclic structure (Y)* (cm^3/mol)	*Apparent molar volume of fused ring moiety (Z)* (cm^3/mol)
4,6-O-ethylidene-D-glucose 144·9 (2% w/w conc.)	D-Xylose 93·80 (3% w/w conc.)	51·10
4,6-O-ethylidene-D-galactose 138·2 (4% w/w conc.)	L-Arabinose 91·84 (3% w/w conc.)	46·36
D-Glucurono-6,3-lactone 103·1 (3% w/w conc.)	Tetrahydrofuran 75·87 (3% w/w conc.) + 1·0 (for 2 OH groups)	26·23[b]

(b)

Observed apparent molar volume (X) (cm^3/mol)	*Calculated apparent molar volume[a] (Y)* (cm^3/mol)	*Apparent molar volume of pseudo ring moiety (Z)* (cm^3/mol)
2,5-Anhydro-D-mannitol 115·3 (1·6% w/w conc.)	2,5-Anhydro-D-mannitol 110·9	4·40
2,5-Anhydro-D-glucitol 117·1 (3% w/w conc.)	2,5-Anhydro-D-glucitol 110·9	6·20
1,5-Anhydro-D-mannitol 110·1 (3% w/w conc.)	1,5-Anhydro-D-mannitol 109·5	0·60
D-Galactono-1,4-lactone 113·0 (3% w/w conc.)	D-Galactono,1,4-lactone 106·6	6·40
D-Glucono-1,4-lactone 113·6 (3% w/w conc.)	D-Glucono-1,4-lactone 106·6	7·00
D-Mannoheptulose 127·2 (3% w/w conc.)	D-Mannoheptulose 127·0	0·20

[a] Obtained from results of Table 2.
[b] In calculating this value the effects of two OH groups in the tetrahydrofuran ring moiety were accounted for (0·50 cm^3/mol contributed by each OH group).
$(X) - (Y) = (Z)$

accordance with prediction (Shamil *et al.*, 1987) but it also shows some bitterness. Table 4(a) quantifies the effects of fused ring structures and Table 4(b) quantifies the (much smaller) effects in the pseudo-cyclic structures created by intramolecular hydrogen-bonding. D-manno-heptulose is listed for comparison as it contains a side chain (like the 1,4-lactones) which might have exhibited a pseudo-cyclic effect. However, its extremely low contribution (0·2 cm^3/mol) indicates absence of any pseudo-cyclic structure. Similarly, 1,5-anhydro-D-mannitol does not form any pseudo-cyclic structure (Table 4(b)).

The intramolecular hydrogen bonding of a substance observed in solution may not occur when the substance is in the crystalline state which may give rise to differences between calculations based on solid density (true specific volume) and solution densities (apparent specific volumes). Table 5 shows that apparent specific volumes are similar but always slightly smaller than true specific volumes due to size advantage conferred by the water on molecular packing (between water molecules). The one exception in Table 5 is 2,5-anhydro-D-mannitol whose apparent specific volume is greater than its true specific volume, underlining its marked disturbance of water molecules possibly by the pseudo-cyclic behaviour suggested in Table 4.

It has previously been reported (Shamil *et al.*, 1987) that apparent specific volume is a prime determinant of taste quality and this may be interpreted as depth of penetration of a solute into different specific regions of taste

TABLE 5
True and Apparent Specific Volume

Substance	*True molar volume*[c] (cm^3/*mol*)	*True specific volume* (cm^3/*g*)	*Apparent molar volume* (3% *w/w conc.*) (cm^3/*mol*)	*Apparent specific volume* (3% *w/w conc.*) (cm^3/*g*)
2,5-Anhydro-D-mannitol	109·4[a]	0·666 4[a]	115·3[b]	0·702 4[b]
L-Ascorbic acid	106·8	0·606 3	106·6	0·605 2
Furfuryl alcohol	86·84	0·885 2	83·91	0·855 4
Furfural	82·88	0·862 5	78·95	0·821 6
Creatinine	85·05	0·751 9	84·05	0·743 0
D-Glucono-1,5-lactone	110·6	0·620 9	107·8	0·605 1
Tetrahydrofuran	81·29	1·127	75·87	1·052

[a] Calculated by assuming that the density of solid 2,5-anhydro-D-mannitol = 1·5 g/cm^3.
[b] Measured at 1·6% w/w conc.
[c] Calculated using molecular weight and density of crystalline solute.

TABLE 6
Discrimination of Basic Tastes by Apparent Specific Volume[a]

$\phi V/m.wt.$[b] (cm^3/g)	*Taste region*
~0 to ~0·33	Salt
~0·33 to ~0·52	Sour
~0·52 to ~0·71	Sweet
~0·71 to ~0·93	Bitter

[a] From Shamil *et al.* (1987)
[b] See Table 1.

epithelium (Table 6). Molecules with low apparent specific volumes are highly compatible with water structure (salt and acid) and are therefore conveyed to deeper layers of the taste epithelium than are sweet and bitter substances (high apparent specific volumes). This explanation assumes that water molecules themselves have the best access to receptors and presumably hydrated protons (acids) and hydrated simple ions (salts) are next. Sweet and bitter receptors probably lie in the outermost regions and signal the arrival of larger stimulus molecules.

The prediction of taste from chemical structure and solution properties appears to be a possibility but calculations may be confounded by interactions of the stimuli in solution. Table 7 illustrates this last point with two compounds.

In the case of the first compound (2,5-anhydro-D-mannitol), clearly the observed apparent specific volume predicts the taste more accurately than does the calculated apparent specific volume. Calculations must therefore take into account structural determinants of solution behaviour.

TABLE 7
Prediction of Taste by Observed and Calculated Apparent Specific Volumes

Sample	*Observed apparent specific volume* (3%, *w/w*) (cm^3/g) *and Predicted taste*	*Calculated apparent specific volume*[a] (cm^3/g) *and Predicted taste*	*Perceived taste*
2,5-Anhydro-D-mannitol	0·702 4 Sweet–bitter	0·675 6 Sweet	Sweet–bitter
D-Mannoheptulose	0·605 2 Sweet	0·604 2 Sweet	Sweet

[a] Obtained from results of Table 2.

It is well known (Birch & Catsoulis, 1985) that open chain polyols (e.g. sorbitol) have much higher apparent specific volumes than corresponding cyclic structures of similar molecular weight (e.g. D-glucose). Also 5-membered ring skeletons are smaller than 6-membered ring skeletons. Therefore it is of interest to compare the 1,4 and 1,5 lactones depicted in Table 3. D-glucono-1,4-lactone (5-membered ring) has a higher apparent specific volume than D-glucono-1,5-lactone (6-membered ring). This underlines the complex interactions generated by the side chain in the 1,4-lactone, interpretable as a pseudo-cyclic effect (Table 4). Interestingly, only the 1,4-lactone has a bitter taste.

CONCLUSIONS

5-Membered ring structures exhibit taste properties which can be anticipated from a knowledge of their structures, solution properties and interactions with water. Apparent specific volume measurement constitutes a useful measure of direct disturbance of water structure by sapid molecules. Together with stereo-structure it offers an explanation of effectiveness of a sapophore and possible means whereby taste could be predicted.

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