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STRUCTURAL FUNCTIONS OF TASTE IN THE SUGAR SERIES: CYCLOHEXANE POLYOLS AS SWEET ANALOGUES OF THE SUGARS

INTRODUCTION

SHALLENBERGER'S sweetness hypothesis (Shallenberger et al., 1969; Shallenberger, 1966; Shallenberger and Acree, 1967) relates the sweetness of polyhydroxy ring structures to their AH,B systems where AH is a proton donor moiety and B is a proton acceptor. In the sugars, for example, the axial-equatorial and diequatorial α-glycol groupings fulfil the geometrical requirements for eliciting the sweet response, whereas the cis or trans diaxial arrangements are sterically disposed to prevent the effect.

Shallenberger's evidence has been criticized (Birch et al., 1970; 1971) because it has been accrued with the acid of reducing sugars, which, due to their free anomeric centers, equilibrate rapidly to mixtures of isomers. Nevertheless the quantitative examination of glycosidic structures has recently (Birch et al., 1971) supported the truth of the hypothesis.

If diequatorial or gauche arrangements of α-glycol groupings can cause sweet effects in ring structures, cyclohexane polyols present an obvious choice for experimental study. These molecules, being devoid of ring oxygen atoms, are simpler structures than the sugars and are not subject to mutarotational isomerisation when dissolved in the mouth. On the other hand, cyclohexane polyols resemble the sugars in being conformationally less rigid than analogous chair conformations of cyclohexane or a hypothetical pyranoid ring devoid of hydroxyl substituents (Stoddart, 1971).

This paper reports the sensory properties of some cyclohexane polyols containing from one to six hydroxyl substituents in relation to their configuration, conformation and analogy with the sugars.

EXPERIMENTAL

THE FOLLOWING cyclohexane polyols were obtained as gifts from Professor S.J. Angyal, New South Wales; Professor G.E. McCasland, San Francisco; and Professor L. Anderson, Madison, Wisc.:

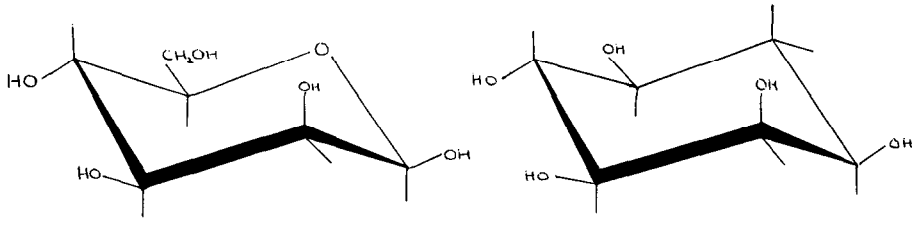
Cyclohexane 1,2/4,5 tetrol	– Chiroinositol
(±) Viboquercitol	+ Chiroinositol
Alloinositol	D-(–)-Bornesitol
Mucoinositol	D-(+)-Pinitol
	Quebrachitol

D-Protoquercitol was extracted from common oak acorns (*Quercus robur L*) obtained locally. L-viboquercitol was prepared from D-protoquercitol (Angyal et al., 1962). Epiinositol was prepared from epi-myo-inosose (Reymond, 1957) which was itself prepared from myoinositol (Posternak, 1936). Neoinositol was prepared from epiinositol (Angyal et al., 1962). Myoinositol was obtained from British Drug House Chemicals, Poole, Dorset; all diols were obtained by fractional crystallization of commercial samples of cyclohexane 1,2- 1,3- and 1,4-diols obtained from Robertson Bros. Ltd., West Bromwich, Staffs.

Panellists were selected and trained according to a previous publication (Birch et al., 1972), and were asked to place a few mg of each substance on the tongue and to comment whether they were trace sweet (Tr.), sweet (S), intensely sweet (SS), trace bitter (tr.), bitter (B), or intensely bitter (BB). The decisions listed in Table 1 are those obtained in at least 70% of total judgments, each panellist carrying out duplicate tasting sessions. The total number

Table 1—Sensory properties of cyclohexane polyols

Compound	Sweetness	Bitterness
Cyclohexane-1-ol	0	B
Cyclohexane cis 1,2 diol	0	B
Cyclohexane trans 1,2 diol	0	B
Cyclohexane cis/trans 1,3 diol	0	B
Cyclohexane cis 1,4 diol	0	B
Cyclohexane trans 1,4 diol	0	B
Cyclohexane 1,2/4,5 tetrol	0	0
(+) Cyclohexane 1,3,4/2,5 pentol [(+)-proto Quercitol]	tr	0
(–) Cyclohexane 1,2,4/3,5 pentol [(–)-vibo Quercitol]	tr	0
(±) Cyclohexane 1,2,4/3,5 pentol [(±)-vibo Quercitol]	S	0
Cyclohexane 1,2,3,4,5/6 hexol [epi Inositol]	tr	0
Cyclohexane 1,2,3,4/5,6 hexol [allo Inositol]	S	0
Cyclohexane 1,2,3/4,5,6 hexol [neo Inositol]	tr	0
Cyclohexane 1,2,3,5/4,6 hexol [myo Inositol]	tr	0
Cyclohexane 1,2,4,5/3,6 hexol [muco Inositol]	tr	0
(+) Cyclohexane 1,2,5/3,4,6 hexol [(+) chiro Inositol]	S	0
(–) Cyclohexane 1,2,5/3,4,6 hexol [(–) chiro Inositol]	S	0
3-0-methyl-myoinositol [D-(–)-Bornesitol]	S	0
3-0-methyl-(+) chiroinositol [D-(+)-Pinitol]	S	0
2-0-methyl-(–) chiroinositol [Quebrachitol]	S	0



β-D-mannose Epi-inositol

Fig. 1—Analogy of epi-inositol and β-D-mannose.

of panellists was ten. Each panellist tasted all 20 substances listed in the Table once each, at one session, rinsing with distilled water between substances, and pausing 1 min before passing on to the next substance.

RESULTS & DISCUSSION

THE RESULTS show that many of the inositols and other substances listed in the Table are sweet but their sweetness varies enormously. Epiinositol, for example, is only trace sweet even though, like many other structures presented in Table 1, it contains several possible AH,B systems meeting Shallenberger's (1969) gauche or diaxial requirements for α-glycol groups. This does not, however, invalidate Shallenberger's hypothesis since particular combinations of hydroxyl configurations around the ring may sterically prevent binding of AH,B systems to the taste bud protein. On the other hand, lack of sweetness in epiinositol may be explained by intramolecular hydrogen bonding in accordance with Shallenberger's own observations (Shallenberger et al., 1969; Shallenberger, 1966; Shallenberger and Acree, 1967).

Epiinositol is, as stated, trace sweet, and is an analogue of β-D-mannose (Fig. 1). Like 1-deoxy mannose, however, epiinositol is not bitter and this is strong supporting evidence of our previous deduction (Birch and Lindley, 1973) that bitterness in β-D-mannose is due to interaction of the β-anomeric hydroxyl group with the ring oxygen atom.

Substitution of a methyl group at position 3 of (+)-chiroinositol gives rise to (+) pinitol without loss of sweetness. Similarly substitution of a methyl group at position 2 of (−)-chiroinositol gives quebrachitol without loss of sweetness. These results suggest that since no change of sweetness or bitterness occurs after these substitutions, one of the nonmethylated hydroxyl groups may be AH in the AH,B system. Myoinositol, which is slightly sweet, is an analogue of β-D-mannose, β-D-galactose and α-D-glucose (Fig. 2). On the other hand 1,2/4,5 cyclohexane tetrol, which is also an analogue of α-D-galactose, is without taste (Fig. 3). Since the equatorial hydroxyl group at position 5 of the tetrol is smaller than the primary alcohol group in the analogous sweet α-D-galactose it would presumably offer no steric hindrance to binding. Also the methylene group which, in the tetrol, replaces the ring oxygen atom of α-D-galactose, does not prevent binding because D-viboquercitol (see below) is very sweet. Therefore we conclude that the third hydroxyl group of α-D-galactose is essential for sweetness in accordance with Hodge's recent observation (Hodge et al., 1972).

Among the cyclohexane pentols (quercitols or oak sugars) we have examined D-protoquercitol, L-viboquercitol and the crystalline racemic mixture D,L-viboquercitol. Only the last of these three is significantly sweet and so must be due to the D-viboquercitol which we have not, as yet, obtained as a pure enantiomorph. D-viboquercitol, as we have previously reported (Birch and Lee, 1971), is an analogue of α-D-glucose (Fig. 4) and therefore is predictably sweet, whereas L-viboquercitol has an axial hydroxyl group below the plane of the ring (Fig. 4) at position 5 which may be responsible for its lack of binding to the taste bud protein. D-viboquercitol has a strong sweet-

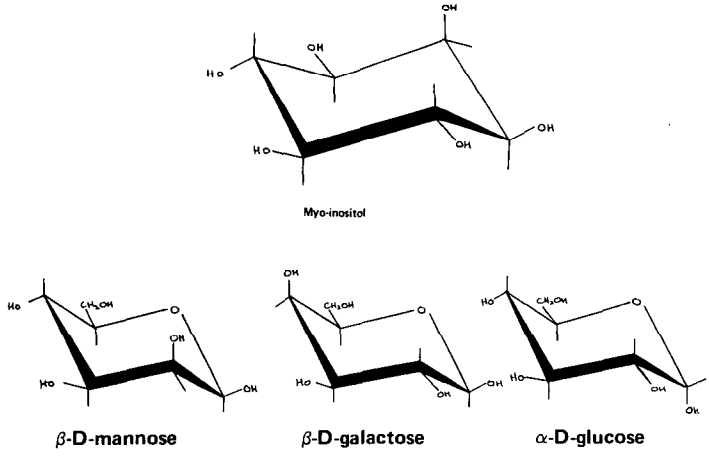


Fig. 2—Analogy of myoinositol, β-D-mannose, β-D-galactose and α-D-glucose

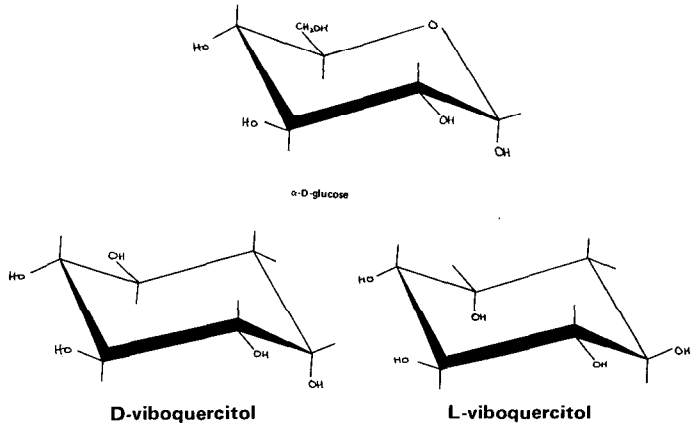


Fig. 4—Analogy of D-viboquercitol and α-D-glucose.

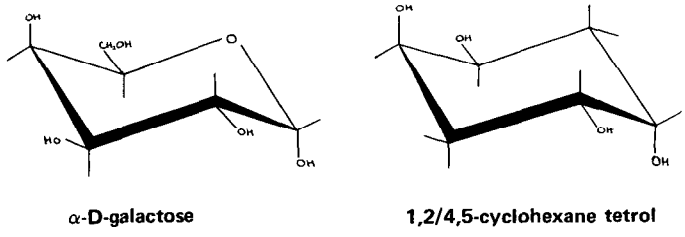


Fig. 3—Analogy of 1,2/4,5-cyclohexane tetrol and α-D-galactose

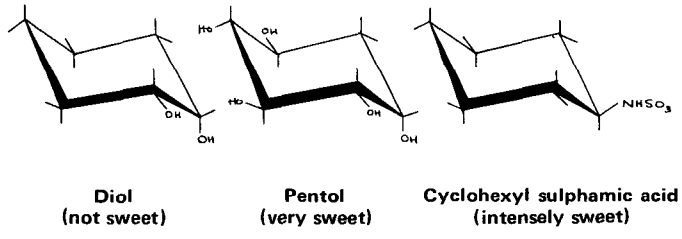


Fig. 5—Organoleptic properties of three related cyclohexane structures.

ness (judged between that of sucrose and fructose by the intensity of the D,L-mixture) but one less hydroxyl group than the inositols which have been tested. On the other hand all the cyclohexane derivatives with fewer hydroxyls (2–4) show no significant sweetness despite all possessing suitable AH,B systems. We can only explain these results by assuming that these molecules align themselves differently on the protein surface due to their greater hydrophobicity; hence some or all of the binding sites in such types are lipophilic in character. Kier (1972) has recently emphasised the significance of this third steric requirement of a lipophilic or "dispersion" site in any molecule capable of eliciting the sweet response and the tripartite functioning of an AH,B system and lipophilic site has been referred to by Birch and Shallenberger (1973) as "multiple group stereogeometry." This is a new concept and implies that combinations of many substituents at different points in the sugar ring may concertedly affect the total sensory properties of the molecule. The greater frequency of sweetness among the methoxy inositols reported here, and D-viboquercitol can presumably be explained on this basis.

If these substances had been tasted as solutions rather than crystals we would anticipate (as in previous studies) no qualitative differences, due to the intrinsic stability of the cyclitol structures. Some differences in intensity might occur due to absence of the hydrogen bonding which exists in the crystal lattice.

In studying many different carbohydrate structures we have never encountered a molecule with more than twice the sweetness of sucrose. Hence, although a polar moiety is likely needed to elicit sweetness, the preferable structural feature of saporific molecules may be an intact cyclohexane ring with a polar substituent, including an AH,B system, outside the ring (Fig. 5). No bitterness was observed in any substances containing more than two hydroxyl groups. Cyclohexanol and the diols were all bitter and devoid of sweetness, a feature which may again be possibly ascribed to the lipophilicity of these substances. The artificial sweeteners saccharin and cyclamic acid both possess bitterness as well as sweetness, as an intrinsic property of the molecule, which is in each case more lipophilic than either the polyols or the sugars.

CONCLUSIONS

CHANGES in configuration in polyhydroxy cyclohexanes cause alteration in their sweetness values from those of the sweetest known sugars down to nothing. These changes cannot be explained simply on the basis of hydrogen bonding and imply changes in binding mode due to alterations in the lipophilic character of the molecules.

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