Molecular Basis of Sweetness

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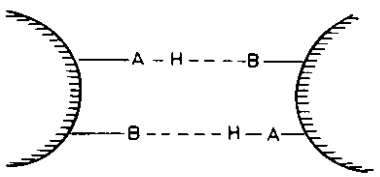
Summary: Some of the theories in the perception of sweetness are reviewed. The sweetness of some chlorodeoxy sucrose and galactosucrose derivatives is examined in relation to conformation and configuration. The presence of more than one 'glucophore' system in these derivatives is proposed.

Introduction

It is generally accepted that a primary event in the elicitation of the sweet taste response is the interaction of a sweet substance with the exterior of a proteinaceous receptor site on the tongue. Hence, it is obvious that in order to understand the true nature of this interaction we need to know the chemical and stereochemical features of sweet compounds and the topology of the receptor site. The molecular nature of sweeteners is generally well understood, but the stereochemical knowledge of the receptor site is still obscure. Until this knowledge is available, the sweet taste response of a substance can only be rationalised on the basis of its molecular structure. However unsatisfactory this approach may be it does provide an explanation as to why certain compounds are sweet. In this article, some of the existing hypotheses on the perception of sweetness will be discussed. These theories will be extended to explain the intense sweetness of some of the chlorodeoxysucrose and galactosucrose derivatives.

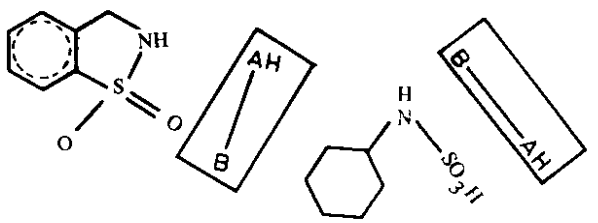
The Relationship between Structure and Sweetness

In 1967, Shallanberger and Acree[1] proposed that the saporous unit of all sweet tasting substances was a bifunctional group consisting of a hydrogen bond donator (AH) and a hydrogen bond accepter (B) with a A-H proton to B distance of about 3 Å. The sweet taste is initiated by intermolecular hydrogen bonding between A-H and B and similar groups on the receptor site (Fig. 1). This A-H, B theory was extended to such compounds as saccharin, cyclamates and acetosulpham (Fig. 2 Table 1) and more significantly to amino acids, where in general D-series are sweet while their enantiomorphs in the L- series are bitter. To overcome this stereochemical requirement, they further suggested[2]



A H, B System

Fig. 1 (Shallenberger and Acree, 1967)



Saccharin Cyclamate

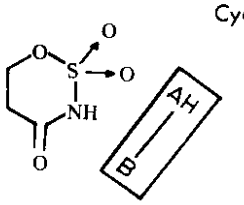


Fig. 2 Acetosulpham

Table 1. *Relative Sweetness of Organic Compounds (sucrose = 1)* *

Cyclamate	30 – 80
Aspartame	100 – 200
Saccharin (sodium)	200 – 700
Acetosulpham	130
6-Chloro-D-tryptopham	1000
Neohisperidin dihydrochalcone	2000
1-n-propoxy-2-amino-4-nitrobenzene	4000

* Sweetness depends upon concentration, temperature, pH, medium and sensitivity of taste.

that the AH unit (NH_3^+) and its B unit (C=O) are hydrogen bonded to their counter-parts on the receptor site in such a way that side chains of the D- series are accommodated whereas those of the L- series are not (Fig. 3). Their theory fails to explain the large difference in the relative sweetness of many known compounds.

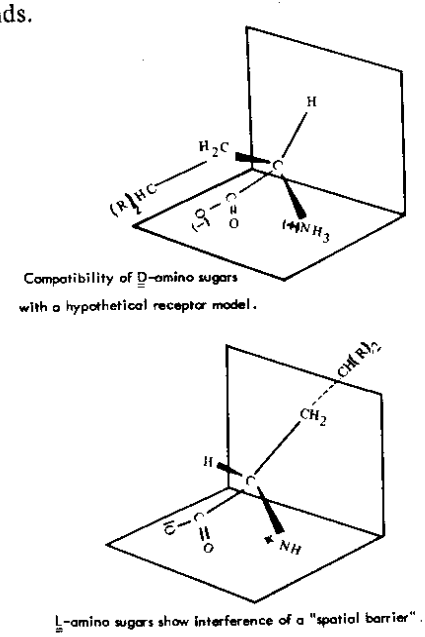


Fig. 3

In 1972, Kier[3] put forward the concept of the "third binding site" (X = lipophilic in nature), located 3.5 Å from A (of AH) and 5.5 Å from B (Fig. 4). Thus, the intense sweetness of 1-n-propoxy-2-amino-4-nitrobenzene (Fig. 5) can be explained on the basis of polarisibility of the group at 1-position (the third site,X) acting in association with the ortho hydrogens (AH) to the nitro group (B). The need for such a 'glucophore' system (Fig. 4) is supported by structure-activity studies of peptides[4], dihydrochalcones[5], by the loss of sweetness on inverting the hydroxyl group at C-4 of sucrose[6] and by the 300-fold increase in the sweetness of D-tryptophan on introducing a 6-chloro group[7]. The importance of hydrophilic-lipophilic balance in determining the sweetness of a molecule has also been considered. Deutsch and Hasch[8] related the sweetness of various 2-amino-4-nitrobenzene derivatives to their partition coefficients between water and octanol.

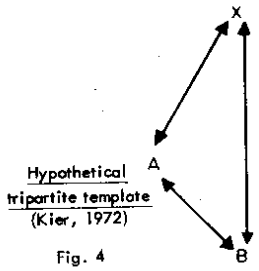


Fig. 4

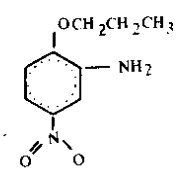
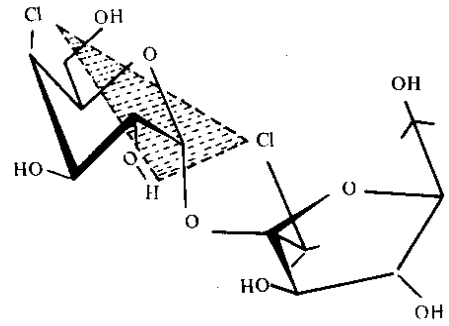


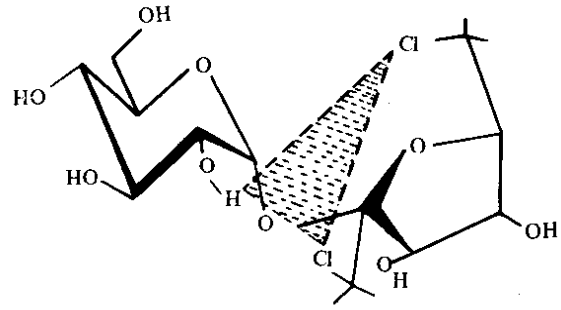
Fig. 5

The surprising discovery[9] that 1,,4,6,6'-tetrachloro-1',4,6,6'- tetradeoxygalactosucrose was 200-fold sweeter than sucrose led us to synthesise[10,11] and to probe the relationship between structure and sweetness of various chlorodeoxy sucrose and galactosucrose derivatives. Shallenberger's AH,B theory and Kier's[3] tripartite template (AH,B and X) has been considered to explain the intense sweetness of 1',4-dichloro-1',4-dideoxygalactosucrose (Fig. 6), 1',6'-dichloro- 1',6'-dideoxysucrose (Fig. 7) and 1',4,6'-trichloro-1',4,6'-trideoxygalactosucrose (Fig. 8). The concept of the presence of more than one 'glucophore' system has been introduced.[11]



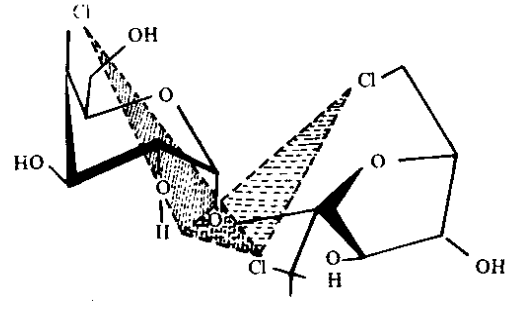
1',4-Dichloro-1',4-dideoxygalactosucrose

Fig. 6



1',6'-Dichloro-1',6'-dideoxysucrose

Fig. 7



1',4,6'-Trichloro-1',4,6'-trideoxygalactosucrose

Fig. 8

On the basis of the results shown in Table 2 , it has been suggested that the presence of 1'-chloro substituent is critical for intense sweetness, and since it can only act as acceptor of an hydrogen bond from the receptor site, this is the B unit of the glucophore on the triangle model (Fig. 4). The equatorial 2-hydroxyl group on the glucopyranosyl moiety must then act as AH. The close proximity of the 1'-and 2-hydroxyl groups in sucrose is supported by Brown and Levy's neutron diffraction studies.[12] The presence of an axial lipophilic group (chloro) at C-4 of the preferred chair conformation of the glucopyranosyl moiety also appears to be critical for sweetness intensification, hence this position is assigned to the lipophilic, locking group X. The molecular models (Figs. 6,7, and 8) are in approximate agreement with both Shallenberger's AH,B system and Kier's[2] tripartite template. The combined effect of the two glucophores on the sweetness intensification of 1,4,6 -trichloro-1 ,4,6 -trideoxy-galactosucrose (Fig. 8) was supported by the fact that it was the sweetest compound in the series.

Table 2. *Relative Sweetness of Sucrose and Galactosucrose Derivatives**

Sucrose	1
*Galacto*sucrose	not sweet
1 -chloro-1 -deoxysucrose	20
4-Chloro-4-deoxy*galacto*sucrose	5
6-Chloro-6-deoxysucrose	bitter
6 -Chloro-6 -deoxysucrose	20
1 -4-Dichloro-1 ,4-dideoxysucrose	600
1 ,6 -Dichloro-1 ,6 -dideoxysucrose	500
1 ,4,6 -Trichloro-1 ,4,6 -trideoxy*galacto*sucrose	1000
1, 4,6,6-Tetrachloro-1,4,6,6-tetradeoxy-galactosucrose	200

*Using a 10% (w/v) aqueous solution of sucrose (sweetness = 1).

Conclusion

Whilst several hypotheses exist to explain the sensation of sweetness, none offer a completely satisfactory explanation that will account for the nature of interactions between sweet compounds and taste receptors. More research is needed to reveal the physiochemical character of the taste buds.

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