Chapter 1

Chemical Aspects of Sweetness

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Introduction

Chemical aspects of sweetness embrace molecular theories of chemoreception as well as simple structure: activity relationships of defined classes of sweetener. Chemical and physicochemical interactions probably affect both the quality and the intensity of sweet taste response, and the molecular structure of a selected sweetener will govern both its suitability and stability in a particular food system. Much of the commercial interest in the subject of sweetness has centered on finding an alternative to sucrose with a view to matching its ideal taste properties and effort has concentrated on selected and/or modified sugars, proteins and peptides, flavonoids, glycosides, saccharin and acesulphame.

The considerable amount of structural and synthetic chemical work of the past two decades has led to commercial success and further promise and has advanced our understanding of chemoreception mechanisms. The work of neurophysiologists, anatomists, and psychophysicists has benefited from an understanding of the behaviour of molecules and their likely interaction with receptors. The involvement of "active sites" or pharmacophores in the sensory effects of sapid molecules is a modern concept that has stimulated the efforts of many research groups. Both gustatory and olfactory responses may originate in similar pharmacophores but sweetness is generally considered a simple taste phenomenon. This chapter therefore concentrates on chemical aspects of sweet taste.

Theories of Sweetness

The earliest recorded theory of sweetness is probably that of Theophrastus in *De Sensibus* (Stratten 1964). He describes its origin in "small round molecules" and attributes the idea to Democritus the Atomist about 500 BC.

Early this century theories of sweetness centered on solubility, "sapophoric groups" (e.g. OH and NH_2) and other simple chemical explanations (Moncrieff

J. Dobbing (ed.), *Sweetness*

1967). Cohn (1914) used the ideas of multiple hydroxyl groups and sapophores[1] to explain sweetness and, following this and the chemistry of dyestuffs, Oertly and Myers (1919) developed a theory of auxoglucs[2] and glucophores[3]. This postulated the presence of the two different kinds of group in the same molecule as a prerequisite for the sweetness response. Oertly and Myers (1919) listed putative auxoglucs and glucophores and some of their suggestions do seem to be partly justified by research in the 1970s and 1980s. However, most of these early theories did not explain the sweetening power of intense sweeteners such as saccharin.

Beck (1943) suggested that the sweetness of sugars correlated well with the ratio, sum of atomic volumes: molecular volume. This interesting idea touches on the use of parachors[4] to predict trends of homologous series in a given chemical class and it is both surprising and unfortunate that so little attention has yet been paid to the implications of Beck's suggestion. Some of the very recent structure: activity studies in both sugars and peptides seem to be re-exploring this approach.

Probably all substances with sapid effects must possess some water solubility in order to gain access to receptors. On the other hand it is known that many lipophilic substances are much sweeter than the natural (hydrophilic) sugars, so Deutsch and Hansch (1966) have attempted to correlate sweetness with partition coefficient. The sapid substance is thus imagined as binding with a hypothetical sweet receptor located on the taste cell membrane. The lipid nature of this membrane necessitates a favourable partition coefficient for effective accession. Other theories to explain sweet taste have been electronic vibration (Kodama 1920) and enzyme activity (Baradi and Bourne 1951). The latter theory has not excited much interest but the recent finding of Schiffman et al. (1985) of adenosine involvement in receptor activity may restimulate the search for enzyme intermediation.

Quite the most important hypothesis to explain the chemical basis of sweetness has been that of Shallenberger and Acree (1967), who used a previous observation of hydrogen bonding in relation to sweetness (Shallenberger 1963) to develop the concept of an AH,B glucophore. According to Shallenberger and Acree (1967), all sweet substances possess this unit (Fig. 1.1), in which A and B are each electronegative atoms and AH acts as an acid while B acts as a base. The AH,B unit then forms a doubly hydrogen-bonded complex with a similar AH,B system on the taste receptor. A separation of 2.86 Å between the centres of the atomic orbitals of A and B appears to be ideal for sweetness, and probably the entire molecular geometry, as well as the AH,B system, governs the strength of the hydrogen-bonded complex and both the quality and the intensity of the sweet taste response.

Kier (1972) extended the AH,B theory of sweetness by introducing the concept of a third, lipophilic binding site on the molecule, usually termed 'γ'. This site was supposed also to create a favourable partition coefficient facilitating accession of the sapid stimulus to the lipophilic environment of the taste cell membrane. The idea of a tripartite AH,Bγ glucophore is now often quoted to explain sweetness (Hough

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1. *Sapophore:* A molecular feature giving rise to a basic taste.
2. *Glucophore:* One of an essential pair of molecular features needed for sweetness (the other is an auxogluc).
3. *Auxogluc:* One of an essential pair of molecular features needed for sweetness (the other is a glucophore).
4. *Parachor:* The parachor is related to the apparent molar volume (ϕV) and the surface tension (γ) by the expression: $[P] = \phi V \cdot \gamma^{1/4}$. In other words the parachor may be viewed as equal to the apparent molar volume if the surface tension were to remain at unity.

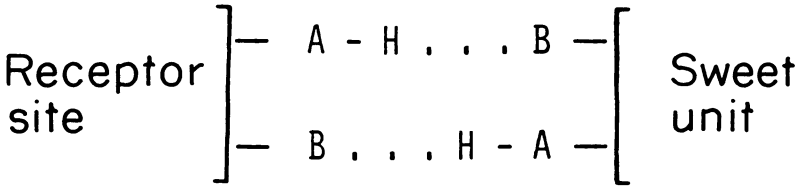

Fig. 1.1. The Shallenberger and Acree (1967) AH,B glucophore.

1985) but there seems little reason to over-complicate Shallenberger and Acree's (1967) original simple and elegant theory by extending it in this way. The role of lipophilicity in enhancing sweetness is undisputed and γ may be viewed as contributing to the orientation and accession of a sapid stimulus to the receptor. However, the idea of γ as a binding site of the glucophore is unnecessary and, indeed, no such site is obvious in the sugars, inositols or polyols; yet the quality of their sweetness response in unsurpassable.

Chemical Classes Which Cause Sweetness

Chemical classes which cause sweetness (Table 1.1) include sugars, glycosides (and modified sugars, e.g. polyols), amino acids, peptides and proteins (and modified types), coumarins, dihydrochalcones, ureas and other nitrogenous compounds, substituted aromatic substances and certain salts. There is clearly no categorical pattern in the chemical class of molecule able to elicit the sweet response and in some classes, e.g. inorganic salts, there is no apparent glycophore. On the other hand certain broad

Table 1.1. Chemical classes and sweetness[a] (sucrose = 1)

Class	Order of sweetness (Molar basis)
Simple sugars	0.1–2.0
Hydrogenated sugars	0.1–2.0
Chlorodeoxy sugars	0–2600
Terpenoids and their glycosides	0–1000
Dihydrochalcones	0–10 000
Peptides	0–30 000
Proteins	0–300 000
Nitroanilines	0–2350
Sulphamates	0–26
Oximes	0–750
Isocoumarins	0–200
Saccharins	(0–1000)[b]
Acesulphames	(10–250)[b]
Tryptophans	(0–1300)[b]
Ureas	(0–250)[b]

[a] References: van der Heijden et al. (1985a,b), Birch et al. (1971), Compadre et al. (1985), Birch et al. (1980)
[b] These figures are on weight basis

chemical features (e.g. polarity, lipophilicity, chirality, molecular size and shape) are evidently important for many known sweeteners and give strong clues in the search for structure : activity relationships.

Most of the chemical synthesis in sweetness research has centered on modification of sugars, peptides (and proteins) and dihydrochalcones, and a guiding principle throughout has been the Shallenberger and Acree AH,B theory. Probably some hundreds of derivatives of these three types are now available (Birch et al. 1971; Birch and Parker 1982; Grenby et al. 1983).

In almost all classes of sweet molecule possible AH,B glucophores may be recognised but it is rare for them to be unequivocally located. The inorganic salts (e.g. lead and beryllium) provide an interesting exception. However, salts are heavily hydrated in solution and the hydration shells which surround each molecule may themselves constitute suitable AH,B systems.

Chemical synthesis and modification of new sweeteners, principally in the United States, United Kingdom, Ireland, The Netherlands and Japan, has established many structure : activity relationships (de Vos et al. 1985; Soejarto et al. 1982; Dubois et al. 1984; Compadre et al. 1985). The subject has been excellently reviewed by Beets (1978). Although the products of synthetic work are numerous, few have been toxicologically cleared for human consumption. Those which are suitable differ in their chemical and physical properties and are conveniently grouped into those which confer body and viscosity to foods, like the sugars (*bulk sweeteners*), and those which have much more sweetening power than the sugars (*intense sweeteners*). The latter are used at such low concentrations that they confer no body. Table 1.2 lists the new permitted sweeteners in the United Kingdom (HMSO 1983). Quite the most important of these is aspartame (L-aspartyl L-phenylalanine methyl ester), which has already been widely used in food formulation. One problem is its limited storage stability in acid foods and a solution to this problem is of considerable economic importance. Recently Fuller et al. (1985) have in fact published the synthesis of 12 new *N*-(L-aspartyl)-1,1-diaminoalkanes ranging in sweetness from 5–1000 times the sweetness of sucrose, all of which are stable to hydrolysis.

Chemical modification to increase sweetness is often unsuccessful because the products turn out to be bitter. Sometimes molecules are truly bitter-sweet and may elicit such effects because of the proximity of receptor sites (Birch and Mylvaganam 1976). Chlorination of sugars, for example, often leads to intensely bitter products (Dziedzic 1980) but sucrose itself yields a number of deoxy chloro-derivatives (Table1.3) ranging from 5 to 2200 times the sweetness of sucrose (Hough 1985). The explanation of this remarkable enhancement is not easy but may emerge from a study of solution properties (Mathlouthi et al., to be published).

Table 1.2. Permitted sweeteners in the United Kingdom (HMSO 1983)

Intense sweeteners	Bulk sweeteners
Acesulphame K	Hydrogenated glucose syrup
Aspartame	Isomalt
Saccharin	Mannitol
Sodium saccharin	Sorbitol
Calcium saccharin	Sorbitol syrup
Thaumatin	Xylitol

Table 1.3. Taste properties of some chlorodeoxy sugars (Hough 1985)

Compound	Taste[a]
1'Chloro-1'-deoxy sucrose	Sweet (20)
4-Chloro-4-deoxy galactosucrose	Sweet (5)
6-Chloro-6-deoxy sucrose	Bitter
6'-Chloro-6'-deoxy sucrose	Sweet (20)
4,1',6'-Trichloro-4,1',6'-trideoxy galactosucrose	Sweet (650)
4,1',4',6'-Tetrachloro-4,1',4',6'-tetradeoxy galactosucrose	Sweet (2200)

[a] Figures in parentheses are the times sweeter than sucrose.

Quality, Intensity and Persistence of Sweetness in Relation to Chemical Structure

Although a large number of intensely sweet molecules have now been synthesised, there are many problems about the quality of their sweetness. There is no currently permitted sweetener that possesses the ideal sensory quality of sucrose, though the alleged quality differences among the sugars themselves may be due to impurities. Problems of quality include bitterness, sourness, cooling and menthol or liquorice-like taste. More subtle effects could result from diffferences in surface tension, viscosity, body and tactile response. By far the most important quality effects, however, are the temporal characteristics, which are manifested as both delayed reaction times and prolonged sweet sensations (*persistence*). Every new intense sweetener synthesised appears to suffer the disadvantage of a long persistence, and with the intense protein sweeteners this may extend to 20 or 30 min. It is not known whether the phenomenon is due to a "hysteresis" effect of the receptor or whether persistence of stimulus molecules themselves is responsible, but unless the persistence of sweeteners is properly understood, there seems to be little hope of solving the problem. Delayed reaction time is also a problem and this is difficult to measure accurately, being of the order of 1 s or less, but depending on the number of papillae stimulated (Halpern 1986).

So far there are no clear indications of the effect of chemical structure on temporal characteristics of the sweet response, but a study of taste interactions and solution properties of the sweeteners is an avenue for further exploration (Birch and Shamil, to be published).

Interactions of Molecules and Tastes

The phenomenon of basic taste change is well illustrated in the sugars, which can easily be converted, by substitution, into bitter substances (Clode et al. 1985). Even a simple configurational change at a single asymmetric carbon atom causes the sweet-to-bitter transition. Thus β-D-glucopyranose is sweet whereas β-D-mannopyranose is

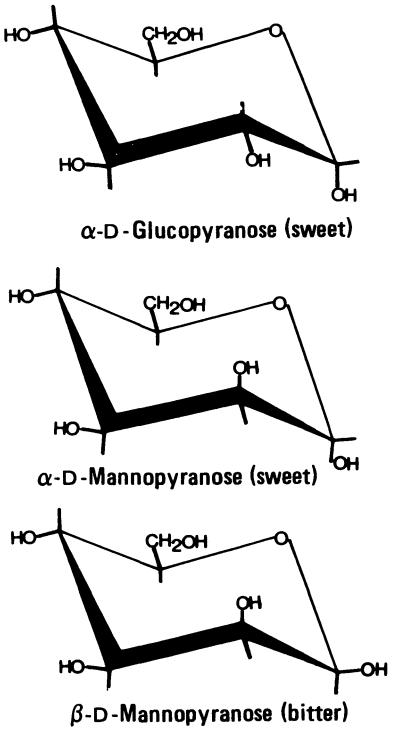

Fig. 1.2. Configurational change and taste.

bitter (Fig. 1.2), so the two basic tastes are fundamentally associated in some way. With bitter-sweet substances (e.g. methyl α-D-mannopyranoside) it has been suggested (Birch and Mylvaganam 1976) that the two types of receptor may be simultaneously spanned by one molecule, which indicates their close proximity.

Although the basic tastes are psychophysically discrete (Bartoshuk 1977; McBurney and Bartoshuk 1973), they interact in mixtures (Bartoshuk 1975 and Chap. 3, this volume) so that the perceived intensity may be different from that of a single component of the mixture. Certainly sweetness lowers the intensity of bitterness and vice versa (Bartoshuk 1975; Birch et al. 1972), but when two sweet substances are mixed the result is less clear. The apparent synergism or suppression of the mixture may be a logical outcome of the two substances' individual intensity power functions (Bartoshuk 1977). If sensorial interaction does occur between sugars, it is certainly not due to interactions between the sugar molecules themselves, as can be seen, for example, by optical rotation measurements. This raises the interesting possibility that the sugar molecules in a mixture may exert different effects on water structure, which in turn affect taste (Mathlouthi et al., to be published). The well reported differences (Bartoshuk 1977) in water taste after adaptation may be related to such effects.

Munton and Birch (1985) have used intensity-time studies of mixtures of two sugars to determine their "effective concentrations". Interestingly the least sweet sugar, in the mixtures tested, appeared to be dominant in the mixture (i.e. the sugar which was the most effective stimulator) and this could be related to its compatibility

Table 1.4. Dominance of sweeteners in binary mixtures (Munton and Birch 1985; Yamaguchi et al. 1970)

Sucrose	: Sorbitol[a]
Sucrose	: Xylose[a]
Sucrose	: Maltose[a]
Sucrose	: Galactose[a]
Lactose	: Glucose[a]
Glucose	: Galactose[a]
Sucrose	: Glucose[a]
Sucrose	: Mannitol[a]
Sucrose[a]	: Saccharin
Fructose	: Glucose[a]
Fructose	: Xylose[a]
Fructose	: Sorbitol[a]
Xylose[a]	: Sodium cyclamate
Sucrose	: Glycine[a]
Mannitol[a]	: Saccharin

[a] Indicates dominant sugar in mixture

with water structure (Birch and Shamil, to be published). A molecule which is highly compatible with water may be viewed as causing the least disturbance or displacement of water molecules and a good measure of this is its apparent molar volume. Yamaguchi et al. (1970) have also observed dominance[5] of one sugar in a mixture but without considering the persistence of response. Table 1.4 lists some results of dominance studies.

The interaction of stimulus molecules with water is of such direct importance to sweet taste response that many related physical parameters should be taken into account (Lawrence and Ferguson 1959). Viscosity, surface tension, and water activity are examples of properties that might affect taste results. The total volume of solution presented to a panellist will affect both the intensity and persistence of response (Birch et al. 1982).

The Fundamental Chemoreception Mechanism

Shallenberger and Acree's (1967) AH,B theory suggests that one molecular feature of a sweet molecule (*a glucophore*) interacts with a sweet receptor. Transduction then occurs and a neural impulse is sent to the brain. If the AH,B concept is correct it ought to be possible to identify the AH,B glucophores in different molecules and to use this information to elucidate similarities and differences of structure : activity patterns among defined classes of sweetener. In practice this is very difficult because most sweet molecules can adopt an almost unlimited number of conformations. Therefore simple cyclic molecules, such as the sugars which adopt a favoured conformation, are the best models in which to conduct a glucophore search. In the sugars, AH,B systems are α-glycol groups, but there are several possible candidates in each molecule. For example, Shallenberger and Acree (1967) assigned the 1,2 α-glycol group as the

5. Operationally, dominance of one or other sugar in a mixture may be viewed as the matchability of its psychophysical power function (measured alone) with that of the mixture. Thus the "effective concentrations" of each of the sugars in a mixture can be calculated.

AH,B system of D-fructopyranose, the sweetest simple sugar, on the basis that OH-2 is the most acidic proton. However, this conclusion is possibly now questionable (Birch et al. 1986, unpublished work) because D-fructopyranose may orientate itself on the taste receptor analogously to D-glucopyranose, in the favoured chair conformation, and its 1,2 α-glycol system would then be unable to bind. The best models for elucidating AH,B systems of sugar molecules are the α-D-glucopyranosides. When oxygen atoms are eliminated stepwise around the ring (Birch and Lee 1974), it is found that only the 3-deoxy derivative exhibits loss of sweetness. Thus OH-3 in glycopyranoside structures must constitute B in the Shallenberger and Acree AH,B system. Substitution of the molecules (Birch 1976) indicates that OH-4 is the primary AH. When the deoxy derivatives of α,α-trehalose and methyl α-D-glucopyranoside are compared they show completely parallel sets of sensory properties in corresponding molecules. This provides a striking illustration of the chemical basis of sweetness as well as a location of the AH,B system.

The binding of a sweet molecule to a receptor via an AH,B glucophore does not in itself explain all the facets of the sweet response. In particular the temporal characteristics of sweetness (reaction time and persistence) probably ensue from other mechanisms. The molecule must accede to the micro-environment of the receptor before it can activate it with an AH,B system, and lipophilic characteristics may facilitate such accession. The great persistence of some of the newly available sweetening agents could be explained by a localised concentration of stimulus molecules at or near to the receptor. This has been clearly established, for example, in insect chemoreception, and persistence can result from prolonged stimulation by a number of molecules in localised concentrations or "stores" until they are depleted. It seems logical to view these localised concentrations as organised for cellular activity. Thus an "orderly queue" hypothesis has been proposed (Birch et al. 1980) to explain how stimulus molecules might be stored and utilised consecutively. Molecules emerging at the head of the queue trigger the ionophore sequentially and the process continues until the queue is emptied of stimulus molecules. Length of queues then governs persistence time whereas the rate of passage through a queue governs reaction time. Accession of stimulus molecules to queues is probably enhanced not only by lipophilicity but also by compatibility with water structure (Birch and Catsoulis 1985; Birch and Shamil, to be published). This introduces an interplay of hydrophilic and hydrophobic forces in the initial stages of taste chemoreception.

The fundamental mechanism of taste chemoreception is still not understood because taste receptors have not yet been isolated and characterised. Considerations of accession of stimuli and activation of receptors suggest that there are at least two stages of the taste chemoreception process and detailed comparisons of stimulus molecules, in homologous series of sweeteners, can indicate how these separate stages might take place.

New Approaches to Sweetness Chemoreception Studies

Probably no substance can be tasted unless it is first dissolved (in water or oral fluid), so water itself is probably involved in a number of different ways in the taste response. Water acts not simply as a vehicle for carrying stimulus molecules to the receptor, but also as an extremely active hydrogen-bonding agent. Sugar molecules

are therefore heavily hydrated in solution though they differ in their degrees of hydration due to differences in the equatorial and axial configurations of their hydroxyl groups. The apparent molar volume (ϕV) of a sugar gives a measurement of its apparent displacement of water molecules. Heavily hydrated sugar molecules have low (ϕV) values and are therefore highly compatible with water structure (Birch and Catsoulis 1985; Birch and Shamil, to be published).

A modern approach to the study of sweetness chemoreception is to consider the interactions of physico-chemical variables which can explain molecular structure and solution properties. Both the effect of the solute on the solvent and the effect of the solvent on the solute must be considered (Mathlouthi et al., to be published). Using this approach it may be noted that the dominant sugar, in mixtures of two, is the one with the smaller (ϕV) value (Birch and Shamil 1986). This does not simply mean that the smaller molecule has a size advantage for access to the receptor, but rather that it is more compatible with water structure and is therefore better transported into the micro-environment of the receptor. Over the entire field of basic tastes, a useful index is specific apparent volume (ϕV/mol. wt.). Table 1.5 lists some specific apparent volumes of known tastants which pass from salty (at the top of the table) down to bitter. Since specific apparent volume represents apparent displacement of water by unit of sapid substance, the results in Table 1.5 show qualitative changes of response according to compatibility with water structure. Molecules with good compatibility (e.g. salts) may be transportable to deeper layers of receptors than, say, sweet and bitter molecules, which may reach only shallow receptors. In accordance with this suggestion Hiji and Ito (1977) have shown that sweet response may be selectively eliminated in rat tongues by pronase treatment, leaving the other basic tastes unaffected.

In a profound new study of structure: activity relationships in homologous series of sweeteners, van der Heijden et al. (1985a,b) have calculated minimum, maximum and optimum distances between putative AH,B and γ sites. Their calculations lead them to the conclusion that nitroanilines, sulphamates, oximes, isocoumarins and dipeptides bind with at least three different classes of receptor. A similar study with saccharins, acesulphames, chlorosugars, tryptophans and ureas also suggests more than one type of sweet receptor. However, van der Heijden et al. (1985a,b) have confined their calculations to interatomic distances and bond torsion angles. They

Table 1.5. Specific apparent volumes and taste

Substance	Mol. wt.	Apparent molar volume, ϕV (cm^3/mole)	Sp. app. volume (ϕV/mol. wt.)	Taste
Ferric chloride	162.22	26.01	0.160	Iron-salt
Sodium chloride	58.44	17.21	0.294	Salt
Monosodium L-glutamate	169.1	76.86	0.455	"Umami"
Ortho phosphoric acid	98.0	44.64	0.456	Sour
D-Gluconic acid	196.16	101.1	0.515	Sour
Acesulphame K	201.17	160.0	0.592	Sweet
Sodium Saccharin	241.2	142.8	0.592	Sweet
D-Fructopyranose	180.16	107.2	0.595	Sweet
D-Galactose	180.16	109.0	0.605	Sweet
Sucrose	342.3	208.3	0.608	Sweet
Sorbitol	182.17	116.2	0.638	Sweet
Methyl β-D-xylopyranoside	164.13	116.9	0.713	Bitter-sweet
Quinine, HCl	360.9	277.8	0.768	Bitter

assume that the 3,4 α-glycol group is the sweet glucophore of chlorosugars but take little or no account of the role of water in the sweet response (Mathlouthi et al., to be published).

The behaviour of sugar molecules in water solution can be conveniently followed by optical rotation measurements and Shallenberger (1982) has undertaken chiral computations in the sugars by summing individual contributions of asymmetric carbon atoms and the helical contributions of ring substituents. This approach leads to prediction of favoured conformation in sugar molecules and provides a sensitive probe of sugar–water interaction.

Yet another new approach to the study of sweetness is to observe the effect of taste modifiers. Both gymnemic acid and ziziphin depress sweetness and the effect may be related to their surface active properties (Adams 1985). This, once again, underlines the importance of solution properties.

Conclusions

1. The complete chemical interpretation of sweetness has not yet been achieved.
2. In certain types of conformationally defined molecule, glucophores have been tentatively located. This implies that these molecules are orientated in a particular manner on the receptor.
3. All intensely sweet molecules are more persistent than sugars. An explanation of the phenomenon of persistence is based on an orderly localised concentration of stimulus molecules.
4. All sweet effects are mediated by water. Therefore solution properties and hydration of sweet stimulus molecules are now under study in an atempt to elucidate the mechanism of taste chemoreception.

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