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The AH,B glycophore and general taste chemistry

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When considered jointly, all tastes (sweet, salt, bitter, sour) are variations on a common electrostatic mechanism, and the primary distinction among them can be traced to the symmetrical nature of the interaction between the substance and the taste receptor. Sourness is a dissymmetric interaction between the hydronium ion (an acidophore) and the taste receptor, whereas saltiness is a concerted symmetrical electrostatic interaction betwen the Na^+ and Cl^- ions (the halophore) and the receptor. Sweetness is elicited through a bilaterally symmetrical and concerted dipolar interaction between a glycophore and the receptor, while bitterness can be traced to either dissymmetric ionic or dipolar interactions between a picrophore and the receptor. As no products are ever formed, taste phenomena are collectively grouped as being due to electrostatic recognition interactions that can occur between a substance and the receptor without the need for chemical binding. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Taste has long been described as a chemical sense, which can simply mean that taste is caused by chemicals. However, the term can also mean that tastes are initiated by chemical interactions. If this is the case, then general chemical principles and theory must apply.

In perusing the literature on taste, one of the first things to become obvious is that advances in the knowledge of taste neatly parallel advances in chemical theory (an observation of T. E. Acree). The ionization theory developed by Faraday and Arrhenius led to the first taste classification; i.e. the sour and salt tastes are generally caused by substances that ionize in solution, whereas the sweet and bitter sensations are elicited by substances that generally do not ionize (Cohn, 1914). The classification is the first indication that distinct chemical reactions might be responsible for different tastes, or at least for saltiness and sourness versus sweetness and bitterness.

For sweetness, Cohn recognized the need for discrete functional groups within the structure of a compound, and noted that these groups usually occurred in pairs. The pair was collectively called a *glucogene*. Subsequently, Oertly & Myers (1919), through application of dyestuff chemical theory, proposed that the glucogene had two complementary but different chemical functions. One was therefore described as an auxogluc, and the other described as a glucophore, and neither was capable of eliciting sweetness without the other.

When Kodama's (1920) recognition of the need for 'vibratory hydrogen', in order to impart sweetness to a compound, is then applied to the bipartite glucogene, it becomes clear that the auxogluc is in some way functioning as a proton donor and the glucophore as a proton acceptor (see also Warfield, 1954). If Kodama had been aware of hydrogen bonding theory in 1920, there is little question in my mind that he then would have described the sweet taste mechanism as 'intermolecular hydrogen bonding'. The auxogluc proton donor would have become AH, and the glucophore B, in an AH,B system. Alas, hydrogen bonding theory did not become readily known until about the middle of this century, but when it did, it seemed to neatly tie into previous observations on relations between sweetness and structure (Shallenberger & Acree, 1967).

In the meantime, the resonance theory of Linus Pauling was developed and it was observed by Tsuzuki *et al.* (1954) that compounds with the highest sweetness potential also had the largest resonance energies. The inductive effect of certain groups and substitutions in the structure of a compound including those with a hydrophobic bonding effect (Nemethy, 1967) can then lead to higher resonance energy, and Ferguson & Childers (1960) took this to be an explanation for the high potency sweetness and/or bitterness of some compounds.

Interestingly, the application of hydrogen and hydrophobic bonding theory, and the notion of inductive effects, to high-potency taste applies only to tastants that do not generally ionize (i.e. the sweet and bitter substances). It does not apply to salty and sour substances. If the role of induction, caused mainly by the electron withdrawing capacity of certain groups in the structure of organic compounds, is valid, then one might expect high taste potency to occur only among

the sweet and bitter organic compounds. To the best of my knowledge, this is true. An increase in the saltiness and sourness of a compound is brought about only by increasing the concentration, but, among sweet and bitter substances, taste potency can be increased by increasing the concentration and/or by increasing the chemical activity of the saporous functions. Such relations strongly indicate that the basic tastes can indeed be differentiated and classified according to the nature of the chemical reactions that elicit them.

In attempting to do this (Shallenberger, 1993), it became clear that another powerful theoretical tool, used to develop chemical theory, also applied to taste. That tool is the notion of symmetry, and its first cousin, chirality. Their application has led, among other things, to Dalton's atomic theory, the development of the periodic table, the recognition of mirror image structural form of compounds, the elucidation of the structure of sugars, and even the elucidation of the nature of molecular orbitals.

In retrospect the reason why the principles of symmetry had not earlier been applied to taste chemistry is somewhat of a mystery, particularly in view of the fact that over a century ago, Pasteur established that symmetry, or lack of it (dissymmetry, chirality) applied to the taste of certain amino acids, and it seemed safe to assume that it applied to the other tastes too, even beginning with tastes caused by ionizable substances.

NATURE OF TASTE CHEMICAL REACTIONS.

In order to deduce the role of symmetry in taste chemistry, the basic tastes were reexamined, beginning with sourness.

Sourness

In solutions of equal normality, all acids are equally sour. (Pfaffmann, 1959). In other words, 'weak acids', which do not completely dissociate in solution, taste just as sour as those that do, or 'strong acids' (Harvey, 1920). Therefore, sour taste is entirely a function of the potential hydrogen (hydronium) ion concentration, and not the hydrogen ion concentration (pH) *per se*. Thus, the chemical mechanism is analogous to the titration of an acid, by a base, to a neutral end point (neutralization reaction). Although the pH of a weak and strong acid at the same normal concentration are quite different, their titration coefficients are the same, and so is sourness potential. For sour taste, however, it has to be the taste receptor that serves as the 'base' for titration purposes, because no products are formed. If products formed, a mixed taste would result. Using the n/e (nueleophilic/electrophilic) notation of Belitz *et al.* (1981) for the chemical character of a bipartite taste receptor, the chemical mechanism for the sour sensation is shown in Fig. 1.

With this mechanism, acids that dissociate totally (HCl), or only partially (acetic acid), would nevertheless be equally sour, as chemical equilibria and mass action phenomena

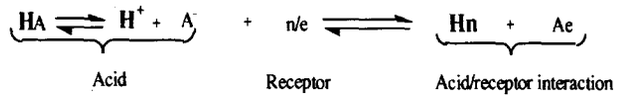

Fig. 1. Interaction of an acid (HA) with a nucleophilic/electrophilic (n/e) taste receptor to elicit sour taste.

are clearly operative, and this effectively exhausts the total acid potential of the weak acid. For sourness, the simplest taste, there does indeed seem to be a chemical reaction to elicit the sensation but, because there is no product, it is a pseudo-acid/base titration phenomenon.

In a conventional acid/base titration, the role of the acid and the base are equally important to product formation, i.e., the equation is balanced, or symmetrical. From the standpoint of sour taste however, where there is no tangible product, the importance of the hydrogen ion far outweighs that of the attendant anion, and in this respect, the taste reaction is unbalanced, or dissymmetric. This feature of sour taste chemistry is indicated in Fig. 1 using bold type for the hydrogen ion.

Taken one step further, the hydrogen ion can also be described as an acidophore (Gr. *phoros*, to carry), or a substance that elicits sourness. Because the hydrogen ion is the only 'structural' acidophore, 'high potency' sour substances are not possible, and sourness potency is a function of the potential hydrogen ion concentration only. It would also seem that topological requirements for the proton receptor (n) are unnecessary. For topology to be operational in the sourness response would require that the (n) receptor must be smaller than the hydrogen ion, which is not structurally possible.

Whenever the tongue has been treated with miracle fruit extracts, and acids then become sweet to the taste, sweetness intensity is also independent of the nature of the acid (Kurihara, 1971). Acid sweetness potential in this case therefore stoichiometrically mimics the sourness potential. Thus, when acids are rendered sweet by treatment with miracle fruit extract the sweetness modality would seem to be elicited by a reaction not unlike the pseudo-acid/base titration that elicits sourness, but in the former case, both the nucleophilic and electrophilic components of the sapid substance have equal importance, and the bipartite concerted interaction is symmetrical.

Saltiness

Saltiness is also elicited by ions, but unlike the case for sourness, both the anion and the cation play a significant role (Kionka & Strätz, 1922; Moncrieff, 1967). There is also a general consensus that only sodium chloride elicits a 'true' salt taste. Other salts have mixed tastes, which is abundantly clear to persons restricted to a low sodium diet. Along with a saltiness note, and beginning with the nearest chemical relative, KCl, those tastes are described as 'unpleasant' (sour and/or bitter). It would seem that there is only one true halophore (Gr. *halo*, salt), and it is the collective combination of the sodium and chlorine ions. An approximate equation for the general saltiness of a metallic salt is shown in Fig. 2.

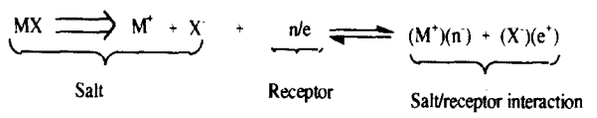

Fig. 2. Interaction of an anion (X^-) and cation (M^+) with a nucleophilic/electrophilic (n/e) taste receptor to elicit salt taste.

In Fig. 2, a metallic cation and a non-metallic anion are shown to interact simultaneously with an n/e receptor to initiate the taste sensation. The salt taste reaction is analogous to a conventional electrostatic interaction among ions, such as the precipitation of silver chloride when a NaCl solution is treated with silver nitrate. In the taste reaction, however, there is no precipitate (product).

For the 'true' salt taste, the sodium and chlorine ions need to be substituted for the metallic and non-metallic ions shown in the equation. As the role for either the anion or the cation for the taste of NaCl is about the same, on either side of the equation, neither M nor X in the equation appears in bold type. In fact; in their role of eliciting saltiness, the combination Na^+/Cl^- seems to be as balanced (symmetrical) as an antipodal pair of ions can possibly be. When the anions and cations have significant size and electronic property differences, mixed tastes, particularly bitterness/saltiness, become apparent (Shallenberger, 1993).

A feature that the two lowest members of the metallic salt series have in common is that in dilute solutions, sodium and potassium chlorides taste distinctly sweet (Bartoshuk *et al.*, 1978). The reason for this seems to be related to the hydration properties of ions in dilute solution (Shallenberger, 1993). Nevertheless, a chemical-mechanism interrelation among the four basic tastes again appears as an intrinsic symmetry attribute for the nature of the interaction. As with sourness, no high potency salty substances are known, and the magnitude of the sensation is a function of concentration alone. It is also difficult to envisage just what form a topological receptor for saltiness might take.

Bitterness of salts

Because the bitter taste is also assigned to some salts, an approximate electrostatic equation for their bitterness is shown in Fig. 3.

Equation 3 for the bitterness of metallic salts would be identical to that for saltiness if it were not for the emphasis on either the anion in one case, or the cation in the other. Both interactions are dissymmetric. There does not appear to be any products formed. Examples of unequal bitter combinations are KCl for the chlorine ion and NaI for the sodium ion. Taken together, such

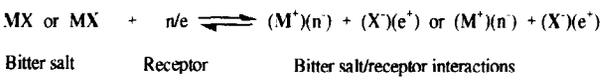

Fig. 3. Interaction of a anion (X^-) and cation (M^+) with a nucleophilic/electrophilic (n/e) taste receptor to elicit bitter taste.

ionic pairs can be considered to be a picrophore (Gr. *pikros*, bitter).

As with sourness and saltiness, it is difficult to an envisage a topological receptor for the bitter taste of salts, and high-potency bitterness does not seem to occur among salts (inorganic substances).

Sweetness

All sweet tasting organic substances are dipolar compounds, and the mechanism for the sweetness of dipolar compounds has been proposed to be a concerted intermolecular hydrogen bonding interaction (Shallenberger & Acree, 1967). It occurs between a proton donor (AH)/proton acceptor (B) of a sweet tastant and a commensurate AH and B at the receptor, as shown in Fig. 4. Here, Cohn's glucogene is labelled as a glycophore (Gr. *glyc*, sweet). The glucophore of Oertly and Myers is the B moiety, and the auxogluc is AH.

The interaction in Fig. 4 is shown in equation form in Fig. 5. The subscripts g and r in Fig. 5 indicate the glycophore and receptor respectively, and the superscript $\delta^{+,-}$ indicates the dipole function.

The role of symmetry is especially manifested in the sweet taste response. The dipole functions must be of nearly equal, but opposite charge. Charge imbalance leads to either an admixture of sweetness and bitterness or, as we shall subsequently see, strong imbalance leads to only bitterness. Thus, there are indeed cases where AH,B is present in the structure of a compound, and yet the compound is devoid of sweetness.

The second role of symmetry in sweet taste is particularly intriguing. Actually, it is the role of dissymmetry (chirality) that is intriguing. The fact that D-asparagine tastes sweet, while the L-antipode does not was established by Piutti (1886). In a note appended to Piutti's paper, Pasteur was led to state that the receptor for asparagine sweetness must therefore be chiral (dissymmetric), as it was capable of distinguishing between asparagine enantiomers. As a result of a long period of time, it somehow came to be tacitly assumed that D- and L-sugars must also have different tastes. A published note to the effect that the L-series of sugars were

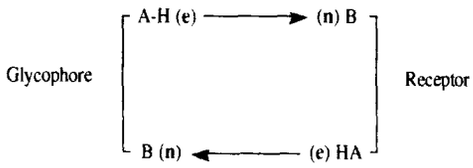

Fig. 4. Interaction of a sweet compound's AH (e) unit, along with a B (n) unit with a nucleophilic/electrophilic (n/e) or AH,B taste receptor to elicit sweet taste.

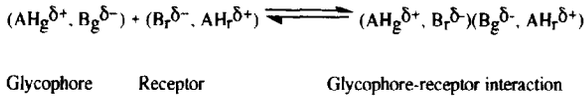

Fig. 5. Equation form of interaction of a sweet compound's AH (e) unit, along with a B (n) unit with a nucleophilic/electrophilic (n/e) or AH/B taste receptor to elicit sweet taste.

tasteless (while the enantiomers were sweet) first appeared (Boyd & Matsubara, 1962) nearly 75 years later. If the L-sugars were indeed tasteless, then the AH,B tenet is not valid. The reason why this should be so is manifested again in symmetry considerations. As a two dimensional bipartite unit, enantiomeric AH,B units are made congruent by a simple rotational operation. In other words, if the AH,B tenet is valid, then the enantiomeric forms of the sugars must generally taste alike.

When a series of L-sugars was assembled (courtesy of N. K. Richtmyer) it was found that the L-forms did indeed taste sweet (Shallenberger *et al.*, 1969), and the fact that every earlier investigator who had first synthesized an L-sugar accurately reported that it tasted sweet, was rediscovered. Two notable examples are Emil Fischer (1890) (L-glucose is purely sweet) and Wolfrom & Thompson (1946) (L-fructose is very sweet).

It was at this point that we became aware of how complicated the sweetness/structural dissymmetry relation really was. For example, not all D- and L-amino acids were respectively sweet and bitter. Some amino acid enantiomers were either equally sweet, equally bitter, or the bitter/sweet taste attributes were reversed.

To account for the sweetness of the D- and L-sugars vs the case for the sweet D- and bitter L-amino acids, we (Shallenberger *et al.*, 1969) proposed that erection of a spatial barrier at the receptor site can resolve that problem. The barrier is shown in Fig. 6.

Shortly thereafter, Kier (1972) added a third hydrophobic component to the glycophore (Fig. 7). Designated as γ, the relation to AH,B generates a scalene, or skewed, triangular arrangement. The receptor for such a glycophore is then the structural diastereoisomer of the glycophore shown in Fig. 7.

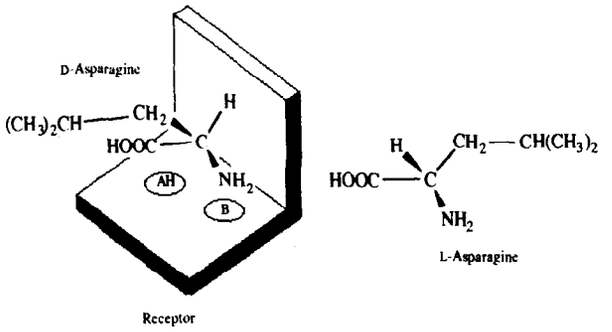

Fig. 6. A receptor spatial barrier to prevent L-asparagine from interacting with the receptor AH,B unit.

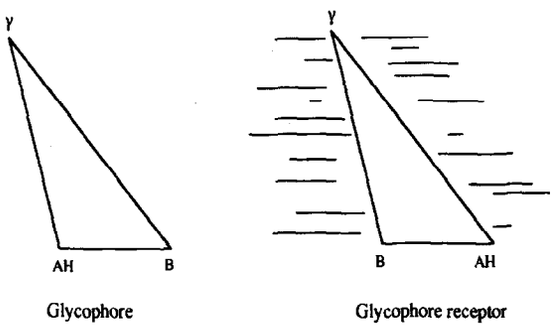

Fig. 7. The planar tripartite AH,B,γ glycophore of Kier (1972), and the diasterisomeric receptor for it.

A second option became available to account for the sweetness of sugar enantiomers and the tastlessness of L-asparagine. In the second option, steric hindrance is yet operative, but is due to the innate structure of the amino acids and is not a feature of the receptor site. In other words, because of the bulk of the rest of the molecule, AH,B of some L-amino acids point in the wrong direction for appropriate interaction with the receptor AH,B. Asparagine is a case in point, as shown in Fig. 8.

When AH,B of the L-amino acid is lined up with AH,B of the receptor, the back of the molecule faces the receptor AH,B, and precludes any concerted interaction. Resultant monopolar interactions are still possible, however, and these can then lead to a bitter note. Put another way, the side chain of an L-amino acid can effectively preclude an L-amino acid's AH,B group from interacting concertedly with a planar receptor AH,B.

It is the latter manifestation of a 'spatial barrier' that seemed to be correct. Hereafter, the plot thickens, but the opportunity arose to apply to taste even another established chemical principle, that of the idea of prochirality.

The occurrence of prochirality was recognized by Ogston (cf. Bentley, 1978) as a type of recognition chemistry responsible for transforming a seemingly symmetrical compound into one that is chiral, at least as far as an enzyme transformation site is concerned.

The notion of prochirality or pseudochirality originated with the observation (Ogston, 1948) that an enzyme, such as alcohol dehydrogenase is able to distinguish between the two protons of a symmetrical substrate, ethyl alcohol. Alcohol dehydrogenase (ADH) selectively removes a specific methylene (—CH_2) proton (asterisked), and a hydroxyl proton from ethyl alcohol to form acetaldehyde, and does so repeatedly when the reaction is reversed and brought forward again (Fig. 9).

Thus, with labelled protons, ethanol seems to be dissymmetric. By the same token, the enzyme aconitase readily distinguishes between the two CH_2COOH groups of citric acid, a symmetrical compound. There are many other examples.

There is no inherent three-dimensional configurational dissymmetry in the ethanol structure. The so-called

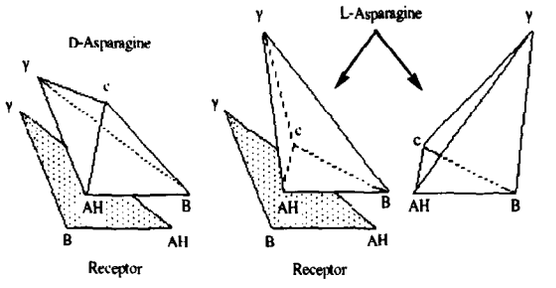

Fig. 8. Interaction of D-asparagine with a sweetness receptor, and inability of the enantiomer to interact with the receptor due to steric hindrance imposed by the L-amino acid's side chain (c).

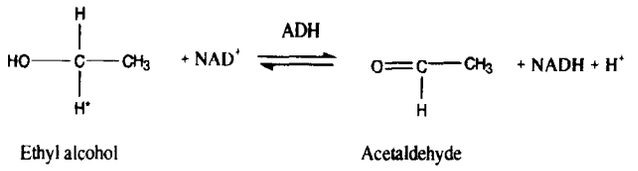

Fig. 9. Action of alcohol dehydrogenase on ethanol to form acetaldehyde.

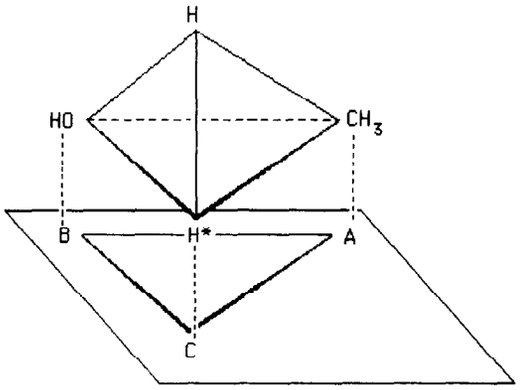

Fig. 10. 'Dissymmetric' recognition interaction of ethanol with an alcohol dehydrogenase receptor.

dissymmetry is imposed at the recognition level of the reaction prior to enzymic transformation. Because of steric hindrance, the alcohol dehydrogenase receptor ABC in Fig. 10 recognizes only the asterisked proton of ethyl alcohol, thus rendering a seemingly symmetrical compound into one that is chiral.

An implication of prochirality is that either of the two ethanol protons can be viewed as being prochiral. By substituting either one of them with a fourth ligand the molecule will become chiral.

The salient prochiral feature of sweetness chemistry is that the case recognized by Ogston is *reversed*, and the sweetness receptor can appear to transform a chiral compound into one that is seemingly symmetrical. The consequences of the situation mandate that the initial chemistry of sweet taste occurs in 'flatland', and it must also be a recognition type of functional group arrangements and functional group interactions. Binding is neither required, nor essential, which serves to explain the extremely low energy requirements for the sweetness of sugars (Lancet & Ben-Arie, 1991).

When everything known about the sweetness of substances is taken into account, particularly the chiral anomaly that arises with respect to the sweetness of enantiomeric amino acids and sugars, its resolution indicates that there is no need for a topologically defined receptor.

High potency sweetness

If a compound contains a group or grouping appropriately located in the molecule so as to have an inductive effect on the glycophore, AH/B, sweetness potency is enhanced. Some such groups are a halogen atom, an NO_2 group, and even a centre of unsaturation. As chloroform sweetness is derived in part from the electron-withdrawing capacity of the chlorine substituents, which render the lone proton 'acidic', it is not now too surprising to learn that sugar chloro-derivatives can be endowed with highly potent sweetness. Generally, the inductive effect is about equal on both AH and B, and the symmetry for the equation for sweetness is maintained, but sweetness potency is magnified.

Again, there seems to be little need for a topologically defined receptor to account for high-potency sweetness. While analogies to receptor/substrate binding, through lock and key mechanisms, are attractive, they serve in the final analysis, to promote a chemical transformation on the substrate, or to elicit a pharmacological effect. In taste chemistry, the substrate is not transformed, nor is there a direct physiological effect.

Bitterness of organic compounds

Among the bitter organic substances are caffeine, brucine, phenylthiocarbamide (PTC) etc. In general, bitter-tasting organic substances have a basic reaction nature. Small alterations in the structure or composition of an organic compound are also sufficient to convert a sweet taste to bitter, and vice versa. Perhaps the most intriguing examples are dulcin vs PTC (Fig. 11) and α-D- vs β-D-mannose (Fig. 12).

The only difference between dulcin and PTC is substitution of a sulfur atom for an oxygen atom. Both can be viewed as a nucleophilic site, and along with the NH_2 group, constitute an AH,B unit. In the case of PTC, however, and with respect to nucleophilicity, the sulfur atom is not as strong as an oxygen atom. It would seem that the electronic bilateral symmetry for the sweetness of dulcin has now been altered, and in effect PTC is a 'soft' base.

An even more subtle difference exists between the two mannose anomers. For the α-D-anomer, the hydroxyl group at carbon atom number one is perpendicular to,

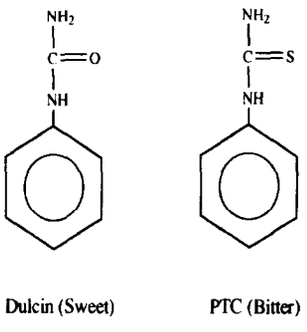

Fig. 11. Dulcin versus PTC.

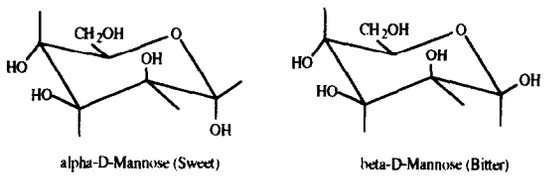

Fig. 12. Alpha-D-mannose versus beta-D-mannose.

and 'beneath' the average plane for the ring. For the β-D-anomer it is 'above' and parallel to the average plane for the ring (Fig. 12).

In effect, the configuration is unique among sugar structures as three contiguous oxygen atoms occupy a common plane to create an extremely unfavourable (unbalanced) dipole moment. β-D-mannose is now also a 'soft' base, and might be expected to taste bitter, whereas the alpha-anomer is not a 'soft' base, and might be expected to taste sweet.

High potency bitterness

Organic substances also have potential for high-potency bitterness, which is not true for bitter-tasting salts (where inductive effects are not possible). The picrophore for bitterness seems, in many instances, to be similar to the AH,B unit for sweetness (Kubota & Kubo, 1969), but it is a dissymmetric AH,B, as proposed for PTC. The reason for high potency bitterness would appear to be that the complex structure of an organic compound gives rise to the potential for dissymmetric inductive effects to occur, either by virtue of an innate structure, or through substitution with appropriate electron withdrawing groups. Denatonium chloride is an excellent example.

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