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Taste recognition chemistry

Robert S. Shallenberger

Cornell University, Geneva, NY (USA)

Abstract: The basic tastes (sweet, salt, sour, and bitter) have common chemical features, and are initiated by chemical recognition reactions with the receptor that are transmitted through water. Although no chemical products are formed, the tastes are differentiated by the symmetrical nature of the interactions. Sweetness results from a symmetrical anti-parallel dipolar interaction, and true saltiness from symmetrical anti-parallel ionic interactions. On the other hand, sourness is elicited by a dissymmetric interaction between the hydrogen ion and a nucleophilic component of the receptor. Bitterness arises when either dipolar organic or ionic inorganic compounds have a dissymmetric saporous unit that leads to a dissymmetric interaction with the receptor.

GENERAL PROPERTIES OF TASTE

The purpose of the five classic senses, and the general chemical nature of the basic tastes, has long been the object of study and speculation. Although many different senses are recognized, the purpose and function of sight, hearing, touch, taste, and smell is well established (ref. 1). They serve to afford an assessment of the nature of the immediate environment. Although the nature of the stimuli differ, a nerve impulse is generated, and the initial interaction energy is many powers of ten *lower* than the energy of the nerve signal. Sensory response systems therefore possess an amplification mechanism (ref. 2). The response to sensory stimuli is also rapid, and taste is perceived within 50 milliseconds. As the stimuli for all tastes is transmitted through water, water solubility is prerequisite for all tastes.

CHEMICAL NATURE OF TASTE

Taste is classified as a chemical sense simply because the four basic tastes are caused by different chemicals. Other chemical senses are olfaction, and the common chemical sense, and they are readily distinguished from the mechanical senses of sight, touch, and hearing. The mechanism by which chemicals elicit a specific sensation, such as sweet, salt, sour or bitter, is arguable. One school of thought is that there are receptors that are specific for each taste. This would make taste unique among the senses as the other senses do not display receptor specificity. For example, there are no specific receptors for different colors, different sounds, or different textures. Nevertheless, geometric receptors of varying size, shape, and complexity have been proposed to account for the wide variety of chemical substances capable of eliciting sweetness alone (sugars, salts, amino acids, peptides, oximes, proteins, etc.).

The receptor for sweetness proposed by Temussi et al. (ref.3) is a shallow contour model within which most sweetening agents seem to fit. In this model it is proposed that the better the fit, the higher the sweetness potency of a substance will be. Still other three-dimensional sweetness receptors have been suggested (refs. 4 and 5), and one (ref. 6) is unique in that it contains eight different sites. In this case it is proposed that sweetness potency is proportionate to the number of sites that interact with the sweetener. The primary objective leading to the development of the latter model was derivation of a reason for high-potency sweetness. Unfortunately, and because it is so complex, the model is incapable of making any stereochemical distinction between D-asparagine (sweet) and L-asparagine (tasteless).

In the final analysis, the need for a three-dimensionally defined (space-filling) sweetness receptor is open to question. Lock and key, or complex fits between a tastant and a receptor, is not commensurate with either the speed with which tastes are perceived, or with the role a sensory response plays in evaluating the immediate environment. Moreover, the derivation of an explanation for the anomalous tastes of some enantiomers is of fundamental importance to the elucidation of taste chemistry mechanisms (ref. 7). To be valid, any taste theory, or model, must be able to account for the taste characteristics of the enantiomeric sugars and amino acids.

Other taste features that a valid taste theory or receptor model must be able to explain are: (1) The fact that high-potency taste occurs only among the *organic* substances that elicit the sweet and bitter taste modalities. (2) The fact that only minor alterations in the composition, but not the shape, of a substance will change the taste from sweet to bitter, or *vice versa*. For example, the mere substitution of a sulfur atom for an oxygen atom in the structure of dulcin will change the taste from sweet to bitter. (3) The

fact that dilute solutions of sodium chloride, below the threshold concentration for saltiness, are as sweet as sucrose. (4) Treatment of the tongue with extracts of the miracle berry (*Synespalum dulcifum*) causes acids to taste sweet, and sweetness potential parallels the acid's potential hydrogen ion concentration. (5) The taste of mixtures of substances is analytic, i.e. no new tastes are generated, and the taste of the individual components of a mixture can be identified. (6) The recognition thresholds of pairs of substances in admixture are proportionately elevated, a fact that establishes that there is competition between tastants for a common receptor.

In an attempt to account for the aforementioned features of taste, it was proposed (ref. 7) that the different tastes are elicited by different chemical tastant-receptor interactions, all of which are variations on a common electrostatic theme. It was also proposed that chemical interactions do not require either binding with, or space-filling geometric congruence with special receptors, even for sweetness. In those cases where the tastant-receptor interactions were electronically balanced (symmetrical), the resulting taste was either sweet or salty. When the interactions were unbalanced (dissymetric), they were characteristic of the sour and bitter tastes. The symmetrical/dissymetrical taste classification was made all the more plausable by the fact that the chemical interactions responsible for different tastes do not lead to the formation of chemical products. If they did, all water soluble substance would have a mixed tastes, and the notion that there are four empirical primary tastes probably never could have been derived.

It was also proposed (ref. 7) that high-potency taste can be expected to occur only among sweet and bitter organic substances because the forces responsible for high potency taste are inductive, and can only occur over the framework structure of a complex organic compound. As the chemical principles of mass action and chemical equilibria apply to all tastes, the general mechanism for non-binding taste initiation was described as *taste recognition chemistry*, i.e., an interaction that is transmitted through water. The recognition mechanism neatly complements those applications of chemical theory to taste that have been made in the past, and which have served to greatly improve general understanding of taste chemistry processes.

CHEMICAL THEORY APPLIED TO TASTE

When ionization theory first appeared, it led Cohn (ref. 8) to observe that the sour and salt tastes are generally caused by substances that ionize in solution, whereas the sweet and bitter sensations are usually caused by substances that do not ionize. That simple classification indicated, at the very outset, that different chemical reactions are probably responsible for the different tastes. Cohn also proposed that a pair of functional groups (a *glucogene*), contained within the structure of an organic compound, were needed to elicit sweetness. Oertly and Myers (ref. 9), then assigned complementary, but different chemical functions to the component parts of the glucogene. Without describing those functions, one was designated to be an *auxogluc*, which was usually a hydrogen atom, and the other was designated to be a *glucophore*. Each was stated to be incapable of eliciting sweetness without the other. Parenthetically, the observation of Oertly and Myers came about through application of dystuff theory, and it is now known (ref. 10) that a third component is needed in order for a substance to possess dye activity . The third component serves to impart water solubility to the substance. Subsequently, Kodama (ref. 11) recognized the need for "vibratory hydrogen" in order to impart sweetness to a compound, and it soon became clear that the auxogluc acts primarily as a proton donor, while the glucophore functions as a proton acceptor (see also ref. 12).

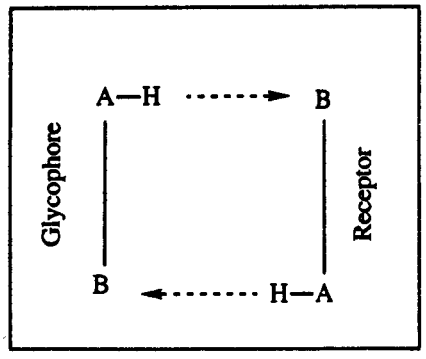

Fig. 1. Concerted interaction between glycophore and receptor dipoles.

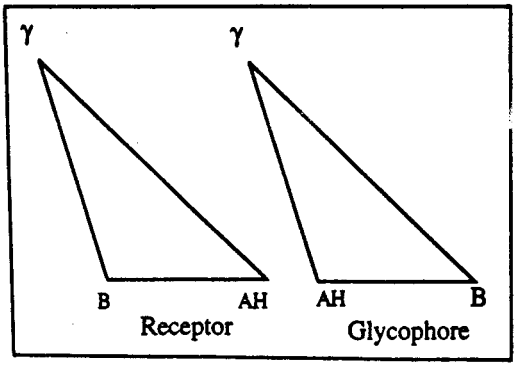

Fig. 2. The tripartite glycophore and receptor.

With the advent of hydrogen bonding theory, the glucogene common to all sweet organic substances came to be described as an AH,B hydrogen bonding system (ref. 13), now described (ref. 7), as a *glycophore* (Gr. *glyc*, sweet; *phoros*, to carry)[a]. As shown in Fig. 1, it was proposed that sweet taste is elicited by concerted intermolecular, antiparallel hydrogen bonding between glycophore and receptor dipoles. The vicinal hydroxyl groups of sugars and other polyols, and also the amino acid group of amino acids, peptides, and proteins are among the usual dipolar systems that were recognized as glycophores. Among the more unusual dipolar glycophores are the unshielded proton and an adjacent chlorine atom in chloroform, and the ring hydrogen atom *ortho* to an oxime group of perillaldehyde oxime.

One criticism directed toward the AH,B theory was that it had no predictive power. Additionally, and because the glycophore was merely a bipartite unit, it could not account for the purported "fact" that the L-sugars are "tasteless." As initially proposed, the AH,B theory would require that the L-sugars must taste sweet, which seemed to be a flagrant violation of the tenet that only the natural forms of enantiomers can possess biological activity. When the present author (ref. 14) found that L-sugars do in fact taste sweet, the credibility of the AH,B thesis was reestablished. Subsequently, it was found that every investigator who first reported the synthesis of an L-sugar had also duely recorded that it tastes sweet.

Still another criticism directed toward the AH,B thesis was that it offered no explanation for high-potency sweetness. The proposal that served to initiate resolution of these problems was made by Kier (ref. 15) to the effect that the glycophore contains a third component. Kier proposed that the third component is a dispersion site X, and is capable of participating in charge-transfer or dispersion bonds. The suggestion also led to distance parameter assignments for the tripartite glycophore, which established the basis by which the glycophore is rendered chiral. In essence the three sites had the form of a scalene triangle, which possesses two-dimensional chirality. As the third glycophore component needed to also function as an inductive group, and to impart an element of lipophilicity to the sweet molecule, it was later designated as γ (ref. 17)[b].

When a functional counterpart to the third glycophore component is incorporated into the receptor, also as a third component with lipophilic (or hydrophobic) properties, the relation between the tripartite receptor and the tripartite glycophore came to be designated as shown in Fig. 2. The relation between the labeled scalene structures is one of two-dimensional *diastereoisomerism*, or stereoisomers that are not enantiomers. The glycophore and the receptor could then be positioned to interact (the superpositioning of one over the other) through a slide operation. The chirality attributes now displayed by the tripartite glycophore and receptor, although of two-dimensional nature only, served to established the basis for resolving the long-standing sweetness chiral anomaly associated with the three-dimensional chirality displayed by the enantiomeric forms of the sugars and amino acids (ref. 7).

RESOLUTION OF THE CHIRAL SWEETNESS ANOMALY

The observation that symmetry, and its first cousin "dissymmetry" (chirality), play an important role in the taste of organic substances was first recognized by Piutti and Louis Pasteur (ref 17) over a century ago. Because the D-asparagine synthesized by Piutti tasted sweet, while the L-form is tasteless, Pasteur proposed that the sweet taste receptor must therefore be dissymmetric[c]. While Pasteur used the term "dissymmetric" to imply that the receptor topography was of three-dimensional nature, it is now known that only certain amino acid enantiomers have different tastes, and that both the D- and L- forms of the sugars are sweet. Thus, while the sweetness receptor might very well be dissymetric, it had to be a special form of disymmetry that applied to the enantiomers only under special conditions. The type of dissymmetry that might be recognized only part of the time is the dissymmetry that may be displayed by

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[a] Similarly the saporous units of a salty substance are a halophore (Gr. *hals*, salt), for a bitter substance a picrophore (Gr. *pikros*, bitter), and the hydrogen ion is simply an acidophore.

[b] The Greek letter for c, hence the glycophore components are a mixed form of A,B,C. The Greek letter "gamma" also serves to indicate that one function of γ, as a component of the glycophore and the receptor, is that of a "greasy" or lipophilic component.

[c] Pasteur used the term "dissymmetric" to indicate that certain chemical structures and objects (e.g., a spiral staircase or regular helix), while appearing to be quite symmetrical, were nevertheless not superposable upon their mirror-image. Hence, "left" and "right" forms were possible. As superposibility is the absolute criterion for proof of symmetry, Pasteur coined the term "dissymetric" to describe those structures that seemed to be symmetrical, and yet were non-superposable. The current term is "chirality."

the surfaces of objects (ref. 7). In other words, it must be only the *faces* of the molecules containing the glycophore that are chiral, and function to elicit sweet taste. Whether the overall space-filling shape of the molecule is chiral or symmetrical is immaterial because the form of chirality that is operative in sweet taste chemistry is contained in only two-dimensions ("flatland"), and its manifestation in only two dimensions leads to intriguing taste consequences.

One established form of two-dimensional (plane or surface) chirality is known as *prochirality*. In this case molecules that are *symmetrical* are transformed in certain biological reactions in such a manner as to suggest that they are in fact chiral (ref. 19). For examplr, ethanol is a symmetrical molecule, and yet in the formation of acetaldehyde from ethanol, the enzyme alcohol dehydrogenase always interacts with the same proton. Put another way, the enzyme recognizes that the two ethanol protons are somehow "different," or that ethanol is in some way "chiral." At the outset of the enzyme-substrate interaction the planar tripartite alcohol dehydrogenase receptor (Fig. 3) recognizes only the face of the ethanol molecule that contains the proton labled H-2, the CH_3 group, and the OH group of the "plus" form. This happens because only these three groups can be positioned (by rotation) over, and directed *toward* the planar receptor H, CH_3, and OH sites. CH_3 and OH of the so-called entiomer "Minus ethanol" can be positioned over their appropriate receptor sites (slide operation), but H-2 is then directed *away* from the receptor, and incapable of interacting with it. It is this phenomenon that causes the perfectly symmetrical ethanol molecule to seemingly appear to be chiral when acted upon by the enzyme. Such prochiral behavior of symmetrical molecules has now been observed for a large number of biochemical interactions (ref. 20).

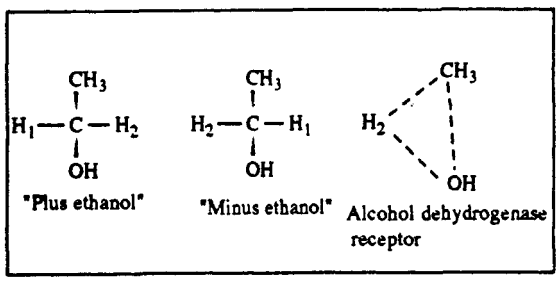

Fig. 3. Ethanol "enantiomers" and the planar receptor for the "plus" enantiomer.

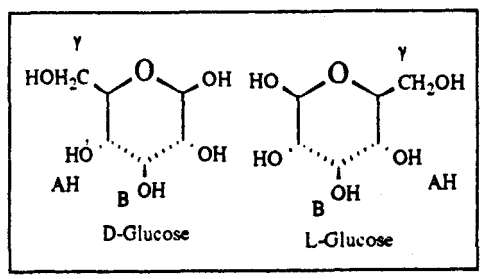

Fig. 4. The common AH,B,γ tripartite glycophore in glucose enantiomers.

If selected faces of a symmetrical molecule can exhibit surface chirality, i.e., prochirality, it follows that selected faces of a chiral molecule can also display two-dimensional symmetry, i.e., they are *prosymmetrical* (ref. 7). Prosymmetrical surface phenomena are operative in those cases where the taste of enantomers is alike, as for D- and L-glucose. Although they are indeed spatial enantiomers, the faces of D- and L-glucose that contain the glycophore are identical. The congruence derives from the fact that there are no steric barriers to impede interaction of either glycophore with the tripartite receptor (Fig. 2). As shown in Fig.4 the *planes* formed by AH,B,γ for D- and L-glucose are made commensurate for interaction with the tripartite receptor by either a slide operation (D-glucose) or by a simple rotation operation (L-glucose). This is not the case for amino acid enantiomers with different tastes. The tripartite glycophore of D-asparagine is commensurate with the tripartite receptor shown in Fig. 2, but the carbon chain for the L-structure impedes tripartite interaction of the L-glycophore with the receptor.

In the first attempt to account for the sweetness disparity between D- and L- asparagine it was proposed (ref. 14) that a spatial barrier, as a component part of the receptor, might prevent L-asparagine from interacting with it. From the prosymmetrical and prochiral considerations presented above, however, it would now appear that there is indeed a steric barrier that governs the taste attributes of the enantiomeric asparagine compounds, but the steric barrier is imposed by the framework structure of L-asparagine, and is not a structural feature or component of the receptor.

SYMMETRY IN TASTE CHEMISTRY INDUCTION

The symmetry principle that plays a major role in governing the nature of the weak interactions characteristic of the different tastes is known as *bilateral symmetry*, or the combination of "left" and "right" in proper proportion (ref. 21). When the combination deviates from proper proportion, the symmetry is said to be degraded, and can be described as *bilateral dissymmetry*. To elaborate upon the

notion that tastes are elicited by different chemical interactions with special symmetry attributes, it is held that both a simple dipole, such as an amino acid zwitterion, or any salt (M^+X^-), can serve as examples of bilateral symmetry or dissymmetry (ref. 7). As dipoles and ionic substances are composed of nucleophilic and electrophilic components, either the receptor for ionic or dipolar interactions (both of which are essentially electrostatic) can be designated as *n* and *e* (ref. 22). Alternatively, because the major functional component of the receptor is probably a dipole, it can be designated as AH,B and yet be capable of interacting electrostatically with either dipolar or ionic substances.

Pseudo-chemical equations for the sour, salty, and sweet tastes are given in Table 1, along with examples of known chemical reactions. The latter are distinguished from the taste equations in that they yield a product, and both sides of the equation are electronically balanced *i.e.*, they are symmetrical. On the other hand, and at the outset, taste equations may be either symmetrical or dissymmetrical, depending upon the nature of the interaction between the tastant and the receptor.

Table 1. Equations for the sweet, salty, and sour tastes for comparison with analogous stoichimetric equations.

Taste equation		Analogous stoichimetric equation	
$HA + AH^+,B^- \rightleftharpoons (AH^+)(A^-) + (H^+)(B^-)$		$HCl + Na\,OH \longrightarrow (Na^+)(Cl^-) + (H^+)(OH^-)$	
Acid Receptor	Sourness interaction	Acid Base	Products
$MX + AH^+,B^- \rightleftharpoons (AH^+)(X^-) + M^+(B^-)$		$NaCl + AgNO_3 \longrightarrow (Ag^+)(Cl^-) + (Na^+)(NO_3^-)$	
Salt Receptor	Saltiness interaction	Salt Base	Products
$AH,B + AH^+,B^- \rightleftharpoons (AH^+)(B^-) + (AH^+)(B^-)$		$HOH + HOH \rightleftharpoons$	H H.....OH....OH....
Dipole Receptor	Sweetness interaction	Free water	H-bonded water

Sour taste

The analogous equation for sour taste given in Table 1 is the equation for the titration of an acid with a base to yield a salt plus water, i.e., it is a *neutralization* reaction. Because the equation is electronically balanced, it is symmetrical. In a neutralization reaction, a solution of an acid is titrated to pH 7 by a base, and the titration coefficient is the same for all acids that have the same normal concentration. Whether an acid is weak (only partially dissociated in solution) or strong (completely dissociated in solution), the fact that their solutions have different pH has no bearing on their titratable acidity.

The sour taste equation differs from the neutralization equation in that sourness is assigned only to the interaction between the hydrogen ion and the receptor, and it is easily reversible. The titration equation yields a product, and is irreversible. However, the two equations are alike in that both serve as an index of an acid's total *potential* hydrogen ion concentration (ref. 23). Thus, for both sour taste and the neutralization reaction, chemical equilibria and mass action phenomena are operative. As a consequence, at equal normalities weak acids have the same sourness potential as do strong acids, even though the initial pH of their solutions is different. Sour taste chemistry, and sour taste intensity, is therefore due to the "titration" of the acid by the nucleophilic component of the receptor (B^-). However, and because chemical products are not formed, the overall electronic nature of the sour taste reaction is is easily reversed. It is also bilaterally dissymmetric. The ease with which the reaction is reversed, and the fact that it is transmitted through water, is consistent with the general purpose and function of the taste sense.

Salt taste

Unlike the case for sourness, both the anion and the cation have a role in eliciting the saltiness sensation (ref. 24), but only sodium chloride elicits a "true" salt taste (ref. 25). Other salts have mixed tastes, which is usually described as bitter, medicinal, or unpleasant. Due to the combined ionic size and electromotive potential characteristics of anions and cations, the sodium and chlorine ions have the highest degree of ionic bilateral symmetry that is possible (ref. 7). Thus, for the salt taste equation shown in Table 1, only NaCl would indeed elicit a true salt taste. For other salts, the symmetry of the component ionic pair is degenerate, and the taste is proportionately more "bitter." The salt taste interaction then is analogous to common electrostatic interactions among ions, such as the formation and precipitation of silver chloride when the a saline solution is treated with silver nitrate (Table 1). Because the solubility product constant of silver chloride is so low, the analogous equation is also irreversible. In the true salt taste reaction, because the reaction is so weak, no products are discernible, and the interaction is easily reversible, and is essentially symmetrical.

Sweet taste

Sweet tasting organic substances are usually dipolar compounds, and the taste equation for sweetness shown in Table 1 is a linear depiction of the interaction shown in Fig. 1, *i.e.*, a concerted intermolecular hydrogen bonding interaction between a proton donor (AH) and a proton acceptor (B) of a sweet tastant interacting with a sterically commensurate AH and B at the receptor (refs.7, 13). A more complete expression of the dipolar chemistry for the sweetness recognition interaction is:

$$(AH_\gamma{}^{\delta+}, B_\gamma{}^{\delta-}) + (B_r{}^{\delta-}, AH_r{}^{\delta+}) \rightleftharpoons (AH_\gamma{}^{\delta+}, B_r{}^{\delta-})(B_\gamma{}^{\delta-}, AH_r{}^{\delta})$$

The subscripts γ and r indicate the glycophore and receptor respectively, while the superscript δ indicates a dipolar electrostatic function.

Both the sweetness equation and the analogous stoichiometric equation shown in Table 1 are characterized by weak initial interactions and easy reversibility, but unlike sourness and saltiness, *both* equations are devoid of products, unless the interaction analogy happens to lead to a change of state. The formation of the tridymite form of water as the repeating unit in the structure of ice (Fig. 5), serves as an analogous sweetness example, but is still easily reversible. Another stoichiometric sweetness example is the propensity for the lower molecular weight aldehydes and ketones to dimerize (ref. 26), as shown in Fig. 6. The union of two molecules of glycolaldehyde to form a dimer is characteristic of crystalline form of the substance. However, upon dissolution in water, the glycoaldehyde dimer rapidly

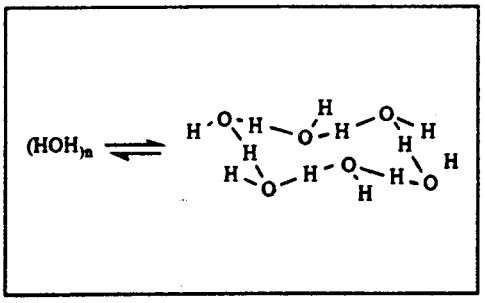

Fig. 5 Formation of the tridymite form of water.

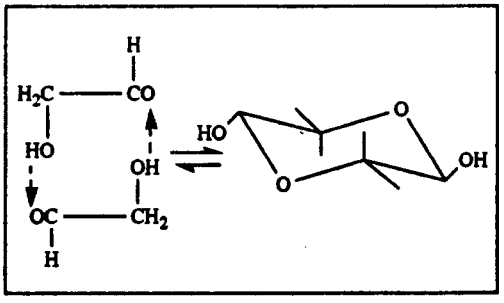

Fig. 6. Dimerization of glycolaldehyde.

reverts to the monomeric form. Although these "products" afford the crystalline form of the substances, they nevertheless are examples of the type of interactions characteristic of the initial chemistry of sweetness.

The symmetry attributes of sweetness are manifested in symmetrical dipolar properties, such as found for the sugars and neutral amino acids. Deviations from dipolar symmetry leads to increasing bitterness and culminate in compounds that are essentially asymmetric in that they possess either a positive or negative monopolar function only. Picric acid, or the alkaloidal substances are examples examples of compounds that have asymmetrical taste properties.

ROLE OF WATER IN TASTE RECOGNITION CHEMISTRY.

One reason for the requirement that a tastant must be soluble in water is that water is needed for a tastant to gain access to the receptor. A second reason is that the tastant-receptor interactions are transmitted through water, and as a consequence are all the more easily reversible. For sourness and saltiness, the interaction is essentially electrostatic, but with distinguishing symmetry attributes. For sweetness, the mechanism of transmission through water is also electrostatic, and probably occurs through bilaterally symmetrical cooperative hydrogen bonding, or (O-H····O-H····O-H····O-H) and (H-O···H-O···H-O···H-O). As a sequence of only six bonds can nearly double the energy of a single hydrogen bond, the process of cooperative hydrogen bonding can be expected to lead to a significant energetic advantage, or amplification (ref. 27).

Without question, many of the seemingly anomalous aspects of taste neatly resolve through the application of the notion of recognition phenomena transmitted through water. Foremost among them is that such phenomena are surface phenomena, and the sweetness chiral anomaly associated with the taste of enantiomers can be explained through application of two-dimensional prosymmetry and prochirality principles. Secondly, recognition interactions, because they are transmitted through water can in fact take place over a distance, an established feature of other sensory phenomena. The interactions also occur rapidly, which precludes the need for either binding or lock and key types of congruency between a tastant and receptor.

While analogies to receptor/substrate binding through lock and key mechanisms are attractive, they serve, in the final analysis, to promote biochemical transformations of substates, or to elicit pharmocological effects. In taste chemistry, because the interactions are recognition interactions only, substrates are not transformed, new products are not generated, and no physiological property has ever been associated with the taste of substances. If an organic compound contains a group or grouping appropriately located in the molecule so as to have a strong inductive effect on the glycophore AH/B for sweetness, or on the picrophore for bitterness, taste potency can be expected to be enhanced exponentially. Some such groups are halogen atoms, an NO_2 group, and even a center of unsaturation.

In conclusion, reasons for the interrelations among the tastes become clear when the basic tastes are assigned to different chemical recognition reactions. Among them is the fact that treatment of the tongue with extracts of the miracle fruit not only causes acids to taste sweet, but their sweetness intensity is directly proportionate to their sourness intensity (ref. 28). The latter is, of course, due to equilibrium phenomena that allow weakly dissociated acids to function as strong acids in taste interactions. Due to hydration characteristics, dilute solutions of sodium chloride and potassium chloride, i.*e.*, at concentrations below those required to elicit saltiness, taste distinctly sweet (ref. 29). The observation is in accord with the symmetry requirements proposed not only for true saltiness, but also for sweetness. The bitterness of substances, whether elicited by organic compounds, or by salts other than sodium chloride, is also in accord with the aforementioned recognition interactions. In all cases of bitterness, symmetry seems to be degraded or broken. This is due either to lack of a symmetrical dipole function, or because of a disparity in the size and electromotive potential properties of individual ions. When an organic compound is transformed from sweet to bitter by simple substitution, as in the case for dulcin, it would appear that the symmetry of the dipolar grouping required for sweetness is simply degraded.

REFERENCES

1. O. Lowenstein. The Senses, pp. 12-14, *Penguin Books*, Baltimore (1966).
2. G.J. Henning, In Gustation and Olfaction (G. Ohloff and A.F. Thomas, eds.)pp. 239-242. Academic Press, London and New York (1971).
3. P.A. Temussi, F. Lelji, and T. Tancredi. In *Sweeteners. Discovery, molecular design, and chemoreception* (D.E. Walters, F.T. Orthoefer, and G.E. Dubois, eds.) pp. 143-161. ACS Symposium series 450 (1991).
4. H. Rohse and H.-D. Belitz. In *Sweeteners. Discovery, molecular design, and chemoreception* (D.E. Walters, F.T. Orthoefer, and G.E. Dubois, eds.) pp. 176-192. ACS Symposium series 450 (1991).
5. J.C. Culbertson and E. Walters. In *Sweeteners. Discovery, molecular design, and chemoreception* (D.E. Walters, F.T. Orthoefer, and G.E. Dubois, eds.) pp. 214-223. ACS Symposium series 450 (1991).

6. J.-M. Tinti and C. Nofre. In *Sweeteners. Discovery, molecular design, and chemoreception* (D.E. Walters, F.T. Orthoefer, and G.E. Dubois, eds.) pp.206-213. ACS Symposium series 450, 1991.
7. R.S. Shallenberger. *Taste Chemistry*. 613 pp.Blackie Academic & Professional, London, (1993).
8. G. Cohn . *Die Organischen Geschmackstoffe*. F. Siemenroth, Berlin (1914).
9. E. Oertly and R.G. Myers. *J. Am. Chem. Soc.* **41**, 344-7 (1919).
10. M.C. Bonneau. (1955) J. Chem. Educ. 72, 724-25 (1995).
11. S. Kodama. (1920). *J. Tokyo Chem. Soc.* **41**, 495-534 (1920).
12. R.B Warfield, R.B. *Abstr. Papers Am. Chem. Soc.* 126th Meeting Div. Agric. and Food Chem., p. 15A (1954).
13. R.S. Shallenberger and T.E. Acree.*Nature* **216**, 480-82 (1967).
14. R.S. Shallenberger, T.E. Acree and C.Y. Lee. Nature 221, 555-6 (1967).
15. L.N Ferguson and L.G. Childers. (1960). *J. Org. Chem.* **25**, 1971-5 (1960).
16. L.B.Kier. *J. Pharm. Sci.* **61**, 1394-7 (1972).
17. R.S. Shallenberger and M.G. Lindley. Food Chem. **2**, 145-53 (1977).
18. M. A. Piutti. *C.R. Acad. Sci., Paris* **103**, 134-7 (1886).
19. A.G. Ogston. Nature 162, **963** (1948).
20. R. Bentley. *Molecular Assymmetry in Biology*, Academic Press, New York (1969).
21. H. Weyl. *Symmetry*, pp. 4-5. Princton Univ. Press (1952).
22. H.-D. Belitz, W. Chen, H. Jugel, W. Stempfl and H. Wieser. *In Flavour '81*, (P. Schreier, Ed.) pp. 741-55. W. DeGruyter, Berlin (1981).
23. R.B Harvey . *J. Am. Chem. Soc.* **42**, 712-4 (1920).
24. H. Kionka and F. Strätz, (1922). *Arch. Exp. Path.* **95**, 241-57 (1922).
25. C. Pfaffmann, C. (1959). In *Handbook of Physiology-Neurophysiology I.* (J. Field, Ed.). Am. Physiol. Soc., Washington, DC, pp. 507-33 (1959).
26. R.S. Shallenberger. *Advanced Sugar Chemistry*, pp.64-68. Avi Pub. Co., Westport, CT (1982).
27. G.A. Jeffrey. In *Sweet Taste Chemoreception*. p.9 (M. Mathlouthi, J.A. Kanters, and G.G. Birch, eds.) Elsevier Applied Sci., London (1993).
28. K. Kurihara. In *Handbook of Sensory Physiology. IV. Chemical Senses. 2. Taste.* pp. 363-78. (L.M. Beidler, Ed.). Springer-Verlag, Berlin (1971).
29. L.M. Bartoshuk, C. Murphy and C.T. Cleveland. *Physiol. Behav.* **21**, 609-13 (1978).