

A structure common to sweet-evoking compounds

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It is hypothesized that the property common to all sweet-evoking compounds is that of being a proton acceptor. Furthermore, the initial step of this mechanism is suggested as being the removal of protons from gustatory receptor sites.

The purpose of this paper is to suggest a chemical structure which is common to all compounds which evoke the sweet quality. The first clue was offered by Höber and Kiesow (1898) who reported that bases were sweet over a reasonable concentration range, above which they became "biting." They concluded that the hydroxyl ion was responsible for the sweet quality. Their finding was confirmed and their conclusion supported by Renqvist (1919). The next logical step was to say that the hydroxyl ion is responsible for sweet in all inorganic compounds. However, a number of dissimilar compounds are also sweet-evoking, but do not appear to have hydroxyl ions in their structures. These compounds are mainly the beryllium salts (Renqvist, 1919) and various other salts at low concentration, e.g., NaCl, KCl, and LiCl (Höber & Kiesow, 1898; Renqvist, 1919; Dzendolet & Meiselman, 1967a). Dzendolet and Meiselman (1967b) suggested that the sweet-evoking property of the latter salts is due to the result of an ion-water interaction, specifically with the cation of these salts. This interaction, which results in the "localized hydrolysis" of Harned and Owen (1950, p. 385), will be described in detail to show how it leads to the sweet-evoking property of inorganic compounds in general. Specifically, the hypothesis proposed here is that sweet-evoking inorganic salts have the hydroxyl ion present in their structures.

Although the various cations mentioned above are not ordinarily considered as possessing a hydroxyl ion structure, they do acquire it in solution by the localized hydrolysis just mentioned. The cation-water interaction initially leads to a structure shown in Fig. 1a, in which water molecules are oriented about the cation with the oxygen atoms nearest the cation. This orientation results because of the attraction between the positive charge of the cation and the negative charge associated with the oxygen atom. In addition, the hydrogens are repelled because of their positivity. Harned and Owen (1950, p. 385) pointed out that a strong interaction between the cation and the water molecules results when the electrical field of the cation is intense, either because of a smaller size of the ion for a given electrical charge, e.g., the lithium ion compared

with the sodium, or because of an increased charge coupled with the same or a smaller sized ion, e.g., the divalent beryllium ion compared with the monovalent lithium ion. The result of a strong interaction is to repel one, or possibly more, hydrogen ions or protons away from the layer of oriented water molecules surrounding the cation. This process can be represented by the structure in Fig. 1b. In addition, the proton will be aided in being repelled from this layer, if a proton acceptor, such as a base or other similar ion, were also present in the solution. In this case, the proton will oscillate between these two structures. It is clear that this localized hydrolysis does lead to a structure which contains the hydroxyl ion, and it is this structure which is responsible for evoking the sweet quality.

The saliva also plays a role in this mechanism. The saliva is somewhat basic and, thus, serves as a proton acceptor. If it were not basic, the repelled proton resulting from the cation-water interaction would not be removed very far, and the hydroxide-like structure would not be maintained.

The mechanism just described is assumed to be at work in dilute solutions of lithium, potassium, and sodium salts, with soluble beryllium salts, and also with lead acetate. Beryllium salts would be

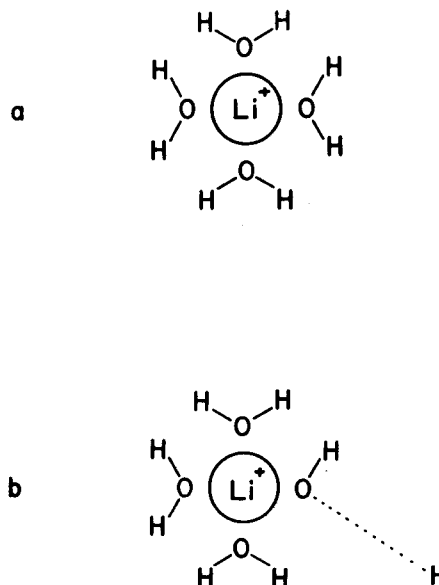


Fig. 1. Showing in a the orientation of water molecules around a lithium ion, and in b, the repulsion of a proton from one of the water molecules.

very interesting to study in detail, except for the fact that they are poisonous. Information concerning them will have to be limited to that existing in the older literature. The same is true for lead acetate, and for potassium fluoride, for the same reason.

The action of a proton acceptor in the stimulus can be seen in the data of Dzendolet and Meiselman (1967b, Fig. 4). The figure shows the percentage of sweet quality reports as a function of cation concentration, with the sulfate salts of lithium and potassium, and the chloride salts of the same cations as stimuli. The sulfates show a less steep negative slope than do the chlorides, and the function intercepts the abscissa at a somewhat higher concentration. This behavior can be attributed to the fact that sulfate ion is a stronger proton acceptor than chloride ion, and is able to help pull away more protons from the water layers surrounding these cations than can the chloride ion.

With the beryllium salts, a sour quality is reported at concentrations higher than those evoking sweet (Hober & Kiesow, 1898). This behavior is similar to that of lithium salts (Dzendolet & Meiselman, 1967a), and to potassium fluoride (Renqvist, 1919). The explanation proposed here is that the protons which were repelled from the water sheath are finally of sufficient concentration so that they cannot be fully neutralized by the saliva, and these protons then stimulate the sour receptors. The appearance of sour occurs primarily with compounds which are able to repel their protons strongly, either because of a high density of charge for the cation, or because of the presence of a strong proton acceptor, e.g., fluoride ion.

The foregoing has been concerned only with a description of the property of the chemical stimulus which is necessary for it to evoke the sweet quality. The next step of interest is to consider the mechanism whereby this proposed structure interacts with the gustatory receptor. Beidler (1954) postulated the existence of discrete sites on the gustatory receptor membrane. The stimulus material was assumed to be adsorbed at these sites. An adsorption process had also been postulated earlier by Renqvist (1919). Beidler derived a quantitative expression for this adsorption process, based on the chemical mass-action law. However, his result was based on an assumption holding only for concentrated solutions. Dzendolet (1967) extended the derivation to include dilute solutions. The result, when it was evaluated by using Beidler's electrophysiological data for NaCl solutions, could best be interpreted in terms of a dissociation reaction at the lower stimulus concentrations, rather than an adsorption process. In other words, some material appeared to be released from the receptor sites at these lower concentrations. The stimulus concen-

tration at the transition between the adsorption and dissociation reactions corresponded approximately to the concentration below which NaCl solutions are usually reported by humans as being sweet. Cohen, Hagiwara, and Zotterman (1955) were the first to propose the possibility of a dissociation reaction as the cause of the "water taste" in animals. They suggested the chloride ions might be the material released from the receptor membrane.

In view of the following points: (1) the hypothesis that a hydroxyl-like structure is sweet-evoking; (2) the fact that such a structure attracts hydrogen ions; and (3) the support for the existence of a dissociation reaction at low concentrations of certain inorganic salts, it is suggested that the initial step in the process for evoking the sweet quality is the removal of protons which are attached to sites on the receptor membrane. It is further hypothesized that the proton acceptor would have to come into reasonably close proximity to the receptor site for the proton removal to take place. Also, anions which are proton acceptors themselves could work directly on the receptor sites, in addition to acting indirectly by influencing the cation-water interaction.

A further step is to see if the hypotheses developed above for inorganic compounds have meaning if applied to organic ones. It is immediately clear that there is as much diversity in the organic structures which evoke sweet as in the inorganic, e.g., the differences between the various natural sugars, and saccharin or other artificial sweeteners. It is also clear that the hydroxide hypothesis used for the inorganic compounds cannot be applied directly to the organic ones because the hydroxide ion, with its negative charge, does not occur in the organic compounds of interest, although the OH grouping is present in many sweet compounds, as first pointed out by Cohn (Moncrieff, 1951, p. 347). The structure of glucose, Fig. 2, is an example showing the numerous OH groups which are present in sugars.

In this consideration of organic compounds, it is first necessary to discuss the concept of a base.

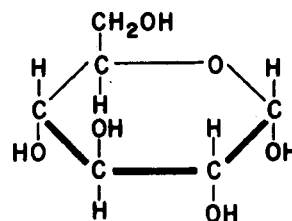
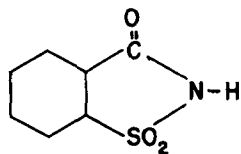
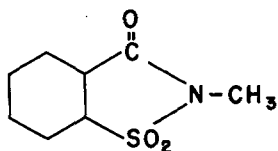


Fig. 2. The Haworth three-dimensional representation of glucose, showing the numerous OH groups. The plane of the six-membered ring is perpendicular to the plane of the page, with the heavy lines being nearest the reader. The vertical lines are in planes parallel to the plane of the page.



saccharin



N-methyl saccharin

Fig. 3. Structures of saccharin and N-methyl saccharin. The presence of the methyl group is hypothesized as not allowing the nitrogen atom to approach closely enough to a receptor site to remove a proton.

A base was first defined in terms of its properties, primarily its reactions with other compounds. The use of the hydroxyl ion to define a base was introduced later. A similar situation was also true of the concept of acidity and its relationship to the hydrogen ion. The hydroxyl ion definition of a base was extended by Bronsted and Lowry (Hermans, 1954, p. 191) to include any chemical structure, either molecular or ionic, which is a proton acceptor.

In order to apply the new hypothesis to organic compounds, it is necessary to modify it by saying that sweet-evoking compounds are proton acceptors, i.e., bases in the Bronsted and Lowry sense, rather than hydroxyl ion structures. This modification avoids the necessity for the sweet compound to have a negative charge as is implied with the hydroxyl ion structure.

Kortüm and Bockris (1951, p. 316) have pointed out that it is only nitrogen, oxygen, and fluorine atoms which can confer the basic property upon a compound, by virtue of the electronic structures of these atoms, i.e., possession of a free electron pair. Thus, it is primarily the activity of these atoms which is important to the sweet-evoking property of a compound.

Data reported by Hevesy (1948, p. 86) can be interpreted as showing that the OH groups of sugar behave in a manner similar to the water molecules of a cation-water structure. Hevesy showed that there was a rapid exchange of deuterium, one of the heavy isotopes of hydrogen, with the protons in the OH groups of sugar in water solution. This ex-

change could happen only if a proton of the OH group left the immediate vicinity of its oxygen atom. Because the oxygen atoms attracted the deuterium, it is clear that sugar is a proton acceptor, which is consistent with the proposed hypothesis. Hevesy generalized this behavior of exchanging protons for deuterium to include all organic compounds with an OH group, or an NH_2 group, i.e., an amine. This classification is consistent with the previously mentioned statement that all proton acceptors must have either an oxygen or a nitrogen atom present.

Although the hypothesis of a sweet compound as a proton acceptor explains why so many diverse-appearing organic compounds are sweet, certain further assumptions must also be made in order to explain changes in the sweetness of compounds as a function of substitutions in their structures. These assumptions cover two main types of effects. The first is a blocking or screening effect, and one possible mechanism for it is by the placement of a group on the primary proton-accepting atom of a compound, so that the molecule cannot approach the receptor sites closely enough to remove a proton. If the primary atom in saccharin is assumed to be the nitrogen, then it is this blocking effect which is the cause for N-methyl saccharin to be tasteless. The formulas of the two compounds are shown in Fig. 3.

A second possible mechanism for the blocking effect is the association of molecules in solution. Association takes place by means of hydrogen bonding between a hydrogen atom on one molecule, with the oxygen or nitrogen atom of another molecule, generally of the same species. Various numbers of molecules can be involved in such a molecular association, including the possibility of long chains in compounds such as acetamide, i.e., OCHNH_2 (Sundara, 1941). Another example of association in solution is that of urea, shown in Fig. 4. Urea is similar to acetamide, but it appears to associate in shorter chains. The dotted lines in Fig. 4 represent hydrogen bonds between the oxygen and hydrogen atoms of separate molecules. Because the oxygen or nitrogen atoms which are involved in molecular

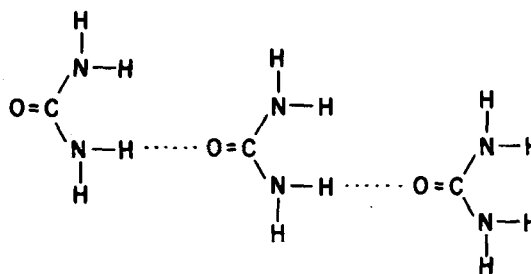


Fig. 4. Representation of the molecular association of urea molecules in solution by means of hydrogen binding which is represented by the dotted lines.

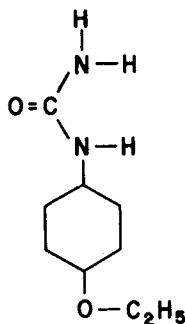


Fig. 5. Showing the structure of dulcin and its relationship to that of urea (Fig. 4), in support of the argument that dulcin also associates in solution.

association are also those which cause a molecule to be sweet-evoking, it is clear that such association will reduce the sweetness of a compound.

Sundara (1941) has pointed out that a decrease in the concentration of a solution will lead to a decrease in molecular association. Figure 5 shows the structure of dulcin. Its relationship to urea (Fig. 4) can be seen and, therefore, dulcin should associate in solution much like urea. Dilution of a solution of dulcin should decrease its association, and lead to an increase in sweetness. It has been observed that saccharin and dulcin both increase in sweetness with decrease in concentration (Moncrieff, 1951, p. 144). It is more likely that the nitrogen atoms are involved in these compounds rather than the oxygen, because symmetrically substituted methyl groups on the two nitrogens of urea produce a bitter compound, whereas substitution of two methyl groups on only one nitrogen produces a very sweet compound (Moncrieff, 1951, p. 323).

The second type of effect involves the changes in the internal distribution of electrons in a molecule

as a function of substitution of various groups in the molecule. Many mechanisms, e.g., the inductive and electrostatic effects, would undoubtedly be involved to various extents. In general, the importance of this type of effect is presumed to be how the distribution of electrons about the proton-accepting atom is influenced, i.e., whether its proton-accepting power is enhanced or diminished. Because of the complex nature of these various mechanisms, this effect will not be discussed in this article.

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