

Molecular Structure and Sweet Taste

R. S. Shallenberger and T. E. Acree

A structural unit common to sweet-tasting compounds is an AH and a B unit where H is an acidic proton and B is an electronegative atom or center. The distance between the proton and B is about 3 Å. There are a variety of functional groups which satisfy these requirements. In the sugars, this group is the glycol unit, in the gauche conformation, to satisfy the distance requirement. Hence, sugar

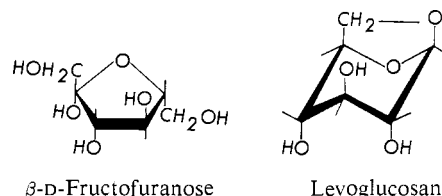
sweetness varies with either configuration or ring conformation. The probable AH,B units for amino acids and a variety of sweet-tasting organic and inorganic compounds are given. Although there are other chemical features associated with the ability of a compound to elicit sweet taste, the AH,B unit is an essential requirement.

When the structure of the sugars is related to their chemical reactivity, the conformation of the sugar molecule plays an important role. The shape of pyranoid and furanoid rings is manifested in the stereostructure of vicinal OH (glycol) groups and this structure is the feature which governs not only the possibility for reaction of a sugar with many inorganic, organic, and biochemical compounds, but also, the rate of the reaction; and if the reaction is reversible, it governs the position of the equilibrium. The sweet taste-eliciting structure of the sugars is the glycol group (Shallenberger, 1963). We believe that the initial chemistry of the reaction whereby sugars elicit sweet taste is also affected by the stereochemical attributes of the sugars, and that this structural variation serves to explain the variance in the sweet taste of the sugars.

A pyranoid sugar molecule may exist in two chair-like conformations, and in a cycle of skew boat-like forms (Bhacca and Horton, 1967). In these various ring conformations, the conformation of the substituent glycol OH groups is vastly altered. Figure 1 shows this feature of D-glucose pyranoid conformational structure where the conformation and perspective of the glycol group at carbon atoms 1 and 2 is emphasized. These OH groups for both the α -D- and the β -D- anomer in the favored C₁ conformation have a projected angle of 60°, and this arrangement is known as the gauche glycol conformation.

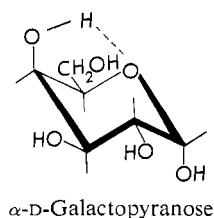
From a study of ring conformations, we have deduced that the gauche glycol conformation is the sugar structure which is best suited to elicit sweet taste. A projected angle of 120° may be attained by trans-vicinal OH groups on a furanoid ring. β -D-Fructofuranose is an example of this situation, and this compound is much less sweet than the β -D-pyranose tautomer (Tsuzuki and Yamazaki, 1953). The trans-vicinal OH groups of levoglucosan have the anti-glycol conformation (projected angle 180°), and this compound is void of sweet taste. Hence, projected angles of

greater than 60° for vicinal glycol OH groups appear to be too far apart to elicit sweet taste. Other model compounds could be cited, but only these two are shown to illustrate this tenet.



Eclipsed vicinal OH groups (projected angle, 0°) are, on the other hand, sterically disposed to participate in a fairly strong intramolecular hydrogen bond (Kuhn, 1952), and this situation appears to restrict the ability of a compound to elicit sweet taste (Shallenberger, 1963, 1964a,b). β -D-Fructofuranose can serve as the example for this case also. The vicinal OH groups at carbon atoms 2 and 3 are nearly eclipsed (depending upon the furanoid conformations), but this is probably true of cis-vicinal OH groups on any furanoid ring. In general, as the projected angle between vicinal OH groups decreases from the 60° angle of the gauche conformation, the OH groups become more prone to participate in an intramolecular hydrogen bond.

A third example of how the stereodisposition of a sugar OH group affects sweetness is when an OH group is able to hydrogen bond the ring oxygen atom. The OH group at carbon atom 4 of α -D-galactose, and at carbon atom 2 of α -D-mannose is so positioned (Foster, 1961), and these sugars are only about one-half as sweet as α -D-glucose.



The corollary to the thesis that sugar sweetness varies with the conformation of vicinal OH groups, and also, with

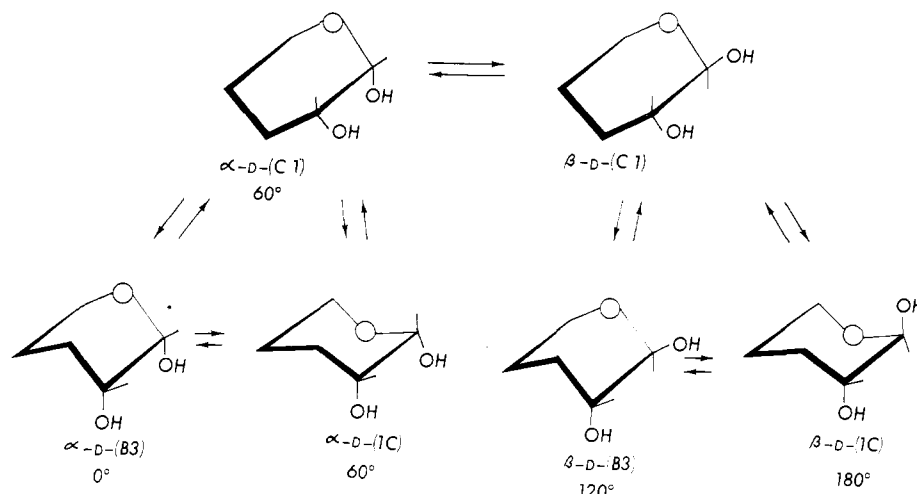


Figure 1. Glycol conformations of D-glucose in various ring conformations

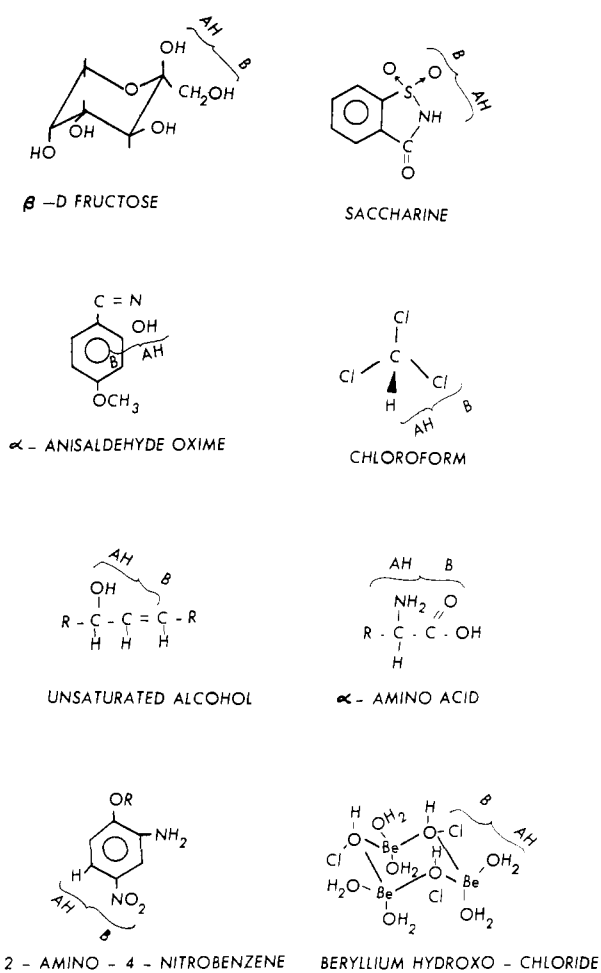
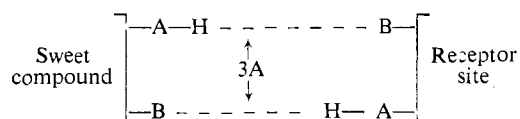


Figure 2. Representative compounds which taste sweet, and the AH,B system responsible

Projected vicinal $\text{OH}_1 - \text{OH}_2$ angles for α -D- and β -D-glucopyranose in selected conformations

the degree with which an OH group may participate in an intramolecular hydrogen bond, is that the initial chemistry of the sweet taste response is probably due to intermolecular hydrogen bond formation (Shallenberger, 1964a). In other words, the gauche sugar glycol group can be viewed as an AH and a B system (Shallenberger and Acree, 1967). The symbols used are those which are conventionally used

(Pauling, 1960; Pimentel and McClellan, 1960) to define and describe the hydrogen bond. The fact that an AH,B system is a dual "hard" acid and "hard" base unit, which would be particularly prone to react with another hard acid-hard base unit (Pearson, 1963) at the taste bud receptor site is particularly pertinent to this discussion.



If that is indeed the case, then the great variety of other compounds which taste sweet must meet the requirements defined for the sweet sugar glycol group. In particular, other sweet compounds need to possess an AH,B system analogous to the glycol group. They must have an AH proton, which is slightly acidic, within a B orbital distance of 3 A. Calculations made from molecular models suggest that this is the case for a number of diverse, but sweet-tasting compounds (Shallenberger and Acree, 1967). Selected compounds which taste sweet are shown in Figure 2, where the AH,B unit is shown in brackets. A number of different AH,B systems are illustrated. Briefly, for the sugars, it is a hydroxyl proton and a vicinal hydroxyl oxygen atom. The unit shown for β -D-fructopyranose is probably the most effective in this respect.

In saccharine and the cyclamates, AH is the imino group and B a sulfoxide oxygen atom. For α -anisaldehyde oxime, it is the oxime OH group and the π -bonding cloud of the benzene ring. McClellan (1968) suggested that the benzene ring might serve as a B moiety in an AH,B saporous unit. That suggestion resolved the anomaly of why α -anisaldehyde oxime tasted sweet whereas the β -isomer is tasteless. In the latter instance, the AH proton, B distance is in considerable excess of 3 A.

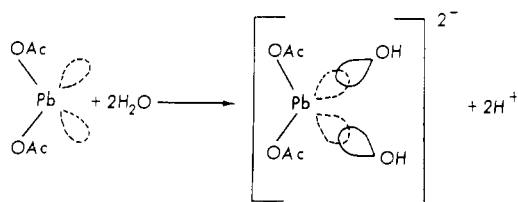
Halogenated acyclic carbon compounds taste sweet when they contain an acidic proton. The methine group of chloroform is the AH moiety, and the halogen atom is the B moiety. In the case of unsaturated alcohols, sweet taste occurs when the OH group is alpha to a double bond (Murahashi, 1938). Here again, AH is OH, but the unsaturated center serves as the B moiety. An amine proton and a carboxyl group oxygen atom serve as the system for the sweet-tasting amino acids.

The alkoxy-2-amino-4-nitrobenzene series of compounds, which vary in their sweet taste depending upon the identity

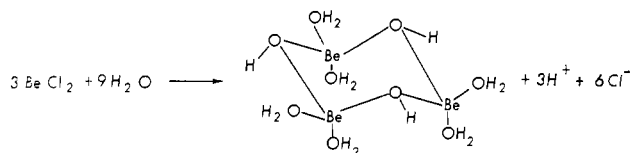
of R (Figure 2), are an example where AH is probably an aromatic ring and ring proton, and the B moiety is a nitro oxygen atom. Here, the other end of the molecule may also be an AH,B unit.

Inorganic molecules which taste sweet are dilute solutions of potassium and sodium chloride, and sodium and potassium hydroxide. Dzendolet (1968) has proposed that the ability of the sodium and potassium ion to elicit sweet taste is probably related to the formation of hydration shells, but every ion in water probably has hydrated structure. We cannot, of course, describe an AH,B system for such complexes since knowledge of the structure of hydrated metallic ions is very limited.

However, two other "inorganic" molecules which taste sweet, but which are very toxic, do appear to possess the postulated AH,B unit. These are lead acetate (sugar of lead) and compounds of beryllium (glucinium). Compounds of beryllium and lead acetate do not dissociate in the usual manner (Britton and Meek, 1931; Kakihana and Sillen, 1956). Instead they form complex hydroxo ions. A simplified structural description of the manner in which lead acetate probably dissociates is shown below, where two "unfilled" lead tetrahedral orbitals are occupied by the orbitals of the hydroxyl ion.



It is possible that this lead acetate-hydroxo ion has an OH group as AH, and B is an oxygen atom belonging either to a second OH group, or to an acetate oxygen atom. Kakihana and Sillen (1956) showed that when beryllium chloride is dissolved in water, the polynuclear ion $\text{Be}(\text{OH})_3^{2+}$ is the predominant form, and that the most likely structure would be that it forms a hydrated six-membered ring.



The hydrated six-membered ring contains in itself a probable AH,B system, but since the hydrated ring structure shown above needs to be in equilibrium with the hydroxo-

chloride complex (these solutions are acidic), this complex is shown in Figure 2, along with the AH,B unit. Not all bonds shown for these cyclic beryllium complexes are single covalent bonds, of course, but rather an overlapping of complete and unfilled orbitals, as suggested for the lead acetate-hydroxo complex.

This AH,B theory of sweet taste fits the energetic requirements of the Beidler (1963) taste equation, and has been used by Dastoli (1968) to demonstrate how a protein isolated from bovine taste buds may complex with sweet-tasting compounds. It has also been employed to explain why the sensation of sweetness is a lingering sensation (Deardon, 1968) and has been used by McClellan (1968) to predict that benzyl alcohol (with OH as AH and the π -bonding system of the benzene ring as B) should taste sweet. A chief criticism of the theory has been that the AH,B model is not tripartite, to account, in part, for the "stereospecificity" of the taste bud receptor site. Comments to indicate that the third-dimensional feature of the site is probably a spatial barrier are discussed elsewhere (Shallenberger *et al.*, 1969).

LITERATURE CITED

- Beidler, L. M., in "Olfaction and Taste," p. 133, Pergamon Press, Oxford, 1963.
 Bhacca, N. S., Horton, D., *J. Am. Chem. Soc.* **89**, 5993 (1967).
 Britton, H. T. S., Meek, F. H., *J. Chem. Soc.* **1931**, p. 2831.
 Dastoli, F., *New Sci.* **37**, 465 (1968).
 Deardon, J. C., *New Sci.* **37**, 628 (1968).
 Dzendolet, E., *Percept. Psychophys.* **3**, 65 (1968).
 Foster, A. B., *Ann. Rev. Biochem.* **30**, 45 (1961).
 Kakihana, H., Sillen, L. G., *Acta Chem. Scand.* **10**, 985 (1956).
 Kuhn, L. P., *J. Am. Chem. Soc.* **74**, 2492 (1952).
 McClellan, A. L., Chevron Research Corp., Richmond, Calif., personal communication, 1968.
 Murahashi, S., *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **34**, 155 (1938).
 Pauling, L., "The Nature of the Chemical Bond," 3rd ed., Cornell University Press, 1960.
 Pearson, R. G., *J. Am. Chem. Soc.* **85**, 3533 (1963).
 Pimentel, G. C., McClellan, A. L., "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, 1960.
 Shallenberger, R. S., *Agr. Sci. Rev.* **2**, 21 (1964b).
 Shallenberger, R. S., *J. Food Sci.* **28**, 584 (1963).
 Shallenberger, R. S., *New Sci.* **23**, 569 (1964a).
 Shallenberger, R. S., Acree, T. E., *Nature* **216**, 480 (1967).
 Shallenberger, R. S., Acree, T. E., Lee, C. Y., *Nature* **221**, 555 (1969).
 Tsuzuki, Y., Yamazaki, J., *Biochem. Z.* **323**, 525 (1953).

Received for review October 10, 1968. Accepted February 10, 1969. Presented at Symposium on Importance of Nonvolatile Compounds in Flavor, Division of Agricultural and Food Chemistry, 156th meeting, ACS, Atlantic City, N. J., Sept. 1968. Journal Paper No. 1659, New York State Agricultural Experiment Station, Cornell University, Geneva, N. Y. 14456.