Sweetness-Structure Correlation in Carbohydrates[1]

J. R. DANIEL[2] and Roy L. WHISTLER, Department of Biochemistry, Purdue University, West Lafayette, IN 47907

ABSTRACT

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Some of the concepts of molecular connectivity and graph theory are used to show a relation between the structures of carbohydrates and their relative sweetness. A third order connectivity index, $^3\chi_m$, calculated for a sugar structure is in direct relation to sugar sweetness. Correlations between calculated $^3\chi_m$ index value and relative sweetness are shown for simple sugars, glycosides, methyl ethers of sugar glycosides, pentoses, pentitols, hexoses, hexitols, sugar enantiomers, and several other classes of carbohydrate sweeteners. Most of the correlations show good correspondence. The index may be useful as a tool to aid in the design and selection of new, sweet synthetic carbohydrates.

Sugars have given humans and animals the pleasure of sweetness for millions of years, starting possibly with the occurrence of natural honey. Sweetness in honey is contributed mainly by the carbohydrate D-fructose, present at a level of about 38%. Today numerous developments have been made in carbohydrate sweeteners. High-fructose corn syrup production from starch by the sequential action of glucoamylase and isomerase has become a new industry of nearly five billion pounds per year in the United States and is developing rapidly in other industrial nations. Carbohydrate sweeteners with noncariogenic properties, such as xylitol and maltitol, are presently of interest, and search is underway for other noncariogenic or even nonmetabolizable sweeteners. Sweeteners of a carbohydrate nature are attractive because they have high possibilities for being nontoxic.

This interest in carbohydrate sweeteners has focused attention on gustatorial receptors for sweetness and especially on molecular structures required to stimulate sensors that recognize and respond to sweetness.

Sweetness Theory and Molecular Connectivity

A significant advance toward recognition of a molecular structure required for sweetness was made by Shallenberger and Acree (1967), who postulated the need for a glucophore structure involving AH and B, hydrogen donating-hydrogen accepting points, in the correct spatial arrangement to allow interaction with a complementary pair of hydrogen-bonding groups at the taste receptor locus.

Kier (1972) extended the glucophore structure by requiring a third but lipophilic point of contact between substrate and its gustatory receptor. The new lipophilic point, designated X, may also be a polarizable atom or group. The geometric relationship between the three structural points is shown in Fig. 1.

The Shallenberger-Acree-Kier AH-B-X glucophore is important as a first designation of a molecular structural required for sweetness. It is heuristic in that the structure is not a sufficient requirement for sweetness nor can the glucophore indicate degree of sweetness.

In an attempt to extend the proposal and to obtain a quantitative relation between molecular structure and sweetness in the carbohydrates, we have modified the concept of molecular connectivity, a part of mathematical graph theory, by insertion of terms to characterize chiral centers and by summation of appropriate molecular subgraphs. The resulting formulation provides a relatively good quantitative relation between structure and degree of sweetness of carbohydrates. In addition, the formulation allows some latitude for predicting sweetness in carbohydrates.

Molecular connectivity, described by Kier and Hall (1976), correlates organic molecular structure with molecular physical properties such as solubility, boiling point, heat of atomization, and molecular polarizability.

In molecular connectivity, nonhydrogen, noncarbon atoms are assigned a specific number, ie, the vertex valence δ_i, where δ_i is the atom's number of valence-shell electrons minus the number of hydrogen atoms normally attached. For carbon atoms, δ_i is the number of atoms to which the carbon is bound minus the number of hydrogens on that atom, resulting in a "hydrogen-suppressed" (hydrogens not represented) graph. Said in another way, δ_i of carbon is the number of other atoms, except hydrogen, bound to the carbon atom.

A number χ for an entire molecule can be calculated from the sums of $^0\chi$, $^1\chi$, $^2\chi...^n\chi$. Thus, for ethylene glycol, O-C-C-O, the vertex values are 5, 2, 2, 5, respectively. The $^3\chi$ path term for the molecule is the reciprocal of the square root of the multiplied vertex values; namely, $(5 \times 2 \times 2 \times 5)^{-1/2}$ or 0.1. For 2-propanol, the $^3\chi$ cluster term is $(1 \times 3 \times 5 \times 1)^{-1/2} = 0.26$. Cluster terms characterize the chiral centers of carbohydrates.

Use of this concept to create for each sugar a number that might be indicative of its degree of sweetness has much appeal. To obtain this possibly definitive molecular value, $^n\chi$, one must assign values to vertices, δ, that reflect chiral configuration and to construct and sum subgragh values for known partial molecular contributions.

Because Shallenberger and Acree (1967) propose that the saporous units in sugars are highly dependent on vicinal dioxygen groupings, one can logically make all OCCO subgraph terms a part of the sweetness contribution to the molecular $^n\chi$ term. To incorporate Kier's lipophilic sites (1972), all OCCC′ paths with no common CC path are included, where C′ is a methyl or methylene unit. Giving weightings to chirality where it is known to affect sweetness is also appropriate. α-D-Glucopyranose is sweeter than β-D-glucopyranose (Shallenberger and Acree 1971). Hence, the O-1 oxygen is assigned a δ_i value that is smaller for the α-D-form ($\delta = 4$) than for the β-D-form ($\delta = 6$). Due to the inverse square root nature of the equation, smaller δ_i values give rise to larger $^n\chi$ values. Because D-mannose and D-galactose are less sweet than D-glucose (Shallenberger and Acree 1971), the value assigned to axial secondary (2°) hydroxyls should reflect this decrease; hence, $\delta^{2°}_{ax}$ is 6 and $\delta^{2°}_{eq}$ is 4. Since ring oxygens seem to depress sweetness (Birch 1976), they are given the δ_i value of 8. Because of the difference in
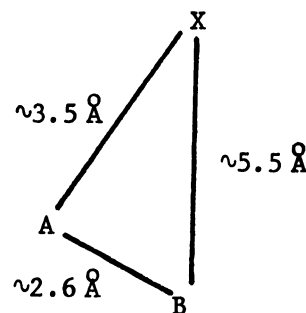
Fig. 1. Approximate geometry of the tripartate glucophore for sweetness according to the Shallenberger-Acree-Kier model.

sweetness of maltitol and cellobiitol (Lee 1979), the glycosidic oxygens are assigned δ_{ax} of 7 and δ_{eq} of 9, respectively. Ether linkages at secondary positions are assigned δ_{ax} of 9 and δ_{eq} of 7. Because glycosides are less sweet than free sugars, glycosidic oxygens are given δ values larger than 6. Oxygens at primary positions contribute little to sweetness (Birch 1976) and are assigned the usual molecular connectivity value of 5 if the hydroxyl is free or 6 if etherified. Assigned δ_i values are compared with normal molecular connectivity (MC) χ_i values in Table I.

To determine the χ value for a molecule, all OCCO paths, all distinct OCCC' paths with no common C-C paths, and all chiral (cluster) terms are counted, to provide an equation $^3\chi = OCCO + OCCC' + cluster$ (Table II). For better comparisons between carbohydrates of different molecular weight, the molecular $^3\chi_m$ value is calculated by dividing $1,000\ ^3\chi$ by the molecular weight of the carbohydrate.

The chiral terms individually relate to the configuration of each ring carbon atom and in total to the unique configuration of the carbohydrate.

Using the values in Table I, α-D-glucopyranose may be drawn as shown in Fig. 2. The $O_1C_1C_2O_2$ contribution is calculated as:
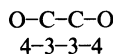
$$O-C-C-O$$
$$4-3-3-4$$

The product of the subgraph valences ($4 \times 3 \times 3 \times 4$) is 144 and its inverse square root is 0.083. The process is repeated for all OCCO subgraphs in the molecule, and the inverse square roots of the

products are summed to yield the total OCCO value, which for α-D-glucopyranose is 0.432. Similar calculations for the OCCC' term give 0.118 and for the chiral terms, 0.430. Then $^3\chi = OCCO + OCCC' + chiral = 0.980$ for α-D-glucopyranose. To properly compare sugars of different molecular weight, the $^3\chi$ values times 1,000 are divided by molecular weight and shown as $^3\chi_m$, which is 5.44 for α-D-glucopyranose.

General Correlations

Calculated $^3\chi_m$ values for several sugars are shown in Table III (Shallenberger and Birch 1975). Relative sweetness values here and elsewhere are taken from the literature and thus are subjective values from individuals, groups, and test panels rather than fixed values. They should sometime be determined by a single, properly designed and conducted test with a properly constituted panel. α-D-Anomers are sweeter than β-D-anomers and have larger $^3\chi_m$ values. This is not a prediction but a consequence of assigned terms; none-the-less, it provides a check that large $^3\chi_m$ values will correlate with intense sweetness, whereas smaller $^3\chi_m$ values will indicate compounds of lesser sweetness. As shown later, sufficiently small $^3\chi_m$ values may correlate with tasteless, bittersweet, or bitter compounds.

Glycosides become increasingly bitter with increasing aglycon chain length or molecular weight (Birch and Lindley 1973). The $^3\chi_m$ values and gustatory responses for alkyl and aryl α- and β-D-glucopyranosides are compared in Table IV. The table shows that $^3\chi_m \geq 4.85$ correlates with sweet taste, $4.85 > ^3\chi_m > 4.5$ correlates with a mixed bitter-sweet response, and $^3\chi_m < 4.5$ correlates with bitter taste.

Introduction of methyl ether groups into sugar structures is generally accompanied by a decrease in sweetness (Lindley and Birch 1975). Several such relations are shown in Table V.

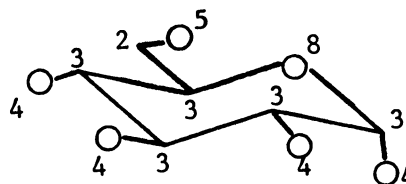Methyl α-D-glucopyranoside is sweet with no trace of bitterness,

TABLE I
Comparison of Vertex Valencies (δ) in Molecular Connectivity (MC) Theory and in Stereo (S) MC as Used Here

Atom or Group	δ	
	MC	SMC
Anomeric OH		
Axial	5	4
Equatorial	5	6
2° OH		
Axial	5	6
Equatorial	5	4
Ring ether	6	8
Anomeric OR		
Axial	6	7
Equatorial	6	9
2° Ether		
Axial	6	9
Equatorial	6	7
1° OH	5	5
1° OR	6	6
$-CH_3$	1	1
$-CH_2$	2	2
$-\overset{\mid}{\underset{H}{C}}-$	3	3
$-\overset{\mid}{\underset{\mid}{C}}-$	4	4

TABLE II
Subgraphs Counted to Yield $^3\chi_m$

Contribution	Subgraph
Shallenberger[a]	O-C-C-O
Kier[b]	O-C-C-C' (C' = 1° or 2°)
Chiral	$\overset{X\diagdown \diagup Y}{\underset{Z}{\mid}C}$

[a]Shallenberger and Acree 1967.
[b]Kier 1972.

Fig. 2. Numbering of atoms in α-D-glucopyranose according to the theory of stereomolecular connectivity.

TABLE III
Relative Sweetness[a] and $^3\chi_m$ Values

Sugar	Relative Sweetness	$^3\chi_m$
β-D-Fructopyranose	180	6.94
Sucrose	100	6.18
α-D-Glucopyranose	40–79	5.44
β-D-Glucopyranose	<α-anomer	5.33
α-D-Mannopyranse	32	5.12
α-D-Galactopyranose	32	5.09
β-D-Galactopyranose	21	4.94

[a]From Shallenberger and Birch 1975.

TABLE IV
Comparisons of Taste and $^3\chi_m$ for α-and α-D-Glucopyranosides

Oxygen Substituent	α-Anomeric		β-Anomeric	
	$^3\chi_m$	Taste	$^3\chi_m$	Taste
H	5.44	Sweet	5.33	Sweet
$-CH_3$	4.89	Sweet	4.82	Sweet-bitter
$-C_2H_5$	4.56	Sweet-bitter	4.50	Bitter
$-C_3H_7$	4.27	Very bitter	4.21	Very bitter
$-C_4H_9$	4.02	Very bitter	3.96	Very bitter
$-C_6H_5$	3.70	Bitter	3.65	Bitter
$-CH_2C_6H_5$	3.51	Very bitter	3.46	Very bitter

its monomethyl ethers are sweet with a trace of bitterness, and its dimethyl ethers are uniformly bitter. These observations seem to indicate that the lower end of the bittersweet range may be as low as a $^3\chi_m$ of 4.00. However, a good qualitative correlation is seen between $^3\chi_m$ and the sweetbitter response.

The lines of demarcation between sweet, bittersweet, and bitter compounds, as judged by their $^3\chi_m$ values, are not sharp. The change is gradual and necessarily leads to borderline predictions that may be erroneous.

Alditols are an important class of sweetening agents. Xylitol is known to possess useful sweetening and noncariogenic properties (Makinen and Scheinin 1972). Other glycitols may likewise have useful properties and perhaps the sweeter ones can be sorted out by application of stereomolecular connectivity.

Comparison of $^3\chi_m$ values for several pentoses and their penitols are shown in Table VI. D-Ribitol and D-xylitol have greater $^3\chi_m$ values than either parent, and D-arabitol and D-lyxitol have $^3\chi_m$ values intermediate between the parent anomers. Such taste relationships were experimentally observed by Moskowitz (1971), who found D-ribitol and D-xylitol to be sweeter than D-ribose and D-xylose, respectively. He also observed that D-arabitol was less sweet than D-arabinose. No sweetness data is available for the D-lyxose-D-lyxitol pair. Thus, the existing sweetness values are in qualitative agreement with the calculated $^3\chi_m$ values. The relative sweetness values for D-xylitol, D-ribitol, and D-arabitol of 1.34, 0.83, and 0.63, respectively (Moskowitz 1971) are in good agree-

ment with their $^3\chi_m$ values. Values are relative to $1M$ D-glucose, which has a value of 1.0.

The $^3\chi_m$ values for D-glucitol, D-mannitol, and D-galactitol and their parent anomeric aldohexopyranoses are also given in Table VI. Although the table shows $^3\chi_m$ data for only three sugars, the values calculated for all eight aldoses and the derived alditols have greater $^3\chi_m$ values for the glycitol than for either parent anomer. The relative sweetness values (Lee 1977) for D-glucitol, D-mannitol, and D-galactitol are 54, 62, and 46, respectively. The $^3\chi_m$ values for mannitol and D-glucitol do not correlate with relative sweetness. This misordering is undoubtedly due to the simplicity of the mathematical formulation, affected also by assumptions that are not necessarily valid for all sugar alcohols. So far, however, this is the only misordering observed.

Recent work by Kearsley et al (1980) has confirmed that the sugar alcohols of D-xylose, D-glucose, D-galactose, lactose, and maltose are sweeter than those of the parent sugars. However, these workers find, contrary to the relationship indicated by the $^3\chi_m$ value, that cellobiitol is somewhat less sweet than cellobiose.

The relationship between $^3\chi_m$ and the relative sweetness values (Beck 1978) for three important dietary disaccharides are given in Table VII. Here the sense of the calculation is qualitatively correct; that is, the larger the $^3\chi_m$ value, the greater the relative sweetness.

Specific Structural Correlations

The rules for calculating $^3\chi_m$ values for D- and L-sugars are the same and predict that D- and L-isomers should be isosweet. Shallenberger et al (1969) have obtained experimental evidence to support this prediction (Table VIII). The sweetness values in the table are on an arbitrary scale and are valid only for comparisons

TABLE V
Comparisons of Taste and $^3\chi_m$ for Some Methyl Ethers of Methyl α-D-Glucopyranoside

Glycoside Derivative	Sweetness[a]	Bitterness[a]	$^3\chi_m$
Parent	S	O	4.89
6-O-Me	S	tr	4.52
3-O-Me	S	tr	4.24
2-O-Me	S	tr	4.20
4-O-Me	S	tr	4.13
4,6-di-O-Me	O	B	3.85
2,3-di-O-Me	O	B	3.68
3,4-di-O-Me	O	B	3.60

[a] S = sweet, O = no response, tr = trace, B = bitter.

TABLE VI
$^3\chi_m$ Values for Some Penitols and Hexitols and Their Parent Anomers

Pentitol and Pentoses	$^3\chi_m$	Hexitol and Monosaccharides	$^3\chi_m$
D-Ribitol	5.43	D-Glucitol	6.03
α-D-Ribose	5.32	α-D-Glucose	5.44
β-D-Ribose	5.15	β-D-Glucose	5.33
D-Arabitol	5.29	D-Mannitol	5.74
β-D-Arabinose	5.45	α-D-Mannose	5.12
α-D-Arabinose	5.27	β-D-Mannose	4.99
D-Xylitol	6.04	D-Galactitol	5.64
α-D-Xylose	5.79	α-D-Galactose	5.09
β-D-Xylose	5.61	β-D-Galactose	4.94
D-Lyxitol	5.29		
α-D-Lyxose	5.39		
β-D-Lyxose	5.24		

TABLE VII
Comparison of Relative Sweetness and $^3\chi_m$ for Important Dietary Disaccharides[a]

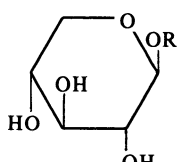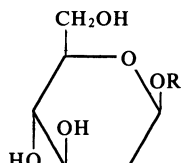| Disaccharide	Relative Sweetness	$^3\chi_m$
Sucrose	100	6.18
α-Maltose	50	5.13
α-Lactose	40	4.83

[a] From Beck 1978.

TABLE VIII
Relative Sweetness Data for Enantiomeric Forms of Monosaccharides[a]

Sugar	Relative Sweetness of Form	
	D	L
Arabinose	5.2	5.6
Xylose	4.6	4.4
Glucose	5.4	6.0
Rhamnose	4.6	6.5
Mannose	4.9	5.0
Galactose	5.6	6.0

[a] From Shallenberger et al 1969.

TABLE IX
Effect of a Hydroxymethyl Group at C-5 of a Pyranose Ring[a]

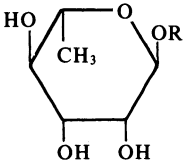| Disaccharide[b]	Relative Sweetness
	80
	70

[a] From Dick et al 1974.
[b] R =
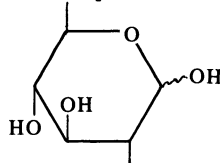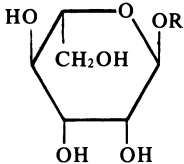
TABLE X
Effect of Reduction of the C-6 Methylol Group to C-6 Methyl[a]

Sugar[b]	Relative Sweetness[c]

10.2

0.07

[a] From Kaniya et al 1976.
[b] R = CH₂OH
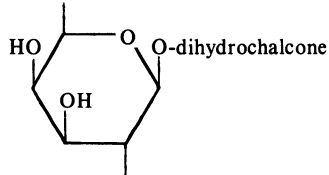
[c] Saccharin = 1.0.

between D- and L-isomers *of the same sugar*; hence, they are not valid for comparing sweetness with other sugars.

The proposed structure-sweetness relationship predicts a marked dependence of sweetness on sugar ring conformation. This is intuitively obvious when considered from the point of view of sugar-taste receptor theory, but no perfect experimental example exists. However, the introduction of a bitter component into the gustatory response to 1,6-anhydro-β-D-glucose (Lee and Birch 1975) is reflected in its relatively lower $^3\chi_m$ value (4.42) compared to that of β-D-glucose (5.33).

Few sugars of absolutely known ring conformation or anomeric configuration have been tested for sweetness. In these calculations, the ring is drawn as its thermodynamically most stable conformer and $^3\chi_m$ calculated on this basis. The δ_i values, and hence $^3\chi_m$, are highly dependent upon ring conformation. That such an assumption has not led to serious errors in the correlation of sweetness and $^3\chi_m$ shows its validity and usefulness.

The theory allows isolation of selected structural moieties and an examination of their contribution to the sweetness of molecules as reflected in their percentage contribution to $^3\chi_m$. For example, deoxy, methylene and methyl, groups contribute greatly to sweetness, as do quaternary carbon atoms such as those in D-fructose and sucrose. The proper number and geometry of vicinal dioxygen components is also of great importance. Thus, this formulation agrees with the Shallenberger-Acree-Kier model of sweetness regarding those factors that are of greatest importance in eliciting sweet taste.

The formulation predicts that introduction of a hydroxymethyl group at C-5 of a pyranose ring will depress sweetness. A comparison of the disaccharide sweeteners (Dick et al 1974) in Table IX shows this to be the case. Additionally, Birch et al (1981) have shown that L-arabinose is sweeter than D-galactose and D-xylose is sweeter than D-glucose (at 35–45° C). These pairs of sugars are also distinguished by the presence or absence of a CH₂OH group at C-5 of the pyranose ring.

The formulation predicts that reduction of hexoses or hexosides to their 6-deoxy derivatives should result in increased sweetness. Comparison of the dihydrochalcone glycosides (Kamiya et al 1976) in Table X shows that this prediction is born out. Also, Birch and coworkers (1981) have shown 6-deoxy-D-galactose (D-fucose) to be

sweeter than D-galactose. However, they find that 6-deoxy-D-glucose (D-quinovose) is less sweet than D-glucose at temperatures less than 45°C. In general, the formulation appears to have some value in correlating sweetness with molecular structure. The $^3\chi_m$ values do not strictly order all sugars in known order and ratio of sweetness. This can possibly be remedied by the use of additional $^n\chi_m$ terms and regression analysis. The formulation has quantitative difficulty in handling carbohydrate derivatives with atoms other than C, H, and O. This may be remedied by gathering additional data on sweet compounds containing atoms other than C, H, and O. In predicting sweetness of reducing sugar, one has difficulty deciding whether to use $^3\chi_m^\alpha$, $^3\chi_m^\beta$, or a $^3\chi_m$ weighted to reflect the anomeric equilibrium in solution. That is, can the formulation be used to predict the sweetness of "crystalline" sugars or the sugar mixture as it occurs in equilibrated solution? Lastly, the theory has some difficulty with the more flexible furanose ring systems.

We believe, as judged by the number of positive sweetness-($^3\chi_m$) correlations found, that the formulation has merit as a correlative, and possibly predictive, tool in sweetness research. We are currently engaged in further research to refine the theory and to reinforce its theoretical foundation.

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