Structure–Property Relationship in Sweeteners

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Most characteristic sweet and nonsweet sulfamates, aldoximes, (arylsulfonyl)alkanoic acids, and carbohydrates were selected by discriminant analysis of structural attributes. The three-dimensional models of chosen molecules were fitted into a sweet-taste receptor model. Two hydrogen bonds and one interaction or one hydrogen bond and two interactions with receptor wall are critical conditions for sweet molecules. The importance of molecular bulkness and the steric factor for sweetness is also discussed.

INTRODUCTION

During the past few years it has become fashionable to reduce the uptake of natural sugar or replace it by various sweeteners. Among them saccharine, perilartines (aldoximes), cyclamates, and dipeptides could be mentioned. Searching for new substances resembling sucrose's taste and all organoleptic properties is in progress. Aspartame is a commercially used sweetener from a group of dipeptide esters which is approximately 200 times more sweet than sucrose and has a very similar sensory profile.[1] Compounds having even better characteristics should be invented. Any prediction of new compounds or classes of sweeteners must be based on the relationship between chemical structure and taste, knowledge of the receptor cavity shape, and interactions between receptor and sweet molecule, blended into a theory of sweet taste.

The aim of this paper is to add some new elements to the existing theory of sweet taste[2–7] through the computer aided fitting of the models of various sweet and nonsweet molecules into proposed receptor sites.[7] Molecular models will be generated by ALCHEMY III software for a set of molecules from different chemical classes. Molecules of interest will be choosen by discriminant analysis of the attributes describing chemical constitution and will represent average (or higher) sweet or nonsweet molecular character. The analysis of interaction between a sweet or a nonsweet molecule and a receptor site in terms of hydrogen bondings and hydrophobic interactions despite the molecular frame will be provided.

SUMMARY OF SWEET-TASTE THEORIES

Many attempts have been made in the past decade to give an interpretation of the sweet taste on the basis of the molecular structure of sweet compounds.[2] The first successful correlation among sucrose, amino acids, sacharine, chloroform, nitroanilines, etc., was found by Schallenberger and Acre[3] who proposed that the perception of sweetness was due to intramolecular hydrogen bonding with the receptor site. The common unit in sweet compounds was described as an AH···B system, in which AH is a proton donor and B is a proton acceptor separated[4] by a distance of 2.8–4 Å in all known sweet molecules. In addition a spatial barrier in the receptor site has been invented[5] at a distance of approximately 3 Å from the line joining AH and B, where the spatial barrier represents a simple geometric feature.

The weekness of this theory is the reliance on neglecting the importance of both the three-dimensional shape of the given molecule and the limitation imposed by the sheer (equilibrium) volume of the active site. It becomes clear that apart from the nature of the AH···B system, a third molecular feature is essential for perception of sweetness. Kier proposed[6] the existence of a point at the apex of a triangle whose basis is the AH···B entity, capable of dispersion bonding.

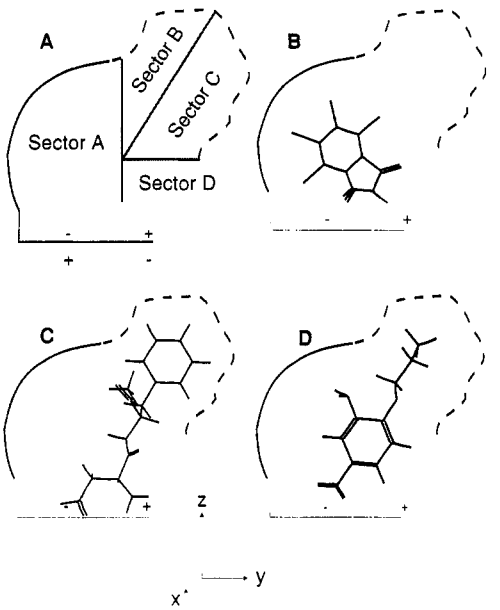

Figure 1. (A) Temussi model of sweet receptor in y–z plane, and our convention of the division into four sectors A–D. (B) Saccharine in receptor. (C) Aspartame in receptor. (D) 2-Propoxy-5-nitroaniline in receptor.

Most recently, Temussi and co-workers[7] attempted to map the receptor site on the basis of several substituted saccharines and the most preferable conformer of aspartame (L-aspartyl-L-phenylalanine methyl ester) *as molecular molds*. The main features of the proposed theory can be summarized as follows. The principal electronic factor in the site is the AH···B entity of Schallenberger, supported by the very flat hemihedral cavity. Figure 1 shows the Temussi model of the sweet receptor in the y–z plane. The continous line refers to identified perpendicular walls derived by combining the shapes of some sweet and nonsweet hologeno-saccharines[8] (Figure 1B). The dashed line shows only minimum contours for critical geometrical features of the receptor when active sites are interacting with apolar groups of such tastants as aspartame, 2-propoxy-5-nitroaniline (Figure 1C,D, respectively), tolylurea derivatives, and others.[9] An important corollary of this receptor model is that one side of the site, opposite to the defined one, is partly open. This circumstance may explain

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Table 1. Most Characteristic Sweet and Nonsweet Sulfamates Selected by DA

no.[a]	substituent	taste	CS[b]	interaction with receptor
1	*n*-Pr	sweet	−2.27	in sector C at the end
13	Me–cyclo-Pr	sweet	−3.85	in sector C
16	*n*-pentyl	nonsweet	0.67	beyond the barrier in sector C
38	1-Me, 1-cyclohexyl	nonsweet	1.72	none, cyclohexyl in open sector D
34	i-Pr	nonsweet	0.39	none

[a] Number in a set. [b] Canonical score.

Table 2. Most Characteristic Sweet and Nonsweet Aldoximes Selected by DA

no.[a]	substituent	taste	CS[b]	interaction with receptor
5	4-H, C(H,Me,OMe)	sweet	−1.17	in sector B/A and C
23	4-H,COMe	sweet	−1.17	in sector B/C
25	4-H,OEt	sweet	−1.17	in sector B/C
18	4-H,C(Me,OMe,CH_2–OMe)	nonsweet	1.42	–OMe invades the walls in sector A/B
19	5-H,C(H,Me,OMe)	nonsweet	0.31	substituent beyond the wall in A
35	4-H,C(Me,Me,OCOMe)	nonsweet	1.42	invades the wall in sector C

[a] Number in a set. [b] Canonical score.

Table 3. Most Characteristic Sweet and Nonsweet (Arylsulphonyl)(cyclo)alkanoic Acids

no.[a]	substituents	taste	CS[b]	interaction with receptor
16	i-Pr, Me	sweet	2.47	i-Pr with sector A, Ph with C
5	i-Pr, H	sweet	3.52	i-Pr with sector A, Ph with C
27	2,2-diMe-c-Pr	sweet	0.83	cycle with sector A, Ph with C
11	Me, Me	nonsweet	−2.07	none with sector A, Ph with C
20	c-pentyl	nonsweet	−1.53	none with sector A, Ph with C
27	n-Pr, n-Pr	nonsweet	−2.11	none with sector A, Ph with C

[a] Number in a set. [b] Canonical score.

Table 4. Most Characteristic Sweet and Nonsweet Carbohydrates

no.[a]	compound	taste	CS[b]	interaction with receptor
1	saccharose	sweet	−0.45	6 CH_2OH with sector A, pyranose with sector B/C
27	glucose	sweet	−1.19	6 CH_2 OH with sector A
13	1′,6′,4-trichlorogalactosaccharose	sweet	−2.87	6 CH_2 OH with sector A, pyranose with sector B/C
21	trechalose	sweet	−0.46	6 CH_2 OH with sector B, ring with sector C and partly with D
25	4,6-dichlorotrechalose	nonsweet	3.38	
26	mannitol	nonsweet	1.30	none (too small)
5	1-chlorosaccharose	nonsweet	0.54	

[a] Number in a set. [b] Canonical score.

why even bulky substituents out of the main molecular frame have no influence on the taste of some sweet molecules.

It seems fair to conclude that the Temussi model for active sites of the receptor of the sweet taste can be used to explain the taste of the best known sweet compounds and can be helpful in the choice of the first synthetic targets of prespective analogues of known sweeteners or even in the design of new sweeteners.

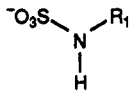
To facilitate further description of the results and discussion, *we divided the receptor into four well distinguished sectors designated by letters A–D (see Figure 1A)*. The receptor wall in sector A has been exactly defined by Temussi.[7] Sectors B and C describe wall contours in the direction of the z axis and are not yet finally defined. Sector D represents the open part of the receptor in the direction of the y axis.

SELECTION OF SWEET AND NONSWEET COMPOUNDS MOST CHARACTERISTIC IN A GIVEN CLASS BY DA OF STRUCTURAL FRAGMENTS

The full description of applied discriminant analysis (DA) and the results achieved will be given in a separate paper.[10] We used DA (forward stepwise) included in CSS STATISTICA/w (by Stat Soft Inc., Tulsa, OK) to determine which variables in multivariate space discriminate between two or more naturally occurring groups of objects.[11,12] In our case we used a data matrix of the format $r \times c$, wherein raw members of a particular class were characterized by variables describing structural fragments present (1) or absent (0) in a given molecule. In a particular class (except carbohydrates), the molecular frame is constant. Thus variables describe substituents, the place of substitution, the length of the carbon chain, the size of ring, additional multiple bonds, the presence of specific molecular fragments, etc. We do not apply in our research molecular measures such as bond length, angles, shape and volume parameters (e.g. in a form of STERIMOL,[13] DISCO,[14] SPERM[15]), topological indices, or connectivity indices[16] used by other authors. In the last column of the data matrix we introduce information on taste known from sensory measurements or elucidations published in the literature.

In this paper only the most important information and key results are presented for a particular class of sweet compounds in the form of a list of structural attributes, a list of variables entered in discriminant function, the percentage of correct assignements, and canonical scores (CSs in Tables 1–4). CSs visualize the positions of sweet and nonsweet compounds along a discriminant function axis and allow selection of the most interesting compounds for further 3-D analysis.

A. Sulfamates. A group of 50 sulfamates was used from the work of Myiashita et al.[17]

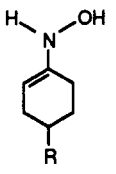


Sulfamates

The structure of substituent R has been described by six attributes, (1) aliphatic chain, (2) n-Pr or n-Bu, (3) β-substituted alkyl, (4) α-substituted alkyl, (5) cyclopentyl or cyclohexyl, and (6) substituted cyclopentyl or cyclohexyl, and one variable, (7) molar refraction (standarized).

Successful discrimination with 90% correct assignments has been obtained when five attributes are used (in order of entrance to the model): 2–5–1–7–4. Canonical scores computed for each compound and its mean value for sweet (–1.50) and nonsweet (0.75) class allowed selection of representatives for further 3-D analysis. The names of these compounds, their characteristics, and final conclusions are presented in Table 1.

B. Aldoximes. A set of 51 aldoximes, derivatives of cyclohexene aldehyde and some noncyclic aldehydes, was selected from the literature.[18–20]



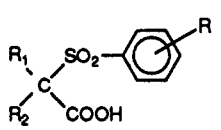
Aldoximes

Their structure has been described using a nine-dimensional space of structural attributes: (1) cyclohexene ring, (2) substituent at C-4, (3) short chain (1–3 C) at C-4, (4) substituent at C-5, (5) –OMe, (6) –OH, (7) an additional olefinic bond, (8) ring heteroatom (O or S), and (9) unsaturation in the substituent.

DA selects only three variables which discriminate between sweet/nonsweet molecules with 88% correct assignments. The variable supporting sweet taste is a short chain at C-4, while variables supporting nonsweet tastes are larger substituents at C-4 and an additional olefinic bond.

Canonical scores computed for each aldoxime, and its mean value for sweet (–1.02) and nonsweet (0.78) classes, allowed selection of the best representatives for further 3-D analysis. The names of these compounds, their characteristics, and final conclusions are presented in Table 2.

C. (Arylsulfonyl)(cyclo)alkanoic Acids. A group of 30 sulfonylalkanoic acids were taken from literature.[21–22]



(Arylsulfonyl)(cyclo)alkanoic acid

The structures of substituents R_1 and R_2 on the alkanoic carbon and in the aromatic ring have been described by attributes which are not listed here. DA includeds only five of them into final solution: R_1 short straight chain, R_1 ring, R_1 α-branched chain, chlorine atom in the molecule, and $R_1 = R_2$.

Successful discrimination has been achieved for 93% of the cases. All sweet compounds were classified as sweet. Canonical scores computed for each compound and its mean value for sweet (2.00) and nonsweet (–0.80) classes allowed selection of representatives for further 3-D analysis. The names of these compounds, their characteristics, and final conclusions are presented in Table 3.

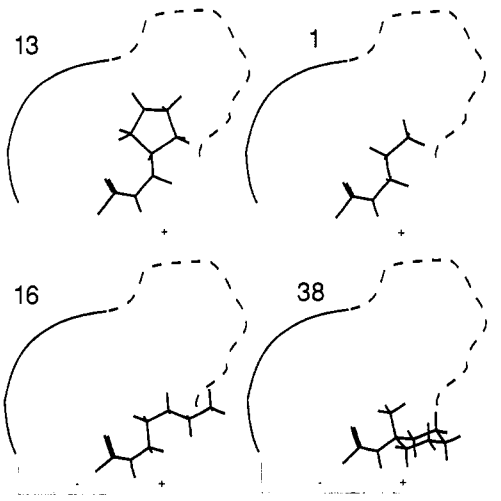


Figure 2. Projection of sweet (**13** and **1**) and nonsweet (**16** and **38**) sulfamates into receptor model.

D. Carbohydrates. A set of 63 carbohydrates, derivatives of saccharose, galactosaccharose, maltose, trechalose, and other mono- and disaccharides unsubstituted or chlorinated with a known taste[23–24] (25 nonsweet, 38 sweet) were selected for DA. Their structures have been described by 32 attributes characterizing various aspects of chemical constitution, e.g., conformation, configuration of pyranose and furanose rings, hydroxy groups, chlorine atoms, sequences of bonds and bridges, etc.

DA selects eight of the most important attributes, which discriminate sweet and nonsweet carbohydrates with overall correct assignments of 80%. The following features were included in the discrimination function: *Z*, four OH groups; *E*, 2,3-diOH; *C*, 1- or 6-Cl; *V*, *x*OH, $(x + 1)CH_2Cl$ trans; *H*, two chlorine atoms; *G*, one chlorine atom; *S*, 2,3-trans substituents; *T*, pyran ring.

Canonical scores computed for each carbohydrate and its mean value for sweet (–0.50) and nonsweet (1.20) classes allowed selection of the best representatives for further 3-D analysis. The names of these compounds, their characteristics, and final conclusions are presented in Table 4.

THREE-DIMENSIONAL ANALYSIS OF SWEET AND NONSWEET MOLECULES[25]

A. Sulfamates. Sulfamates have two distinguished active centers: acidic AH in the form of a SO_3^- group, and basic B in the form of a –NH– group. The geometry of the centers is identical with that in well-known saccharine.

The minimum energy conformers of different sulfamates shown in Table 1 were fitted to the model site for the sweet taste receptor proposed by Temussi.[7] Two sweet sulfamates **1** and **13** and two nonsweet ones **16** and **38** are shown in Figure 2, together with the receptor pattern. Hydrophobic parts of sweet sulfamates **1** and **13** interact with the receptor wall in sector C, near its junction with open sector D. The *n*-pentyl group in **16**, a nonsweet sulfamate, invades the receptor wall in sector C. One or two last carbons in the chain should be beyond the receptor wall.

(Methylcyclohexyl)sulfamate **38** could not interact with any part of the receptor, and the cyclohexyl ring occupies the open sector D. From the other side the isopropyl group in **34**

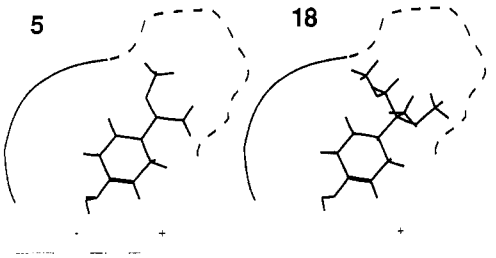


Figure 3. Projection of sweet **5** and nonsweet **18** aldoximes into receptor model.

is too small to give a hydrophobic interaction with any receptor sector. We might conclude the following:

(1) The good fit of sweet sulfamates **1** and **13** to the receptor and the superposition with nonsweet sulfamate **16** allow one to define exactly the part of the wall in sector C (the bottom).

(2) The presence of the open sector D in the receptor site has been proved by nonsweet sulfamate **38**; its cyclohexyl group is located there along the *y* direction.

B. Aldoximes. Aldoximes have only one strong active center able to interact through hydrogen bonding with the appropriate site of the receptor. Strong basic center B is formed by the –NH–OH group. One can assume that the vinyl hydrogen in the cyclohexene ring is weak acidic center, supporting the strong one.

Compounds having only one center or two centers but of very different strengths can be sweet.[8,9] In such cases very good fittness of the molecule into the receptor site is of critical importance. Then, dispersion forces and hydrophobic interaction are effective enough to create a sweet impression.

The minimum energy conformers of different aldoximes listed in Table 2 were fitted to the receptor site for sweet taste proposed by Temussi. Sweet aldoxime **5** and nonsweet **18** are shown in Figure 3 together with the receptor pattern. Two groups, methyl and methyl from –OMe in **5** resembling *n*-propoxynitroaniline, show two hydrophobic interactions with sector C, and sector B (in part close to sector A, respectively). Two other sweet aldoximes listed in Table 2, **25** and **23**, may interact with receptor walls of sectors B and/or C (upper edge).

Large and bulky substituents in **18** have not enough space with either sector A/B nor C (assuming rotation of the substituent) to fit into the receptor cavity. For that reason it is not sweet. Substituents in aldoxime **19**, located at carbon atom C-5, violate the receptor wall in sector A, and again do not allow the molecule to fit into the receptor cavity. The ester group in nonsweet aldoxime **35** overlaps strongly with the receptor wall in sector C.

The above arguments support the conclusion that, in the case of nonequilibriated centers AH···B, steric interactions or hindrance of the hydrophobic part of the molecule is of key importance for sensory properties. Strong hydrophobic and dispersion links between tastant molecule and the receptor compensate weaker hydrogen bonding forces between the receptor and the hydrophilic moiety of the molecule.

C. (Arylsulfonyl)(cyclo)alkanoic Acids. Carboxylate ion in the title compounds has only a single hydrogen bonding center in the molecule. There is no basic center. According to Temussi[7] the AH···B moiety has mainly the locking function. It is conceivable that only half of this entity might be sufficient to lock a given molecule in the receptor cavity, provided that the sterical fit of the molecule to the site is particulary good and effective.

The minimum energy conformers of different acids listed in Table 3 were fitted to the receptor site and are shown in Figure 4.

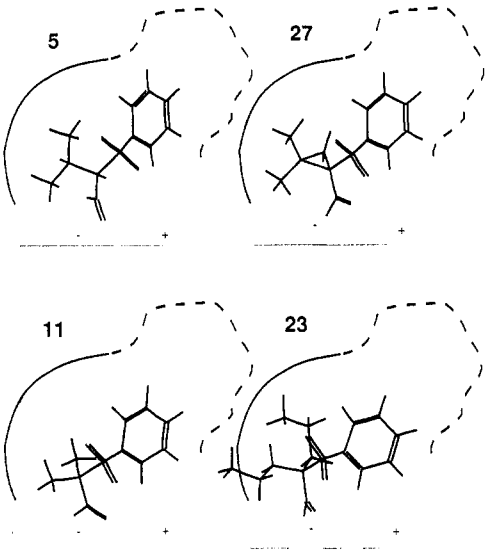


Figure 4. Projection of sweet (**5** and **27**) and nonsweet (**11** and **23**) (arylsulfonyl)alkanoic acids into receptor model.

Sweet acids **16** and **27** strongly interact with sectors A and C of the receptor through London dispersion forces. It seems in **27** that both methyl groups in sector A are a critical distance from the wall, and the tastant molecule can perfectly fit the cavity. The isopropyl group in **5** fits the receptor site very well. Derivatives **11** and **23** are nonsweet. This could be explained by inspection of Figure 4. Two methyl groups in **11** do not provide efficient interaction with sector A. However in acid **23** at least one *n*-propyl chain hinders interaction with wall in sector A.

The above observations support the conclusion that in molecules having only half of the Schallenberger entity (AH or B) the critical for sensory property is the remaining part of the molecule. With half of a Schallenberger moiety, two hydrophobic groups interacting with the receptor are necessary to give a sweet taste (**5**, **16**, **27**). If only one such possibility exists (**11**, **20**), the molecule is not a sweet one.

D. Carbohydrates. Carbohydrates constitute a class which is much more flexible with respect to the defined AH···B entity. Fits of minimum energy conformers of different carbohydrates in the receptor site led us to different conclusions than those in the literature.[9] The fitting of saccharose into the receptor in agreement with the literature assignment of AH···B violates the Schallenberger barrier. In addition the lack of logically explainable interactions with the receptor wall is evident. The difference deals with the assignment of AH···B centers in carbohydrates. Our idea is to assign a hydroxy group at C-4 as the basic center B and a hydroxy group at C-3 as the acidic center AH, in saccharose **1**, glucose **27**, trechalose **21**, and other carbohydrates, contrary to other authors. This assumption allows us to fit the above carbohydrates into the receptor and achieve good superposition with aspartame and saccharine molecules without violating the Schallenberger barrier. Figure 5 shows also very effective interaction of carbohydrates with the wall in sector A, as in saccharine.

Saccharose **1**, trechalose **21**, and trichlorogalactosaccharose **13** (see Table 4), besides having good interaction with sector A, interact also with sectors B and/or C. We assume in compound **13** 4-Cl as the B center and 3-OH as the AH center. The three-dimensional fit indicates also very effective interaction with sector C.

On the grounds of our interpretation we disagree with the theory of Kier[5] who proposed a fixed geometrical pattern of AH···B and the site of interaction between the molecule and

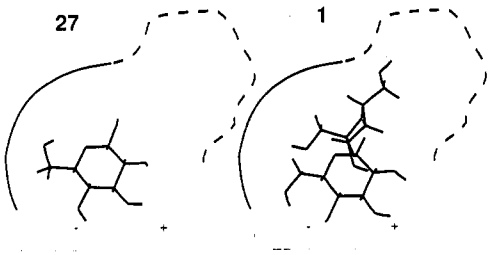


Figure 5. Projection of glucose **1** and saccharose into receptor model.

the receptor. Up to now, the only proof for failure of Kier's proposal was saccharine, tolylourea, and dulcine.

CONCLUSIONS

Discriminant analysis allows selection of the most important molecular fragments supporting sweet and nonsweet taste and most characteristic sweet and nonsweet representatives in four families of organic compounds. Selected compounds were used for further studies of the relationship between taste, three-dimensional chemical structure, and the pattern of sweet taste receptor.

Sulfamates and carbohydrates have both centers provided by Schallenberger theory, basic and acidic in proper distance. In aldoximes a strong basic center is present; however, only the potential presence of a weak acidic center might be assumed. (Arylsulfonyl)alkanoic acids show only an acidic center. It may be concluded that the presence of the AH···B moiety in a molecule is not a critical condition for sweet impression. Two hydrogen bondings or even one hydrogen bond between the molecule and the sweet taste receptor locks the molecule in the cavity of receptor. The necessary requirements for sweet molecules are in addition to hydrogen bond(s) interaction with one or two sectors of the receptors A, B, and C, respectively. Division of the receptor's cavity into sectors A–D has been invented by us to simplify discussion and for better consistency of reasoning.

Sector D is completely open and can accommodate large groups or parts of the molecule. Thus sweet taste results from three interactions between molecule and receptor. Interaction with sectors A–C are controlled by the geometry of the receptor size (fixed) in the plane *yz* and the bulkiness of the molecule. Only molecules which can fit rather tightly into the receptor are potentially sweet. Too small and too large molecules are not sweet. The nature of said interaction depends on the steric factor, hydrophobic forces, van der Waals forces, and London forces. In our opinion the literature description of AH···B centers in carbohydrates does not correspond with the three-dimensional model. We propose the opposite designation of both centers in saccharose and glucose. As a result a much better fit between carbohydrates, aspartame, and saccharine occurs.

We assume that the receptor's cavity in sector A is especially effective in the process of taste perception. There is no doubt that sectors A–C are not equal in sweet taste reception and organoleptic profiling; however, this is only a qualitative conclusion that should be supported in the future by a quantitative approach.

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