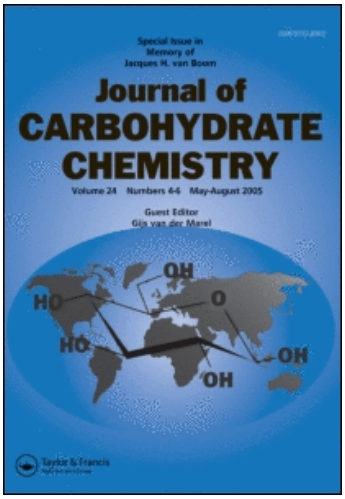

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Molecular Mechanisms of Sweet Taste. V. Sucralose and Its Derivatives

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MOLECULAR MECHANISMS OF SWEET TASTE. V.

SUCRALOSE AND ITS DERIVATIVES

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ABSTRACT

Chloro-deoxy-derivatives of sucrose, especially the intensely sweet 4,1',6'-trichloro-4,1',6'-trideoxy-*galacto*-sucrose (Sucralose) and its derivatives, have been investigated in their peripheral interactions with a helical proteinaceous receptor model using computer graphics. In common with other high intensity sweeteners, they show multiple couplings with different side chains of the amino acid residues in the receptor protein.

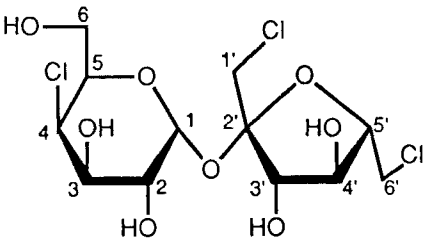
INTRODUCTION

We have developed a sweetener mechanism based on a simple hypothetical model of an α-helical proteinaceous receptor with L-asparaginyl (**AH** and **B** sites) and L-prolinyl residues at the N-terminus and adjacent sites.[1] This three dimensional model accounts for the activity of practically all known sweet compounds, including chiral molecules, and their variations in intensity from one to several thousand times, by virtue of the interactions or bindings to the side chains emerging from the α-helix.[2,3,4] Our proposed model has been deduced from structure - sweetness relationships, on a chirality basis, of both sweet and

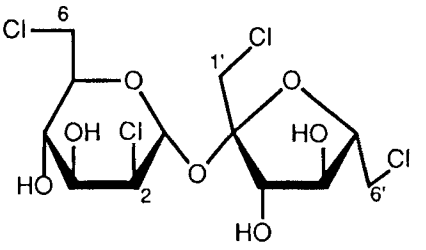
their isomeric non-sweet compounds. A pleated sheet or random coil protein cannot fulfil the demands of chiral sweet molecules. The receptor site may well be a valley or fissure within a convoluted polypeptide chain, similar to the active sites of many enzymes, but the substrate requirements for the sweetness sensation range from small molecules, such as chloroform, to polypeptides and macromolecular proteins. Hence our choice of a peripheral site, at this stage, as a simple but plausible model until the active site is identified; if necessary, our computer graphics can then be transformed, with minor modifications, to an interior active site since the stereochemical requirements of the substrate - receptor will be similar. Especial interest is centred on the intensely sweet 4,1',6'-trichloro-4,1',6'-trideoxy-*galacto*-sucrose (Sucralose)[5] and its derivatives (Fig. 1).

The preceding study[2] on sucrose revealed two glucophoric bifunctional entities ($\mathbf{AH_S/B_S}$) of Shallenberger-Acree type[7] at 1'-OH($\mathbf{AH_S}$)/2-O($\mathbf{B_S}$) and 3'-OH ($\mathbf{AH_S}$)/2-O($\mathbf{B_S}$). The former acted in conjunction with three of Kier's hydrophobic sites[8] at 1'-CH_2($\mathbf{X_S}^4$), 6-CH_2($\mathbf{X_S}^5$) and 6'-CH_2($\mathbf{X_S}^8$) and the latter with two such centres at 1'-CH_2($\mathbf{X_S}^4$) and 6-CH_2($\mathbf{X_S}^5$). The multiple hydrophobic interactions enable the sucrose molecule to form dispersion bonds with different side chains of the receptor, which often results in an enhancement of sweetness.[2,3,4] The configurations of the glucophoric triads ($\mathbf{AH_S/B_S/X_S}^4$, $\mathbf{AH_S/B_S/X_S}^5$ and $\mathbf{AH_S/B_S/X_S}^8$) were found to be in the expected clockwise orientations.[9]

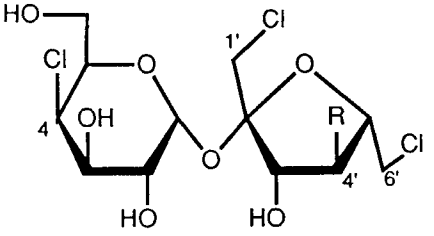
Strong enhancement of sweetness of sucrose has been achieved by replacing specific hydroxyl groups, namely those at C-4, C-1', C-4' and C-6', in the glucosyl and the fructoside units of sucrose, but not at the 6-OH group, with highly lipophilic chlorine atoms.[10] These intensely sweet derivatives are 4'-chloro-4'-deoxysucrose (2 X sucrose),[11] 4-chloro-4-deoxy-*galacto*-sucrose (5 X),[12,13] 4',6'-dichloro-4',6'-dideoxysucrose (5 X),[14] 1'-chloro-1'-deoxysucrose (20 X),[12] 6'-chloro-6'-deoxysucrose (20 X),[12] 6,1',6'-trichloro-6,1',6'-trideoxysucrose (25 X),[9] 1',4'-dichloro-1',4'-dideoxysucrose (30 X),[11] 4,6'-dichloro-4,6'-dideoxy-*galacto*-sucrose (50 X),[15] 1',6'-dichloro-1',6'-dideoxysucrose (76 X),[9] 1',4',6'-trichloro-1',4',6'-trideoxysucrose (100 X),[11] 4,1'-dichloro-4,1'-dideoxy-*galacto*-sucrose (120 X),[9] 4,4',6'-trichloro-4,4',6'-trideoxy-*galacto*-sucrose (160 X), [14] 4,6,1',6'-tetrachloro-4,6,1',6'-tetradeoxy-*galacto*-sucrose (200 X),[12,16] 4,1',4'-trichloro-4,1',4'-trideoxy-*galacto*-sucrose (220 X), [14] 4,1',6'-trichloro-4,1',6'-trideoxy-*galacto*-sucrose (Sucralose, 650 X),[12] 4'-deoxy-4'-fluoro-sucralose (1,000 X),[11,17] 4'-chloro-4'-deoxysucralose (2,200 X),[17,18] 4'-bromo-4'-deoxysucralose (3,000 X)[17,19] and 4'-deoxy-4'-iodo-



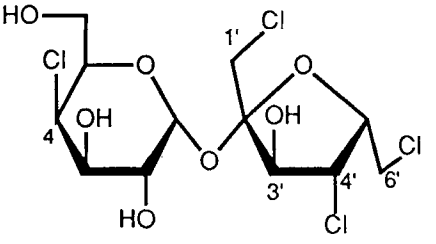
Sucralose (650 x sucrose)



2,6,1',6'-Tetrachloro-2,6,1',6'-tetradeoxy-*manno*-sucrose (not sweet)



4'-Substituted-4'-deoxysucralose
R = H (150 x), OCH_3 (300 x),
F (1,000 x), Cl (2,200 x),
Br (3,000 x) and I (7,500 x)



4-Chloro-4-deoxy-α-D-galactopyranosyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-sorbofuranoside (200 x)

Figure 1. Molecular structures of tri- and tetra-chlorosucroses.

sucralose (7,500 X)[17,19] (**Fig. 1**). We have now applied computer graphics to study of the interactions of sucralose and related derivatives with the receptor helical model.

RESULTS AND DISCUSSION

There are five OH groups on C-2, C-3, C-6, C-3' and C-4' in the sucralose molecule (**Fig. 1**). Concerning the primary 6-OH group, the influence of the

substituent at the C-6 position was found to be critically dependent on its size rather than the presence or absence of an oxygen capable of participating in the hydrogen bonding.[20] In fact, 6-deoxysucralose is 400 times sweeter, whilst 6-chloro-6-deoxysucralose is only 200 times sweeter than sucrose.[21] The removal of the 4'-OH group is not detrimental to sweetness, indeed an increase in the size and hydrophobicity of the C-4' substituent from H (deoxy, 150 X)[21] to *O*-CH_3 (300 X),[21] F, Cl, Br and I resulted in a remarkable increase of sweetness.[20] The remaining glucosyl equatorial 2-OH, 3-OH and fructosyl 3'-OH groups are therefore the only candidates for the AH_S and B_S components.

Assuming that the hydrophobic Cl and CH_2 components of the sucralose molecule reside on one face of the molecule, in common with other high intensity sweeteners, models reveal that interaction can occur only where this hydrophobic face confronts the receptor. Three AH_S/B_S pairs, namely 3-OH/2-O, 2-OH/3'-O and 3-OH/3'-O, among six possible AH_S/B_S pairs, can be eliminated from our considerations, owing to the unfavourable counterclockwise arrangements[9] of the $AH_S/B_S/X_S$ triads. Furthermore, due to the strictly restricted distance (2.5 - 4.0 Å)[7] between the AH_S and B_S sites, the 3'-OH/3-O (ca. 5.6 Å) can be discounted, leaving only two AH_S/B_S pairs, that of 3'-OH/2-O and 2-OH/3-O as significant to the molecular mechanism. However Hooft et al.[22] have designated the 2-OH/3-O to the **AH/B** of Sucralose from calculations of molecular mechanics and dynamics: the glycosidic linkage of sucralose ($\Phi = -152°$) is very different from sucrose ($\Phi = -60°$) but they predict that the major conformation for sweetness has $\Phi = +60°$. Likewise Lichtenthaler and Immel[23] favour the 2-OH/3-O as **AH/B** from a computer aided study of molecular electrostatic potentials and lipophilic potentials of sucralose, with the lipophilic **X**-site on the outside of the fructosyl unit (see, however, our comments about C-4 above).

It is noteworthy that sucralose-3',4'-epoxide was found to be not sweet.[21] However, a conformational deformation of the furanose ring, caused by the epoxidation, was insufficient to prevent the dispersive interactions between models of the sucralose molecule and the receptor. This observation suggests that the fructosyl 3'-OH is an essential component for sweetness. Also, 2,1'-dichloro-2,1'-dideoxy-*manno*-sucrose[11,24,25] and 2,6,1',6'-tetrachloro-2,6,1',6'-tetradeoxy-*manno*-sucrose[10,26] (**Fig. 1**) were not sweet, which suggest that the glucosyl 2-OH is also essential for sweetness in sucrose derivatives, thus favouring 3'-OH/2-O as **AH/B**.

The Fourier transformation infrared spectrum of sucralose revealed a sharp absorption characteristic of a free OH group which was assigned to the 3-OH, hence it is not engaged in an intramolecular hydrogen bond.[9,27] The X-ray

crystal structure analysis of sucralose demonstrated the presence of an intramolecular hydrogen bond between the 2-OH and 3'-OH,[28] and SIMPLE ^{1}H NMR spectroscopy (secondary isotope multiplet NMR of partially labelled entities) revealed that the 2-OH is a proton acceptor and the 3'-OH is a proton donor in the 3'-OH ···· 2-O hydrogen bond.[9,28] In a dilute aqueous solution, the internal hydrogen bond is probably cleaved, and the isolated partners are ready to form two new external hydrogen bonds with the highly electron-deficient $NH_3^+(\mathbf{AH_r})$ and the electron-rich $\underline{C}\underline{O}NH_2(\mathbf{B_r})$ components of the N-terminal L-asparginyl residue of the helical receptor protein, respectively. Clearly, little structural change will take place when sucralose is transformed from the intramolecularly hydrogen-bonded form to the bi-intermolecularly hydrogen-bonded complex that links the sucralose molecule to the receptor protein,[9] since there is only a slight rotation about the central interglycosidic C-1-O-C-2' bond.[29]

An early attempt to explain the intense sweetness of sucralose involved the 1'-Cl as the proton accepting component $(\mathbf{B_S})$[12] of two glucophoric $\mathbf{AH_S/B_S/X_S}$ triads. This proposal could account for the sweetness of chloroform, in which one Cl and another Cl play roles as the $\mathbf{B_S}$ and $\mathbf{X_S}$[4], respectively, and the electron deficient H acts as the $\mathbf{AH_S}$, but since chloroform is not very sweet, the proton accepting power of the Cl substituent was assumed to be weak, compared to that of an O substituent. Indeed, our infrared spectroscopic study[30] has revealed that the proton accepting power of Cl is only 6 – 22% of that of O, when phenol is used as the proton donating component of the hydrogen bond. Thus, the Cl substituent can scarcely participate in a formation of hydrogen bond with the receptor in a case where the OH and Cl groups coexist in the same molecule, such as sucralose and its derivatives.

Hence, we have studied the two most probable $\mathbf{AH_S/B_S}$ pairs, namely 3'-OH/2-O and 2-OH/3-O, respectively, and their interactions with the receptor helix by computerized molecular modellings. Using the $\mathbf{AH_S/B_S}$ pair of 3'-OH/2-O, the two intermolecular hydrogen bonds between the sucralose molecule and the receptor exhibit proper distances and correct bond angles. That is, by constraining the distances and angles of the two intermolecular hydrogen bonds: $\mathbf{AH_r}(NH_3^+)$ ···· $\mathbf{B_S}$(2-O) and $\mathbf{B_r}(\underline{C}\underline{O}NH_2)$ ···· $\mathbf{AH_S}$(3'-OH), to be 2.9 ± 0.1 Å[31]; 180 ± 16°[32] and 2.8 ± 0.1 Å[31]; 160 ± 20°[33], respectively, favourable interactions between sucralose and the receptor are generated with energy minimizations by the molecular mechanics program MAXIMIN 2 in SYBYL system.[34] As shown in Fig. 2,* the two adjacent hydrophobic sites at 1'-CH_2 and 1'-Cl of the fructosyl unit

* Figs. 2-5 appear on pages 1091 and 1092.

interact with the side chains of the 4th(X_r^4) and 8th(X_r^8) amino acid residues of the receptor protein, respectively, counting from its N-terminus. The axial 4-Cl of the glucosyl unit interacts with the side chain of the 5th(X_r^5) amino acid residue. Furthermore, the 4'-OH of the fructosyl moiety appears to play an important role as a proton donor (AH_s^4) in the formation of an additional hydrogen bond with a side chain of the 4th amino acid residue of the receptor. This is not surprising, since there is a peak of preference for an acidic amino acid residue, such as aspartic acid (28/214) or glutamic acid (40/214) in the 4th position of the helical protein.[35,36] A hydrogen bond between the 4'-OH (AH_s^4) and the COO^- (B_r^4) of the 4th glutamic acid residue is favourable, but not between similar groups and a 4th aspartic acid residue, owing to its shorter side chain length. The formation of this hydrogen bond, COO^- ···· HO: 2.8 Å ; 160° (2.5 – 2.8 Å[37]; 180 ± 16°[32]) requires a pseudo-rotation of the furanoid ring[38] and a slight rotation about the central interglycosidic C-1-O-C-2' linkage.[29] This is probably assisted by the formation of a weak internal hydrogen bond between the 6-OH and 6'-Cl: 3.1 Å; 164° (2.86 – 3.21 Å[39]). The 6'-Cl, centered on the fructosyl unit now occupies a position external to the active site of the receptor. The existence of an internal 6 → 6' hydrogen bond is supported by the reduced sweetness of 6-deoxysucralose (400 X)[21] which cannot form such a hydrogen bond. The sucralose conformation which we employed in our receptor model had $\Phi = \theta$(C-1g-O-1g-C-2f-O-5f) = -76.9° for the closest contacts; the angle Φ was determined by computer analysis. The various assignments for the interactions of sucralose with the receptor sites are listed in **Table 1**.

Moreover, the reduced sweetness of 4'-deoxysucralose (150 X)[21] and 4'-*O*-methylsucralose (300 X)[21] is reasonably explained by using the above mentioned assignment. Thus, deoxygenation of the 4'-OH prevents the formation of hydrogen bond (AH_s^4 ···· B_r^4) and reduces the sweetness, whilst *O*-methylation eliminates hydrogen bond formation, but retains a dispersion bond between the *O*-CH_3(X_s^4) and the X_r^4 component, thus exhibiting only moderately reduced sweetness, compared to that of the parent sucralose.

In the AH_s/B_s pair of 2-OH/3-O, when the two intermolecular hydrogen bonds between sucralose and the receptor: $AH_r(NH_3^+)$ ···· B_s(3-O) and $B_r(\underline{C}\underline{O}NH_2)$ ···· AH_s(2-OH) are constrained to be 2.9 ± 0.1 Å[31]; 180 ± 16°[32] and 2.8 ± 0.1 Å[31]; 160 ± 20°[33], respectively, only one hydrophobic site: 4-Cl(X_s^5) has good contact with the side chain of the 5th(X_r^5) amino acid residue of the receptor, but the other two hydrophobic sites: 1'-Cl and 6'-Cl have positions remote to the binding sites of the receptor. Furthermore, the 4'-OH is remote from the side chain of

Table 1. Interaction sites between sucralose and its derivatives with the receptor.

	AH_S/B_S	AH_S^4	X_S^4	X_S^5	X_S^8
Sucralose (650 X)*	3'-OH/2-O	4'-OH	1'-CH_2	4-Cl	1'-Cl
4'-Deoxy-4'-fluoro-sucralose (1,000 X)	3'-OH/2-O	——	1'-CH_2, 4'-F	4-Cl	1'-Cl
4'-Chloro-4'-deoxy-sucralose (2,200 X)	3'-OH/2-O	——	1'-CH_2, 4'-Cl	4-Cl	1'-Cl
4'-Bromo-4'-deoxy-sucralose (3,000 X)	3'-OH/2-O	——	1'-CH_2, 4'-Br	4-Cl	1'-Cl
4'-Deoxy-4'-iodo-sucralose (7,500 X)	3'-OH/2-O	——	1'-CH_2, 4'-I	4-Cl	1'-Cl

* Intensity of sweetness is given in parenthesis (sucrose = 1).

the 4th amino acid residue of the receptor (**Fig. 3**), and formation of the cardinal extra hydrogen bond between the 4'-OH and the acidic side chain of the 4th amino acid residue of the receptor was ruled out. Therefore, we conclude that the choice of 2-OH/3-O as the AH_S/B_S pair for the sucralose molecule is not favourable.

Examinations of models of 4'-deoxy-4'-halo-sucraloses reveal a total of six interaction sites, in each case, using the 3'-OH/2-O as the AH_S/B_S components, as shown in **Fig. 4** and **Table 1**. The dispersion bond formation between the 4'-substituent and the X_r^4 is probably assisted by the formation of weak intra-molecular hydrogen bond between the 6-OH and 6'-Cl, as seen in the case of sucralose. Also, there is a close relationship between the intensity of sweetness and van der Waals radius of the 4'-substituent, viz. H (1.00), F (1.35), Cl (1.80), Br (1.95) and I (2.15 Å), as well as their hydrophobicities. Hence, the contact surface area of the 4'-substituent with the X_r^4 influences the strength of the attractive force with the receptor, thereby playing an important role in the enhancement of sweetness. In fact, the 4'-substituent has a contact with the X_r^4 site with a conformational change caused by the pseudo-rotation of the furanoid ring[37] and the rotation about the interglycosidic C-1-O-C-2' linkage.[29] As a result, the 6'-Cl occupied an external position to the binding site of the receptor.

Inversion of the configurations at C-3' and C-4' of 4'-chloro-4'-deoxy-sucralose results in a reduction in sweetness. Thus, 4-chloro-4-deoxy-α-D-galactopyranosyl 1,4,6-trichloro-1,4,6-trideoxy-β-D-sorbofuranoside (200 X)[9] (**Fig. 1**) shows only one tenth of the sweetness of the fructoside isomer (2,200 X).[17] The participation of the epimerized 3'-OH as the AH_S component is allowed by the conformational flexibility of the stimulus molecule around the inter-glycosidic C-1-O-C-2' bond, but as a result, the 4'-Cl is now remote from the receptor site (X_r^4). The interaction pattern of the compound with the receptor [3'-OH(AH_S)/2-O(B_S), 1'-Cl(X_S^4) and 4-Cl(X_S^5)] has only two hydrophobic binding sites (**Fig. 5**), thus eliciting the reduced sweetness, compared to the fructoside isomer which has the four hydrophobic binding sites with the receptor (**Table 1**).

CONCLUSION

A conformational study by computer graphics of the interaction between sucralose with a helical protein receptor has revealed that the most favorable case for high intensity sweetness involves participation of the AH_S/B_S pair of 3'-OH/2-O in concert with multiple hydrophobic attractions with side chains of the peptide constituents and another intermolecular hydrogen bond between the proton donating 4'-OH(AH_S^4) and a proton accepting side chain of the 4th amino acid residue, such as a glutamyl residue, of the receptor. Thus, the 1'-CH_2 interacts with the 4th amino acid residue (X_r^4), the 4-Cl interacts with the 5th amino acid residue (X_r^5) and the 1'-Cl has a contact with the 8th amino acid residue (X_r^8) of the receptor. The formation of the additional intermolecular hydrogen bond is probably assisted by a possible occurrence of a weak intramolecular hydrogen bond between the 6-OH and 6'-Cl in the sucralose molecule.

4'-Deoxy-4'-halo-sucraloses have six interaction sites with the receptor helix, in each compound, with the same AH_S/B_S pair of 3'-OH/2-O, and a close relationship is noted between the intensity of sweetness and the contact area of the 4'-halo substituent with the 4th amino acid side chain (X_r^4). The *sorbo*-isomer of 4'-chloro-4'-deoxysucralose showed reduced sweetness, because of fewer hydrophobic attractions. The important 4'-Cl is now remote from the binding site of the protein receptor.

The alternative AH_S/B_S pair at 2-OH/3-O did not show a good profile in the sweetener - protein helix, due to its poor fit in the complex. Thus, without a participation of the 4'-components in the interaction with the receptor, it is

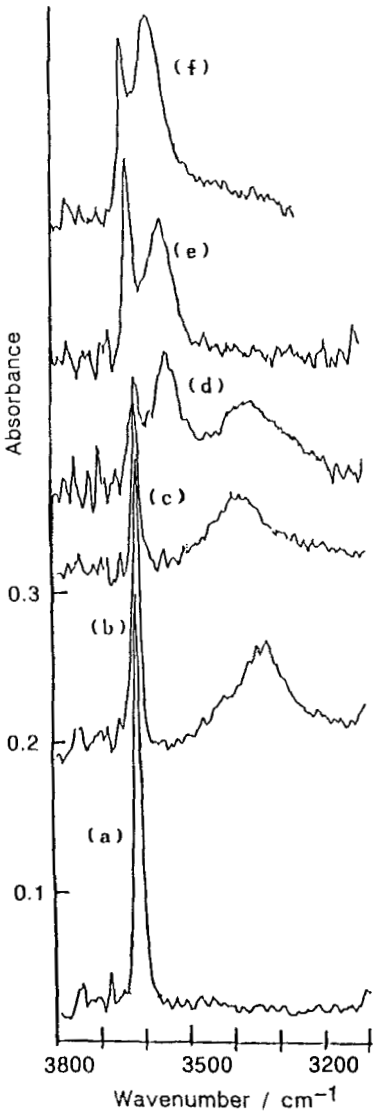
impossible to explain the enhancement of sweetness in the 4'-halogenated derivatives of sucralose as well.

EXPERIMENTAL

We have compared the proton accepting powers of several compounds in their formation of hydrogen bonds with a common proton donor, namely phenol. The comparison was made by examining infrared spectra of three-component system, each of which consisted of the proton donor (phenol) and a proton acceptor (dipentyl ether or another) in carbon tetrachloride. Phenol, carbon tetrachloride, dipentyl ether, pentyl alcohol, pentyl chloride and pentyl bromide were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), and pentyl fluoride and pentyl iodide were purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin, U. S. A.). The instrument used was a Shimadzu IR-460 spectrometer, and the sample solution was placed in a CaF_2 cell with an optical path length of 1 mm. The results are shown in **Fig. 6**.

When phenol is dissolved in CCl_4 and its concentration is as low as 0.015 M, only one bond-stretching band (a free O-H) was observed at 3616 cm^{-1} [**Fig. 6** (a)]. On adding a proton acceptor (dipentyl ether) to the solution, an intensity of the free O-H band was lowered, and a new band appeared at lower frequency (3328 cm^{-1}) [**Fig. 6**(b)] which was assignable to a hydrogen-bonded O-H stretching vibration. The proton accepting power of a proton acceptor may be estimated by (1) how great is an amount of the shift of the hydrogen-bonded O-H frequency from the free O-H frequency, and /or (2) how small is an amount of the proton acceptor necessary to add for causing an occurrence of the hydrogen-bonded O-H band. As determined from an inspection of **Fig. 6**, the proton accepting powers are in the following order: dipentyl ether > pentyl alcohol > pentyl iodide > pentyl bromide > pentyl chloride > pentyl fluoride. In the present examination, pentyl fluoride showed no proton accepting power, even when phenol was dissolved in neat pentyl fluoride without CCl_4, there appeared only its free O-H band at 3616 cm^{-1}.

It should be pointed out that dipentyl ether causes the O-H ···· O band, in CCl_4 solution containing phenol, at a lower frequency than the free O-H with a large shift, such as 288 cm^{-1}, and that this band appears with only 0.10 M of the ether. An equilibrium constant of phenol - dipentyl ether association is estimated to be 4.8 M^{-1} in CCl_4 at 20°C. On the other hand, pentyl chloride causes the OH ···· Cl band at 3552 cm^{-1}, which is lower than the free O-H frequency only 64



(1) Phenol in CCl_4. (b) Phenol + dipentyl ether(0.1M) in CCl_4. (c) Phenol + pentyl alcohol(0.1M) in CCl_4. (d) Phenol + pentyl iodide(3.8M) in CCl_4. (e) Phenol + pentyl bromide(2.7M) in CCl_4. (f) Phenol + pentyl chloride(4.1M) in CCl_4. The optical path length was 1 mm, the temperature was kept at 20°C, and the concentration of phenol in CCl_4 was 0.015M in each cases.

Figure 6. *Infrared absorption spectra of dipentyl ether, pentyl alcohol, pentyl iodide, pentyl bromide and pentyl chloride with phenol in* CCl_4.

cm^{-1}. In addition, the concentration of pentyl chloride must amount to 4.1 M to cause an occurrence of the OH ···· Cl band. An equibrium constant of the phenol – pentyl chloride association is estimated to be 0.29 M^{-1}. Thus, the proton accepting power of pentyl chloride is estimated to be weaker than that of dipentyl ether by one order of a magnitude.

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REFERENCES

1. T. Suami and L. Hough, *J. Carbohydr. Chem.*, **10**, 851 (1991).
2. T. Suami and L. Hough, *J. Carbohydr. Chem.*, **11**, 953 (1992).
3. T. Suami and L. Hough, *Food Chem.*, **46**, 235 (1993).
4. T. Suami and L. Hough, *Food Chem.*, **47**, 267 (1993).
5. L. Hough, S. P. Phadnis, R. Khan, and M. R. Jenner, *Brit. Pat.* 1.543.157 (1977); *Chem. Abstr.*, **87**, 202019v (1977).
6. T. Suami, *Pure Appl. Chem.*, **59**, 1509 (1987).
7. R. S. Shallenberger and T. E. Acree, *Nature*, **216**, 480 (1967).
8. L. B. Kier, *J. Pharm. Sci.*, **611**, 1394 (1972).
9. L. Hough and R. Khan in *Progress in Sweeteners,* T. H. Grenby, Ed.; Elsevier Applied Science: London/New York, 1989, pp 97–120.
10. C. E. James, L. Hough, and R. Khan in *Progress in the Chemistry of Organic Natural Products,* W. Herz, H. Grisebach, G. W. Kirby, and Ch. Tamm, Eds.; Springer Verlag: Wien/New York, 1989, pp 117–184.
11. G. Jackson, M. R. Jenner, R. A. Khan, C. K. Lee, K. S. Mufti, G. D. Patel, and E. B. Rathbone (Tate & Lyle), *Brit. Pat.* 2.104.063 (1982), *Eur. Pat. Appl.* EP 73.093 (1983); *Chem. Abstr.*, **99**, 54127j (1983).
12. L. Hough and R. Khan, *Trends Biol. Sci.*, **3**, 61 (1978).
13. L. Hough, S. P. Phadnis, R. A. Khan, and M. R. Jenner, *Brit. Pat.* 1.543.167 (1976).
14. L. Hough and R. Khan, The relationship between sweetness and the molecular structure of sucrose and its derivatives, Reims lecture, Sept. 2–6 (1991).
15. G. Jackson, M. R. Jenner, and R. Khan (Tate & Lyle), *Brit. Pat.* 2.101.989 (1982), *Eur. Pat. Appl.* EP 67.535 (1982); *Chem. Abstr.*, **98**, 161107d (1983).
16. L. Hough and S. P. Phadnis, *Nature,* **263**, 800 (1976).
17. C. K. Lee, *Adv. Carbohydr. Chem. Biochem.*, **45**, 199 (1987).

18. C. K. Lee, *Carbohydr. Res.*, **162**, 53 (1987).

19. G. Jackson, M. R. Jenner, R. A. Khan, C. K. Lee, K. S. Mufti, G. D. Patel, and E. B. Rathbone, *Brit. Pat.* 8.211.427 A (1982).

20. M. R. Jenner in *Sweeteners,* D. E. Walters, F. T. Orthoefer, and G. E. DuBois, Eds.; ACS Symp. Ser., **450**, 68 (1990).

21. Private communications.

22. R. W. W. Hooft, J. A. Kanters, and J. Kroon in *Sweet-Taste Chemoreception,* M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds.; Elsevier Applied Science: Amsterdam, 1993, pp 11–19.

23. F. W. Lichtenthaler and S. Immel in *Sweet-Taste Chemoreception,* M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds.; Elsevier Applied Science: Amsterdam, 1993, pp 21–61.

24. C. K. Lee (Tate & Lyle), *Eur. Pat. Appl.* EP 50.952 (1982); *Chem. Abstr.*, **97**, 145225q (1982).

25. C. K. Lee (Tate & Lyle), *US Pat.* 4.405.654 (1983); *Chem. Abstr.*, **100**, 33495b (1984).

26. M. Mathlouthi, A. M. Seuvre, and G. G. Birch, *Carbohydr. Res.*, **152**, 47 (1986).

27. J. A. Kanters, R. L. Scherrenberg, B. A. Leeflang, J. Kroon, and M. Mathlouthi, *Carbohydr. Res.*, **180**, 175 (1988).

28. J. C. Christofides, D. B. Davies, J. A. Martin, and E. B. Rathbone, *J. Am. Chem. Soc.*, **108**, 5738 (1986).

29. C. Meyer, C. H. du Penhoat, and S. Perez, Conformational flexibility of sucralose, Symposium on Conformational Studies of Oligosaccharides, Polysaccharides and Glycoconjugates, Le Croisic, Loire-Atlantique, France, June 29–July 2, 1992, Abstract VI–5; C. Meyer, S. Perez, C. H. du Penhoat, and V. Michon, *J. Am. Chem. Soc.*, **115**, 10300 (1993).

30. M. Tsuboi, *Bull. Chem. Soc. Jpn.*, **25**, 60 (1952).

31. G. E. Schulz and R. H. Schirmer in *Principles of Protein Structure ;* Springer Verlag GmbH & Co. KG: Wien, 1979, p 35.

32. P. M. Dean in *Molecular Foundations of Drug-receptor Interaction* ; Cambridge Univ. Press: Cambridge, England, 1987, p 93.

33. G. A. Jeffrey and W. Saenger in *Hydrogen Bonding in Biological Structures* ; Springer-Verlag: Berlin/Heiderberg/New York, 1991, p 18.

34. Tripos Associates, Inc., St. Louis, Missouri, SYBYL 6.0 (1993).

35. L. G. Presta and G. D. Rose, *Science,* **240**, 1632 (1988).

36. J. S. Richardson and D. C. Richardson, *Science,* **240**, 1648 (1988).

37. G. C. Pimentel and A. L. McClellan in *The Hydrogen Bond* ; Reinhold Publishing Co.: New York, 1960, p 282.

38. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison in *Conformational Analysis* ; Interscience Publishers, John Wiley & Sons, Inc.: New York/London/ Sydney, 1965, pp 200–206.

39. G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures* ; Springer-Verlag: Berlin/Heidelberg/New York, 1991, p 29.

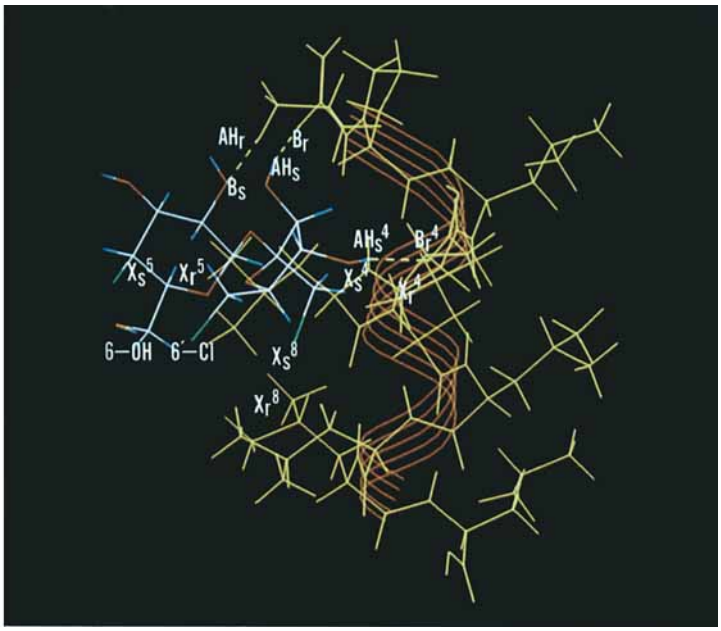

Figure 2. Interactions between sucralose and the receptor model, using 3'–OH/2–O as the AH_S/B_S pair. The α–helix of the receptor is illustrated in yellow colour. The stimulant skeleton is illustrated by white lines, chlorines in green, oxygens in red and hydrogens in blue colour.

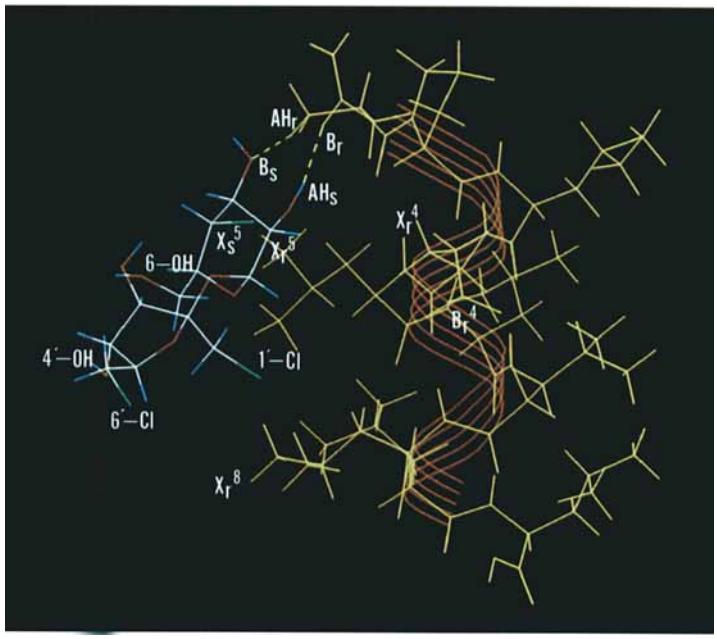

Figure 3. Interactions between sucralose and the receptor model, using 2–OH/3–O as the AH_S/B_S pair. Colour illustrations are same as **Fig. 2.**

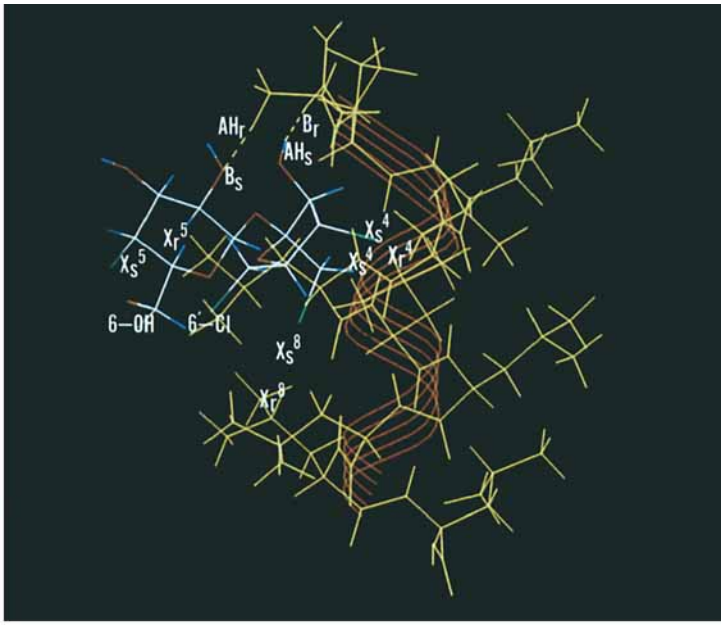

Figure 4. Interactions between 4'–chloro–4'–deoxy–sucralose and the receptor model, using 3'–OH/2–O as the AH_S/B_S pair. Colour illustrations are same as **Fig. 2.**

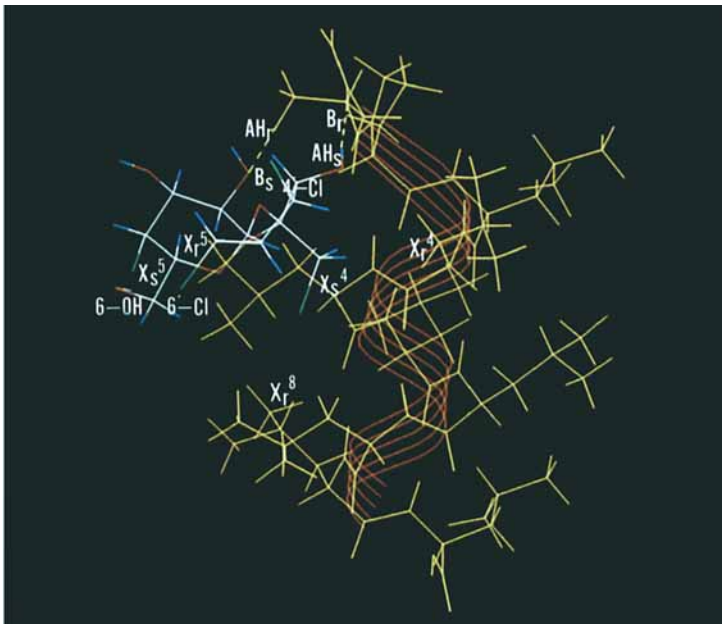

Figure 5. Interactions between 4–chloro–4–deoxy–α–D–galactopyranosyl 1,4,6–trichloro–1,4,6–trideoxy–β–D–sorbo–furanoside and the receptor model, using 3'–OH/2–O as the AH_S/B_S pair. Colour illustrations are same as **Fig 2.**