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Molecular mechanisms of sweet taste 8*: saccharin, acesulfame-K, cyclamate and their derivatives

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The sweetness values of saccharin, acesulfame–K and cyclatmate have been rationalised on the basis of molecular models of their multiple interactions with our α-helical protein receptor, in which the hydrophobic attractions within a crevice of the helix are critical for both sweetness and intensity. The study was carried out by modelling of the host–guest molecules, joined by hydrogen bonds and assessment of their non-bonded hydrophobic interactions, as determined by three-dimensional computer graphics. Both enhancement and loss of sweetness in these disulphoxide derivatives were then interpreted on this basic premise. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Extensive structure-taste studies on three well-known commercial sweeteners, namely saccharin [**1**, R = R′ = H; Na salt of 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide] (>300×sucrose), acesulfame–K [**2**, R = H, R′ = CH_3; K salt of 6-methyl-1,2,3-oxathiazin-4 (3*H*)-one 2,2-dioxide] (130×sucrose) and sodium cyclamate [**3**, $R^1 = R^2 = R^3 = R^4 = R^5 = H$; Na salt of cyclohexyl-sulphamic acid] (30~40×sucrose) afforded data on the binding sites that initiate sweetness (Moncrieff, 1967; Walter and Mitchell, 1986; Lee, 1987; Hough, 1993; Shallenberger, 1993; Spillane *et al.*, 1996). In each sweetener there is a good evidence that the NH-SO_2) moiety acts as the proton donor ($\mathbf{AH_S}$)/proton acceptor ($\mathbf{B_S}$) unit (Clauss and Jensen, 1973; Pautet and Nofre, 1978; van der Heijden *et al.*, 1985), since any substitution at the imino group (NH) eliminates sweetness.

The notation used in the present article is as follows. A proton-donating component is $\mathbf{AH_S}$ and a proton accepting component is $\mathbf{B_S}$; a subscript letter **s** means the stimulus molecule while **r** indicates the receptor helix. A superscript number, such as **4**, **5** and **8**, indicates the numbering of the amino acid residue of the receptor, where the binding occurs with the stimulus molecule. For example, $\mathbf{X_S^8}$ is a hydrophobic binding site of the stimulus molecule, which contacts the 8th amino acid residue of receptor helix, and $\mathbf{X_r^4}$ indicates the 4th amino acid residue of the receptor.

The X-ray crystal structure analysis of these sweeteners revealed that one of the S-O groups has a torsion angle of 60° with the N-H group, placing the proton 2.8 Å from the oxygen atom (Okaya, 1969; Cain and Kanda, 1972; Lee, 1987), as required for the $\mathbf{AH_S/B_S}$ unit.

The hydrophobic site ($\mathbf{X_S}$) for saccharin (**1**; R = R′ = H) was assigned by Kier (1972) to C-4 of the benzene ring, whilst van der Heijden *et al.* (1985) placed it centrally on the double bond that is common to both the benzene and heterocyclic rings. The $\mathbf{X_S}$ component of acesulfame (**2**, R = H, R′ = CH_3) was located at the 6-CH_3 group (Shallenberger, 1993). In the case of sodium cyclamate (**3**; $R^1 = R^2 = R^3 = R^4 = R^5 = H$), the $\mathbf{X_S}$ site was placed at C-3 (or C-5) which is ~3.6 Å from the imino nitrogen atom (Kier, 1972; Lee, 1987), and also central in the cyclohexane ring (van der Heijden *et al.*, 1985).

We have now applied computer-mediated three-dimensional molecular modelling to a study of interactions of these important sweeteners with our proposed α-helical protein receptor, since this stereospecific receptor model accounts for the sweetness, and its intensity, of a diverse range of chiral sweeteners,

*For Part 7 see Suami *et al.* (1997).
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including α-amino acids, sugars, sucralose, aspartame, sucrononic acid and significantly the proteins, Monellin and Thaumatin (see Parts 1–7). The highly specific lock-and-key motif of enzyme binding is implicated in these interactions.

MATERIALS AND METHODS

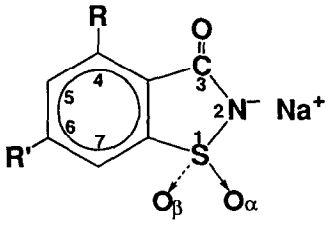
The present work was carried out on a Silicon Graphics workstation, using the computer programs SYBYL 6.1a (TRIPOS Inc., St Louis, Missouri, USA, 1995). Initial co-ordinates for saccharin (**1**, R = R′ = H) (Okaya, 1969), acesulfame-K (**2**, R = H, R′ = CH_3) (Paulus, 1975) and sodium cyclamate (**3**, $R^1 = R^2 = R^3 = R^4 = R^5 = H$) (Cain and Kanda, 1972) were generated from their chemical structures and those for the receptor model were produced for an idealized α-helical protein having L-asparaginyl and L-prolyl residues at the *N*-terminus and adjacent site, respectively, followed by poly-L-leucine in a right-handed α-helix, as described in Part 7 (Suami *et al.*, 1997).

Systematic docking procedures between the sweeteners and the receptor model were carried out by using the SYBYL conformation system, which allows for a graphic surveillance of the process. The method is based on a robot arm (or crankshaft) built by hydrogen bonds between the sweetener and the α-helical receptor protein. The docking study is reduced to a conformational analysis procedure, such as an energy minimization to avoid severe steric conflicts.

The molecular models for the sweetener–receptor complexes were constructed as described in Part 7, with (1) 1:1 stoichiometry, (2) the intermolecular hydrogen bond between the *N*-terminal NH_3^+ of receptor helix ($\mathbf{AH_r}$) and the S→O (or S-O$^-$) of disulphoxide derivatives ($\mathbf{B_S}$) (2.01 Å and ca. 160°), and (3) the intermolecular hydrogen bond between the $CONH_2$ group of a side chain of the *N*-terminus of receptor ($\mathbf{B_r}$) and the N$^-$H$^+$ (or N-H) of disulphoxide derivatives ($\mathbf{AH_S}$) (1.91 Å and 160°) (Taylor *et al.*, 1984; Jeffrey and Saenger, 1991).

All of the disulphoxide derivatives described herein are utilised as salts which in solution will be in equilibrium with the acidic forms. The proportions of acid to salt (or cationic sweetener) will vary according to pH of its solution, hence the differences in sweetness listed for the free acids and salts of saccharin, acesulpham-K and cyclamate (Shallenberger, 1993). In all cases, the sweetness of the salt of the cationic form of the disulphoxide sweetener is higher than the free acidic form, because it is the cationic form that interacts initially with the receptor to bind the host and its guest together. For convenience we have calculated the interatomic distances of the various sweeteners and their derivatives for their unionised acidic forms, but the values for the cationic forms are very closely related (Tables 1, 3, 5).

Table 1. Interatomic distances (Å) in saccharin



Saccharin (1, R=R'=H)

	S→O_α	S→O_β	C=O	H-4	H-5	H-6	H-7
N$^-$H$^+$	2.56	3.25	2.52	4.83	6.52	6.65	5.18
S→O_α		2.52	4.03	5.51	6.25	5.48	3.45
S→O_β			4.55	5.61	6.30	5.45	3.35
C=O				2.89	5.18	6.20	5.66
H-4					2.50	4.32	5.00
H-5						2.48	4.32
H-6							2.50

RESULTS AND DISCUSSION

Distances between N$^-$(**H**$^+$) and S→(**O**) atoms of saccharin (**1**, R = R′ = H) and acesulfame-K (**2**, R = H, R′ = CH_3 were determined (Tables 1 and 3) in order to validate the $\mathbf{AH_S}$ (N$^-$H$^+$) and $\mathbf{B_S}$ (S→O) components. The N$^-$(**H**$^+$) and S→(**O**α) were separated by 2.56 Å in saccharin (**1**, R = R′ = H) and 2.52 Å in acesulfame (**2**, R = H, R′ = CH_3), which should be compared with the accepted distance of 2.5–4.0 Å (Shallenberger and Acree, 1967). The orientation of $\mathbf{AH_S}$ (N$^-$H$^+$)/$\mathbf{B_S}$(S→$\mathbf{O}_\alpha$)/$\mathbf{X_S}$ components was observed to be in the favourable clockwise arrangement for sweetness, when viewed from the receptor side (James *et al.*, 1989); the alternative NH/S→$\mathbf{O}_\beta$/$\mathbf{X_S}$ triad was in the unfavourable counterclockwise mode.

When saccharin (**1**, R = R′ = H) was combined with the receptor model by two intermolecular hydrogen bonds [$\mathbf{B_S}$(S→O_α)····$\mathbf{AH_r}$ and $\mathbf{AH_S}$(N$^-$H$^+$)····$\mathbf{B_r}$], the stimulus molecule settled into a crevice that was surrounded by the 4th, 5th and 8th amino acid residues of the helical receptor model. Previously the hydrophobic binding site ($\mathbf{X_S}$) was assigned to the 4-CH of the benzene ring by Kier (1972), but the present study revealed alternative sites, with both the 5-CH ($\mathbf{X_S^8}$) and 6-CH ($\mathbf{X_S^8}$) in close contact with the 8th amino acid residue of the receptor helix thereby completing the glycophoric triad(s), which induced an appearance of sweet taste, Further, the presence of a proton-donating group ($\mathbf{AH_r'}$) at the 4th position of the receptor, such as L-aspartic acid, L-glutamic acid, L-serine or L-threonine residue, as suggested by studies on sucrose derivatives (Suami *et al.*, 1994), could give rise to a third auxillary hydrogen bond between the $\mathbf{B_S'}$ (C = O) of saccharin (**1**, R = R′ = H) and the $\mathbf{AH_r'}$ (the carboxyl or hydroxyl group but not a carboxylate anion) of the receptor.

Each of the H-4, H-5, H-6 and H-7 of saccharin (**1**, R = R′ = H) can be substituted by a Cl atom with retention of sweetness (Rohse and Belitz, 1991). When the 4-Cl derivative (**1**, R = Cl, R′ = H) was combined with the receptor as described above, both the 4-Cl (X_S^8), and 5-CH (X_S^8) made close contact with the 8th amino acid residue of the receptor, thus establishing the favourable glycophoric triad(s) for sweetness. The 5-Cl and 7-Cl derivatives accomplished analogous glycophoric triads necessary for sweetness (Table 2).

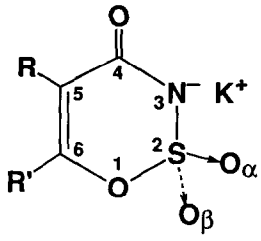
When substituents at the 6-position were CH_3, NH_2, F (van der Waals radius: 1.35×10^{-8} cm), Cl (1.8×10^{-8} cm) or Br (1.95×10^{-8} cm), sweetness was retained although the chloride and bromide each had a bitter aftertaste. These 6-substituted saccharins were accommodated within the crevice surrounded by the 4th, 5th and 8th amino acid residues of receptor, making close contact with the 8th amino acid residue of the receptor, thus retaining sweetness.

On the other hand, when the 6-substituent was OCH_3, OC_2H_5, $NHCOCH_3$ or I (van der Waals radius: 2.15×10^{-8} cm) group, the derivatives were not accommodated due to the bulkiness of the 6-substituent. Hence they failed to accomplish the glycophoric triad, resulting in a lack of sweetness.

The initial interaction, between the sweetener and the receptor involves the formation of the intermolecular hydrogen bond between the proton acceptor of the sweetener (B_S) and the proton donor of receptor (AH_r), and this bond is ionic. Simultaneously the hydrophobic X_S and X_r components interact by van der Waals forces. The second intermolecular hydrogen bond can then be formed but only when the receptor's B_r site is precisely located at the required distance and angle to the AH_S component of the sweetener (Taylor *et al.*, 1984; Jeffrey and Saenger, 1991).

When the 6-ethoxy derivative (**1**, R = H, R′ = OC_2H_5) forms the first inter-molecular hydrogen bond between the S→O_α (B_S) and the NH_3^+ (AH_r), the 6-OEt (X_S) group makes contact with the 5th and 8th amino acid residues (X_r). Moreover, the 5-CH and 7-CH each make contact with the 8th and 5th amino acid residues of the receptor, respectively. In this position, the N^-H^+ group (a potential AH_S component) is remotely located, ca. 2.1 Å away and at ca. 100° to the B_r component of the receptor. It is unable to form the second intermolecular hydrogen bond and hence is not sweet (see Table 2).

Table 3. Interatomic distances (Å) in acesulfame-K



Acesulfame-K (2, R=H, R'=CH3)

	S→O_α	S→O_β	C=O	H-5	6-CH_3
N^-H^+	2.52	2.36	2.39	4.20	5.19
S→O_α		2.48	4.00	4.53	4.39
S→O_β			4.25	5.03	4.71
C=O				2.63	4.81
H-5					2.81

A similar, situation to the 6-ethoxy derivative (**1**, R = H, R′ = OC_2H_5) is that of phthalimide which is tasteless (Hollerman, 1923; Lee, 1987), despite the fact that the acidic N-H ($K_a = 5\times10^{-9}$) of phthalimide can function as a proton donor (AH_S) and the C=O group as a proton acceptor (B_S). Its 3-CH (X_S^5) and 4-CH of the benzene ring (X_S^5) bind to the 5th amino acid residue of receptor, with the 5-CH (X_S^8) in contact with the 8th amino acid residue of receptor, but the N-H (a potential AH_S component) is remote from the B_r component of the receptor (ca. 2.0 Å and ca. 90°). Therefore phthalimide cannot establish the essential second intermolecular hydrogen bond, and the glycophoric triad for sweetness is incomplete. The optimal dihedral angle

Table 2. Assignments of $AH_S/B_S/X_S$ to saccharin and its derivatives[a]

	AH_S	B_S	X_S^5	X_S^8	Taste
Saccharin	N^-H^+	S→O_α	—[b]	H-5 and H-6	Sweet
6-Me deriv.	N^-H^+	S→O_α	—	H-5 and 6-Me	Sweet
6-NH_2 deriv.	N^-H^+	S→O_α	—	H-5 and 6-NH_2	Sweet
6-F deriv.	N^-H^+	S→O_α	—	H-5 and 6-F	Sweet
4-Cl deriv.	N^-H^+	S→O_α	—	4-Cl and H-5	Sweet
5-Cl deriv.	N^-H^+	S→O_α	—	5-Cl and H-6	Sweet and bitter
6-Cl deriv.	N^-H^+	S→O_α	—	H-5 and 6-Cl	Sweet and bitter
7-Cl deriv.	N^-H^+	S→O_α	7-Cl	H-5 and H-6	Sweet and bitter
6-Br deriv.	N^-H^+	S→O_α	6-Br and H-7	H-5 and 6-Br	Sweet and bitter
6-I deriv.	—	S→O_α	6-I and H-7	H-5 and 6-I	Non-sweet
6-OMe deriv.	—	S→O_α	6-OMe and H-7	H-5 and 6-OMe	Non-sweet
6-OEt deriv.	—	S→O_α	6-OEt and H-7	H-5 and 6-OEt	Non-sweet
6-NHAc deriv.	—	S→O_α	6-NHAc and H-7	H-5 and 6-NHAc	Non-sweet

[a]Hamor (1961); Moncrieff (1967); Temussi *et al.* (1978); Rohse and Belitz (1991); Shallenberger (1993).
[b]—indicates no contact with the receptor.

Table 4. Assignments of $AH_S/B_S/X_S$ to acesulfame-K, its analogues and derivatives[a]

	AH_S	B_S	X_S^4	X_S^5	Relative[b] sweetness
Demethylated cpd. (K salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—[c]	H-6	20×
5-Me analogue (Na salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—	H-6	20×
Acesulfame-K (K salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—	6-Me	130×
5-Me-acesulfame (Na salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—	6-Me	130×
6-Et-5-Me analogue (Na salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—	6-Et	130×
6-Et analogue (Na salt)	N^-H^+	$S{\rightarrow}O_\alpha$	—	6-Et	150×
5-Et-acesulfame (Na salt)	N^-H^+	$S{\rightarrow}O_\alpha$	5-Et	6-Me	250×

[a]Clauss and Lohaus (1972); Clauss and Jensen (1972, 1973); Clauss *et al.*, 1976; Crosby and Wingard (1979); Rohse and Belitz (1988).
[b]Sucrose = 1; Relative to 4% (by weight) sucrose.
[c]—indicates no contact with the receptor.

between the proton-donating group (AH_S) and the proton-accepting group (B_S) in saccharin is ca. 60° (Shallenberger and Acree, 1967; Lee, 1987; Spillane, 1991), but the angle in the phthalimide molecule is close to 0°.

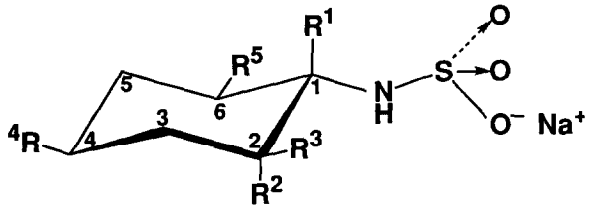
The sweetness mechanism of acesulfame-K (**2**, R = H, R′ = CH_3) (ca. 130×) was similarly interpreted. The N^-H^+ and $S{\rightarrow}O_\alpha$ groups were assigned to the AH_S and B_S components, respectively, with the 6-CH_3 group playing, the role of the X_S^5 component, thus completing the glycophoric triad, AH_S (N^-H^+)/B_S ($S{\rightarrow}O_\alpha$)/X_S^5 (6-CH_3), for sweetness.

The parent compound (**2**, R = R′ = H; K salt: of 1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide) is less sweet (20×) (Clauss and Jensen, 1973), because the smaller, 6-H-substituent, compared to the 6-CH_3 group of acesulfame (**2**, R = H, R′ = CH_3), resulted, in a reduction of strength of the hydrophobic attractive force with the receptor. The 5-Me analogue (**2**, R = CH_3, R′ = H) is less sweet (20×), since its 5-CH_3 group does not contact the receptor; hence the H-6 is the sole hydrophobic binding component, and is similar to **2** (R = R′ = H).

The 5-Me-6-Et analogue (**2**, R = CH_3, R′ = C_2H_5) is much sweeter (130×), because the larger 6-C_2H_5 group contacts the 5th amino acid residue of the receptor. It is noteworthy that the 5-Me-6-Me derivative (**2**, R = R′ = CH_3) showed a similar sweetness (130×) to acesulfame (**2**, R = H, R′ = (CH_3) and the 6-Et analogue (**2**, R = H, R′ = C_2H_5) is a little higher (150×). The 5-Et-6-Me derivative (**2**, R = C_2H_5, R′ = CH_3) appears to be anomalous, because of its higher sweetness (250×) Crosby and Wingard, 1979). However the 5-C_2H_5 group (X_S^4) provides an additional interaction with the 4th amino acid residue of the receptor, in addition to that between the 6-CH_3 group and the 5th amino acid residue of the receptor, thereby strengthening the binding force to the receptor, with the consequent enhancement of sweetness (Table 4).

The conformation of sodium cyclamate (**3**, $R^1 = R^2 = R^3 = R^4 = R^5$ = H) is flexible in contrast to the above sweeteners; hence the interatomic distances between two constituent atoms were determined with that chair conformation which made good contact with the receptor helix (Table 5). The N-(**H**) and S-($\mathbf{O}^-$) atoms were separated by 3.02 Å in agreement with prior assignments as the AH_S and B_S components, respectively. There are six possible binding sites with *axial* (*ax*) H-2 and H-4 functioning as X_S^4 components, and *equatorial* (*eq*) H-5 and H-6 as X_S^5 components, as well as the two intermolecular hydrogen bonds: $B_S(SO^-)$ ···· AH_r and AH_S (N-H) ···· B_r, completing the glycophoric $AH_S/B_S/X_S$ triad(s) for sweetness (Table 6).

Table 5. Interatomic distances (Å) in sodium cyclamate



Sodium cyclamate (3, R^1=R^2=R^3=R^4=R^5=H)

	S-O^-	H-1	H-2		H-3		H-4		H-5		H-6	
		ax	*ax*	*eq*	*ax*	*eq*	*ax*	*eq*	*ax*	*eq*	*ax*	*eq*
N-H	3.02	2.46	3.73	3.83	4.89	5.59	5.16	5.96	4.35	4.78	2.97	2.45
S-O^-		2.59	3.83	2.58	4.22	4.94	5.91	6.32	5.19	6.29	4.88	4.66

Table 6. Assignments of $AH_S/B_S/X_S$ to sodium cyclamate and its derivatives[a]

	AH_S	B_S	X^4_S	X^5_S	X^8_S	Taste
Cyclamate	N-H	S-O$^-$	*ax* H-2 *ax* H-4	*eq* H-5 *eq* H-6	—[b]	Sweet
1-Me deriv.	—	S-O$^-$	*ax* 1-Me	*ax* 1-Me	—	Non-sweet
cis-2-Me deriv.	N-H	S-O$^-$	*ax* 2-Me	—	—	Sweet
trans-2-Me deriv.	N-H	S-O$^-$	*eq* 2-Me	—	—	Sweet
trans-4-Me deriv.[c]	—	S-O$^-$	—	—	*eq* 4-Me	Non-sweet
(1/2,6)-2,6-Di-Me deriv.[c]	—	S-O$^-$	*eq* 2-Me	*eq* 6-Me	—	Non-sweet

[a]Unterhalt and Böschemeyer (1972, 1975).
[b]—indicates no contact with the receptor.
[c]Since the configurations of compounds were not defined in the literature (Unterhalt and Böschemeyer, 1972), their tentative configurations were used for the coupling studies with the receptor model.

The replacement of *ax* H-1 atom of sodlutn cyclamate by a methyl group resulted in a loss of sweetness (Unterhalt and Böschemeyer, 1972). When sodium 1-methylcyclamate (**3**, $R^1=CH_3$, $R^2=R^3=R^4=R^5=H$) was coupled with the receptor model by forming the intermolecular hydrogen bond between $\mathbf{B_S}$ (SO^-) and $\mathbf{AH_r}$ of the receptor, the hydrophobic *ax* CH_3 group on the C-1 position (X^4_S and X^5_S) made close contacts with both side-chains of the 4th and 5th amino acid residues of the receptor. At this point, the N-H group (the potential $\mathbf{AH_S}$ constituent) was inaccessible to the $\mathbf{B_r}$ component of receptor, being remotely located from the $\mathbf{B_r}$ site. In the absence of this second intermolecular hydrogen bond, compound **3** ($R^1=Me$, $R^2=R^3=R^4=R^5=H$) was devoid of sweetness (Table 6).

Sodium *cis*- and *trans*-2-methylcyclamates have the same degree of sweetness as sodium cyclamate (Unterhalt and Böschemeyer, 1975). Coupling studies between *cis*-2-methylcyclamate (**3**, $R^2=CH_3$, $R^1=R^3=R^4=R^5=H$) and the receptor model revealed that there was a good fit between them, having the two intermolecular hydrogen bonds: $\mathbf{B_S}(SO^-)$ ···· $\mathbf{AH_r}$ and $\mathbf{AH_S}$(N-H) ···· $\mathbf{B_r}$, and a hydrophobic interaction between the *ax* CH_3 group in the C-2 position ($\mathbf{X^4_S}$) and the receptor's $\mathbf{X^4_r}$. Thus, the glycophoric $\mathbf{AH_S/B_S/X_S}$ triad for sweetness was completed (Table 6).

Also, docking studies between *trans*-2-methylcyclamate (**3**, $R^3=CH_3$, $R^1=R^2=R^4=R^5=H$) and the receptor model showed close contacts between the *eq* CH_3 group in the C-2 position ($\mathbf{X^4_S}$) and the receptor's $\mathbf{X^4_r}$, as well as the required duo of inter-molecular hydrogen bonds, thereby completing the glycophoric triad for sweetness (Table 6).

Sodium *trans*-4-methylcyclamate (**3**, $R^4=CH_3$, $R^1=R^2=R^3=R^5=H$) showed a similar interaction pattern with the receptor model to 1-methylcyclamate. That is, the intermolecular hydrogen bond between $\mathbf{B_S}$ (SO^-) and $\mathbf{AH_r}$, and hydrophobic interaction between the *eq* CH_3 group in the C-4 position and the receptor's $\mathbf{X^8_r}$ were formed, but the N-H proton (the potential $\mathbf{AH_S}$ component) was not accessible to the $\mathbf{B_r}$ site. Thus, the essential glycophoric triad was not established, resulting in a disappearance of sweetness (Table 6).

Likewise, when (1/2,6)-2,6-dimethylcylcamate (**3**, $R^3=R^5=CH_3$, $R^1=R^2=R^4=H$) was linked to the receptor by the intermolecular hydrogen bond ($\mathbf{B_S}$ ···· $\mathbf{AH_r}$), the two hydrophobic interactions arose between the *eq* CH_3 in the C-2 position and $\mathbf{X^4_r}$, and between the *eq* CH_3 in the C-6 position and $\mathbf{X^5_r}$. However, it failed to complete the glycophoric triad, because the distance and angle between the NH (potential $\mathbf{AH_S}$) and the $\mathbf{B_r}$ component were unacceptable. Hence this cyclamate derivative was devoid of sweetness (Table 6).

CONCLUSION

A computer modelling study of the host–guest relationship between various sweeteners, including saccharin, acesulfame-K and cyclamate, and our suggested receptor model, an α-helical, right-handed protein, accounts for then, sweetness and the activities of various derivatives and analogues. Highly stereoselective non-bonded attractive forces between hydrophobic sites of the sweeteners within a crevice of the helical receptor are essential for sweetness to occur. Larger substituents at crucial positions on the sweet molecules can prevent completion of the $\mathbf{AH_S/B_S/X_S}$ triad, resulting in non-sweet molecules.

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