Chemical Senses Vol.10 no.1 pp.73–88, 1985

Structure-activity relationships in sweeteners. II. Saccharins, acesulfames, chlorosugars, tryptophans and ureas

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Abstract. The previously introduced conceptual parameters (α, δ, ω and S) to describe the stereochemical requirements for organic compounds to taste sweet, were now applied to another series of sweeteners and to some well-known potent substances. With the help of an adapted STERIMOL computer program, the positions of relevant, hydrophobic side chains were determined in ureas, saccharins, tryptophans, chlorosugars and acesulfame derivatives in relation to their AH-B moieties. The results obtained were compared with previous findings for five other homologous series of sweeteners. There is evidence to suggest that 6-substituted acesulfame derivatives and saccharin employ the same receptor site. δ in 5-substituted acesulfame derivatives coincides with that of sulphamates calculated earlier. δ in 6-chloro-D-tryptophan was found to be at equal distances from H and B, a position which was earlier also observed for the methyl ester group in aspartame. In the dulcin series of the urea derivatives, two AH-B moieties can be distinguished: the HN-CO group gives rise to α, δ and ω's which fit in the earlier calculated nitroaniline receptor site, while for the OC-NH_2 group they are located near those found for isocoumarins. The chlorine atoms in 1',6'-dichlorosucrose are located above and below the plane of the pyranose ring at almost the same positions with respect to the OH groups at positions 3 and 4 (in fact, two equal δ's), which are supposed to form the AH-B moiety. The high relative sweetness values of 1',6'-dichlorosucrose and 1',4,6'-trichlorogalactosucrose are most probably due to the fact that both sweeteners can interact with the receptor site in two ways (as such and upside-down). It is remarkable that the average δ positions belonging to sweeteners with similar AH-B moieties are located very close to each other.

Introduction

Recently, we published some new concepts to describe the stereochemical requirements for representatives of a series of sweeteners to taste sweet (van der Heijden *et al.*, 1985). The α, δ and ω conceptual parameters introduced represent the minimum, optimum and maximum distances from the third binding sites in sweeteners to the corresponding AH-B moieties. Moreover, we calculated S values, which are the shortest distances between the position of any atom and the plane formed by the A, H and B atoms of the AH-B moiety. The distances mentioned could be calculated with the help of the STERIMOL computer program (Verloop *et al.*, 1976). The calculations indicated that there are several receptor sites with narrow clefts with a maximum height of ~0.6 nm (van der Heijden *et al.*, 1985).

We decided to extend our studies to other homologous series of sweeteners and to well-known potent representatives, namely (i) 6-chloro-D-tryptophan; this is a very potent sweetener but there is no homologous series; (ii) urea derivatives, especially those containing the p-alkoxyphenyl moiety (dulcin series); (iii) saccharins, although only a limited number of relevant representatives is known; (iv) acesulfame derivatives; in this series many compounds have been synthesized, except those necessary for the precise determination of ω; and (v) chloro-

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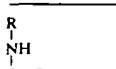
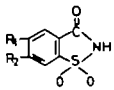
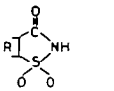
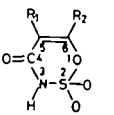
Table I. Sweet and non-sweet tasting derivatives of urea (dulcin series), saccharin and 5/6-substituted oxathiazinondioxides (acesulfame analogues)

Sweetener	Compound no	R	Relative sweetness on weight basis	References
 Ureas (dulcin)	1	-O-C-C	Sweet	Beets (1978)
	2		<250	
	3		250	
	4		Slightly sweet	This publication
	5		Tasteless	
 Saccharins		R1 R2		
	6	-H -H	450	Beets (1978)
	7	-H -O-C	Tasteless	Crosby *et al.* (1979)
	8	-O-C -H	Bitter	Bambas (1952)
	9	-O-C -O-C	Sour/bitter	
 Saccharins	10		1000	Trummlitz *et al.* (1980): Rossy *et al.* (1980); Hromatka and Binder (1976)
	11		250	
	12		350	
	13		150	
	14		550	
	15		1000	
 Oxathiazinondioxides (acesulfame analogues)		R1 R2		
	16	-H -H	10	Claus and Jensen (1973)
	17	-H -C	130	
	18	-H -C-C	150	
	19	-H -C-C-C-C	30	
	20	-C -H	20	
	21	-C -C	130	
	22	-C -C-C	130	
	23	-C-C -H	20	
	24	-C-C -C	250	
	25	-C-C -C-C-C	70	
	26	-C-C -C-C-C-C	70	
	27	-C-C-C -C	30	

sugars; there is no homologous series but a number of very potent representatives of sucrose to calculate δ.

Methods

Literature data

All relevant data on the sweeteners investigated were abstracted from the literature (van der Heijden *et al.*, 1985). Relative sweetness values on a weight basis were converted into values on a molar basis. Data relevant to our calculations, are given in Tables I and II.

Calculation procedures

The STERIMOL computer program has been described earlier (Verloop *et al.*,

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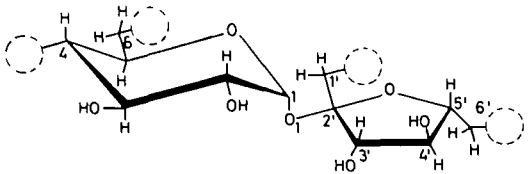
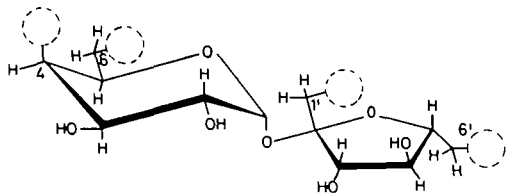
Table II. Sweet and non-sweet tasting sucrose and 'galacto' sucrose chloro derivatives.

Sweetener	Compound	Cl instead of OH on				Relative sweetness on molar (weight) basis
		4	6	1′	6′	
(Chloro)sucrose(s)	**28**	·	·	·	·	1 (1)
	29	·	·	●	·	22 (20)
	30	·	·	·	●	22 (20)
	**31**	·	●	·	·	Bitter
	32	·	·	●	●	600 (500) 91 (76)[a]
	33	·	●	·	●	0 (0)
	34	●	●	●	●	140 (100)
	35	·	●	●	●	130 (100)[b]
(Chloro)galactosucrose(s)	**36**	·	·	·	·	0 (0)
	37	●	·	·	·	5.5 (5)
	**38**	●	·	●	·	722 (600) 145 (120)[a]
	39	●	·	●	●	2600 (2000) 845 (650)[a]
	40	●	●	●	●	281 (200)
	41	●	●	·	●	5.2 (4)[b]

[a]Jenner, 1980.
[b]Tate and Lyle Ltd., 1977; all other compounds: Lee, 1979.

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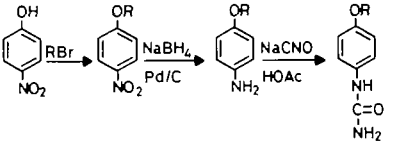
1976). The input for the program only consists of a general formula and a number of torsion angles for the compound. The program itself selects valence angles and appropriate bond distances. However, for more complex molecules, such as saccharin, some deviating bond distances are then produced. Therefore, the subroutine COORD (ex Philips Research Laboratories, Eindhoven, The Netherlands), which offers the advantage of introducing valence angles, bond distances and torsion angles ourselves, was incorporated in the STERIMOL routine in such a way that the program could be run according to its original or adapted form. For all data the program runs through sequential calculations and the values obtained are transcribed when the COORD subroutine is used.

Synthesis of model compounds

The 4-propoxy- and 4-butoxyphenylureas (**4** and **5** in Table I) were synthesized according to the following scheme (R = C_3H_7 or C_4H_9):



Intermediates and final products were characterized by m.s., i.r. and n.m.r. Compound **4** was obtained as shiny crystals; m.p. 149°C; n.m.r. (d6-acetone): δ 1.00 (tr), 1.75 (sextet); 3.88 (tr), 6.82 (broad d), 7.39 (broad d). Compound **5** was also obtained as shiny crystals, m.p. 143 – 144°C.

Analysis of the structures of sweeteners

Tryptophans

D-amino acids taste sweet in contrast with the L-isomers which have a bitter taste, especially those with long side chains (Beets, 1978). D-tryptophan, which is 19 times sweeter than sucrose on a molar basis, becomes dramatically sweeter when one or two chlorine atoms are introduced at one or both positions 5 and 6 of the benzene nucleus (Kornfeld *et al.*, 1974; Eli Lilly and Company, 1972a,b). Substitution at other positions on the indole ring or side chain was generally ineffective.

In the series of tryptophans, there are no examples known for our α and ω conceptual parameters. Therefore, we had to confine ourselves to 6-chloro-D-tryptophan of which the chlorine atom is expected to occupy the δ position, as this compound is 1300 times sweeter than sucrose (on a weight basis).

It is generally accepted that the AH-B glucophore in amino acids can be assigned to the NH_3^+ and the COO^- groups (Beets, 1978). Calculations indicate there are five AH-B pairs fulfilling the requirements for AH-B in the sweet taste perception. For α, we decided to designate the carbon atom of the CH_2 group in $-CH_2-CH(NH_3^+)-COO^-$ because D-alanine is sweet.

The results of our calculations are given in Table III and Figure 1. The two con-

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Table III. Distances (nm) of atoms in 6-chloro-D-tryptophan *versus* the AH-B moiety (see Figure 1).

Atom	Conformation	Conceptual parameters	AH-B moieties 1	2	3	4	5
Cl	I	δH	0.940	0.940	1.004	1.004	0.877
		δB	1.032	0.890	1.032	0.890	1.032
		δA	0.915				
		S value	0.856	0.853	0.475	0.065	0.804
Cl	II	δH	0.844	0.844	0.755	0.755	0.720
		δB	0.775	0.818	0.775	0.818	0.775
		δA	0.748				
		S value	0.277	0.224	0.744	0.748	0.131
CH_2	I/II	αH	0.266	0.266	0.336	0.336	0.266
		αB	0.367	0.267	0.367	0.267	0.367
		αA	0.246				
		S value	0.245	0.189	0.077	0.088	0.242
		HB	0.318	0.332	0.264	0.377	0.386

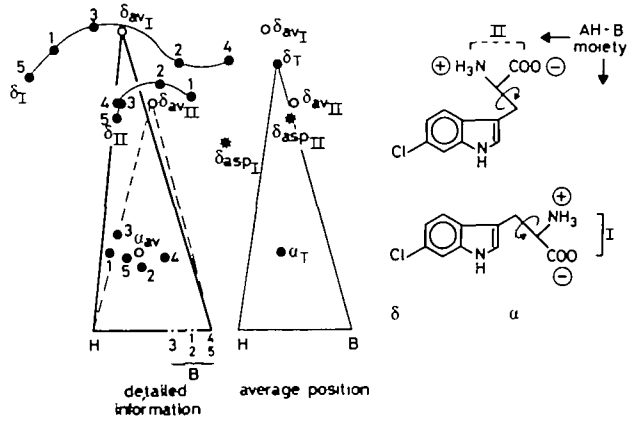

Fig. 1. Location of α and δ *versus* the AH-B moiety (conformations I and II) in 6-chloro-D-tryptophan (see Table III). The average positions of δ_I, δ_{II} and α are also given in the overall average (right) together with the position of the methyl ester group in aspartame (δ_{asp}).

formations, which can arise through rotation about the bond between the side chain and the indole ring, give δ1 to δ5 positions which are somewhat scattered for conformation I but fairly close together for conformation II. It is striking that the average positions of α_T and δ_T are almost at equal distance from H and B.

Recently, Schiffman *et al.* (1981) suggested that D-tryptophan and aspartame employ similar receptor sites. This suggestion, which was based on cross-adaptation experiments, prompted us to compare several δ positions of 6-chloro-

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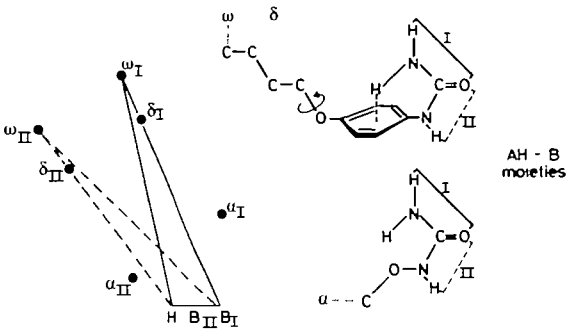


Fig. 2. Location of α, δ and ω *versus* the AH-B moieties I and II in urea derivatives (compound **5** and methoxy-urea); see also Table IV.

D-tryptophan with that of the methyl group of the ester moiety in aspartame. We have already indicated that the distances of this methyl ester group to both the AH group and the B group of the AH-B moiety are ~0.65 nm (van der Heijden *et al.*, 1979). Also the most recent calculations indicate that the position of the methyl ester group in aspartame (considering AH-B moiety II) is indeed very close to the position of the chlorine atom in 6-chloro-D-tryptophan.

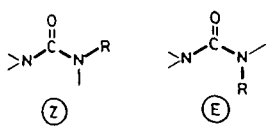
Urea derivatives

The urea derivatives can be divided into the dulcin series in which urea has *p*-alkoxyphenyl substituents, and the suosan series, where urea has *p*-nitrophenyl and carboxylic acid groups. Because it is hard to identify the AH-B moiety in the latter series, we restricted our calculations to the dulcin series.

It is striking that Beets (1978) did not refer to the designation of the AH-B moiety of dulcin. In principle, the HN-CO group and the H_2N-CO group can be considered as acting as AH-B moieties (see Figure 2). We decided to take both moieties into account but preferred the H_2N-CO group, moiety I, because of its terminal position in the molecule.

As to the α, δ and ω parameters, we observed in the *p*-alkoxyphenyl series (**2** and **3** in Table I) that the optimum is reached at **3** (dulcin itself) which is 250 times sweeter than sucrose. Hence, δ is represented by the terminal carbon atom. Synthesis and evaluation of **4** and **5** showed that they are slightly sweet and tasteless respectively so that we reach ω at *p*-butoxyphenylurea. For α, we chose methoxy-urea, as **1** is sweet according to Beets (1978).

In the structures of the urea derivatives, one can recognize the E and Z conformations:



According to the literature, especially the phenyl-substituted ureas and thio-ureas are mostly in the E form because of an intramolecular hydrogen bonding between

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Table IV. Distances (nm) between atoms in urea derivatives *versus* the AH-B moiety (see Figure 2).

Conceptual parameters		Torsion angle 0°	90°	180°	270°
AH-B I (II)	HB	←		0.248 (0.231)	→
	AB			0.226 (0.224)	
	HA			0.103 (0.103)	
α I (II)	αH			0.521 (0.241)	
	αB	←		0.447 (0.447)	→
	αA			0.418 (0.226)	
S value				0.003 (0.000)	
δ_I	δH	0.936	0.960	0.932	0.908
	δB	1.002	1.006	0.997	0.992
	δA	0.852	0.870	0.848	0.829
S value		0.025	0.053	0.131	0.053
δ_{II}	δH	0.850	0.841	0.847	0.857
	δB	1.002	1.006	0.997	0.992
	δA	0.791	0.790	0.789	0.790
S value		0.022	0.056	0.134	0.056
ω_I	ωH	1.170	1.210	1.164	1.122
	ωB	1.245	1.253	1.237	1.230
	ωA	1.089	1.121	1.085	1.052
S value		0.093	0.072	0.239	0.073
ω_{II}	ωH	1.094	1.078	1.089	1.105
	ωB	1.245	1.253	1.237	1.230
	ωA	1.037	1.035	1.033	1.033
S value		0.089	0.076	0.242	0.077

the NH_2 group and the phenyl ring, in which situation the -NH-CO-NH_2 group is perpendicular to the phenyl ring (Walter and Ruess, 1971). It is very likely that dulcin exists in this form also because of the electron-donating properties of the *p*-alkoxy group.

The results of our calculations are given in Table IV and Figure 2. The dimensions and shape of the receptor site for ureas with the AH-B moiety I are similar to those found for isocoumarins, except for α which is situated closer to the AH-B group (van der Heijden *et al.*, 1985). When we consider the results with respect to the AH-B moiety II (Figure 2), the data are almost identical to those found for nitroanilines (van der Heijden *et al.*, 1985).

Saccharins

It is generally accepted that the AH-B moiety in the saccharin series (see Figure 3)

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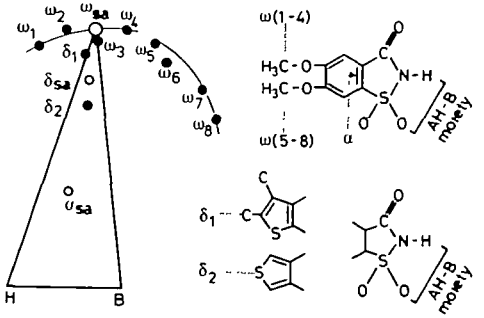

Fig. 3. Location of α, δ and ω *versus* the AH-B moiety in the saccharin series (compound **9**, **15** and **10**). For numbers see Table V.

Table V. Distances (nm) between atoms in the saccharin series *versus* the AH-B moiety (see Figure 3).

Conceptual parameters		Torsion angle 0°	90°	90°	180°
AH-B (HN-SO_2)	HB		0.313		
	AB	←	0.271	→	
	HA		0.092		
α	αH		0.327		
	αB	←	0.313	→	
	αA		0.238		
S value			0.030		
		δ_1 (CH_3 in **15**)		δ_2 (S in **10**)	
δ	δH	0.697		0.573	
	δB	0.668		0.528	
	δA	0.611		0.484	
S value		0.100		0.048	
Code		1	2	3	4
ω (R_1 in **9** = MeO)	ωH	0.698	0.745	0.745	0.789
	ωB	0.733	0.746	0.705	0.719
	ωA	0.621	0.661	0.661	0.699
S value		0.153	0.010	0.230	0.066
Code		5	6	7	8
ω (R_2 in **9** = MeO)	ωH	0.807	0.778	0.778	0.749
	ωB	0.695	0.652	0.608	0.539
	ωA	0.715	0.688	0.688	0.660
S value		0.018	0.145	0.079	0.083

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can be assigned to the HN-SO_2 group (Beets, 1978). Some saccharins can be used for our analysis of α, δ and ω. The input for the COORD program was based on data from the crystal structure of saccharin (Okaya, 1969). Two saccharin derivatives (**10** and **15** in Table I), mentioned in the patent literature by Hromatka and Binder (1975) and Trummlitz *et al.* (1980) were used for δ, because both compounds are, to our knowledge, the most potent representatives. The parent compound saccharin (**6**) is sweet but we do not know whether the compound without the benzene nucleus is also sweet. However, in view of the fact that similar 6-membered ring compounds are sweet (see acesulfame derivatives **16**–**27**), we positioned α in the middle of the bond to which the benzene ring of the saccharins **6**–**9** is attached. The only compounds, which can be used for ω, are the methoxy derivatives **8** and **9**. We calculated the distances of these groups *versus* the AH-B moiety, taking into account torsion angles of 0° and 180° (the methoxy groups are in the same plane as the phenyl ring) and 90° (the methoxy groups are perpendicular to it) (Table V, Figure 3).

For δ_1 of **15** and δ_2 of **10** (Figure 3, see Table I), we also calculated the average position and denoted it as δ_{sa}. As was observed in practically all cases, α and δ are situated within the AH-B-ω triangle; therefore, we constructed the triangle for saccharins in such a way that it would result in an estimated ω position (ω_{sa}).

Acesulfame derivatives

The AH-B glucophore in oxathiazinondioxides (acesulfame derivatives) can reasonably be assigned to the HN-SO_2 moiety. Maximum sweetness was observed for 6-methyl or 6-ethyl derivatives (see Table I). Although a large number of derivatives was synthesized and evaluated, there are no explicit examples for ω. However, a chain length *versus* relative sweetness plot indicates that it will most probably be reached at the hexyl group. For the assignment of α the carbon atom in the ring, to which the substituent is attached, was chosen because the parent molecule is 10 times sweeter than sucrose (Table I).

The data for the COORD program were identical with those published for the crystal structure of acesulfame (Paulus, 1975). The results of our calculations are given in Table VI and Figure 4. We have also taken into account rotations of the side chains of 90° or 180°. The δ and ω concepts then shift in opposite directions away from their original position (see Figure 4).

Chlorosugars

The structure-activity relationships in sugars are difficult to study because (i) sugars are flexible molecules and, in solution, their conformations are difficult to predict; (ii) sugars have a large number of possible AH-B moieties and it is not easy to indicate which one will ultimately interact with the receptor site; and (iii) there is no explicit homologous series. Despite these drawbacks, we did some calculations on chlorosugars, as these are extremely potent sweeteners (see Table II). We had to confine ourselves to δ as there are no examples for α and ω and started from the assumption that the AH-B moiety in sucrose derivatives is formed by the oxygen atoms at equatorial positions 3 and 4 of the pyranose ring (Birch, 1976; Shallenberger and Lindley, 1977), and that the conformation of sucrose

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Table VI. Distances (nm) between atoms in the 5- and 6-substituted acesulfame derivatives *versus* the AH-B moiety (see Figure 4).

Conceptual parameters[a]		Torsion angle 0°	90°	90°	180°
AH-B (5,6)	HB			0.270	
	AB		←	0.243	→
	HA			0.091	
α (5/6)	αH			0.309/0.368	
	αB		←	0.391/0.359	→
	αA			0.228/0.278	
S values (5)		0.055 0.058	0.057	0.054	0.057 0.055
S values (6)		0.011 0.011	0.011	0.011	0.011 0.011
δ (5)	δH	0.554	0.493	0.493	0.422
	δB	0.609	0.575	0.628	0.595
	δA	0.475	0.432	0.432	0.383
S values		0.113 0.119	0.271	0.007	0.164 0.162
δ (6)	δH	0.588	0.586	0.586	0.583
	δB	0.598	0.510	0.568	0.474
	δA	0.502	0.498	0.498	0.495
S values		0.080 0.080	0.116	0.145	0.051 0.051
ω (5)	ωH	1.054	0.958	0.958	0.852
	ωB	1.092	1.035	1.123	1.068
	ωA	0.977	0.914	0.914	0.847
S values		0.281 0.294	0.752	0.040	0.431 0.427
ω (6)	ωH	1.073	1.069	1.069	1.065
	ωB	1.095	1.046	0.950	0.893
	ωA	0.993	0.987	0.987	0.981
S values		0.220 0.220	0.367	0.412	0.175 0.175

[a]Two S values are given because two AH-B planes can be considered in relation to the two O atoms attached to the S atom.

derivatives in solution or during the interaction step with the receptor site is similar to that of the crystal structure of sucrose (Brown and Levy, 1963). The latter assumption is plausible because Bock and Lemieux (1982) found that sucrose in aqueous solution would have pronounced conformational preference for the

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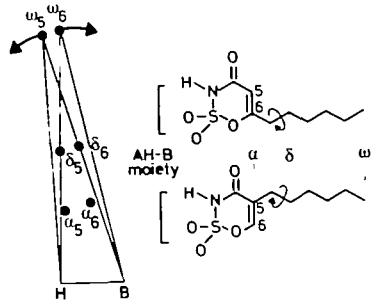

Fig. 4. Location of α, δ and ω *versus* the AH-B moiety in 5- and 6-substituted acesulfame derivatives. The position of ω_5 and ω_6 move into the indicated directions where the torsion angles become larger. See also Table VI.

Table VII. Calculated distances (nm) between chlorine atoms in **32** (1′,6′-dichlorosucrose) *versus* the O_4 and O_3 atoms (O_3-O_4 = 0.283 nm) in the pyranose ring (see Figure 5).

Torsion angles[a]						Code	$Cl_{6'}$ *versus*		Code	$Cl_{1'}$ *versus*	
H | $C_{5'}$	Cl | $-C_{6'}$	O_1 | $C_{2'}$	Cl | $-C_{1'}$	C_1 | O_1-	$C_{3'}$ | $C_{2'}$		O_4	O_3		O_4	O_3
180		30		200		1	0.586	0.692	1′	0.610	0.446
170		0		200		2	0.611	0.717	2′	0.594	0.418
190		60		200		3	0.558	0.662	3′	0.658	0.514
170		60		180		4	0.603	0.715	4′	0.659	0.495
190		0		180		5	0.550	0.659	5′	0.606	0.436
170		0		160		6	0.597	0.698	6′	0.603	0.456
Average value						δ	0.584	0.691	δ'	0.622	0.461

[a]Seen from the left atom to the right atom (notation according to Brown and Levy, 1963); see Table II.

glycosidic linkage near to that for sucrose in the crystalline state.

In our calculations for chlorosucroses it was not possible to take the hydrogen atom of the AH-B moiety into account, not only because its exact position is not known but also because it is not clear whether it is attached to the O_3 or O_4 atom. For this reason, we decided to calculate only the distances of δ to the oxygen atoms (hence the AB moiety). This small difference should be taken into account when comparing the results for chlorosucroses with those of other series.

Information about the crystal structure of sucrose and cited torsion angles in the above-mentioned paper of Brown and Levy (1963) were used for our calculations. We determined the influence of variations of three torsion angles on the positions of the chlorine atoms *versus* the A-B moiety (Table VII).

The results of our calculations are presented in Table VII and Figure 5. The variations in the three torsion angles did not appear to change the δ positions of the chlorine atoms significantly (encircled areas in Figure 5). Furthermore, these

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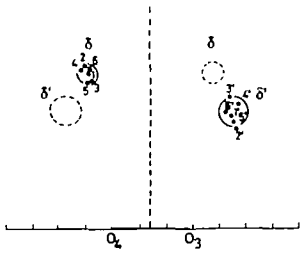

Fig. 5. Locations of the δ's of compound **32** (1',6'-dichlorosucrose) *versus* the O_4 and O_3 atoms: (1 to 6) area for δ position of $Cl_{6'}$; (1' to 6') area for δ' position of $Cl_{1'}$; (broken circles) areas are mirror images (obtained by a 2-fold axis rotation through the C_3-C_4 bond). See also Table VII.

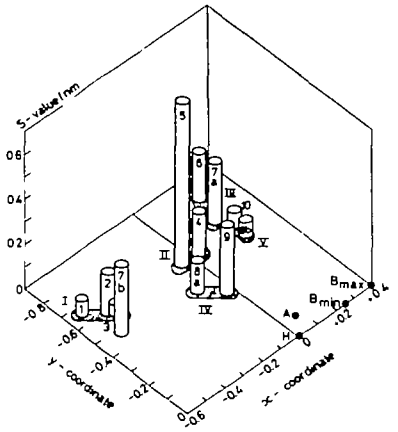

Fig. 6. Three-dimensional view of the positions of δ's in 10 series of sweeteners. For sweeteners **1 – 10** arranged in the groups **I – V**, see Table VIII.

positions are almost identical when a 2-fold axis rotation is performed through the C_3-C_4 bond (Figure 5, reversed positions). If we assume that the ωHB triangle has a ωHB angle >90° (generally observed for practically all series of sweeteners) we may conclude that for compound **30** (6'-chlorosucrose), the AH-B moiety will be formed by HO_4-O_3 and **29** (1'-chlorosucrose) by HO_3-O_4. This assumption is supported by the fact (see Table II) that both compounds are 20 times sweeter than sucrose. The sharp increase in the sweetness of **32** (1',6'-dichlorosucrose) can be explained by the fact that the chlorine atoms lie above and below the plane of the pyranose ring. In this way, the molecule can enter the receptor site in two ways (as such and upside-down) and always has a chlorine atom at the δ position. The data on the sweetness of the chlorogalactosucroses **37 – 41** can be explained in the same way. The chlorine atom at position 4 will form part of the AH-B moiety. Apparently, the bulkiness of the chlorine atom at this axial position is sufficient enough to act together with the equatorial HO_3 group as AH-B moiety.

Discussion

It was not always possible to indicate the positions of all α, δ and ω conceptual

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Table VIII. Coordinates of AH-B moiety and of the average positions of the hydrophobic groups (δ) *versus* the AH-B moieties in 10 series of sweeteners (see Figure 6).

Group	AH-B moiety[a]	Sweetener	δ_x	δ_y	S value
I	H – NO, O – NH	1. Ureas	−0.525	−0.652	0.078
		2. Nitroanilines	−0.450	−0.590	0.188
		3. Oximes	−0.435	−0.555	0.066
II	OH – OH, OH – OCH_3	4. Chlorosugars	0.030	−0.565	0.200
		5. Isocoumarins	−0.060	−0.580	0.730
III	$H_3N^+ - COO^-$	6. Tryptophan	0.230	−0.780	0.224
		7a. Dipeptide esters[b]	0.190	−0.650	0.277
IV	HN – SO	8a. 5-Subst. acesulf.	−0.105	−0.430	0.140
		9. Sulphamates	−0.045	−0.345	0.305
V	HN – SO	8b. 6-Subst. acesulf.	0.224	−0.520	0.065
		10. Saccharin	0.226	−0.590	0.074
–	$H_3N^+ - COO^-$	7b. Dipeptide esters	−0.495	−0.470	0.321
[a]For AH-B:		A	0.065	−0.075	0
		H	0	0	0
		B_{min}	0.250	0	0
		B_{max}	0.400	0	0

[b]Methyl ester group in aspartame

parameters because some relevant representatives of the sweeteners were not available.

We can consider 6-chloro-D-tryptophan as a representative to calculate the δ of D-amino acids known as sweeteners (Beets, 1978). All D-amino acids have the AH-B moiety in common and the chlorine atom (or other substituents) at position 5 or 6 of D-tryptophan is apparently in the right position to interact with the third binding site. We observed that this site is at equal distance from H and B of the AH-B moiety. In our previous studies of dipeptide esters (van der Heijden *et al.*, 1979), we observed that the methyl group of the ester moiety in L-Asp-L-Phe-OMe was also at equal distance from H and B. The recent finding by Schiffman *et al.* (1981) that D-tryptophan and aspartame employ similar receptor sites is in accordance with this finding. As D-amino acids are generally sweet, this means that the position of the site with respect to the AH-B moiety is essential. When looking along the AH-B plane from H to A, the site is situated in or above this plane: this situation was observed in all our studies on sweeteners (van der Heijden *et al.*, 1979, 1985; this publication, Figure 6).

In the urea series, there are two AH-B moieties. Calculations show that the α, δ and ω concepts belonging to the HN-CO group as AH-B moiety, mostly coincide with those of the nitroaniline receptor (van der Heijden *et al.*, 1985). However, if we consider the OC-NH_2 group as AH-B moiety, there is more overlap with the

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isocoumarin receptor site (van der Heijden *et al.*, 1985). Synthesis of N-alkyl-substituted derivatives and conformational analysis of these sweeteners will be necessary to obtain additional information in regard to the actual dimensions of the urea receptor site.

It is surprising to observe that, although torsion angles in chlorosugars were varied considerably, the positions of the chlorine atoms (δ positions) are confined to a narrow area (Figure 5). The high relative sweetness values of 1′,6′-dichlorosucrose (**32**) and 1′,4,6′-trichlorogalactosucrose (**39**) are most probably due to the equivalence of (i) the HO_3 and HO_4 (or Cl_4) groups in the pyranose ring serving as AH-B moiety, and (ii) the positions of the $Cl_{6'}$ and $Cl_{1'}$ atoms *versus* the AH-B moiety above and below the pyranose ring. When **32** and **39** approach the receptor site as such or upside-down, the δ's and the AH-B moieties are available in both situations to stimulate this contact.

It is interesting to compare our findings for acesulfame and saccharin with those for sulphamates (van der Heijden *et al.*, 1985) because all these series have similar AH-B moieties. We can conclude that 6-substituted acesulfame derivatives employ the same receptor site as the representatives of the saccharin series, whereas the δ position of 5-substituted acesulfame derivatives coincides more with that of sulphamates (van der Heijden *et al.*, 1985). Striking in this connection is that 6-substituted acesulfame derivatives have higher sweetness potencies than 5-substituted derivatives while saccharins are more potent than sulphamates. Apparently, for sweeteners containing the HN-SO group as AH-B moiety, hydrophobic groups at δ_6 in acesulfames (Figure 4) and δ_{5a} in saccharins (Figure 3) increase the sweetness potency more than similar groups do at δ_5 in acesulfames (Figure 4) and sulphamates (van der Heijden *et al.*, 1985). Whether the saccharins, acesulfames and sulphamates fit in a common site, cannot be concluded from our present calculations.

Recently, Schiffman *et al.* (1981) postulated that sodium saccharin and acesulfame appear to operate through a similar receptor site, which is in agreement with our data for both series. The shorter distance of ω for sulphamates (~ 0.7; van der Heijden *et al.*, 1985) in relation to that for 5-substituted acesulfame derivatives ($0.9-1.1$, see Table VI) can be attributed to the rapid increase of the S value in the sulphamate series upon extension of the side chain. It might well be that such molecules cannot enter the receptor site for geometrical reasons.

To compare our findings for the five series of sweeteners reported here with those for the five of our previous study (van der Heijden *et al.*, 1985) we determined the coordinates of the average δ positions of the third binding sites in the 10 series of sweeteners *versus* the AH-B moieties. It should be noted that (i) for saccharins, oximes, sulphamates and isocoumarins, we used the average δ positions of the data reported (van der Heijden *et al.*, 1985, this publication); (ii) as for nitroanilines, we determined the δ position using a 45° torsion angle for the alkoxy group *versus* the phenyl ring (van der Heijden *et al.*, 1985); (iii) in the case of ureas, we took the average δ position near those of nitroanilines and oximes (van der Heijden *et al.*, 1985) because these three series of sweeteners have fairly similar AH-B moieties (O-NH or H-NO); (iv) for acesulfame, we differentiated

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between 5- and 6-substituted derivatives; (v) as for tryptophan we calculated for the two groups of five δ positions each the average δ positions and from these ultimate coordinates for δ; (vi) in the case of dipeptide esters we determined the average δ position from the δ values of the conformers A and B with AH-B moiety II (van der Heijden *et al.*, 1985), as those with AH-B moiety I are more or less located on an extension of the line B-H; we also introduced the position of the methyl ester group in aspartame; and (vii) in regard to the chlorosugars, we fixed the S value at 0.2 nm and introduced the distance of the H atom into our calculations; the average coordinates were derived from the positions of the 1′- and 6′-chlorine atoms.

The results are given in Table VIII. It is noteworthy that when the sweeteners are arranged according to similarity in AH-B moiety, the hydrophobic groups have also closely located X- and Y-coordinates. Figure 6 shows a three-dimensional view of the five groups of δ positions *versus* the AH-B moieties based on the data given in Table VIII. We indicated the position of an arbitrary A atom and the positions of B_{min} (0.25 nm) and B_{max} (0.4 nm). When looking along the AH-B plane from H to A, all sites are situated in or above this plane.

It would be interesting to establish whether representatives of each group employ the same receptor site. The results of such a study, for instance by cross-adaptation experiments (Schiffman *et al.*, 1981), might mean a great step forward in the elucidation of the sweet taste perception mechanism.

Acknowledgements

The authors thank Dr. Hoogenstraaten of the Philips Research Laboratories, Eindhoven, for providing the STERIMOL and COORD programs, Drs. J.Heidema for adaptation of those programs, and Mr. J.A.M.Laan for synthesizing the model compounds.

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Received May 1984; accepted August 1984

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