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Structure–Activity Studies on Sulfamate Sweeteners II: Semiquantitative Structure–Taste Relationship for Sulfamate ($RNHSO_3^-$) Sweeteners—The Role of R

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Abstract □ With the use of Corey–Pauling–Koltun space-filling models, measurements of defined parameters (x, y, and z) were made of the R groups in a large number of carbosulfamates, $RNHSO_3^-$. The correlation between sweet and nonsweet sulfamates and the defined parameters for R is good. As a test, 12 new carbosulfamates were synthesized and tasted. The predictions of their sweetness or nonsweetness based on the correlation were >90% correct. To elicit a sweet taste, the R group of the sulfamate should have $x \geq 5.2$ Å and ≤ 7.2 Å and V (*i.e.*, xyz) ≤ 250 Å^3 and probably ≥ 90 Å^3. The receptor site is seen (as for aspartame) as a rather narrow cleft into which R has to fit "properly" or be "locked" so that the AH,B mechanism for initiating the sweet stimulae can operate. Possible applications of this approach are indicated.

Keyphrases □ Sweeteners—structure–activity analysis of sulfamates, the role of R side chains □ Sulfamates—sweeteners, structure–activity analysis, the role of R side chains □ Structure–activity relationships—the role of R side chain on sulfamate sweeteners

Synthetic studies of alternative sweeteners have been given impetus since the ban on cyclamates in 1970 and the apparently unresolved question of the toxicity of saccharin, the only synthetic sweetener presently used worldwide. These studies, aimed at the design of new synthetic sweeteners and a fuller understanding of sweetness, have led to the establishment of structure–taste relationships for some classes of alternative sweeteners (1–3).

Most workers have concentrated on the development of intraclass structure–taste relationships since there is good evidence that different classes of sweeteners act by binding at different receptor sites in the taste buds of the tongue (4). Thus, structure–taste information from one class is not transferable to another class.

BACKGROUND

The structure–activity relationships of sulfamate sweeteners were reviewed in Part I of this study (5). Other investigators (6, 7), using Corey–Pauling–Koltun (CPK) space-filling atomic models, showed that the best $NHSO_3^-$ group conformation for sweet taste stimulation involved an angle (θ) of 60° between the N–H and S–O bonds. The necessity of maintaining this optimal 60° torsional angle for sweetness explains why substitution of an α-hydrogen by an alkyl group at C-1 of an alicyclic ring or aliphatic chain destroys sweetness. Similarly, the lack of sweetness of phenylsulfamate is ascribed to steric hindrance due to an *ortho*-hydrogen of the phenyl ring forcing the aminosulfonate group to adopt a conformation with $\theta \approx 0°$.

Pautet and Nofre (6) measured the lengths of various R groups in $RNHSO_3^-$ and found that for sweetness, R should lie between 5 and 7 Å. In their second paper (7), they suggested, on the basis of a few measurements, that R should have a "half-width" of <4 Å. While this approach is satisfactory for simpler aliphatic and alicyclic systems, it appeared to us to be inadequate for various substituted systems for several reasons:

1. Taste response is a function of the size, shape, and functionality of a molecule, *i.e.*, taste response = f(size, shape, functionality), and any assessment of size and shape should take into account the three-dimensional structure and conformation of the molecule.
2. Several molecules whose R groups have dimensions falling within the limits given by Pautet and Nofre (6, 7) were prepared (and tasted for sweetness), and it was found that they are not sweet (Table I, Compounds 15, 18, 47, and 49).

In the present work, 12 new sulfamates were synthesized. With the use of CPK space-filling models, measurements were taken on these and other sulfamates reported (and tasted) previously. A good correlation existed between sweet/nonsweet sulfamates and the defined parameters for R, so it is possible to predict whether unknown sulfamates will be sweet. Predictions based on the correlation were >90% correct for the 12 sulfamates synthesized.

RESULTS AND DISCUSSION

Measurements were carried out on all known carbosulfamates for which taste data were available. Only those sulfamates whose lack of sweetness could be ascribed to a distortion of the angle θ from 60°, *e.g.*, those substituted at C-1 of a chain or a bridgehead (6, 7), were excluded.

Parameters x, y, and z were defined and measured for each R group; from these values, a measure of the size or three-dimensional structure (V) of R is obtained from the product xyz (see *Experimental*).

Table I lists the sulfamates on which measurements were made. The x, y, z, and V parameters are given together with the literature references. The compounds are listed (Table I) in certain convenient groupings, *e.g.*, straight chain, branched, and increasing ring size.

In Fig. 1, a plot of x (the "length" of R) against V was made using the data for the previously reported sulfamates in Table I. The sulfamates synthesized in the present work (Compounds 15, 18, 20, 21, 35, 41, 43, and 45–49) and those about which predictions were made (Compounds 26–28) were excluded. Figure 1 reveals that nearly all of the sweet sulfamates fall into a rectangle (Fig. 1A) whose boundaries are reasonably well defined on three sides, being ~5.2 and ~7.2 Å on the x axis and ~250 Å^3 on the V axis. The fourth boundary appears to be ≤ 90 Å^3 on the V axis. Almost all of the sulfamates lying outside A are not sweet. Some bitter or faintly sweet sulfamates lie at or near one of the three defined boundaries.

Of the 12 sulfamates synthesized, it could be predicted on the basis of Table I and Fig. 1 that 10 of them would not be sweet and two of them would be sweet (*i.e.*, Compounds 46 and 48). Tasting indicated that these predictions were correct in 11 cases. The one exception was the apocamphane compound (Compound 48), which was bitter. All 12 compounds are shown in Fig. 2. Compound 48 might have been excluded since it is an example of a C-1 substituted sulfamate and, therefore, would not be expected to be sweet due to distortion of the angle θ from 60°. However, it is included because it is bitter and it does lie on a boundary.

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Table I—Space Parameters for R Groups of Carbosulfamates

Compound	R	x, Å	y, Å	z, Å	V, Å³	Reference
1	Ethyl	4.36	3.71	4.06	66.0	16–18
2	*n*-Propyl	5.68	4.19	3.77	89.7	5, 16, 17
3	*n*-Butyl	6.88	4.38	3.77	113.0	16–19
4	*n*-Pentyl	8.12	4.62	3.77	142.0	16, 17
5	2-Methylbutyl	6.68	5.54	5.28	195.0	20
6	3-Methylbuytl	8.00	4.96	5.44	216.0	16
7	Isobutyl	5.40	4.80	6.08	158.0	5, 16, 19, 20
8	Isopentyl	5.64	5.12	6.24	180.0	20
9	Isohexyl	7.40	5.20	6.24	240.0	6
10	Neopentyl	5.40	5.68	6.08	186.0	16
11	Cyclohexyl	5.72	5.03	6.28	181.0	11
12	2-Methylcyclohexyl	6.72	4.96	7.52	250.0	11
13	3-Methylcyclohexyl	5.72	5.03	7.56	218.0	20
14	4-Methylcyclohexyl	6.40	4.98	6.25	199.0	21
15	2,3-Dimethylcyclohexyl	6.92	5.07	7.64	268.0	—[a]
16	2,6-Dimethylcyclohexyl	7.04	5.00	8.64	304.0	21
17	2,5-Dimethylcyclohexyl	6.96	5.07	8.64	305.0	20
18	3,3,5-Trimethylcyclohexyl	5.32	6.64	7.76	274.0	—[a]
19	2-Ethylcyclohexyl	7.08	5.00	8.80	314.0	21
20	4-*tert*-Butylcyclohexyl	7.68	6.25	6.56	315.0	—[a]
21	4-*tert*-Pentylcyclohexyl	8.16	6.69	6.32	345.0	—[a]
22	Cyclopentyl	5.32	4.88	5.96	155.0	21
23	2-Methylcyclopentyl	5.32	4.88	6.72	174.0	20
24	3-Methylcyclopentyl	6.40	5.24	6.28	211.0	19, 22
25	Cyclobutyl	5.04	4.48	5.44	123.0	5, 17
26	3-Methylcyclobutyl	5.68	5.20	5.36	158.0	—[b]
27	2-Methylcyclobutyl	5.40	5.20	6.00	168.0	—[b]
28	Cyclobutylmethyl	5.88	4.96	5.36	156.0	—[b]
29	Cycloheptyl	6.00	5.04	6.88	208.0	5, 21, 23
30	Cyclooctyl	6.64	5.04	7.36	246.0	21, 23
31	Cycloonyl	7.04	5.04	7.68	244.0	20
32	Cyclododecyl	7.64	5.20	8.80	350.0	5
33	Cyclopentylmethyl	6.96	4.90	6.00	205.0	24
34	Cyclohexylmethyl	7.80	5.04	6.36	250.0	20
35	Cyclooctylmethyl	8.24	5.12	7.76	327.0	—[a]
36	1-Cyclopentenyl	5.16	4.08	7.36	155.0	25
37	2-Cyclohexenyl	5.48	5.01	6.02	165.0	25
38	3-Cyclohexenyl	5.48	5.30	6.27	182.0	25
39	2-Cycloheptenyl	6.00	5.17	6.40	198.0	25
40	2-Cyclooctenyl	6.88	5.25	6.92	250.0	25
41	4-Ethenylcyclohexyl	7.88	5.11	6.36	256.0	—[a]
42	Benzyl	7.56	3.68	6.32	176.0	18, 19
43	ac-Tetrahydro-1-naphthyl	6.60	5.12	8.76	296.0	—[a]
44	ac-Tetrahydro-2-naphthyl	7.95	5.04	7.36	295.0	11
45	1-Indane	6.40	5.04	8.72	281.0	—[a]
46	1-Norbornyl	5.92	5.92	5.92	207.0	—[a]
47	*cis*-Myrantyl	6.80	7.68	6.28	328.0	—[a]
48	1-Apocamphane	5.32	7.28	6.40	248.0	—[a]
49	2-Adamantyl	6.76	6.53	6.96	307.0	—[a]
50	1-Adamantyl	5.48	6.53	6.96	249.0	5

[a] Synthesized in the present work. [b] Not synthesized.

In Fig. 3, the 12 compounds are shown with those in Fig. 1 and three unknown compounds. On examination of Fig. 3, a quantitative assessment of the quality and predictive value of the correlation can be made. Of the 47 compounds synthesized and tasted (Compounds 26–28 can be excluded), there is only one nonsweet compound within area A and one sweet compound outside A if those actually on a boundary are ignored. Thus, the taste, *i.e.*, sweet/nonsweet, of 45 of the 47 compounds can be predicted correctly. This finding indicates that Fig. 3 has a 96% chance of correctly predicting the taste of unsynthesized sulfamates.

The correlation between sweet/nonsweet and the defined parameters for R is good and suggests that Fig. 3 can be used to predict whether certain unknown sulfamates will be sweet. Thus, its usefulness in the design of new sweet sulfamates is clear. For example, although Compound 25 is not sweet, it can be predicted that Compounds 26–28 will be sweet.

Plots of either *y* or *z versus V* did not give such a high correlation between sweet/nonsweet molecules and the magnitudes of *y*/*z* and *V*. A few known carbosulfamates were exluded in addition to the group specifically

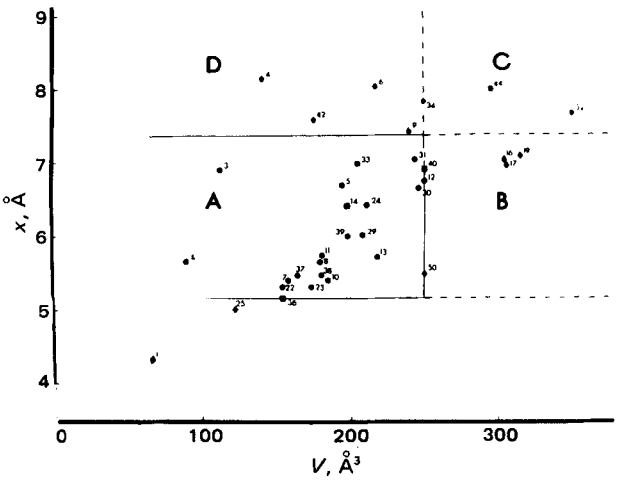

Figure 1—*Plot of the lengths of R (x)* versus V *for reported sulfamates. See Table I for key to compounds. Key:* ●, *sweet;* ♦, *nonsweet; and* ■, *bitter.*

mentioned at the beginning of this section. Thus, for example, *n*-hexylsulfamate and higher homologs were not considered since their *x* parameters ($x = 9.26$ Å for *n*-hexylsulfamate) would place them at the outer limits of the figures and, being nonsweet, they add nothing to the correlation. Some sulfamates that were not tasted were excluded.

The space-filling properties of R (as measured by *V* and *x*) are all important in determining whether or not a molecule is sweet; *V* is not a measure of the molecular volume of R, although the actual volumes of dipeptide ester sweeteners have been measured by immersion in 40% methanol using CPK models (8). The present authors found that the solvent penetrates into the hollows in the models; therefore, it was doubtful if this method could give an accurate assessment of volume (unless the models were hermetically sealed first). Recently, relative sweetness data for 33 dipeptide esters were correlated in a multiparameter equation involving parachor, hydrophobic, and STERIMOL parameters (9).

The *V* parameter can be regarded as the volume generated when *x*, *y*, and *z* are multiplied, *i.e.*, *V* gives the dimensions of the space or receptor site into which R will fit. Thus, although *V* is in part a function of *x*, both parameters are highly meaningful and allow one to explain why some sulfamates are sweet and others are not.

The absence of sweetness of some sulfamates (Fig. 3) can be explained if, as in the case of aspartame (10), the receptor site is seen as a rather narrow cleft (10 Å for aspartame) into which R has to be fitted. Thus, those molecules whose R groups have $5.2 \geq x \leq 7.2$ Å but $V > 250$ Å³ (Fig. 3B) are unable to fit into the receptor site and, therefore, cannot be "locked," and the AH,B mechanism for initiating the sweet stimulus cannot operate. Molecules with $x > 7.2$ Å are too long to fit into the receptor site (Fig. 3D), and molecules with $x > 7.2$ Å and $V > 250$ Å³ (Fig.

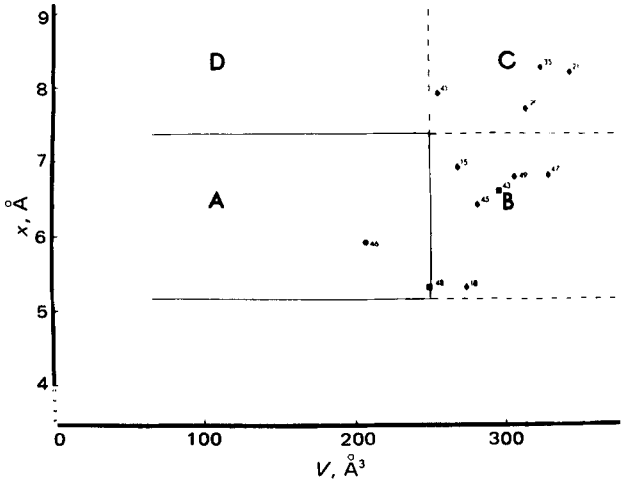

Figure 2—*Plot of lengths R (x)* versus V *for the 12 new sulfamates. See Table I for key to compounds. Key:* ●, *sweet;* ♦, *nonsweet; and* ■, *bitter.*

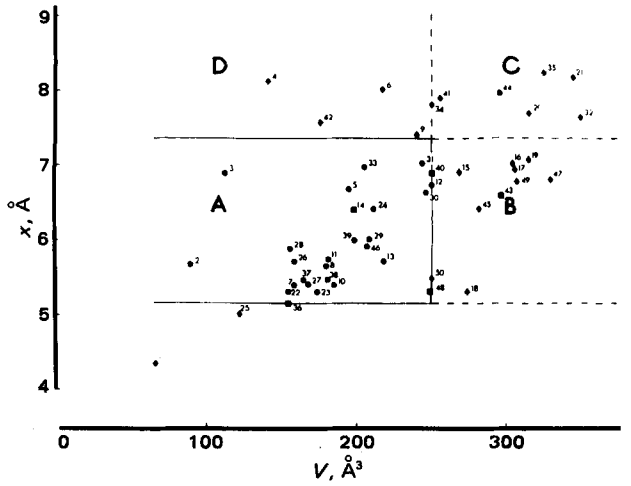

Figure 3—*Plot of the lengths of R (x) versus V for reported, newly synthesized, and some unknown (Compounds 26–28) sulfamates. See Table I for key to compounds. Key: ●, sweet; ♦, nonsweet; and ■, bitter.*

3C) are both too long and too large to be accommodated by the restricted three-dimensional geometry of the binding site. Finally, the few sulfamates with $x < 5.2$ Å and $V < 250$ Å^3 should give a poor fit at the binding site and might not be expected to be sweet.

The approach to structure–taste relationships developed here may be useful in developing such relationships for other types of sweeteners. An attempt is being made to extend it (both by syntheses and measurements on models) to include the large group of sulfamates whose R groups contain one or more heteroatoms. An advantage of the present method is that relative sweetness data are not required. If such data were available, additional patterns or trends might be discernible in Fig. 3. Seen on a broader canvas, the present approach might find application in the wider area of structure–activity relationship studies in chemoreception.

EXPERIMENTAL

Syntheses—All of the sulfamates were synthesized either by reaction of the appropriate amines by the method of Audrieth and Sveda (11) or by the method of Boyland *et al.* (12). Many of the amines were prepared from the corresponding ketones by conversion to their oximes and subsequent sodium–ethanol reduction. All compounds were isolated as their sodium salts, except Compounds 43 and 48, which were purified as their ammonium salts. Compound 48 was prepared from camphor *via* camphorsulfonic acid, camphorsulfochloride, ketopinic acid (13), apocamphane-1-carboxylic acid (14), and 1-aminocamphane (15).

Taste Analysis—All of the sulfamates were tasted by four tasters who were asked to decide whether a solution was sweet or nonsweet, *i.e.*, tasteless or bitter. Prior to commencing, each taster took a concentrated solution of sodium *n*-propylsulfamate, which is very slightly sweet (5, 16). The methodology of the tasting process involved the following: (*a*) rinsing out the mouth with distilled water, (*b*) tasting a concentrated solution of the test sulfamate, (*c*) rinsing out the mouth with distilled water, and (*d*) tasting a concentrated solution of sodium *n*-propylsulfamate. (For many of the compounds taken from the literature and shown in Figs. 1–3, the taste data reported only indicated sweet or nonsweet results.)

Measurements with Models—The atoms making up each side-chain R were arranged in the most stretched conformation. For example, in Compound 12, the methyl group was put into an equatorial position; in Compound 15, the two methyl groups were put *trans* to one another. The side-chain R was positioned on a calibrated straight line (in the plane of the paper) so that the apex carbon (C-1) was superimposed on the zero mark and the remainder of the group was positioned on the line. The group R was clamped in this position, and the measurements (x, y, z) were made in this fixed position.

The length of R (x) could be read off the calibrated line or determined with a vernier. The width of R (z) was obtained by locating the widest points of the chain at right angles to the calibrated line in the x, z plane and dropping perpendiculars from the z axis to these points. The sum of the lengths of the two perpendiculars gave z. The height of R (y) was obtained by locating in the x,y plane (at right angles to the plane of the paper) the highest point of R. Value V, in Å^3, is the volume generated by multiplication of x, y, and z. Where comparison was possible, measurements were usually within 10% of those previously reported (6, 7).

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