Semi-quantitative and Quantitative Structure–Taste Relationships for Carbo- and Hetero-sulphamate ($RNHSO_3^-$) Sweeteners

William J. Spillane* and Maryanne B. Sheahan
Chemistry Department, University College, Galway, Ireland

Seventeen carbosulphamates (eight synthesised in this study) and 23 heterosulphamates (seven synthesised here) have been examined with a view to extending previously developed[1,2] structure–taste relationships for sulphamates ($RNHSO_3^-$). Measurements of defined parameters *x*, *y*, *z*, and *V* ($V = xyz$) for R using Corey–Pauling–Koltun space-filling models for the 17 carbosulphamates have shown that their taste can be predicted in most cases using the previously developed semi-QSAR established. Predictions made from a recent pattern-recognition method study of sulphamate taste are shown to be partially incorrect.

The heterosulphamates were also examined using CPK models and first-order molecular connectivity ($^1x^v$) measurements. The use of linear discriminant analysis on seven subsets of the five variables measured *i.e.* *x*, *y*, *z*, *V*, and $^1x^v$ showed that the subset, *x*, *z*, $^1x^v$ misclassified only three of the 23 heterocompounds, *i.e.* the percentage misclassified was 13%.

Mapping of the sulphamate receptor site on the basis of the measurements carried out suggests that the carbo- and hetero-sulphamates use different sites to bind. This present work brings the database of taste-assessed sulphamates reported to over 120 compounds.

There has been considerable interest over the last decade in the design of synthetic sweeteners and hence in the development of structure–taste relationships for numerous classes of sweeteners.[3] In the area of sulphamate sweeteners many groups are active world-wide in synthesis[4–6] and/or the development of structure–taste relationships.[7–11] The aim of much of this work has been the desire to understand the intraclass molecular structure–activity relationships that govern the sulphamates but in one case, at least, the aims have been more ambitious and interclass relationships have been sought.[9]

Some years ago, building on the idea[12,13] of using Corey–Pauling–Koltun precise space-filling molecular models to examine R in the sulphamates,† $RNHSO_3^-Na^+$, we developed a reliable semi-quantitative structure–taste relationship for the carbosulphamates.[1] Defined parameters, *x*, *y*, *z*, and $V (= xyz)$ for R were measured using the CPK models of the sulphamates. The relationship was then established using taste data for 35 carbosulphamates reported in the literature, and it successfully predicted the taste of 11 of 12 newly synthesised compounds. The development of a QSAR for the correlation of sweet/non-sweet heterosulphamates required the employment of a further parameter namely, first-order molecular connectivity, $^1x^v$.[2] The statistical technique of linear discriminant analysis was applied to the complete group of 33 hetero compounds and analysis was carried out using various subsets of the five available variables, *x*, *y*, *z*, *V*, and $^1x^v$. Seven variable subsets were identified which correctly classified 27 and 28 compounds.

Since we developed our structure–taste sulphamate relationships in the early eighties *ca.* 40 further sulphamates (15 in this work) have been synthesised and assessed for taste. It seemed timely therefore to revisit these relationships and to assess the impact that these new compounds might have on them.

Experimental

Materials.—All amines used were commercially available (Aldrich Chem. Co. and Lancaster Synthesis) and were dried prior to use. Sulphamates were synthesised either by the method of Audrieth and Sveda[14] or Boyland *et al.*[15] They were isolated as their sodium salts except for *N*,*N*-dimethylsulphamate which was isolated as its barium salt. All the sulphamates gave a satisfactory analysis except sodium *N*-benzyl-*N*-methylsulphamate which had C and H well within the limits expected but the N found value was 5.91%. (Calc. for $C_8H_{10}NSO_3Na$: N, 6.75%). I.r. spectra of all the sulphamates prepared were recorded as KBr discs on a Perkin-Elmer 983G spectrophotometer and the usual characterstic bands[16,17] were observed. Some of the sulphamates contained water of recrystallization which gave a broad peak centred at 3 500 cm^{-1} accompanied by a sharp peak at 1 620 cm^{-1}. All sulphamates gave a positive and clean 'sulphamate' test.[18]

Taste Analysis.—Analysis was carried out as previously described[1] and using a similar methodology, except that a 0.5% sucrose solution was substituted for the propylsulphamate solution.

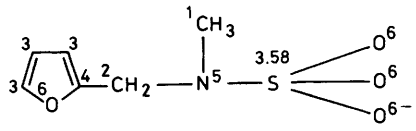
Measurements with CPK Models.—These were carried out as previously described.[1] Replicate measurements were, at least, within 5% (usually better).

Linear Discriminant Analysis.—This was performed as previously shown.[2]

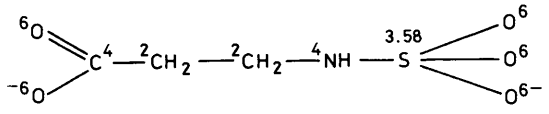
Molecular Connectivity Measurements.[19]—Molecular connectivities of the first order ($^1x^v$) were calculated as previously described.[2] In the previous calculations, a value of 4 was incorrectly used for S and this has been pointed out.[20] The correct value is 3.58 and this is the value which has been used here. The following model calculations illustrate the method of computation.

A ring correction factor of 0.5 has been used for saturated ring compounds, *i.e.* (**31**), (**34**), (**35**), and (**37**)–(**43**).

† In this paper, *carbosulphamate* refers to those sulphamates $RNHSO_3^-Na^+$ in which the *N*-substituent possesses a carbon skeleton; in the *heterosulphamates* the *N*-substituent possesses a carbon skeleton which includes one or more heteroatoms.



$^1x^v = 3(3.58.6)^{-\frac{1}{2}} + (3.58.5)^{-\frac{1}{2}} + (5.1)^{-\frac{1}{2}} + (5.2)^{-\frac{1}{2}} + (2.4)^{-\frac{1}{2}} + (4.3)^{-\frac{1}{2}} + 2(3.3)^{-\frac{1}{2}} + (3.6)^{-\frac{1}{2}} + (6.4)^{-\frac{1}{2}} = 3.3958$



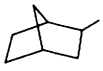
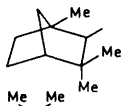
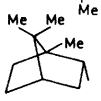
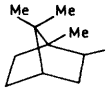
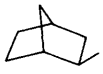
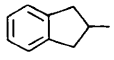
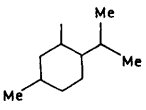
$^1x^v = 3.(3.58.6)^{-\frac{1}{2}} + (3.58.4)^{-\frac{1}{2}} + 2(4.2)^{-\frac{1}{2}} + (2.2)^{-\frac{1}{2}} + 2(6.4)^{-\frac{1}{2}} = 2.5269$

Results and Discussion

The presence of the AH and B centres of the Shallenberger–Acree theory[21] in a tastant molecule is best viewed as a necessary but not a sufficient condition for sweetness. Within every class of sweetener studied, molecules are known which not only have the AH and B centres but also the correct 2.5–4.0 Å separation of these centres and yet do not elicit a sweet taste.[3e] Invoking Kier's 'third' binding site[22] does not get over the problem.

Taste response must be viewed as a function of the size, shape and functionality of the molecules.[3e] In order that the AH, B mechanism for initiating sweet taste can operate, the molecule must be capable of first fitting ('locking') into the receptor site. Molecules that are too large to be accommodated by the binding site will therefore be unable to provide a sweet stimulus though they possess clearly identifiable AH and B centres. Similarly, molecules that are relatively small in size might fit

Table 1. Spatial parameters for R[a] in the carbosulphamates and observed and predicted taste.

		Spatial parameters				Taste[b]		
Compound	R	x/Å	y/Å	z/Å	V/Å^3	Obs.	Pred.[c]	Reference
(1)	Et_2CH–	4.30	4.32	8.64	160.45	N	N	Present paper
(2)	$Ph(CH_2)_2$–	8.62	3.78	6.30	205.24	N	N	Present paper
(3)	$Ph(CH_2)_4$–	10.70	5.60	6.29	376.83	N	N	Present paper
(4)	cyclo-$C_3H_5CH_2$–	4.87[d]	—	—	115.00[d]	FS	N	Present paper
(5)	$R^1 = R^2 = Me$	3.44	3.68	5.92	74.94	N	N	26[e]
(6)	$R^1 = R^2 = Pr^i$	7.20	4.72	6.00	203.97	N	S	Present paper
(7)	$R^1 = R^2 = PhCH_2$	9.92	7.54	6.29	470.45	N	N	Present paper
(8)	$R^1 = PhCH_2$; $R^2 = Me$	7.93	6.08	6.27	302.54	N	N	Present paper
(9)		6.11	5.70	6.15	214.30	VS	S	5
(10)		7.15	5.80	8.45	350.27	N	N	5
(11)		6.79	6.98	7.46	404.05	N	N	5
(12)		6.79	6.98	7.46	404.05	N	N	5
(13)		6.07	5.70	6.07	210.18	N/FS	S	6; 1,27
(14)		6.07	6.70	6.07	210.14	VS	S	6
(15)		7.56	4.72	6.95	248.26	N	N	6
(16)		8.73	5.36	9.36	438.43	N	N	5
(17)	$Me_3C(CH_2)_2$–	5.61	6.15	6.24	215.24	S	S[f]	8

[a] In the general formula $RNHSO_3Na$; compound (5) is the *N*,*N*-disubstituted carbosulphamate $R^1R^2NSO_3Ba$ and compounds (6)–(8) are the *N*,*N*-disubstituted carbosulphamates $R^1R^2NSO_3Na$. [b] N = non-sweet; FS = fairly sweet; S = sweet; VS = very sweet. [c] This work. [d] Estimated by extrapolation (see text). [e] Synthesised previously but tasted here for the first time. [f] Also predicted to be sweet by the method of ref. 8.

Table 2. Spatial parameters and observed and predicted taste for a series of branched carbosulphamates $RNHSO_3Na$.

		Spatial parameters				Taste		
Compound	R	x/Å	y/Å	z/Å	V/Å^3	Obs.	Pred.[a]	Pred.[b]
(18)	$EtC(Me_2)CH_2-$	5.23	6.82	5.81	205.65	?	S	S
(19)	$Me_2CHCH(Me)CH_2-$	6.10	6.26	6.13	234.06	?	S	S
(20)	Et_2CHCH_2-	6.13	4.74	7.22	209.74	?	S	S
(21)	$EtCH(Me)(CH_2)_2-$	8.09	4.96	5.35	214.60	N[c]	N	S
(22)	$Me(CH_2)_2CH(Me)CH_2-$	8.04	4.75	5.18	197.72	?	N	S

[a] This work. [b] Compounds **(18)**–**(22)** and **(17)** (Table 1) were all predicted to be sweet using the method of ref. 8. [c] Ref. 17.

poorly at the receptor site and again the vital mechanism for sweetness may be inhibited.

For aspartame the receptor site is seen as a rather narrow cleft, *ca.* 10 Å.[23] However, it has been suggested[3e] and supported in independent studies[9,24,25] that quite a number of sites may be involved in the binding of various sweet agonists. Van der Heijden[9] has shown that the receptor site used by sulphamates is different to those used by isocoumarin, oxime/nitroaniline and dipeptide sweeteners.

Carbosulphamate Structure–Taste Relationship.—In our previous work[26] we established that in a plot of x (the 'length' of R in $RNHSO_3^-$) *versus* V ($= xyz$) nearly all of the sweet carbosulphamates studied fell into a rectangle, the boundaries of which were reasonably well defined on three sides, being *ca.* 5.2 Å and *ca.* 7.2 Å on the x-axis and *ca.* 250 Å^3 on the V-axis. Most of the sulphamates lying outside this area on the plot were not sweet. It was also noted that some bitter or faintly sweet compounds lay at or near one of the boundaries of this area. Thirty five carbosulphamates reported in the literature and for which reliable taste data were available were used to establish the structure–activity relationship. A further 12 compounds were synthesised and tasted and the taste of 11 of these was successfully predicted using the relationship. Thus the SAR appeared to be >90% successful in predicting taste for carbosulphamates. Such a high predictive power is very good.

In the present work we have synthesised and tasted eight new carbosulphamates and have brought together (see Table 1) a further nine carbosulphamates reported and tasted by other workers.[5,6,8] Measurements of x, y, z, and V together with the observed taste and the taste predicted by our QSAR are included in Table 1.

Compounds **(5)**–**(8)** are actually secondary sulphamates and lack an amino hydrogen and therefore the H of the Shallenberger AH entity is missing and they are hence unlikely to be sweet. They are included however, since it is interesting to note that this lack of sweetness is confirmed in three cases using our QSAR after measurements were made on the R grouping shown. The Figure shows the x *versus* V plot. Examination of Table 1 shows that the taste of the 17 compounds has been correctly predicted in 14 cases. This predictive ability, 82%, is again quite good and if compound **(6)** is omitted this rises to 88%. We had difficulty constructing a model for compound **(4)** but we estimated its x and V dimensions by extrapolation from the earlier plot[1] using the series cyclobutyl-, cyclopentyl-, and cyclohexyl-methylsulphamates. We believe this to be a reliable procedure since many homologous series, not surprisingly, give excellent straight lines in the x *versus* V and related plots.

It is instructive to look at those compounds where our predictions sweet/non-sweet were incorrect. Compound **(4)** which is faintly sweet, is a 'borderline' case falling near the boundary of the 'sweet rectangle' (Figure) and as noted previously a number of bitter or faintly sweet compounds tend to fall near the boundaries.[1] Compound **(6)** might strictly speaking be excluded from our studies since it does not contain an amino hydrogen and is unlikely to be able to engage in the Shallenberger mechanism for sweetness.[1,18] Some years ago we synthesised the *endo*-8,9,10-trinorbornylsulphamate, **(13)**, and we found it to have a faint sweetness.[1,27] The Italian workers,[6] however, clearly include it amongst their non-sweet compounds. It may be that our purchased starting amine was slightly contaminated with the *exo*-isomer **(14)** which would account for the faint sweetness. It should be noted that compounds **(9)** and **(14)** are enantiomers.

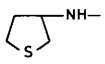
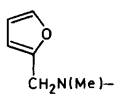
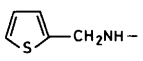
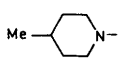
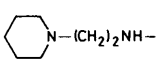
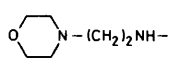
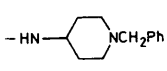
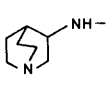
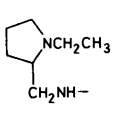
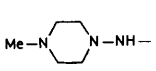
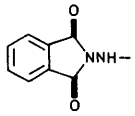
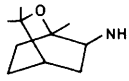
Recently a pattern-recognition method has been employed to classify sweet and non-sweet sulphamates.[8] From this study predictions were made regarding the taste of compounds **(17)**–**(22)** (inclusive). All six compounds were predicted to be sweet and **(17)** was synthesised and found to be sweet.[8] Using our SAR for carbosulphamates, **(17)**–**(20)** should be sweet and **(21)** and **(22)** would not be sweet. It is of interest that compound **(21)** was found to be non-sweet some years ago[17] (see Tables 1 and 2) and the pattern-recognition method may not therefore be as powerful for predicting the taste qualities of sulphamates as has been claimed.[8]

Heterosulphamate Structure–Taste Relationship.—In our earlier work[2] in this area we used a database of 33 heterosulphamates (22 from the literature and 11 synthesised and tasted) to classify sweet/non-sweet compounds. The entire database had to be used in attempts to establish a structure–taste relationship for these compounds since had we restricted it to a smaller number, any relationships found might be less reliable than when the entire group of 33 compounds was used. Hence the opportunity to test the relationship, which was set-up using linear discriminant analysis, was not available. Now, however, using new data from this laboratory and data principally from Pautet's[7] and Nardo's[6] reports (see Table 3) it is possible to test the reliability of the classification arrived at from further application of the analysis.

In the calculation of first-order molecule connectivity, ^1x_v, carried out in our earlier work[2] we rounded off the δ^v value for sulphur (used in the $^1x^v$ calculations) to 4 from 3.58 since all the other values used were integers. This has been queried[20] though use of 4 rather than 3.58 makes little difference in the final $^1x^v$ values obtained and does not effect the conclusions of the previous work. In this work we have used the value of 3.58 (see the Experimental section).

Linear discriminant analysis has been reapplied to the group of compounds in Table 3 using the same five parameters *viz.*, x, y, z, V, and $^1x^v$ and the seven subsets thereof previously used. The results are shown in Table 4. Using the number of misclassified compounds and the spread of misclassified compounds between sweet and non-sweet as criteria of significance one may focus attention on the subsets (y, V, $^1x^v$), (x, z, $^1x^v$) and (x, y, z, $^1x^v$). The first of these (y, V, $^1x^v$) seems unsatisfactory since it

Table 3. Spatial parameters for X and first-order molecular connectivities for XSO_3^- in the heterosulphamates ($XSO_3^-Na^+$).

Compound	X	Spatial parameters				$^1x^v$	Taste[a]	Reference
		x/Å	y/Å	z/Å	V/Å^3			
(23)	$HO(CH_2)_2NH-$	6.04	4.63	3.79	105.94	2.08	N	7
(24)	$HO(CH_2)_3NH-$	7.54	4.50	3.80	128.86	2.58	N	7
(25)	$(MeO)_2CHCH_2NH-$	7.20	5.93	5.70	243.12	2.96	N	7
(26)	$MeO(CH_2)_2NH-$	7.60	4.36	3.80	125.86	2.46	N	7
(27)	$^-O_2C(CH_2)_2NH-$	6.40	4.56	4.93	143.81	2.53	N	7
(28)	$^-O_2C(CH_2)_3NH-$	7.63	4.37	4.95	165.10	3.03	N	7
(29)	$Me_2N(CH_2)_2NH-$	7.39	4.72	6.02	210.19	2.97	N	7
(30)	$MeS(CH_2)_2NH-$	8.11	4.58	3.79	140.77	2.67	S	7
(31)		5.99	4.98	6.01	179.39	2.76	S	7
(32)		7.74	5.15	6.04	240.94	3.39	N	Present paper
(33)		9.28	4.90	5.94	270.53	3.14	FS	Present paper
(34)		5.57	4.52	6.66	167.65	2.76	N	Present paper
(35)		5.66	5.40	6.41	187.65	3.41	N	Present paper
(36)	$EtO(CH_2)_3NH-$	10.08	4.45	3.80	170.11	3.55	N	Present paper
(37)		9.53	4.87	6.43	298.43	4.21	N	6
(38)		8.82	4.98	6.15	269.99	3.79	N	6
(39)		11.69	7.05	6.56	540.91	5.73	N	6
(40)		7.41	5.94	5.86	257.97	4.21	N	6
(41)		7.62	4.96	8.34	315.31	4.18	N	6
(42)		6.18	3.94	5.95	144.80	2.77	N	6
(43)		8.52	4.41	6.08	228.17	3.34	N	6
(44)		9.18	3.58	7.34	241.70	3.82	N	6
(45)		7.15	7.23	7.74	400.38	5.26	N	5

[a] NS = non sweet; FS = faintly sweet; S = sweet.

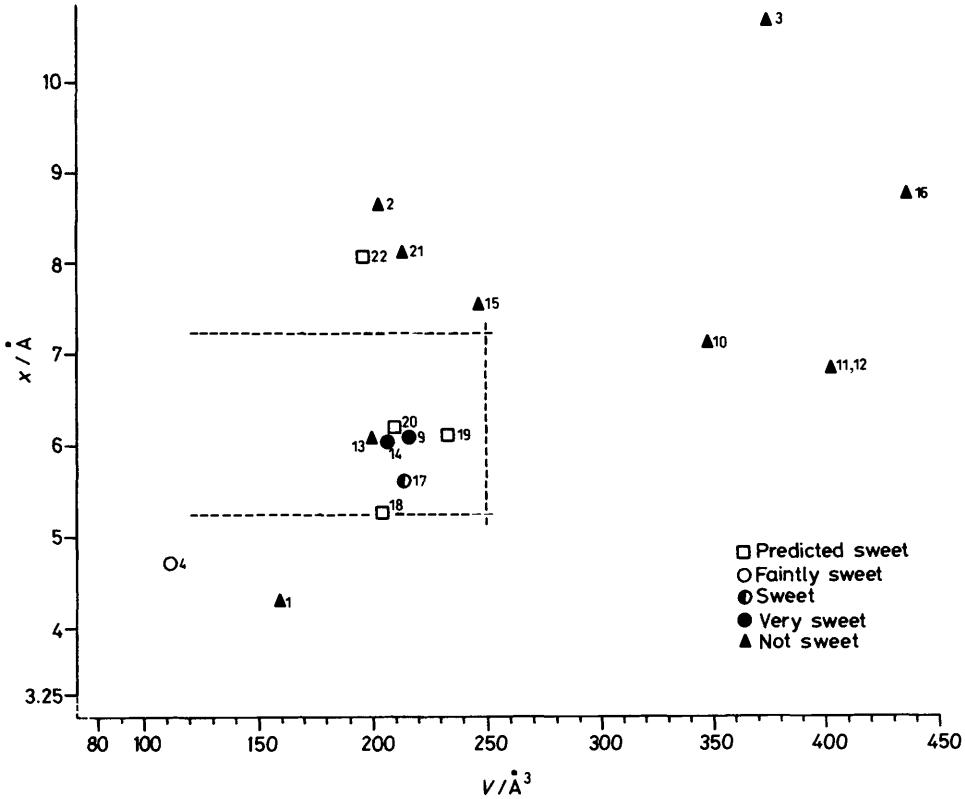


Figure. Plot of x/Å *versus* V/Å^3 for carbosulphamates (**1**)–(**4**) and (**9**)–(**22**); ○ = faintly sweet, ◑ = sweet, ● = very sweet, ▲ = not sweet □ = predicted sweet in ref. 8.

Table 4. Discriminant analysis for best subsets.

Subset	Compounds misclassified: Sweet	Compounds misclassified: Non-sweet	Total misclassified
x, $^1x^v$	(**30**), (**31**)	(**26**), (**36**), (**39**)	5
y, V, $^1x^v$	(**30**), (**31**), **33**)	—	3
x, z, $^1x^v$	(**30**), (**31**)	(**44**)	3
x, z, V, $^1x^v$	(**30**), (**31**), (**33**)	(**44**)	4
x, y, z, $^1x^v$	(**30**), (**31**)	(**44**)	3
x, y, z, V	(**30**), (**31**)	(**35**), (**37**)–(**39**), (**41**), (**44**)	8
x, y, z, V, $^1x^v$	(**30**), (**31**), (**33**)	(**44**)	4

misclassifies the three sweet compounds in Table 3. The subset (x, z, $^1x^v$) is to be preferred to the subset (x, y, z, V) since fewer variables are needed to achieve the same result. This subset (x, z, $^1x^v$) was also the best subset in the original work[2] since it misclassified the least number of compounds (five) in that study.

For the total set of heterosulphamates (56 compounds, from the present study and the previous work[2]), eight are misclassified using the subset (x, z, $^1x^v$). Five of these are from the 13 sweet compounds used and three from the 43 non-sweet. Therefore, while the overall misclassification is 8/56 or 14%, the misclassification of sweet in high (5/13 or 38%) and the misclassification of non-sweet is quite low at 7%.

The five misclassified sweet compounds all contain a sulphur atom in the disulphide or sulphone form *i.e.* compounds (**30**) and (**31**) (Table 3) and the 4-thiacyclohexyl-, 4-thia-4,4-dioxocyclohexyl- and 3-methyl-4-thiacyclohexylsulphamates.[2] These compounds are consistently misclassified (Table 4 and ref. 2), irrespective of the subset used.

Sweet Receptor Site.—Some approximate mapping of the carbosulphamate receptor site can be attempted from consideration of the x, y, and z parameters of the 23 sweet carbosulphamates reported[1] together with compounds (**9**), (**14**), and (**17**) (Table 1). The product xy for these 26 compounds is 31.2 ± 3.32 Å^2. This suggests that the surface area of the receptor site which has to receive the sulphamate R group is *ca.* 30 Å^2. The 'depth' of the site can be gauged from the average z value for the 26 compounds. It is ≃6.2 ± 0.63 Å. A similar analysis for the heterosulphamates using the ten sweet compounds previously reported[2] and compounds (**30**), (**31**), and (**33**) (Table 3) gave an xy value of *ca.* 46.1 ± 14.7 Å^2 and z = 6.3 ± 0.59 Å. This analysis reinforces the idea of different receptor sites being required by different types of sweeteners. Indeed it suggests that even within a class (the sulphamates) different receptor sites are utilised. In view of the large number of sulphamates (>120) which have had their taste qualities assessed in this and other laboratories further SAR work utilising this information may be expected.

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