Development of structure–taste relationships for sweet and non-sweet heterosulfamates †

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A data set of 101 hetero- (both cyclic and open chain) sulfamate sodium salts, whose taste data are known, have been assembled and divided into sweet (S) (20 compounds) and non-sweet (N) (81 compounds) categories. The data set is made up of 56 compounds reported earlier, 32 synthesised in this work and another 13 reported since the earlier publications. Using the parameters x, y and z (measured for the RNH portion of $RNHSO_3Na$ using CPK models) and first order molecular connectivity, $^1\chi^v$ it has been possible to achieve a correct classification rate of approximately 65% using linear discriminant analysis (LDA): a compound is N if $-3.285 + 0.439x + 0.662y + 0.236z - 1.27\,^1\chi^v > 0$ otherwise it would be S. Using quadratic discriminant analysis (QDA) the classification rate increased to approximately 80%. Finally a Tree-based analysis gave an 86% classification rate but performed poorly in classifying correctly the S group of compounds.

In the European Union since 1994 almost twenty intense and bulk type sweeteners have been cleared as food and drink additives and on a worldwide basis a number of others are permitted or are awaiting clearance.[1] Despite this there is still enormous interest in the development of new sweeteners. This interest is driven perhaps mainly by the fact that none of the alternative sweeteners are capable of replacing the mouthfeel and other properties that sucrose brings to food and drinks and that secondly the market for non-nutritive sweeteners is assessed in billions of euros and even a niche share of the market can be very valuable to a manufacturer.

Our particular interest lies in the cyclamate (sulfamate) field and we are part of a wider European group spread over seven countries in sixteen laboratories researching many aspects of sweeteners.[2] Three sulfamate sweeteners, *viz.* *N*-cyclohexylsulfamic acid (cyclamic acid) and its sodium and calcium salts are on the EU list of permitted sweeteners.[3] In our work we have been mainly involved in the development of structure–taste relationships (SARs) for different types of sulfamates of general formula $RNHSO_3^-Na^+$.[4,5] The terms carbo- and heterosulfamates have been used to describe compounds in which R possesses a carbon-only skeleton or a carbon skeleton containing one or more heteroatoms respectively.[6] In the present work we report our latest results in finding structure–taste relationships for an enlarged group of 101 heterosulfamates including 32 newly synthesized in this study and 13 from another laboratory.

Background

Some years ago a structure–taste relationship was developed for a rather limited set of 33 heterosulfamates (13 prepared by us and 20 from the literature) using linear discriminant analysis (LDA).[7] This was subsequently extended to encompass 56 compounds (5 made in this laboratory and 18 from other laboratories).[6] The analysis involved the development of a simple linear discriminant function which classified compounds as sweet (S) or non-sweet (N) using first order molecular connectivities ($^1\chi^v$) and a set of spatial measurements for each sulfamate, determined using Corey–Pauling–Koltun (CPK) precise molecular models of the RNH part of $RNHSO_3^-Na^+$. These measurements gave x (length of R), y (the height of R), z (the width of R) and volume $xyz = V_{CPK}$. The volume may be thought of as the space into which R should fit (be held) to allow the Shallenberger–Acree mechanism of sweetness to operate satisfactorily. The LDA analysis classified 48 out of the 56 compounds (85%) and it classified 40 of the 43 non-sweet compounds correctly (93%). However it performed poorly in the sweet group classifying only 8 out of 13 correctly (62%). Now with an additional 45 compounds available (32 synthesised here and 13 reported in another laboratory[8]) we felt that it was appropriate to revisit these relationships.

Results and discussion

The current position is shown in Table 1, in which each research group involved in heterosulfamate synthesis is identified, and the number of compounds made is given together with references to the work. In all there are now 101 heterosulfamates synthesised and tasted—81 of these have been classified as non-sweet (N) and 20 as sweet (S). The 45 newly synthesised compounds are illustrated in Fig. 1 and in Table 2 the spatial parameters, x,y,z and V_{CPK}, the first order molecular connectivity ($^1\chi^v$), the taste (N or S), the location (see Table 1) and the references to the syntheses are given. These compounds are numbered **57**–**101** in order to preserve the sequential numbering introduced in 1983[7] and continued in 1989[6] (see footnote *a* in Table 2).

Apart from the availability of new compounds several other reasons prompted us to examine the structure–taste relationships of heterosulfamates again. (i) Some doubt has been cast on the reliability of the taste data of Wendt and Winkley[11] following recent work.[18] Therefore it seemed appropriate to repeat the analysis taking five of their compounds **21**–**25** as being non-sweet (in our previous analysis they were considered to be sweet). Each of these compounds lacks a hydrogen on the

† Taste data are available as supplementary data. For direct electronic access, see http://www.rsc.org/suppdata/p2/b0/b002482l/

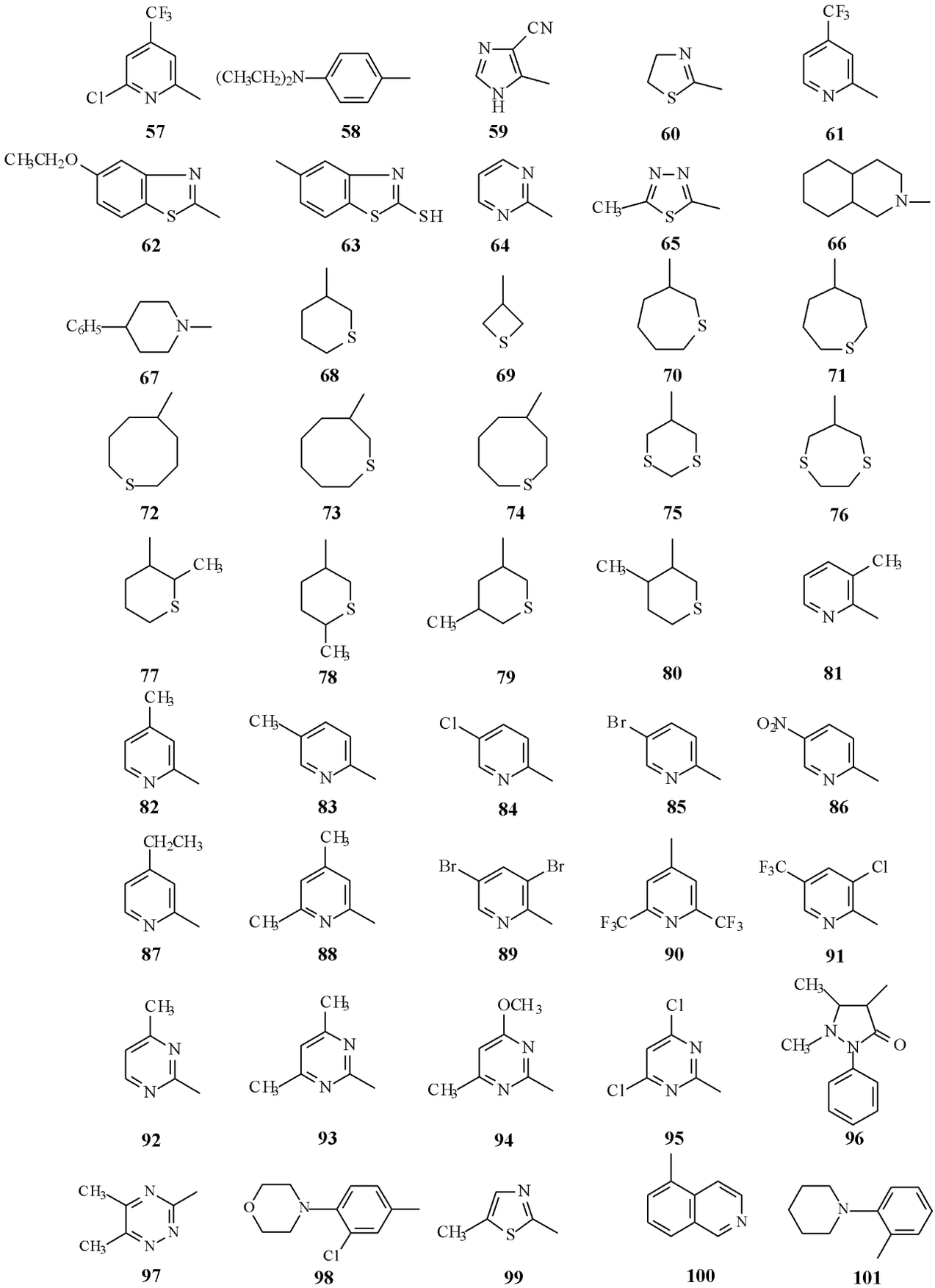

Fig. 1 Structures **57**–**101**. The sodium sulfamate function $–NHSO_3^-Na^+$ is omitted from each drawing but its position is indicated by the solid line. Compounds **57**–**67** and **81**–**101** were prepared in this work; **68**–**80** were prepared by Unterhalt and Moellers.[8]

$–NHSO_3^-$ function and would therefore be expected to be non-sweet.[19] The sixth compound that they made, **11**, does have a hydrogen and an amino function and therefore was left as sweet. (ii) By 1993 eleven heterosulfamates had been made here[20] and the thirteen compounds synthesised by Unterhalt and Moellers[8] were available. However, when we reapplied the

Table 1 Breakdown by group/location of heterosulfamates synthesized

Location No.	List of groups	No. of compounds made	Reference
1	Spillane *et al.* (Ireland) (1983, 1989, present paper)	50	6,7, This work
2	Hurd and Kharasch (US) (1946)	5	9
3	Unterhalt and Boschemeyer (Ger) (1972, 1976)	3	10*a*, *b*
4	Wendt and Winkley (US) (1974)	6	11
5	Thompson (US) (1957)	1	12
6	Yamaguchi (Jap) (1963)	1	13
7	Blicke *et al.* (US) (1954)	4	14
8	Pautet and Daudon (France) (1986)	9	15
9	De Nardo *et al.* (Italy) (1984)	8	16
10	Evangelisti *et al.* (Italy) (1980)	1	17
11	Unterhalt and Moellers (Ger) (1990, 1991)	13	8*a*, *b*
		Total: 101	

Table 2 Spatial parameters for X, first order molecular connectivities for XSO_3^- in the heterosulfamate $XSO_3^-Na^+$, taste of the compound, location of group who synthesized compound and reference

Compound[a]	*x*/Å	*y*/Å	*z*/Å	V_{CPK}/Å^3	$^1\chi^v$	Taste[b]	Location[c]	Reference
57	8.02	4.62	9.33	346	3.65	N	1	Present paper
58	9.55	8.50	6.22	505	4.75	S	1	Present paper
59	7.16	3.42	7.97	195	2.33	N	1	Present paper
60	7.01	3.58	5.43	136	3.18	N	1	Present paper
61	8.10	4.66	7.97	300	3.16	N	1	Present paper
62	12.6	4.30	6.96	377	4.94	N	1	Present paper
63	10.2	4.00	7.73	316	4.74	N	1	Present paper
64	7.29	3.48	6.05	153	2.29	N	1	Present paper
65	7.98	3.75	5.39	161	3.03	S	1	Present paper
66	7.97	4.99	7.26	289	4.98	S	1	Present paper
67	10.4	6.22	6.20	401	5.03	N	1	Present paper
68	7.46	4.80	6.36	228	4.24	S	11	8*a*
69	6.74	4.79	4.96	170	3.24	N	11	8*a*
70	7.68	4.81	7.18	265	4.74	S	11	8*a*
71	7.67	4.96	7.25	276	4.74	S	11	8*a*
72	8.00	4.78	7.11	272	5.24	S	11	8*a*
73	8.12	4.82	7.64	299	5.24	N	11	8*a*
74	8.64	4.90	7.39	313	5.24	N	11	8*a*
75	7.65	4.53	6.42	223	4.97	S	11	8*a*
76	7.89	4.91	7.14	277	5.47	N	11	8*a*
77	7.64	4.96	7.48	284	4.59	N	11	8*b*
78	8.18	5.17	6.30	266	4.57	N	11	8*b*
79	7.52	5.02	7.41	280	4.64	N	11	8*b*
80	7.45	5.18	7.28	281	4.65	N	11	8*b*
81	7.76	3.63	7.40	209	2.85	N	1	Present paper
82	7.81	3.54	7.33	203	2.84	N	1	Present paper
83	8.62	3.52	6.28	191	2.84	N	1	Present paper
84	9.25	3.46	6.24	200	2.91	N	1	Present paper
85	9.52	3.72	6.26	222	3.32	N	1	Present paper
86	9.17	4.79	6.28	276	2.88	N	1	Present paper
87	8.26	5.17	7.97	340	3.41	N	1	Present paper
88	7.93	3.58	8.57	243	3.26	S	1	Present paper
89	9.48	3.74	8.00	284	4.22	S	1	Present paper
90	8.25	5.27	9.80	426	3.88	S	1	Present paper
91	9.14	4.59	7.73	324	3.64	N	1	Present paper
92	7.71	3.56	7.43	204	2.71	N	1	Present paper
93	7.68	3.87	8.56	254	3.13	N	1	Present paper
94	7.79	4.52	9.25	325	3.25	N	1	Present paper
95	7.74	3.46	9.03	242	3.26	N	1	Present paper
96	7.99	3.62	8.42	244	5.09	S	1	Present paper
97	8.16	4.27	10.8	378	3.01	N	1	Present paper
98	12.0	5.98	6.80	488	5.72	N	1	Present paper
99	8.33	4.68	5.93	231	3.15	N	1	Present paper
100	7.74	3.39	8.77	231	3.83	N	1	Present paper
101	7.80	6.42	10.0	519	5.34	N	1	Present paper

[a] The structures, spatial parameters, molecular connectivities and taste data for compounds **1**–**33** can be found in ref. 7 and compounds **34**–**56** are in ref. 6 (numbered as 23–45). [b] N = Non-sweet; S = sweet. [c] See Table 1.

discriminant function previously used[6,7] to these compounds a disproportionate number seemed to be misclassified and, in particular, the interesting thia- and dithiacyclic compounds of Unterhalt and Moellers[8] *viz.* **68**–**80** tended to be misclassified. (iii) On rechecking all our previous calculations using the CPK models and the calculations of molecular connectivity a few errors emerged with the initial 56 compounds. These are now corrected in Table 4 (Supplementary Data) and are the values used in the present study.

Before seeking a new discriminant function using the complete data set of 101 compounds a decision was taken not to use the V_{CPK} values. Since these are calculated from *x*, *y* and *z* it was

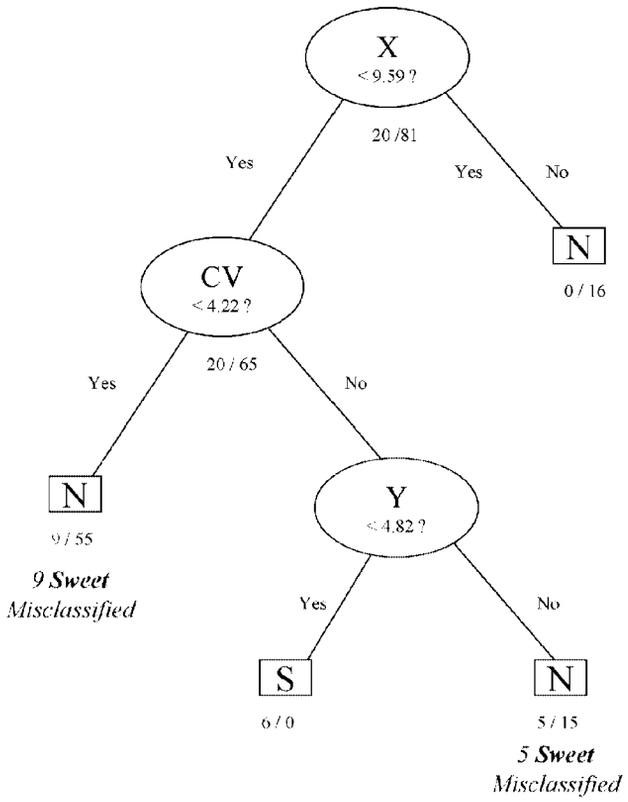

Fig. 2 Sweet (S)/non-sweet (N) classification Tree for all 101 (81N + 20S) sulfamates in the data set.

Table 3 Valence delta (δ^V) values used for heteroatoms in calculating first order molecular connectivity ($^1\chi^v$) for heterosulfamates XSO_3^-

Group[a]	δ^V	Group	δ^V
–NH	4	–O–	6
—N=	6	=O	6
–S–	0.67	O (both nitro)	6
–SH	0.56	F	7
		Cl	0.78
		Br	0.26
=S=	3.58		5
		=N–(pyridine)	5
		≡N	5

[a] Carbon atoms with 0, 1, 2, and 3 hydrogen atoms attached have δ^V values of 4, 3, 2 and 1 respectively.

felt that these three parameters should be adequate to describe the steric effects of R in $RNHSO_3^-Na^+$. Molecular connectivity, $^1\chi^v$, which is said[21] to encode both electronic and spatial effects, was used as before.

Using the Splus 2000 (Mathsoft International) statistical software package a linear discriminant function was found which indicated that a compound would be non-sweet (N) if relationship (1) holds, otherwise it would be sweet (S). Since

$$-3.285 + 0.439x + 0.662y + 0.236z - 1.27\,^1\chi^v > 0 \quad (1)$$

there are 81 N and 20 S compounds in the data set and 26 N and 7 S were misclassified this indicates that 26/81, 32% and 7/20, 35% of non-sweet and sweet compounds respectively were misclassified. Interestingly, if one looks at the misclassification rates for the five main locations/groups (those who report 6 or more compounds) in Table 1 they are as follows: this laboratory 11/50 = 22%, Wendt and Winkley 3/6 = 50%, Pautet and Daudon 0/9 = 0%, De Nardo *et al.* 4/8 = 50% and Unterhalt and Moellers 8/13 = 62%.

Quadratic discriminant analysis (QDA) was performed using the Splus package and gave better results misclassifying only 16/81 = 20% and 4/20 = 20% of the non-sweet (N) and sweet (S) compounds respectively. The misclassification rates for the same five locations as above were respectively 5/50 = 10%, 0/6 = 0%, 1/9 = 11%, 3/8 = 38% and 8/13 = 62%. Thus, all showed improvement except the Unterhalt and Moellers data which had the same seven compounds (**73**,**74**,**76**–**80**) misclassified both in LDA and QDA. These results are quite good especially when one bears in mind the wide diversity of structural types, as indicated in Fig. 1, involved in the analysis. The 101 compounds in the data set are made up of 14 pyridines, 14 thiacyclohexanes, 10 other thiacycles, 11 non-cyclic heterocompounds, 8 piperidines, 7 thiazoles, 5 pyrimidines, 5 pyrrolidines, 5 morpholines and a small number of other types of heterocycles.

Finally we have used a Tree-based approach, again employing the Splus package, as an alternative to LDA and QDA analyses. This approach has become popular in recent years since the publication[22] of CART (Classification and Regression Trees). Tree-based models are so called because the primary method of display is of the form of a binary tree where each observation is passed down the branches of the tree on the basis of a binary decision rule at each split. This approach allows for 'significant interactions' to be identified in a non-hierarchical manner providing insight and understanding into the structure of the data.

The approach is non-parametric, unlike LDA and QDA, and is used to gain a better understanding of the structure of the relationships of the classification variables (*e.g.* x, y, z and $^1\chi^v$) and their interactions in terms of predicting class membership (*i.e.* sweet or non-sweet in this application).

The method involves successive binary recursive partitioning of the data set by identifying, at each partition step, which classification variable best (and significantly) separates out the remaining compounds in terms of class membership. It is essentially a data driven approach and unlike LDA and QDA does not rely on assumptions relating to the covariance matrix.

A Tree-based approach was used on the full data set of 101 compounds and resulted in all 81 non-sweet compounds being classified correctly but 14 of the 20 sweet compounds were misclassified *i.e.* 14/20 = 70%. Four of the 14 misclassified, **4**, **42**, **44** and **90**, were previously misclassified in the QDA analysis. Thus the Tree-based approach gives the best overall result misclassifying only 14 compounds giving a classification rate of 86%. However it is not particularly satisfactory since all the compounds that it misclassifies come from the sweet group of 20 sulfamates. One advantage of it is that it is the only method that has correctly classified almost all the compounds synthesised by Unterhalt and Moellers—only one, **71**, is misclassified. The classification Tree obtained for the 101 compounds is shown in Fig. 2 (in Fig. 2, CV = $^1\chi^v$).

Splitting rules are determined by looking at all possible splits for all variables included in the analysis. The best splitting rule is determined using a quality-of-split criterion based on rank order of all possible splits. Once a best split rule is determined, the procedure repeats the process for each branch node, continuing recursively until further splitting is impossible. Once such a 'maximal' tree is generated, cross validation is used to determine the 'best' tree by comparing misclassification error rates. The best tree in our analysis uses only three classification variables, namely x, y and $^1\chi^v$, has 3 splits and four terminal nodes. The first splitting rule involves the x variable only, where a compound is classified as non-sweet if $x \geq 9.59$ or else is carried down to the next level of the tree. The second splitting rule involves the variable $^1\chi^v$ only, where all unclassified compounds are classified as non-sweet if $^1\chi^v < 4.22$ or else are carried to the final splitting rule where the remaining com-

pounds available for classification are deemed non-sweet if $y \geq 4.82$ and sweet otherwise.

Experimental

Material and methods

All amines used were commercially available (Aldrich Chemical Co., Lancaster Synthesis). Liquid amines were normally distilled over a drying agent to remove water as any water present reacts with the chlorosulfonic acid subsequently used to achieve the sulfamation reaction. Solid amines were used as obtained or, if thought necessary, dried overnight in a heating cabinet at approximately 40 °C. Sulfamates were synthesised either by the method of Audrieth and Sveda[19] or Boyland *et al.*[23] and all were isolated as their sodium salts and purified by successive recrystallization from approximately 93% EtOH. All were free of chloride and sulfate ions and gave a positive and clean 'sulfamate test'.[24] IR spectra of all 32 sulfamates prepared were recorded as Nujol mulls on a Perkin-Elmer 983G spectrophotometer and all showed the usual characteristic bands.[7] Most of the sulfamates crystallized with small amounts of water of crystallization.[19] The presence of water was indicated by a broad peak in the IR at 3500 cm^{-1} accompanied by a sharp peak at 1620 cm^{-1}. Microanalysis for the 32 sulfamates gave C, H and N percentages well within the normal limits *i.e.* ±0.5%, except for the compound **97** which had 22.98 N, 25.74 C and 3.30% H (calc. for $C_5H_7N_4SO_3Na \cdot 0.5H_2O$ 23.82 N, 25.53 C and 3.40% H). Thus the %N is out by 0.84 but the compound gave a good IR spectrum and performed well in the sulfamate test and was free of chloride and sulfate ions and was thus used in tasting.

Taste panel procedure

A basic 'sip and spit' methodology was employed. Solutions for tasting were made up in volumetric flasks using distilled water and tasted within 24 hours of preparation. All taste evaluation was carried out at a room temperature of 18 ± 0.5 °C. Samples were presented to an experienced group of panelists in clean white plastic cups labeled A, B, *etc*. All compounds were tasted at the concentration of 0.01 M, a concentration found to give readily detectable taste. A maximum of five solutions were tasted at any one tasting session and fixed aliquots were used.

In order to determine the tastes properly, standards for the four primary tastes, sweet, sour, bitter and salty were used. The concentration of standards used has been given before.[25] Each standard was tasted at or above its recognition threshold so that a definite taste was detected by each of the panelists. Panelists were also asked to look out for aftertastes. For compounds **57** to **67**, 5 ml samples were given to 4 panelists, for **81** to **97**, 6 ml samples and 7 panelists were used and for **98** to **101**, 10 panelists each took 8 ml samples.

Measurements with CPK models

These were carried out as previously described.[26] For the heterosulfamates, $XSO_3^-Na^+$, measurements were made on the X portion of the compound. The *x*, *y* and *z* dimensions were accurately determined in centimeters using Vernier calipers and then converted to ångströms by dividing by 1.25; the values are given in Å in Tables 2 and 4.

Molecular connectivity measurement

The procedure for calculating first order molecular connectivity ($^1\chi^v$) has been explained and illustrated previously[7] and they have been found to be helpful in correlating structure–sweetness for nitroanilines,[27a] aldoximes[27b] and perillartines.[27c] The heteroatom valence delta (δ^V) values[28] in Table 3 have been used in the present work and the calculations are illustrated for compounds **57**, **69**, **81**, **83**, **99** and **100** in Fig. 3. As in previous calculations a ring connection factor of 0.5 has been subtracted from ($^1\chi^v$) for cyclic compounds.

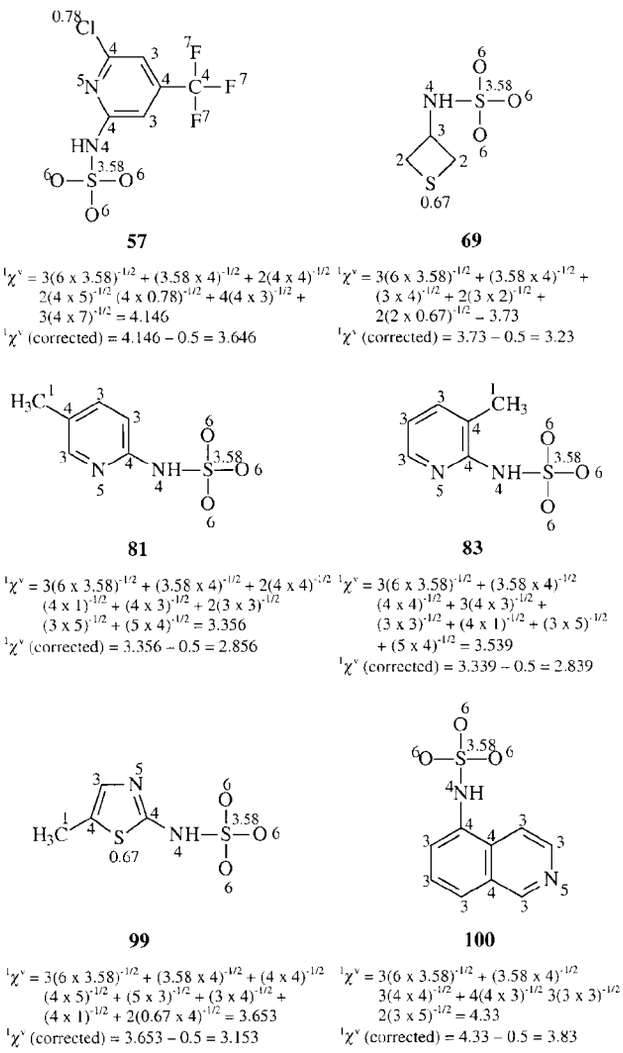

Fig. 3 Molecular connectivity ($^1\chi^v$) calculations for compounds **57**, **69**, **81**, **83**, **99** and **100**.

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