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Further studies on the synthesis and tastes of monosubstituted benzenesulfamates. A semi-quantitative structure–taste relationship for the *meta*-compounds

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Abstract

Twenty-two new sodium monosubstituted phenylsulfamates $XC_6H_4NHSO_3^-Na^+$ have been prepared and characterized. These compounds, and also *para*-tolyl- and phenylsulfamate, have been tasted and their taste properties reported. Taste data are now available for 63 such compounds: 19 *ortho*-, 23 *meta*- (including phenylsulfamate) and 21 *para*-. Using CPK molecular models, measurements of the aromatic portion XC_6H_4– have been made. Exclusive/predominant sweetness and reduced sweetness is mainly found with the *meta*-compounds and a plot derived from the CPK measurements correctly classifies 20 of the 23 (including X = H) *meta*-compounds into sweet and bitter categories, 12 of the 13 sweet compounds (92%) and 8 of the 10 bitter compounds (80%). Using the PC SPARTAN *PRO* molecular modelling program, HOMO and LUMO electronic parameters and aqueous solvation energy E_{solv} were calculated. Linear (LDA) and quadratic (QDA) discriminant analyses were carried out on the 23 compounds using various subsets of the CPK measurements and the above SPARTAN-calculated parameters. A 91% classification rate was achieved using QDA and the subset with the parameters LUMO, E_{solv}, and the CPK measurements, x (length) and z (width) of XC_6H_4–. Apparently, for sweetness, the CPK measurement x of XC_6H_4– needs to be in the range $\sim 5.65 \leqslant x \leqslant \sim 5.95$ Å. Using several of the methods developed, taste predictions were made on some unsynthesised *meta*-phenylsulfamates.

Keywords: Sweet; Benzenesulfamates; Structure–taste relationship; *meta*-aromatics; Bitter; Taste

1. Introduction

Some years ago (Spillane, Sheahan, Simmie, Cunningham, McArdle, & Higgins, 1989) we reported the synthesis of the first sweet-tasting benzenesulfamates and developed a semi-quantitative structure-taste relationship for these. Later this work was extended (Spillane, Ryder, & Sheahan, 1994) to include over 30 monosubstituted aromatic sulfamates (**I**).

The positions (*ortho*-, *meta*- and *para*-) and types of X were varied and strong sweetness was found for some of the *meta*-X-phenylsulfamates. Finding a virtually exclusive sweet taste for some benzenesulfamates was unexpected since, in earlier seminal work (Audrieth & Sveda, 1944), it had been concluded that a reduced (saturated) ring was essential for sweetness. They did report a sweet aftertaste for sodium phenylsulfamate, **I** (X = H) and also, around this time, the sweetness of some aromatic thiazolesulfamates had been reported (Hurd & Kharasch, 1946).

In this paper we report the synthesis, characterisation and taste assessment of 22 new phenylsulfamates, **I**. A semi-quantitative structure-taste relationship for the *meta*-compounds has been extended in this work, using measurements made on Corey–Pauling–Koltun (CPK) molecular models. The sweetness of 12 of the 13 sweet *meta*-compounds and the bitterness of 8 of the 10 bitter *meta*-compounds can be correctly predicted using this semi-QSAR, which involves a plot of x (length of XC_6H_4–) vs. V_{CPK}. Linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA) are also carried out using, not only the CPK parameters, but also the PC SPARTAN *PRO*—calculated HOMO and LUMO electronic parameters and also the aqueous solvation energy E_{solv}.

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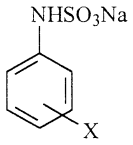

I

2. Materials and methods

2.1. Amines

These were generally available from Aldrich and Lancaster. Other chemicals used were obtained from sources previously cited (Spillane, Sheahan, & Ryder, 1993).

2.2. Synthesis

Amines and reagents were distilled/recrystallized before use and dried. The aromatic sulfamates were synthesised and characterized by the procedures given previously (Spillane et al., 1993). Recently, pyridine-sulfur trioxide complex (Aldrich) has been used directly in pyridine and this has obviated the use of chlorosulfonic acid. Some of the sulfamates listed in Table 1 have been made using sulfur trioxide–pyridine directly. All sulfamates were isolated as their sodium salts, $XC_6H_4NHSO_3^-Na^+$ and were analyzed for C, H and N and all, except the following, were found to have C, H and N within 0.5 of the theoretical percentage: *m*-$F_3COC_6H_4NHSO_3Na.2H_2O$, N theory 4.44, found 3.70. α-Picoline-sulfur trioxide (rather than the more usual pyridine-SO_3) was used in a few cases as the sulfamating agent. Sodium N-*o*-sec-butylphenylsulfamate formed as an oil but, after 9 months at 0 °C it crystallized as a white solid. IR and ^1H and ^{13}C NMR spectra of all compounds were obtained. Some of the products crystallized with varying amounts of water of hydration and allowance was made for this when preparing 0.01M aqueous solutions for tasting. The yields of pure sodium sulfamates varied from 55 to 2%, with an average of 28%. The first 22 compounds in Table 1 are new and *p*-tolyl- and phenylsulfamates (last two compounds in the table) were also remade for tasting.

Table 1
Percentage of assessors giving the taste quality[a] of monosubstituted phenylsulfamates

Sulfamate	pH	No. of assessors	Sweet	Sour	Bitter	Salt	Tasteless	Sweet aftertaste	Predominant taste (⩾50% assessors)
o-CH_2Ph	10.0	8	0	25	75	0	12.5	0	Bitter
m-Bu^t	6.20	10	0	10	60	20	0	0	Bitter
p-Bu^t	6.01	10	10	10	20	20	40	0	–
o-Bu^s	8.92	9	25	0	100	0	0	37.5	Bitter
p-Bu^s	10.4	8	0	50	25	12.5	12.5	12.5	Sour
m-SMe	9.13	8	30	0	20	0	50	0	Tasteless
p-SMe	9.44	9	12.5	12.5	62.5	0	25	25	Bitter
m-NMe_2	8.90	8	0	25	62.5	0	37.5	50	Bitter
p-NMe_2	8.10	8	60[b]	0	30	0	0	0	Sweet
o-C_4H_8NO[c]	6.30	10	0	30	20	20	30	0	–
p-C_4H_8NO[c]	6.46	10	60	10	20	10	0	0	Sweet
o-OPh	10.3	9	25	12.5	37.5	0	50	25	Tasteless
m-OPh	12.1	9	0	12.5	87.5	0	12.5	12.5	Bitter
m-OCH_2Ph	12.2	9	0	0	100	0	12.5	0	Bitter
p-OCH_2Ph	9.37	9	0	0	50	25	50	0	Bitter/tasteless
o-Ph	4.06	10	0	40	50	0	0	0	Bitter
o-COMe	2.60	10	30	60	0	0	0	0	Sour
m-OCF_3	11.1	8	60	0	20	0	40	0	Sweet
p-$NO_2C_6H_4SO_2$	7.53	3[d]	0	0	100	0	0	0	Bitter
p-$C_5H_{10}NSO_2$[e]	11.8	8	25	12.5	62.5	0	0	12.5	Bitter
m-CH(Me)OH	8.92	9	50	25	25	0	25	37.5	Sweet
m-CH_2OH	6.90	8	50	0	25	12.5	50	0	Sweet/tasteless
p-Me	7.10	8	25	37.5	25	0	37.5	12.5	–
H	7.50	8	87.5	12.5	0	0	0	0	Sweet

[a] All compounds were tasted as 0.01 M solutions made in distilled water of pH varying from 5.7 to 5.9.
[b] Delayed sweetness (~5 s).
[c] C_4H_8NO = N-morpholino.
[d] This compound was only given to three tasters because of its extreme bitterness.
[e] $C_5H_{10}N$ = N-piperidinyl.

Table 2
Concentration and pHs of the four primary taste standards

Taste	Standard	Concentration (M)	pH
Sweet	Sucrose[a]	4.4×10^{-2} (1.5%)	5.05
Sour	Citric acid[a]	5.2×10^{-4} (0.01%)	3.69
Bitter	Quinine sulfate[a,b]	6.4×10^{-6} (0.0005%)	5.03
Salt	Sodium chloride[c]	3.4×10^{-2} (0.2%)	5.60

[a] BDH Chemicals.
[b] Quinine sulfate is light-sensitive and its solution was stored in the dark.
[c] Riedel de Haen.

2.3. Taste panel procedure

The procedures and methodology of the tasting procedure for the new compounds and *p*- tolyl and phenylsulfamate were identical to that previously described (Spillane et al., 1994). The standards and their strengths and pHs are given in Table 2. In the corresponding table (Table 1) in the earlier paper (Spillane et al., 1994), two of the molar (M) quantities given were incorrect and these are now corrected in Table 2 in this paper. The strengths of the standards used were always calculated as percentages, wt/ml i.e. sucrose 1.5 g/100 ml, citric acid 0.01 g/100 ml, quinine sulfate 0.0005 g/100 ml and sodium chloride 0.2 g/100 ml and thus the standards used in this work were identical to those used in the previous work. The number of panellists used for each tasting is indicated in Table 1. pH determinations were made using a Jenway model 3310 pH meter, buffered at 4.0, 7.0 and 9.2.

2.4. CPK measurements

Corey–Pauling–Koltun (CPK) space-filling precise atomic models (Barrett, 1979; Boyd, 1976; Harte, 1969; Pautet & Nofre, 1978; Spillane et al., 1994; Walters Pearlstein, & Krimmel, 1986) were used to construct models of each sulfamate synthesised. All measurements were made on the aromatic portion of the molecule only, i.e. XC_6H_4–. The length (x), width (z) and height (y) of XC_6H_4– were measured and a volume, V_{CPK} defined as $x.y.z$. Pautet and Nofre (1978) first employed CPK models of sulfamates in SAR work and this was extended by us (Spillane & McGlinchey, 1981; Spillane, McGlinchey, Muircheartaigh, & Benson, 1983; Spillane et al., 1993). The procedures adopted in building the models and in carrying out the measurements have been detailed in these papers. A full listing of CPK measurements is given in Table 3 for the first 22 compounds, then *p*-tolylsulfamate and, finally, for nine unsynthesised compounds for which taste predictions are made (see later in this paper). The CPK parameters for phenylsulfamate are available (Spillane et al., 1994).

Table 3
CPK measurements for monosubstituted phenylsulfamates

Sulfamate	x (Å)	y (Å)	z (Å)	V_{CPK} (Å^3)[a]
o-CH_2Ph	6.9	7.5	10.8	559
m-Bu^t	6.6	6.0	8.5	337
p-Bu^t	7.8	6.0	6.3	295
o-Bu^s	5.6	9.0	7.0	353
p-Bu^s	8.9	5.6	6.4	319
m-SMe	5.9	4.9	7.9	229
p-SMe	10.1	6.9	3.8	265
m-NMe_2	6.6	3.8	8.6	216
p-NMe_2	7.9	5.5	6.3	274
o-C_4H_8NO[b]	7.7	6.5	9.2	460
p-C_4H_8NO[b]	11.2	6.3	7.6	536
o-OPh	9.6	7.5	8.1	583
m-OPh	10.6	9.4	5.6	558
m-OCH_2Ph	12.1	4.4	7.6	405
p-OCH_2Ph	13.6	6.2	4.7	396
o-Ph	11.2	3.4	6.3	240
o-COMe	7.5	5.4	8.2	332
m-OCF_3	6.8	4.7	8.7	278
p-$NO_2C_6H_4SO_2$	15.8	14.2	8.0	1795
p-$C_5H_{10}NSO_2$[c]	11.8	6.4	7.5	566
m-CH(Me)OH	5.9	8.0	6.1	288
m-CH_2OH	5.8	4.3	8.1	202
p-Me	6.6	3.8	6.3	158
m-CO_2^-	6.3	3.2	7.8	157
m-SO_3^-	6.6	5.1	8.4	283
m-Pr^n	6.3	4.8	9.1	275
m-Pr^i	6.4	6.3	7.5	302
m-Bu^n	6.8	5.8	10.0	394
m-Bu^s	7.0	6.5	9.1	414
m-CH_2CH_2OH	6.3	4.7	8.7	258
m-CH_2F	5.8	4.1	7.3	174
m-CH_2Cl	5.8	5.0	8.2	238

[a] $V_{CPK} = x.y.z$.
[b] C_4H_8NO = N-morpholino.
[c] $C_5H_{10}N$ = N-piperidinyl.

2.5. Molecular modelling of sulfamates

The structures of all 23 *meta*-compounds (including phenylsulfamate), and of the nine unsynthesised *meta*-compounds were built using PC SPARTAN *PRO* software (Wavefunction, 2000). The equilibrium geometry was obtained using the semi-empirical AM1 module within PC SPARTAN *PRO*. A charge of -1 was applied to all of the sulfamates, except in the case where the substituent X = O^-, CO_2^- and SO_3^-; then a charge of -2 was used. The positive sodium counter-ion was not considered. The electronic properties that were calculated within the software were the HOMO and LUMO energies for all of the sulfamates. In addition, the aqueous solvation energy E_{solv} was calculated using the software by the SM5.4 procedure (Chambers, Hawkins, Cramer, & Truhlar, 1996). E_{solv} is actually the sum of the aqueous solvation energy and total energy for each molecule. A full list and values of the parameters are given in Table 4.

Table 4
Electronic and thermodynamic parameters for all *meta*-compounds

Sulfamate	HOMO (ev)	LUMO (ev)	E_{solv} (kcal mol^{-1})
Et	−5.129	3.611	−228.52
OEt	−5.219	3.664	−259.66
O^-	−0.159	8.301	−340.16
COMe	−5.409	2.472	−255.46
NH_2	−5.097	3.686	−220.37
I	−5.420	3.042	−199.28
OMe	−5.183	3.615	−254.60
NO_2	−5.868	1.799	−211.39
CF_3	−5.618	2.822	−369.45
F	−5.379	3.359	−259.39
Cl	−5.385	3.303	−221.89
Br	−5.416	3.196	−210.46
CN	−5.571	2.606	−183.41
Me	−5.119	3.622	−223.23
Bu^t	−5.128	3.605	−232.77
SMe	−5.222	3.104	−217.99
NMe_2	−5.154	3.598	−206.84
OPh	−5.425	2.426	−214.62
OCH_2Ph	−5.340	2.101	−223.92
OCF_3	−5.517	3.169	−414.19
CH(Me)OH	−5.148	3.533	−273.75
CH_2OH	−5.333	3.323	−272.98
H	−5.130	3.701	−216.00
CO_2^-	−2.205	6.830	−390.12
SO_3^-	−2.495	6.370	−440.03
Pr^n	−5.144	3.590	−235.04
Pr^i	−5.135	3.606	−231.95
Bu^n	−5.149	3.585	−240.79
Bu^s	−5.15	3.593	−237.67
CH_2CH_2OH	−5.258	3.434	−280.42
CH_2F	−5.282	3.373	−269.39
CH_2Cl	−5.316	2.982	−230.72

2.6. Statistical analysis

Linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA) have been employed by us previously (Spillane et al., 1983, Spillane et al., 2000) in classifying sweet and non-sweet sulfamates. The variables that were generally used were the CPK parameters, along with first order molecular connectivity, $^1\chi^v$. The semi-quantitative SAR obtained from the x vs. V_{CPK} plot in Fig. 2 is derived from the steric properties of the sulfamates. We have also applied both LDA and QDA to various subsets of x, y and z (the CPK parameters), and HOMO, LUMO and E_{solv} (parameters calculated in PC SPARTAN *PRO*) for the 23 *meta*-compounds (including **I**, X = H). The software used were the statistical packages SYSTAT 10 (SPSS, 2000) and MINITAB (MINITAB, 2000). A correlation matrix was first constructed for all the parameters, which allows us to examine relationships within the data set. Any two parameters that were highly correlated with each other were not used together in the discriminant analysis calculations. In the present case, both HOMO and LUMO parameters were highly correlated ($r = 0.942$) with each other and were not jointly used in LDA or QDA calculations.

3. Results and discussion

In previous work on benzenesulfamates taste assessment of 34 sodium sulfamates was carried out (Spillane et al., 1994) and relative sweetness data are available for four of the *meta*-substituted benzenesulfamates (Spillane et al., 1989). Using the CPK measurements, a limited semi-quantitative SAR was found simply by plotting the x (length) values for the XC_6H_4– portion of each sulfamate, $XC_6H_4NHSO_3Na$ against the corresponding volumes, V_{CPK}. In this plot it was noticed that many of the *meta*-compounds fell on/or close to a line drawn at right angles to the x-axis at $x = 5.8$ Å. A number of these compounds exhibited a strong, clearcut sweetness. The *ortho*- and *para*-compounds prepared tended to fall at x values greater than 5.8 Å and none of them exhibited the strong sweetness shown by some of the *meta*-compounds.

This SAR replaced the previously proposed dihedral angle theory of Pautet and Nofre (1978) (see Spillane et al., 1989, for a discussion) and it also offered a rationale that might explain the strong sweetness of some *meta*-compounds and the lack or relative lack of sweetness of the *ortho*- and *para*-compounds.

The V_{CPK} volumes measured in our work correlated moderately well with theoretical GEPOL calculated van der Waals (V_W) and molecular (V_M) volumes for 24 different sulfamates, giving correlation coefficients (r) of 0.925 and 0.935, respectively (Spillane, Birch, Drew, & Bartolo, 1992). V_{CPK} Volumes also show some correlation with experimentally determined apparent molar volumes (AMV) for 16 sulfamates, giving a correlation coefficient (r) of 0.917 (Spillane, Morini, & Birch, 1992). V_{CPK} volumes are of course different from van der Waals and molecular volumes and neither are they 'swept' or accessible volumes. Since x, y and z are multiplied to obtain V_{CPK} volumes they are in effect describing a rectangular box (mathematically a rectangular parallelpiped).

It seems reasonable to consider that the XC_6H_4– portion of the molecule may have to fit into this rectangular box before the sweet taste mechanism (Shallenberger-Acree, α-helical or multicomponent attachment) can operate. Since many of the *meta*- compounds have x close to 5.8 Å they may very well provide a 'good fit' to the proposed rectangular box and thus will be able to participate fully in a sweet taste mechanism. All of the *ortho*- and *para*-compounds have $x > 6$ Å and they therefore may not be able to give a good fit and hence are not sweet or only show some partial sweetness among other tastes.

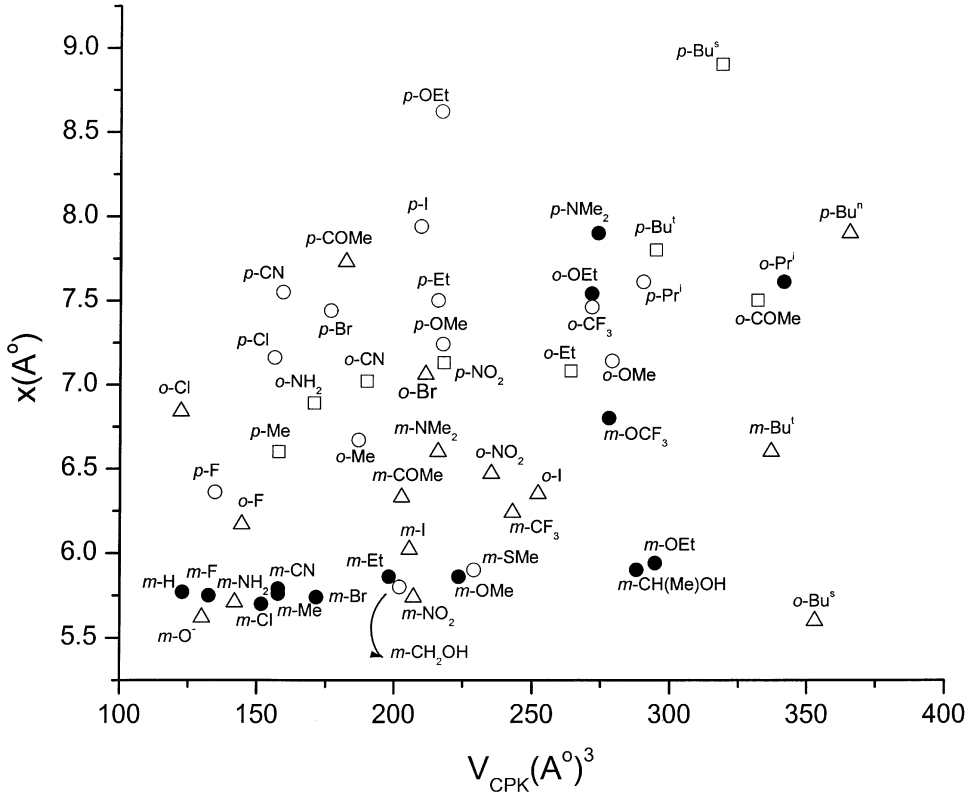

Fig. 1. Plot of x (Å) vs V_{CPK} (Å^3) for sodium phenylsulfamates for which taste data are available. (●) Exclusive or predominant sweetness, (○) reduced sweetness, (Δ) bitterness, (□) other tastes (e.g. sourness, tasteless). Taste data and CPK measurements for compounds shown here and not in Tables 2 or 3 are available in earlier publications (Spillane et al., 1994). Points for the following compounds, taste data symbol, x and V_{CPK} in brackets, were omitted from the figure: *p*-C_4H_8NO (●, 11.2, 536), *m*-OCH_2Ph (Δ, 12.1, 405), *o*-Ph (Δ, 11.2, 240), *p*-$NO_2C_6H_4SO_2$ (Δ, 15.8, 1795), *p*-SMe (Δ, 10.1, 265), *p*-$C_5H_{10}NSO_2$ (Δ, 11.8, 566), *o*-CH_2Ph (Δ, 6.9, 559), *p*-OCH_2Ph (Δ, 13.6, 396) *m*-OPh (Δ, 10.6, 558), *o*-C_4H_8NO (□, 7.7, 460), *o*-OPh (□, 9.6, 583).

In this present work we have synthesised 22 new sodium benzenesulfamates, and characterized these. All 22 new compounds and, in addition, *para*-tolyl and phenylsulfamate, have been tasted. The latter two were included since detailed taste data had not been provided for these by Audrieth and Sveda (1944). The taste data on all 24 compounds, together with the solution pHs, are given in Table 1. CPK models were built and measurements made on the 22 new compounds, on *p*-Me and on nine *meta*-compounds that have not yet been synthesised and tasted (Table 3).

In Fig. 1 an x (Å) vs. V_{CPK} (Å^3) plot has been made and this includes data for all 63 [19 *ortho*-, 22 *meta*- and 21 *para*- plus phenylsulfamate **I** (X = H)] benzenesulfamates for which taste data are now available. Taste data for the benzenesulfamates not made in this present work will be found in our previous papers (Spillane et al., 1989, 1994). Four symbols (see Fig. 1 legend) have been used to indicate taste. Points for a few compounds are not shown since it would extend the figure to an inordinate size. However, the coordinates and taste classifications for these compounds are given in the legend to the figure. As mentioned above, most of the *meta*-compounds lie closer to the V_{CPK}-axis than the *ortho*- and *para*-compounds. Exclusive or predominant sweetness (• symbol) is found mainly in this region. This region can be looked at more closely in Fig. 2, which is an x (Å) vs. V_{CPK} (Å^3) plot for the *meta*-compounds (excluding the two compounds with $x > 6.8$ Å, i.e. OPh, OCH_2Ph). Fig. 2 appears to show that exclusive or predominant sweetness occurs (with one exception) in the area, ~ 5.65 Å $\leqslant x \leqslant \sim 5.95$ Å. However, there are two compounds in this area, *m*-NO_2 and *m*-NH_2, which are very bitter and *m*-SMe, which shows reduced sweetness. The parent phenylsulfamate **I** (X = H) was, surprisingly, found to be immediately quite sweet whereas Audrieth and Sveda (1944) report that it had "only a sweet aftertaste". In fact its sweetness was considered to be very intense and it could be a good candidate for a further relative sweetness assessment. Thus, of the 14 compounds in this area, two show no sweetness at all. It should also be noted that three of the *ortho*-/*para*-compounds displayed predominant sweetness (Fig. 1).

Notwithstanding these considerations, Fig. 2 does give a reasonable SAR for correctly classifying the *meta*-compounds into sweet and bitter categories. Thus, of the 23 *meta*-compounds (including the parent phenylsulfamate **I**, X = H) tasted, 13 are sweet and 10 are bitter

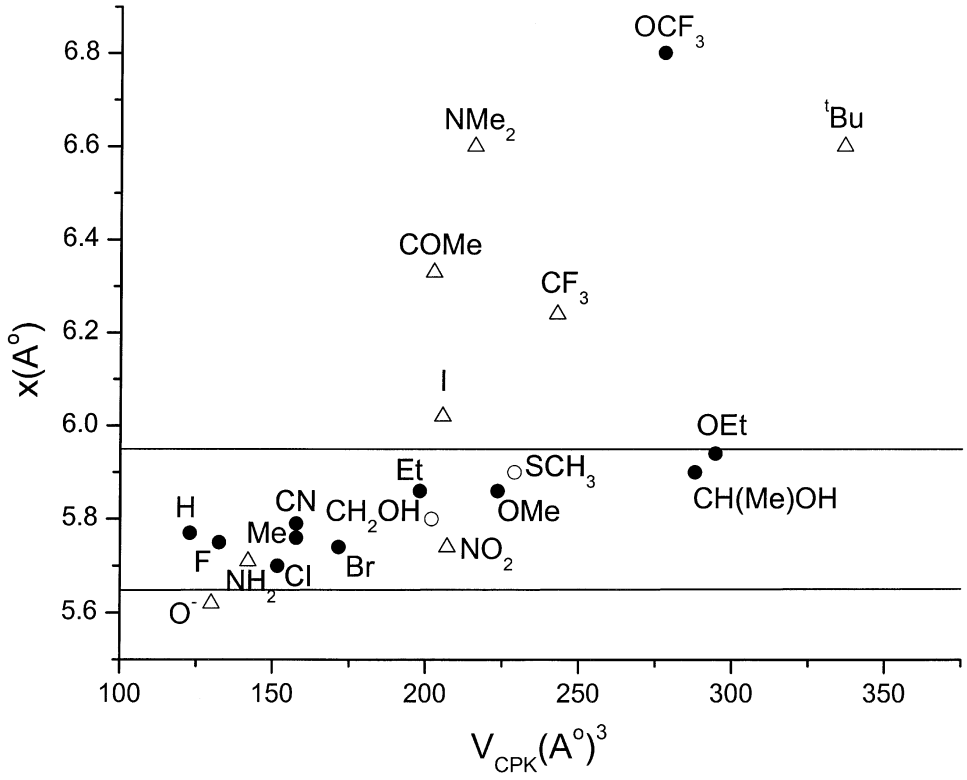

Fig. 2. Plot of x (Å) vs. V_{CPK} (Å^3) for *meta*-substituted phenylsulfamates for which taste data are available. (●) Exclusive or predominant sweetness, (○) reduced sweetness, (Δ) bitterness. The following *meta*-compounds, x, V_{CPK} and taste symbol in brackets, were omitted from this plot: OPh (Δ, 10.6, 554), OCH_2Ph (Δ, 12.1, 405).

Table 5
Classification of 23 *meta*-phenylsulfamates into sweet/non-sweet categories

Subset	Method	Correctly classified		Overall % classified	Misclassified compounds	
		% Sweet	% Non-sweet		Sweet	Non- sweet
x, V_{CPK}	x vs. V_{CPK} plot	92	80	87	OCF_3	NH_2, NO_2
HOMO, E_{solv}, x, z	LDA	100	70	87	–	NH_2, NO_2, CF_3
	QDA	100	60	83	–	COMe, NH_2, I, CF_3
LUMO, E_{solv}, x, z	LDA	92	60	78	OCF_3	COMe, NH_2, NO_2, CF_3
	QDA	100	80	91	–	NH_2, I

and the x/V_{CPK} plot correctly places 12 of the sweet compounds in the defined area (92%) and 8 of the 10 bitter compounds outside this area (80%) (see first entry, Table 5). The three *meta*- compounds that deviate are those with $X = NH_2$, NO_2 (both bitter) and $X = OCF_3$ (predominantly sweet). We have looked at various parameters, such as σ_m, π, E_s and molar refractivity (see Hansch, Leo, & Hoekman, 1995), for all the *meta*-compounds, to try to account for these deviations but have been unable to find a reason.

It is interesting to note that, prior to synthesising and tasting the eight *meta*-compounds made in this work, we were able to predict their tastes, i.e. sweet or non-sweet, correctly, in seven cases, on the basis of having x in the range 5.65–5.95 Å, (the one deviating being *m*-OCF_3 which is predominantly sweet but which would have been predicted to be non-sweet on the basis of an $x = 6.8$ Å).

In an attempt to find an SAR that might give a better classification of these compounds we have calculated electronic parameters, HOMO and LUMO, for all *meta*-compounds, together with aqueous solvation energies, E_{solv} (Table 4) using the molecular modelling software PC SPARTAN *PRO*. LDA and QDA have been applied to various subsets of x, y and z (CPK parameters) and HOMO, LUMO and E_{solv} (SPARTAN—calculated parameters) in an attempt to achieve a better classification or separation between the sweet and non-sweet compounds. After performing both LDA

Table 6
Taste predictions on unsynthesised *meta*-phenylsulfamates

Sulfamate	x, V_{CPK}	LUMO, E_{solv}, x, z QDA	HOMO, E_{solv}, x, z LDA
CO_2^-	N[a]	N	N
SO_3^-	N	N	N
Pr^n	N	N	N
Pr^i	N	N	S[b]
Bu^n	N	N	N
Bu^s	N	N	N
CH_2CH_2OH	N	S	N
CH_2F	S	S	S
CH_2Cl	S	S	S

[a] N, non-sweet.
[b] S, sweet.

and QDA on many different subsets, it becomes apparent that the best subsets for discriminating between the sweet and non-sweet compounds include the variables E_{solv}, x (length) and z (width of XC_6H_4–), along with either the HOMO or LUMO parameters. For the 23 *meta*-compounds, the best parameter subsets, the percentages of correct classifications, and the misclassified compounds are listed in Table 5.

As stated previously, HOMO and LUMO variables were not both used in the same subset, due to their high correlation with each other. From Table 5 it is evident that QDA performed on the subset LUMO, E_{solv}, x and z gives the best classification of all for sweet (100%) and non-sweet (80%) compounds, and also the best overall percentage classification (91%). This is an improvement over the x vs. V_{CPK} SAR. QDA also correctly classifies the *meta*-compound, where $X = OCF_3$, which was misclassified by the x vs. V_{CPK} SAR. Surprisingly, *meta*-iodophenylsulfamate is misclassified in QDA and *meta*-aminophenylsulfamate is misclassified by all subsets. LDA performed on the subset HOMO, E_{solv}, x and z gives a classification rate of 100% for sweet compounds and 70% for non-sweet. Overall 87% of the compounds are correctly classified, similar to the x vs. V_{CPK} SAR.

Using the above established SARs, taste predictions have been made on nine unsynthesised *meta*-compounds; these are listed in Table 6 and their CPK parameters are in Table 3. Using the x vs. V_{CPK} SAR we predict that *m*-CH_2F and *m*- CH_2Cl ought to show exclusive or predominant sweetness as they have $x = 5.8$ Å. The two most effective discriminant classifications achieved may also be used to predict taste, namely LDA performed on HOMO, E_{solv}, x and z, and QDA on LUMO, E_{solv}, x and z. Looking at Table 6 there is good correlation between the taste predictions made by the three subsets. Both discriminant analysis classifications achieved also predict that *m*-CH_2F and *m*-CH_2Cl ought to show predominant sweetness. Additionally *m*-CH_2CH_2OH is predicted to be sweet by the classification rule obtained when using the LUMO, E_{solv}, x and z subset and *m*-Pr^i is predicted sweet when using the HOMO, E_{solv}, x and z subset. Confirmation or otherwise of these predictions will have to await further synthesis.

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