Synthesis and tastant properties of disulfamates. Multisulfamation studies

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Twenty four disulfamates, one trisulfamate, two tetrasulfamates and two monosulfamates have been made. The disulfamates are of two types: $RN(SO_3Na)_2$ (Type A, compounds **1**–**20**) and $NaO_3S(H)NR'N(H)SO_3Na$ (Type B, compounds **21**–**24**) and all except three (which had not been tasted) are new materials. The positions of the $-SO_3Na$ groups in compounds **21**–**23** have been established by the use of model compounds (*e.g.* parent amines, appropriate monosulfamates) and ^{13}C-NMR. Some multisulfamation synthesis leading to compounds **25**–**27** has been carried out. Taste data have been obtained for almost all the sulfamates made and the significance of these in relation to structure–taste studies for sulfamate sweeteners is discussed. In particular, the possibility that the entity $\succ CHN(R)SO_3^-$ might function as a hydrogen source in the Shallenberger–Acree, multicomponent attachment and α-helical protein receptor mechanisms has been examined.

There are over 30 reports in the literature dealing with disulfamates (imidodisulfonates) ranging from the initial work in 1920 of Traube and co-workers[1,2] [who made some basic compounds such as $RN(SO_3K)_2$ (R = Me, Et, Pr)[1,2] and simple hydroxylamine disulfonates such as $MeON(SO_3K)_2$[2,3]] to a current report[4] where 2,2-dinitropropane-1,3-diol [$HOCH_2C(NO_2)_2CH_2OH$] reacts with alkylsulfamates ($RNHSO_3M$) to give, *inter alia*, the disulfamates $MO_3SN(R)CH_2C(NO_2)_2CH_2N(R)SO_3M$. Most reports deal with ionic disulfamates but there are also some reports[5–8] of various disulfamate esters and one[9] of a 'mixed' disulfamate *e.g.* a monobactam which contains a sulfamate ester group (see Fig. 1).

There are a number of reports dealing with tetra- and trisulfamates.[1,10–13] Traube and Wolff[1] report the preparation of the tetrasulfamate $(KO_3S)_2NCH_2CH_2N(SO_3K)_2$. Various hydrazine tri- and tetrasulfonates have been synthesized[11] and in two papers[12,13] Baumgarten describes the preparation of some tetra potassium and barium sulfonate salts of urea,[12] a series of aminoacid disulfonates and one trisulfonate, *N*,*N*′,*N*″-histidylhistidine trisulfonate.[13]

Few reports have focused on the syntheses of disulfamates *per se* apart from the work of Baumgarten,[13] who synthesized seven di-/tri- amino acid sulfonates using pyridine–sulfur trioxide, and Kanetani,[14,15] who used amine–SO_3 adducts and amines to synthesize over 20 disulfamates including **1**–**3** (Fig. 2). Kanetani carried out a detailed study of the effect of the reaction time, temperature *etc.* on the disulfamation reaction.

Disulfamates have found application in a number of areas. Thus, alkanediyl disulfamates [$H_2NSO_2O(CH_2)_nOSO_2NH_2$, $n = 6, 7, 8$] inhibit the growth of malignant cells in mammals,[16] the monobactam sulfamates shown in Fig. 1 are reported to have *in vitro* antibacterial activity,[9] various derivatives of 3,5-bis(sulfoamino)benzoic acid act as anti-inflammatory agents in the treatment of rheumatic fever and rheumatoid arthritis[17] and a number of disulfamates are intermediates in the dyeing industry.[18] Finally the disulfamate aniline-*N*,*N*-disulfonic acid, $PhN(SO_3H)_2$ has been implicated in the mechanisms of both the sulfonation of aniline in conc. sulfuric acid and the rearrangement of phenylsulfamic acid[19] and in the reduction of nitro compounds with sulfite (Piria reaction).[20]

Disulfamates could, since they contain a sulfamate moiety, be sweet compounds and this indicates another possible use.

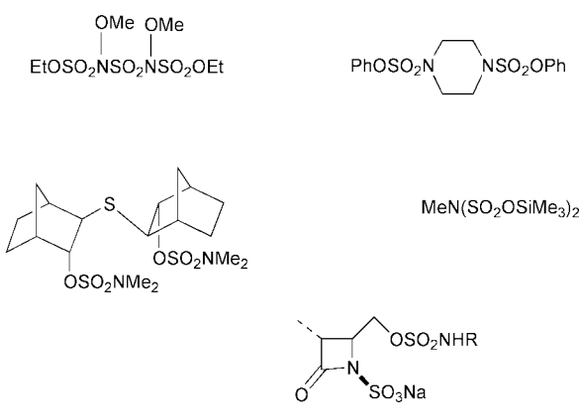

Fig. 1 Some previously reported disulfamate esters (refs. 5–9).

Unfortunately, there are no taste data at all available for all the disulfamates already prepared. In this paper we explore this potential by synthesizing twenty one new disulfamates and three previously made by Kanetani[14] (see Figs. 2 and 3) together with one trisulfamate, and two tetrasulfamates (see Fig. 3). The taste portfolios of 25 of the compounds together with those of two monosulfamates also made in this work for comparison have been assessed.

Results and discussion

The sweet taste elicited by a number of metallic sulfamates [$RN(H)SO_3^-M^+$] has been known for about 60 years.[21] Structure–taste studies have been carried out on sulfamates synthesized with alicyclic, open-chain, aromatic, heterocyclic and hetero open-chain and branched R groups, and a number of the compounds were found to be sweet.[22] The cation, M^+ does not appear to effect the degree of sweetness of a sulfamate.[22] An intact $-NHSO_3^-$ function was considered to be essential for sweetness since it provides a hydrogen and an electronegative center for the operation of the Shallenberger–Acree mechanism of sweetness.[23] However, some years ago a series of heterocyclic sulfides and sulfones containing an $-N(R)SO_3^-$ group were reported to be sweet,[24] and their sweetness has been explained on the basis of the presence of the system $\succ CHN(R)SO_3^-$, in which an α-hydrogen might function

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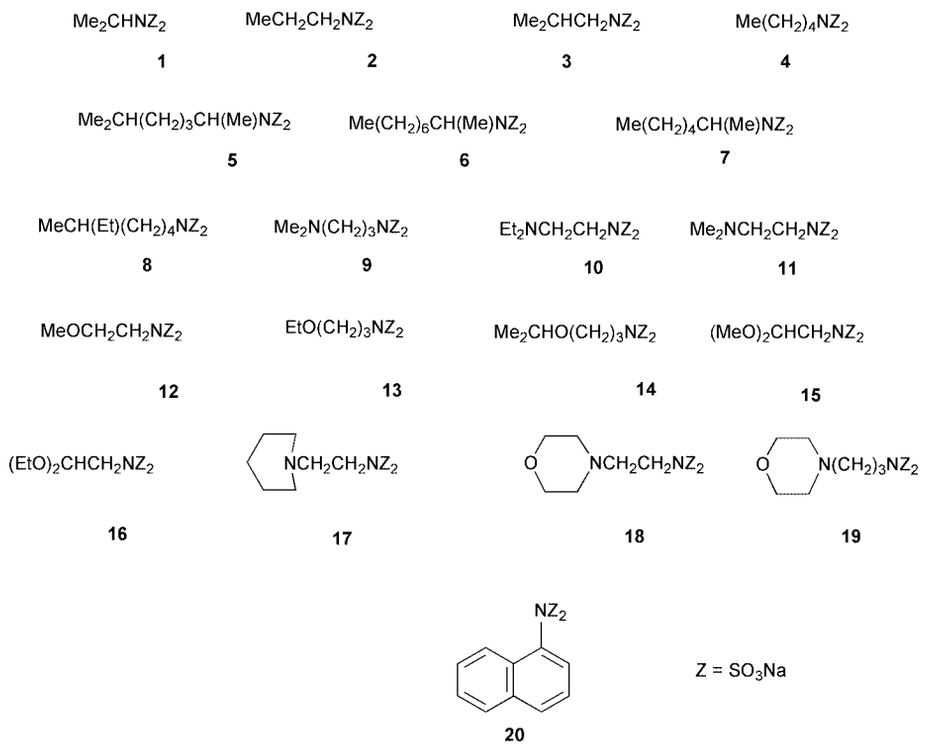

Fig. 2 Type A disulfamates synthesized; Z = SO_3Na.

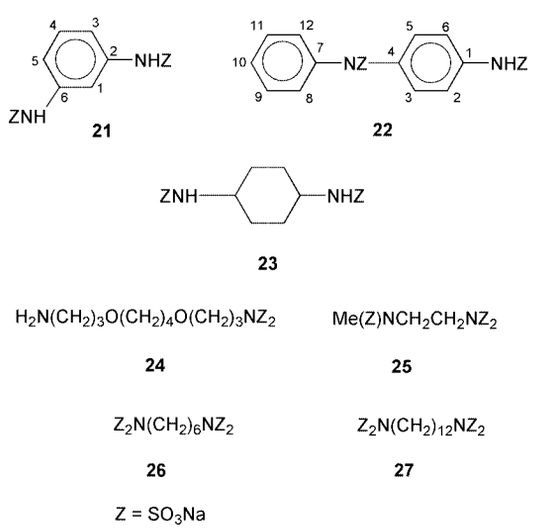

Fig. 3 Type B disulfamates (**21**–**24**) and multisulfamates (**25**–**27**) synthesized; Z = SO_3Na.

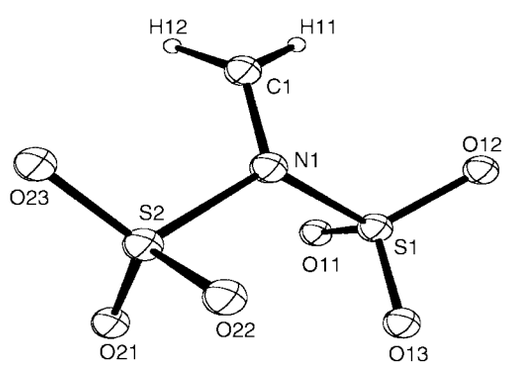

Fig. 4 Schematic representation of $K_2[CH_3N(SO_3)_2]$ from the Cambridge Structural Database.

as a hydrogen source in the Shallenberger–Acree mechanism.[25] The reported sweetness of these compounds has more recently been disputed.[26]

We were interested in testing the idea that an α-hydrogen, rather than a hydrogen on nitrogen, might be able to participate in the sweetness mechanism. The synthesis of disulfamates seems to offer an ideal opportunity to test this since (i) the amino hydrogen is replaced, (ii) a second sulfamate entity is being introduced into the molecule and, given the well-established "sweet-conferring ability" of the sulfamate group, it might enhance sweetness and (iii) we have been able to show that one of the α-hydrogens in $CH_3N(SO_3K)_2$ is within a distance of 3 Å of two of the oxygen atoms and it could therefore act as hydrogen source in the operation of the Shallenberger–Acree mechanism. This was established by downloading from the Cambridge Structural Database the structure for the disulfamate $K_2[CH_3N(SO_3)_2]$ (no. 39971) (see Fig. 4) determined by Kennard *et al.*[27] Using the *ORTEX* (*OSCAIL*) program[28] we obtained the relevant interatomic distances and found that H11–O12 was 2.665 and H11–O11 was 2.916 Å. All other H–O distances were >3 Å and were not considered. It should be noted that H13 was not located in the crystallographic work of Kennard.

Two types of disulfamate have been prepared—Type A [$RN(SO_3Na)_2$, *i.e.* both sulfonates on one nitrogen, *N*,*N*-disulfamates] and Type B [$NaO_3S(H)NR'N(H)SO_3Na$, *i.e.* the two sulfonates on different nitrogens, *N*,*N'*-disulfamates].

All the disulfamates prepared (Figs. 2 and 3) have one or two α-hydrogens at C1, except compound **20** (Fig. 2), which was included because it had not been prepared by Kanetani when he prepared a series of aryldisulfamates.[15] Of the 29 compounds prepared in this work only three compounds (**1**–**3**) have been previously prepared.[1,14] These were resynthesized as standards and also because their taste data was needed for comparison with their monosulfamates, two of which are sweet.

Taste portfolios for 25 compounds, together with percentage yields (for 27 compounds) are given in Table 1. From the taste data in Table 1 it is readily apparent that, though some of the compounds are multisapophoric, none of the 25 compounds tasted display sweetness, apart from a sweet aftertaste in compound **22**. The pHs of most of the 0.01 M solutions for tasting were determined and these are given in Table 1. As would be expected,[23] those solutions that have a predominant sour taste

Table 1 Percentage yield, pH, taste data[a] and percentage of tasters giving the taste quality of disulfamates **1**–**27**

Compound	Yield (%)	pH	Sour	Bitter	Salty	Tasteless	Aftertaste (% of tasters)	No. of tasters	Predominant taste (>50% tasters)
1	42	2.35	100	0	0	0	0	9	Sour
2	15	—	100	0	0	0	0	4	Sour
3	12	—	100	0	0	0	0	4	Sour
4	45	6.2	45	0	67	0	0	9	Salty
5	41	2.3	67	55	0	0	0	9	Sour/bitter[b]
6	20	2.2	89	45	0	0	0	9	Sour
7	21	2.2	100	0	0	0	0	9	Sour
8	60	10.4	0	0	100	0	0	9	Salty
9	16	11.1	0	100	0	0	0	9	Bitter
10	25	11.3	22	78	0	0	0	9	Bitter
11	20	10.8	0	100	0	0	Bitter (33)	9	Bitter
12	45	—	100	0	0	0	0	4	Sour
13	20	8.1	78	22	0	0	0	9	Sour
14	68	10.2	45	0	0	55	0	9	Tasteless
15	15	2.5	78	0	0	22	0	9	Sour
16	54	10.5	0	55	0	45	0	9	Bitter[c]
17	33	—	0	100	0	0	0	4	Bitter
18	36	10.3	0	100	0	0	0	9	Bitter
19	29	10.3	0	0	0	100	0	9	Tasteless
20	30	3.00	0	100	0	0	0	9	Bitter[d]
21	34	—	0	100	0	0	0	4	Bitter
22	46	—	25	100	0	0	Sweet (25)	4	Bitter
23	15	5.9	0	0	0	100	0	9	Tasteless[e]
24	10	—	—	—	—	—	—	—	—[f]
25	13	—	100	0	0	0	0	9	Sour
26	7	—	0	100	0	0	0	9	Bitter[g]
27	10	—	—	—	—	—	—	—	—[f]

[a] All compounds were tasted as 0.01 M aqueous solutions and allowance was made for water of hydration when making up solutions. pH measurements were made using these solutions and an Orion pH meter model 420A buffered at pH 4.0, 7.0 and 9.2. Taste panellists did not detect an initial sweet taste in any of the solutions. [b] An onion-like taste was also reported for this compound. [c] A musty taste was also reported. [d] A taste of mothballs was also reported. [e] A taste of nuts was also reported. [f] Not tasted. [g] Taste of burnt nuts was also reported.

display a definite acidic pH, while bitter solutions give a pH in the alkaline region. The solutions found to be tasteless, *viz*. those of compounds **14**, **19** and **23**, gave pHs of 10.2, 10.3 and 5.9, respectively. In the tasting of compound **5** sourness seemed to predominate over bitterness, thus the pH of 2.3 is reasonable. The one peculiarity arises with the naphthyldisulfamate (**20**) which, despite being exclusively bitter, displays a solution pH of 3.00. One notes, however, that a secondary taste of mothballs was found with this compound and this may be masking a sour taste. In Table 2 data (where available) for the corresponding monosulfamates are compared with those for the disulfamates. In the case of compounds **22** and **23** taste data for the corresponding monosulfamates (**28** and **29**) were obtained in this work (see footnotes, Table 2). From Table 2 it is seen that for compounds **2**, **3** and **23** there is a change in taste on going from the mono- to the disulfamates and for **22** there is no change. Comparison is difficult for other compounds, as when most of the monosulfamate taste data was collected between 11 and 37 years ago it was common to describe compounds that did not give a sweet taste as simply nonsweet,[25,28,34] non sucre,[29,33] or non dolce.[35] However, for compounds **1**, **4**, **9**, **12**, **13**, **15**, **17**–**19** and **22** sweetness is absent in the monosulfamates and disulfamation does not induce sweetness. Simple *meta*-substituted phenylsulfamates are often sweet and hence some sweetness might be expected in **21**, but not in **22**, as sweetness has not been found in *para*- or *ortho*-phenylsulfamates. Some sweet taste might also be expected in **23** and in its monosulfamate **29** since some monosubstituted cyclamate derivatives are sweet,[36] and in fact the monosulfamate **29** has a substantial sweet component.

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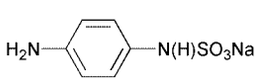

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The di-, tri- and tetrasulfamates **24**, **25** and **26** and **27**, respectively, are long-chain compounds and would be unlikely to be sweet since even a C5 chain hydrocarbon sulfamate is not sweet.[29]

Table 2 Comparison of predominant tastes of di- and multisulfamates with the corresponding monosulfamates

Compound	Taste		Ref.[c]
	Di-	Mono-	
1	Sour	Nonsweet	25
2	Sour	Sweet	25, 29, 30
3	Sour	Sweet	25, 29–31
4	Salty	Nonsweet	29
9	Bitter	Bitter	32
12	Sour	Nonsweet	33
13	Sour	Nonsweet	34
15	Sour	Nonsweet	33
17	Bitter	Nonsweet	35
18	Bitter	Nonsweet	35
19	Tasteless	Nonsweet	32
22 (di), **28** (mono)	Bitter	Bitter[a]	Present work
23 (di), **29** (mono)	Bitter	Bitter/Sweet[b]	Present work

[a] Panellists (4) found this compound to be 100% bitter and to have 25% sweet aftertaste only—therefore its predominant taste is bitter. [b] Panellists (4) found this compound to be 100% bitter and 100% sweet—therefore its predominant taste is recorded as bitter/sweet. [c] Reference to monosulfamate.

The absence of sweetness in the disulfamates does appear to underline the necessity for an imino hydrogen (–NH) in the sulfamate functionality that can actively participate in hydrogen bonding in the dual H-bond theory of Shallenberger and Acree. Substitution of an α-hydrogen, as we have tired to do with the disulfamates, does not work, even though we have shown above that the distance between the –CH– and the oxygen can be within 3 Å, the required AH–B distance of the Shallenberger–Acree theory. A C-bound hydrogen would, of

course, be much less efficient in H-bonding than an –NH or –OH and this is probably an important factor too. In terms of the multicomponent attachment theory of sweetness of Nofre and Tinti,[37] one might assign the alkyl or alkoxy or piperidine or morpholine rings (Fig. 2) as G sites, the α-CH as an AH site and $–SO_3–$ as a B site. On this basis the AH–G distance could be ~3.5 Å and the B–G distance ~5.5 Å, respectively, as required by the theory. One selects a suitable point in G to achieve this. It is difficult to assign other sites (the theory normally requires at least 8 sites) unless one takes one of the SO_3^- groups as a D site.

Using their α-helical protein receptor theory, Suami and Hough[38] have recently examined some cyclamate derivatives and explained very well the sweetness of some and the lack of sweetness in others. In the disulfamates it is relatively easy to pick a glycophoric triad of $AH_s/B_s/X_s$ (using their notation). Thus, AH_s would be the α-CH, B_s one of the $–SO_3^-$ groups and X_s appropriate hydrogens in the R portion. In so far as one can see, therefore, the three main sweetness theories would indicate that the disulfamates might elicit sweetness. The failure to realize this may well be due to the weak H-bonding ability of the $α\text{-}H_s$.[39]

In summary, 29 sulfamates, mainly disulfamates, have been prepared in this work and taste profiles have been obtained for 27 of these. No sweet taste was noted in the disulfamates **1**–**19**, all of which contain the entity $\succ CHN(SO_3Na)_2$ (in which the α-hydrogen attached to carbon might be a source of hydrogen, in place of a hydrogen on nitrogen, for the successful operation of the Shallenberger–Acree multicomponent attachment or α-helical receptor theories of sweetness). Further, the sweetness of several monosulfamates is shown to be destroyed in the corresponding disulfamates and a sweet taste could not be "induced" in a number of nonsweet monosulfamates on their conversion to the corresponding disulfamates. In conclusion, this work is in line with the main body of evidence from earlier studies[21,25,40,41] that indicates that an amino hydrogen is essential for sweetness and it appears to cast additional doubt on the 1974 report that some secondary sulfamates containing an $–N(R)SO_3$ group were sweet.[24]

Experimental

Materials and methods

General. All amines used were commercially available. Liquids were distilled using normal distillation apparatus at atmospheric pressure or using a Kugelrohr distillation unit if the amine had a high boiling point and/or where only small quantities were available. Solid amines were recrystallized using appropriate solvents and dried over P_2O_5 for a period of at least 24 h. 2-Picoline was dried over KOH pellets for 24 h, refluxed, distilled and again stored over KOH pellets. Chlorosulfonic acid was distilled at atmospheric pressure and stored in a dark environment in a suitably-sized bottle. 1-(2-Aminoethyl)piperidine was a gift from Allied Colloids Ltd.

Preparation of disulfamates. The synthesis of the disulfamates was based on Kanetani's procedures.[14,15] Typically, chlorosulfonic acid (0.1 mol, 6.7 ml) was added dropwise to stirred 2-picoline (1.0 mol, 81 ml) at 0 °C under anhydrous conditions. The solution was maintained at 0 °C using an ice-bath with the aid of salt–acetone. The 2-picoline–sulfur trioxide complex was allowed to warm to room temperature with stirring and the amine (0.05 mol) in the minimum amount of 2-picoline was added slowly. The reaction was stirred overnight, after which it was basified to pH ~ 10 using 3 M NaOH. The resulting solution was washed with diethyl ether several times to extract unreacted amine. The remaining aqueous solution was evaporated *in vacuo* to yield the crude disulfamate product. This crude product could then be purified by successive recrystallizations with aqueous ethanol with a pH > 7 (lower pH values tend to cleave off one of the sulfamate groups to give monosulfamate). Recrystallization was repeated until the product was free of sulfate and chloride and gave a clean sulfamate test.[25] The purified material was dried over P_2O_5 *in vacuo* for at least 24 h.

The 2 : 1 ratio of chlorosulfonic acid to amine was stepped up to 2.5 : 1 or 3 : 1 in order to improve yields for the synthesis of compounds **4**, **9**, **11** and **18**–**20**. If more than 10 ml of chlorosulfonic acid was used a MeOH–dry-ice bath was used to lower and maintain the temperature and to allow more rapid addition of the acid.

Preparation of other sulfamates. The monosulfamates **28** (9.2% yield) and **29** (11.3%) were synthesized using a 1 : 1 ratio of chlorosulfonic acid to amine. Interestingly the same ratio easily trisulfamated *N*′-methylethylenediamine to give **25**. Tetrasulfamates **26** and **27** were obtained by using a 4 : 1 ratio of chlorosulfonic acid to amine.

Elemental analyses. Most of the compounds prepared tended to recrystallize with some water of crystallization. This is commonly the case with sulfamates despite lengthy drying.[21,25,29] Microanalyses (C, H and N) for all 29 sulfamates was carried out and S analysis was also performed on compounds **2**, **3**, **12**, **17**, **21**, **22**, **24**, **28** and **29**. C, H, N and S were within the normal limits (±0.5%) except for the following: compound **5**, % N found was +0.59; compound **12**, % N found was −0.69 and % S found was −0.64; compound **21**, % C found was +0.77; compound **22**, % C found was +0.60 and % S found was −0.90; compound **24**, % S was −0.73; and compound **27**, % N found was −0.58. These six compounds gave good IR and NMR spectra, performed well in the sulfamate test and were free of sulfate and chloride ions, and so were used in tasting.

Spectroscopic analyses. IR spectra of all the sulfamates prepared were recorded and these showed the usual SO_3 and NS bands and those sulfamates containing –NH(s) gave absorbances in the range 3400–3190 cm^{-1}. Spectra were recorded on a Perkin-Elmer 983G spectrometer. Proton and carbon-13 NMR were recorded on JEOL 270 and 400 MHz spectrometers, in ppm relative to TMS. Compounds **1**–**20** and **25**–**27** did not give an amino H signal in their ^1H NMR spectra but compounds **21**–**24** did show such a signal. Compounds **21**–**24** may form disulfamates of Type B, having $–SO_3Na$ groups on different nitrogens as illustrated for compounds **21**–**23** (*N*,*N*′-disulfamate), or they could have the two $–SO_3Na$ groups on the same nitrogen (*N*,*N*-disulfamate) as shown for compound **24** in Fig. 3. For **21** δ_C $[(CD_3)_2SO]$ 105.56, 108.69, 128.11 and 143.64 and δ_C for the starting amine phenylene-1,3-diamine $[(CD_3)_2SO]$ 100.18, 103.28, 129.28 and 149.09. Both of these spectra exhibit four carbon signals characteristic of a symmetrically substituted 1,3-disubstituted phenyl ring. Had disulfamation taken place on the same nitrogen, a ^{13}C spectrum with six signals would be anticipated. The signals furthest downfield in both spectra are due to the two tertiary C–N carbon atoms and the upfield shift of 5.45 on sulfamation is due to shielding.

In Table 3 ^{13}C chemical shifts are given for *N*-phenylphenylene-1,4-diamine, the monosulfamate, **28**, and the disulfamate product, **22**. For the diamine spectrum the assignments have been made from calculation of theoretical ^{13}C chemical shifts for this compound using the empirical rules and tables of data of Williams and Fleming.[42] The assignments of the signals at 132.0, 144.0 and 146.9 to the three tertiary carbons were confirmed by the results of a C-*J* resolved spectrum. For the monosulfamate the assignments are also shown and again a C-*J* resolved spectrum confirmed that the three downfield peaks are due to the three tertiary carbon atoms. That the monosulfamate **22** is as shown above is evident by the fact that the C1 signal is, as expected, shifted upfield by 5 ppm, C7 is virtually unaffected and C4 shows an upfield shift of 3.4. Had sulfamation occurred

Table 3 ^{13}C Chemical shifts[a] for *N*-phenyl-1,4-phenylenediamine, the monosulfamate **28** and the disulfamate **22** relative to Me_4Si

$(CD_3)_2SO$	C8/C12	C3/C5	C2/C6	C10	C9/C11	C4	C1	C7
4-Ph(H)$NC_6H_4NH_2$	114.0	115.1	117.3	122.7	129.2	132.0	144.0	146.9
28	115.1	118.4	118.7	121.1	130.0	135.4	139.0	146.7
22	116.8	117.3	120.3	123.1	123.6	129.2	142.7	143.1

[a] 270 MHz.

at the NH between the two rings, considerable shifts in the C7 and C4 signals would have been expected. For **21** a C-*J* resolved spectrum again assigned the three downfield signals as shown. The disulfamate shows a strong upfield shift (6.2 ppm) at C4, whereas at C1 it is only 3.7 and this indicates that it is the *N*,*N*′- and not the *N*,*N*-disulfamate that has been formed.

For **23** δ_C [D_2O, 100 °C] 31.72 and 57.4; for 1,4-diaminocyclohexane δ_C [$(CD_3)_2SO$] 35.26 and 50.0 and for the monosulfamate, **29**, δ_C [$(CD_3)_2SO$] 32.6, 35.1, 49.9 and 52.1. The spectrum of compound **23** had to be run in D_2O to increase its solubility because it was insoluble in $(CD_3)_2SO$. Clearly again, as in the case of **21**, **23** is an *N*,*N*′-disulfamate, and not an *N*,*N*-disulfamate, which would give four signals in its ^{13}C NMR. Compound **24** gave 10 signals in the ^{13}C NMR so it clearly has to be the *N*,*N*-disulfamate as shown in Fig. 3.

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