Basicity of Nitrogen–Sulphur(VI) Compounds. Part 5.[1] Ionization of Trisubstituted Sulphamides

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The ionization equilibria in base of 27 trisubstituted sulphamides, mainly represented by the following series: $X\text{-}C_6H_4NHSO_2NR^2R^1$, where NR^2R^1 = piperidyl, morpholinyl, and NPr^n_2, and $RHNSO_2NR^2R^1$, where R, R^1, and R^2 are cyclo-C_6H_{11}, Ac, and $X\text{-}C_6H_4$ and $X\text{-}C_6H_4$, Ac, and $X\text{-}C_6H_4$, have been studied in 60% v/v ethanol–water using the potentiometric method. In a few cases pK_a values have been determined by the u.v. method. The effect of substituents has been correlated in Hammett plots and values are generally ca. 2.6 (as for an aryl linked nitrogen in sulphonanilide ionizations). The acid-strengthening effect of the acetyl group and the acid-weakening effect of the methyl group are seen in some series.

There are only two reports on measurements of pK_a values for trisubstituted sulphamides.[1,2] In the preceding paper in this series we determined pK_a values for five N'-aryl-NN-dimethyl-sulphamides, $X\text{-}C_6H_4NHSO_2NMe_2$ and obtained a Hammett ρ value of 2.78.[1] Unterhalt and Seebach[2] found that for the corresponding aliphatic series, $RNHSO_2NMe_2$, the pK_a values are about 5 pK_a units less acidic. In view of the paucity of data in this area and because of the structural similarity to sulphonanilides (which also have one ionizable proton) we were prompted to synthesise some further series (including two hetero-series) of trisubstituted sulphamides and determine their pK_a values. In this paper we have employed principally potentiometric and also u.v. methods to examine the equilibria in Schemes 1 and 2 and the results are given in Table 2.
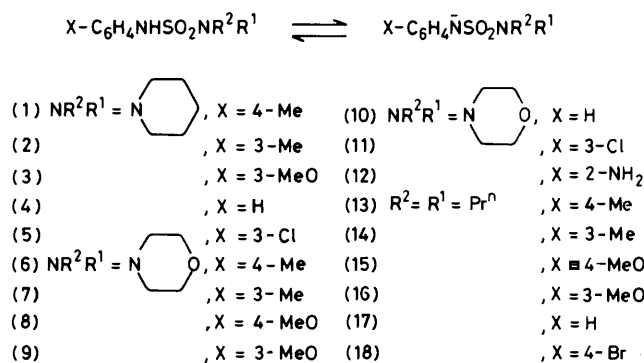
Experimental

U.v. measurements were made on a Perkin-Elmer 124 spectrophotometer at 25 °C. Potentiometric measurements were made with a Pye Unicam 290 MK2 pH meter standardized with buffers of pH 7.0, 10.0, and 12.0. ^{13}C N.m.r. spectra were recorded in a JEOL JNM FX 60 spectrometer and ^1H n.m.r. spectra on a JEOL MH-100 100 MHz spectrometer.
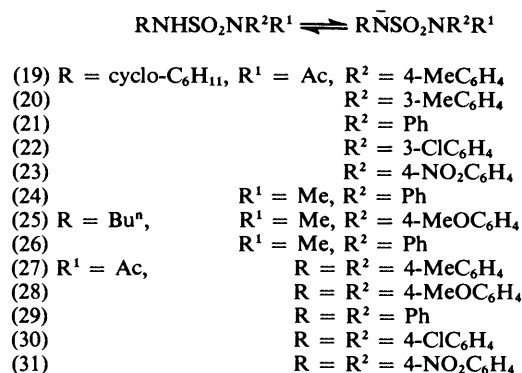
Materials.—Liquid amines were distilled prior to use and solid amines were recrystallized from appropriate solvents. All other solvents and reagents were commercially available and were used as obtained. The potassium hydroxide solutions for the potentiometric and u.v. methods were made up by suitable dilutions with 60% v/v ethanol–water and absolute ethanol of 1M- and 0.1M-KOH Volucon standards. The base solutions were checked by titration.

N-Morpholinyl-[b.p. 65 °C at 1 mmHg (lit.,[3] 76 °C at 3 mmHg)] and N-piperidyl-[b.p. 74 °C at 1 mmHg (lit.,[4] 125 °C at 5 mmHg)] sulphamoyl chlorides were prepared in about 70% yield by the action of distilled sulphuryl chloride on the amines.[3] N-Cyclohexylsulphamoyl chloride was prepared by the reaction of cyclohexylsulphamic acid with phosphorus pentachloride,[5] yield 75%, b.p. 136—140 °C at 0.2 mmHg (lit.,[6] 120 °C at 0.1 mmHg). N-n-Butyl-[b.p. 112 °C at 1 mmHg (lit.,[6] 90 °C at 0.8 mmHg)] and NN-di-n-propyl-sulphamoyl chlorides were prepared in yields of 60 and 80%, respectively, by reaction of the amines with chlorosulphonic acid.[5] The di-n-propylsulphamoyl chloride (lit.,[7] 77 °C at 1.5 mmHg) was not distilled because of its tendency to undergo extensive decomposition; ^1H n.m.r. (CDCl₃) δ 1.0 (t, 3 H), 1.72 (m, 2 H), 3.3 (t, 2 H) (Found: C, 33.0; H, 6.40; N, 6.33. $C_6H_{14}ClNO_2S$ requires C, 36.1; H, 7.02; N, 7.02%).

Most sulphamoyl chlorides have a tendency to decompose on distillation[5,8] possibly because of the presence of some

$$X\text{-}C_6H_4NHSO_2NR^2R^1 \rightleftharpoons X\text{-}C_6H_4\bar{N}SO_2NR^2R^1$$

(1) $NR^2R^1 = $ N(piperidyl), X = 4-Me
(2) , X = 3-Me
(3) , X = 3-MeO
(4) , X = H
(5) , X = 3-Cl
(6) $NR^2R^1 = $ N(morpholino), X = 4-Me
(7) , X = 3-Me
(8) , X = 4-MeO
(9) , X = 3-MeO
(10) $NR^2R^1 = $ N(morpholino), X = H
(11) , X = 3-Cl
(12) , X = 2-NH₂
(13) $R^2 = R^1 = Pr^n$, X = 4-Me
(14) , X = 3-Me
(15) , X = 4-MeO
(16) , X = 3-MeO
(17) , X = H
(18) , X = 4-Br

Scheme 1.

$$RNHSO_2NR^2R^1 \rightleftharpoons R\bar{N}SO_2NR^2R^1$$

(19) R = cyclo-C_6H_{11}, R^1 = Ac, R^2 = 4-MeC_6H_4
(20) R^2 = 3-MeC_6H_4
(21) R^2 = Ph
(22) R^2 = 3-ClC_6H_4
(23) R^2 = 4-$NO_2C_6H_4$
(24) R^1 = Me, R^2 = Ph
(25) R = Bu^n, R^1 = Me, R^2 = 4-$MeOC_6H_4$
(26) R^1 = Me, R^2 = Ph
(27) R^1 = Ac, R = R^2 = 4-MeC_6H_4
(28) R = R^2 = 4-$MeOC_6H_4$
(29) R = R^2 = Ph
(30) R = R^2 = 4-ClC_6H_4
(31) R = R^2 = 4-$NO_2C_6H_4$

Scheme 2.

unreacted phosphorus pentachloride, chlorosulphonic acid, or sulphuryl chloride. Therefore, in subsequent reactions to form sulphamides the undistilled chlorides were used.

Sulphamides (1)—(12) and (19)—(23) (non-acetylated) were prepared by one of the procedures (depending on whether the amine was a solid or a liquid) of Wheeler and Degering.[9] Sulphamides (13)—(18) were prepared by reaction of the di-n-propylsulphamoyl chloride with the amine in dry ether and refluxed for 12 h. If oils were obtained they were eventually solidified in ice. Sulphamides (1)—(18) and (19)—(23) (non-acetylated) were recrystallized from aqueous ethanol. The preparation of the series of NN'-diarylsulphamides (27)—(31) (non-acetylated) has been reported previously.[10]

Preparation of Methylated Sulphamides.—Compounds (25) and (26) were prepared by refluxing overnight *N*-n-butyl-sulphamoyl chloride (2.4 g, 0.014 mol) with the appropriate amine (*ca.* 0.029 mol) in dry toluene (*ca.* 15 ml) and dry ether (*ca.* 15 ml), respectively. The work-up of (25) was as in ref. 9. The compound separated out as an oil which was heavily contaminated with *N*-methyl-*p*-anisidine. The oil was taken up in ether and the solution was extracted with 10% HCl to remove the amine. The ether solution was dried and evaporated under reduced pressure to give an oil which solidified in ice to give a light brown material (0.21 g, 5.3%), m.p. 23—26 °C. The work-up of (26) was similar to that in ref. 9. Recrystalliz-ation twice from light petroleum (b.p. 60—80 °C) gave a white crystalline material (0.4 g, 12%), m.p. 31—33 °C. Compound (24) was synthesised and worked up as in ref. 9.

Preparation of Acetylated Sulphamides.—The following procedure was typical: *NN'*-diphenylsulphamide (0.5 g, 2.0 mmol) and acetic anhydride (1 ml) were stirred at room temperature.[11] On addition of a few drops of concentrated sulphuric acid an exothermic reaction occurred. Stirring was continued for a few minutes and on cooling crude mono-acetylated product (29) crystallized out. The crystals were stirred with benzene, suction filtered, and washed with water. Recrystallization from benzene–light petroleum (b.p. 40—60 °C) gave pure material (0.5 g, 86%), m.p. 156—157 °C (lit.,[11] 164 °C). Compounds (27), (28), (30), and (31) were similarly prepared and isolated. Compounds (19)—(23) did not crystal-lize out on cooling and water (*ca.* 10 ml) was added to the cooled solution whereupon a solid or a gum formed. A solid product was filtered and recrystallized as above. A gum was extracted into ether and the ether solution dried and evaporated under reduced pressure. The crude product was recrystallized from benzene–light petroleum except in the case of (23), which was recrystallized from ethanol.

Characterization of Trisubstituted Sulphamides.—All the trisubstituted sulphamides synthesised are new compounds with the exception of (1), (2), (4), (12), and (29). All the compounds gave satisfactory C, H, and N analyses (± 0.5) except for the following: (4) (Found: C, 53.67; H, 6.39; N, 11.7. $C_{11}H_{16}N_2O_2S$ requires C, 55.0; H, 6.66; N, 11.66%), (6) (Found: C, 51.0; H, 6.25; N, 10.9. $C_{11}H_{16}N_2O_3S$ requires C, 51.6; H, 6.25; N, 10.9%), (10) (Found: C, 48.0; H, 5.70;

N, 11.6. $C_{10}H_{14}N_2O_2S$ requires C, 49.6; H, 5.78; N, 11.6%), (13) (Found: C, 57.5; H, 8.33; N, 9.88. $C_{13}H_{22}N_2O_2S$ requires C, 57.8; H, 8.15; N, 10.4%), (25) (Found: C, 53.6; H, 7.67; N, 10.1. $C_{12}H_{19}N_2O_3S$ requires C, 52.9; H, 7.35; N, 10.3%).

The i.r. spectra of the trisubstituted sulphamides displayed characteristic absorptions[3] (in cm⁻¹): 3 225—3 280 (s, m) (v_{NH}), 1 320—1 340 (m) (v_{SO_2} asym), 1 140—1 150 (s) (v_{SO_2} symm), 1 030—1 080 (m, w) (v_{CN}), and 795—820 (m, w) (v_{SN}). ¹H N.m.r. spectra were measured for some compounds and were readily assignable on the basis of the structures in Schemes 1 and 2.

Potentiometric measurements. pK_a Determinations were carried out as previously described.[1] The initial substrate concentration was 0.0033M in all cases and the strength of the base used was 0.044M-KOH. Allowance was made for dilution caused by the additions of base and where the pK_a values exceeded 10 allowance was made for a_{OH^-} in the pK_a calculations.[12] In calculating a_{OH^-} a value for pK_s of 15.1 was used for the 60% v/v ethanol–water system where a_{OH^-} = antilog (pH − pK_s).[13] pK_a Values were calculated within a range of 25—80% ionization.[14] Observed pH readings were reduced by 0.22 units to allow for the fact that the glass–calomel electrode system used was buffered in aqueous solution.[15] As a test of our method we determined the pK_a of sulphanilamide as 12.05 ± 0.09 (*n* = 5) compared with the literature value of 12.04.[14]

U.v. measurements. pK_a Values were determined by a modification of the standard spectrophotometric technique described by Albert and Serjeant.[16] The initial substrate concentration in the u.v. cell was 1 × 10⁻⁴M in 60% v/v EtOH–H₂O. pH Modification was effected by injections of suitable portions of a 0.1M-KOH 60% v/v EtOH–H₂O solution. Additions were made to both sample and reference cells. After thorough mixing, solutions were scanned from 370 to 220 nm. In the calculation of pK_a values allowance was made for the small decrease in substrate concentration and consequently in absorbance caused by addition of the base. pH Readings were reduced by 0.22 and pK_a values were calculated only for the 30—80% ionization range. When deviation from isosbestic points occurred due to medium effects at higher pH values a graphical method[17] for calculat-ing d_i (absorbance of fully ionized species) was used. In this method a plot of *d* (absorbances of solutions giving isosbestic points) *versus* (*d* − d_M) . a_{H^+}, where d_M is the absorbance of the

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Table 1. Partial ¹³C chemical shifts of non-acetylated and *N*-arylacetylated disulphamides and model compounds

X	R	1	2	3	4	5	6	C=O
4-Me	H	136.70	118.12	129.16	130.85			
4-Me	MeCO	138.71	130.14	129.23	135.85			169.98
3-Cl	H	140.86	116.04	130.46	121.63	133.32	116.82	
3-Cl	MeCO	139.43	128.38	130.98	129.16	133.32	129.42	169.45

		1	2	3	4			C=O
	H[b]	146.60	115.00	128.70	117.90			
	MeCO[b]	138.20	120.40	128.70	124.10			169.50

[a] Shifts relative to Me₄Si. [b] Taken from E. Breitmaier, G. Haas, and W. Voelter, 'Atlas of Carbon-13 N.M.R. Data,' Heyden, London, 1979, vols. 1 and 2.

Table 2. Yield (%), m.p., and potentiometric and u.v. determined pK_a values at 25 °C in 60% v/v EtOH–H$_2$O for trisubstituted sulphamides

Compound	Yield (%)	M.p. (°C)	pK_a	Spread (±)[a]	n[b]
(1)	63	97—99 [c]	11.50	0.06	6
(2)	36	121—123 [d]	11.44	0.04	7
(3)	32	78—80	10.98	0.06	6
(4)	48	85—87 [e]	11.27	0.06	7
(5)	71	123—125	10.15	0.06	6
(6)	72	87—89	10.31	0.06	7
(7)	30	113—115	10.18	0.08	8
(8)	68	112—113	10.39	0.02	7
(9)	34	64—66	9.85	0.06	7
			(9.86)[f]	(0.03)	(7)
(10)	51	103—105	10.17	0.08	7
(11)	45	105—107	9.06	0.07	8
			(9.08)[f]	(0.07)	(8)
(12)	55	152—154 [g]	9.64	0.08	8
(13)	42	79—81	11.48	0.02	7
			[11.60][h]	[0.06]	[8]
(14)	37	31—33	11.33	0.07	7
			[11.49][h]	[0.05]	[8]
(15)	45	44—45	11.43	0.04	7
			[12.07][h]	[0.03]	[6]
(16)	40	37—39	10.99	0.09	6
(17)	42	85—87	11.00	0.03	6
(18)	43	66—69	10.25	0.04	6
(19)	37	82—84	11.28	0.06	7
(20)	62	92—94	11.12	0.06	7
(21)	86	121—123	10.89	0.03	5
(22)	96	110—111	i		
(23)	94	131—133	i		
(24)	70	78—80	13.54	0.09	5
(25)	5.3	23—26	13.31	0.08	8
(26)	12	31—33	13.28	0.06	6
(27)	98	149—150	8.86	0.03	9
(28)	100	177—179	j		
(29)	86	156—157 [k]	8.42	0.07	7
(30)	97	157—158	7.17	0.07	9
(31)	94	175—177	i		

[a] The spread or scatter was calculated as described in ref. 12. ch. I. [b] n = No. of pK_a values averaged to obtain the value given; generally the first and last values were omitted. [c] Lit.,[3] 97—98 °C. [d] Lit.,[3] 123—124 °C. [e] Lit.,[3] 83 °C. [f] The figures in parentheses are for duplicate runs. [g] Lit., 152—154 °C (W. J. Spillane and T. J. Hannigan, *J. Chem. Res. (S)*, 1982, 84). [h] The figures in brackets are for the u.v. method. The analytical wavelength at which absorbances were read was 250 nm for (13), (14), and (15). A second determination on compound (13) using λ = 247 nm gave a pK_a of 11.62, spread 0.04, and n = 7. [i] These compounds hydrolysed too rapidly for measurements to be made. [j] This compound was too insoluble in 60% v/v EtOH–H$_2$O to allow measurements to be made. [k] Lit.,[11] 164 °C.

molecular species, gave a line whose intercept gave d_1. pK_a Values were then calculated in the usual manner (see Results and Discussion section).

Results and Discussion

Site of Acetylation.—Mono-acetylation of (19)—(23) (non-acetylated) was achieved easily by the method of Wohl and Koch.[11] However, the possibility that acetylation occurred at the alicyclic-linked NH rather than the aryl-linked NH had to be considered. Because of the greater acidity of the aryl-NH one would expect acetylation to occur at this site. This was confirmed by [13]C n.m.r. using (19), which has an electron-donating group in the ring, and (22), which has an electron-
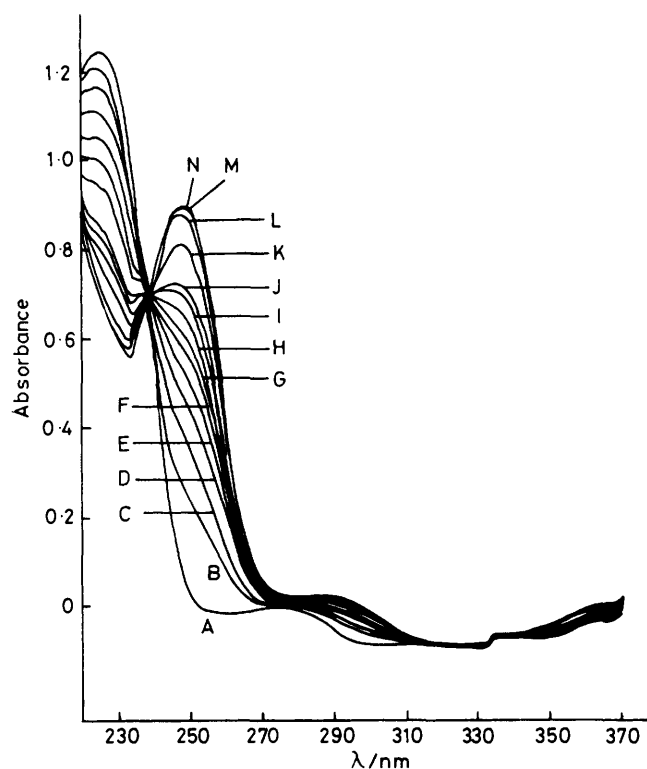

Figure 1. Absorption spectra of compound (13) in 60% v/v EtOH–H$_2$O at various pH values: A, 7.16; B, 10.84; C, 11.19; D, 11.39; E, 11.54; F, 11.64; G, 11.73; H, 11.87; I, 11.97; J, 12.05; K, 12.12; L, 12.33; M, 12.64; N, 12.82

withdrawing group in the ring. The basis of the confirmation was that the largest differences in chemical shifts between acetylated and non-acetylated compounds and between acetanilide and aniline (models for the acetylated and non-acetylated compounds, respectively) occurred at the 1,2, and 4 positions in the aromatic ring (Table 1).

pK_a *Values.*—For reasons of solubility the pK_a values of all the sulphamides in Table 2 were determined in 60% v/v EtOH–H$_2$O. Various aspects of pK_a determination in mixed aqueous solvent systems have been reviewed by Cookson.[17] In the potentiometric method pK_a values above ten were calculated using equation (1) and for pK_a values less than ten a correction for hydroxyl ion activity was not applied and equation (2) was used.

$$pK_a = pH + \log_{10} \frac{[HA] + a_{OH^-}}{[A^-] - a_{OH^-}} \quad (1)$$

$$pK_a = pH + \log_{10} \frac{[HA]}{[A^-]} \quad (2)$$

In the u.v. method equation (3) was used to calculate pK_a values; d_1 is the absorbance of the fully ionized species, d_M the absorbance of the un-ionized species, and d the absorbances of solutions at various pH values. Figure 1 shows a set of typical u.v. spectra for compound (13). For compound (14) good isosbestic points were not obtained at the higher pH values and the method described in the Experimental section for calculating d_1 was applied prior to the use of equation (3).

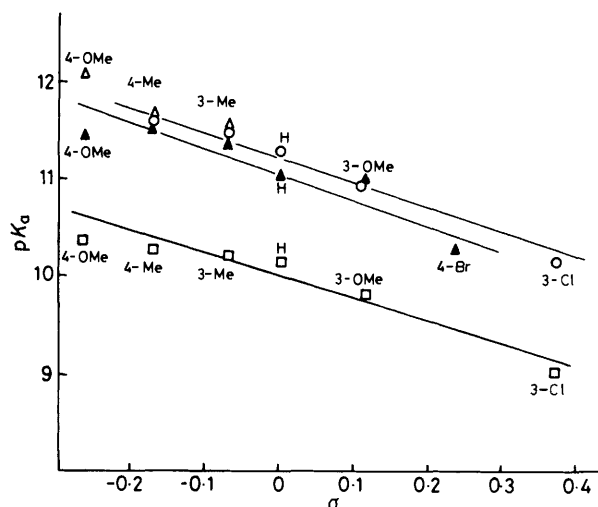$$pK_a = pH + \log_{10} \frac{d_1 - d}{d - d_M} \quad (3)$$

Figure 2. Hammett plots for trisubstituted sulphamide series: compounds (1)—(5) (O); compounds (6)—(11) (□); compounds (13), (15)—(18) (▲); compounds (13)—(15) by u.v. method (△)

The agreement between the potentiometrically determined and the u.v. determined pK_a values is good for compounds (13) and (14) but shows some divergence for (15) (Table 2). The potentiometrically determined value for (15) is probably somewhat in error because at the high pH levels involved in measuring the pK_a of this compound, equation (1) becomes less valid than when it is used to determine the pK_a values of slightly more acidic compounds.[18] It is of interest to note that the mean pK_a reckoned from the u.v. and potentiometric values is about 11.75, which would almost fit the Hammett plot for the ionization (see Figure 2).

The pK_a values for the piperidyl series of sulphamides, (1)—(5), are in much the same range as those for the di-n-propyl series, (13)—(18), but those for the morpholinyl series are about 1 pK_a unit more acidic. This can be attributed to the presence of the electron-withdrawing oxygen atom in the 4-position in the morpholinyl series.

In the case of the two mono-acetylated series, namely (19)—(23) and (27)—(31), the pK_a values were measurable for only three compounds in each series because of rapid hydrolysis resulting in release of acetic acid or insolubility of the sulphamides. The acid-strengthening effect of the acetyl group can be seen in both series. Compounds (19)—(21) are about 0.4 of a pK_a unit more acidic than their non-acetylated analogues [19] and in the di-aryl series, (27), (29), and (30) are 1.70 ± 0.07 pK_a units more acidic than their non-actylated analogues.[1] The acid-weakening effect of methylation on the aromatic NH is seen to be about 2 pK_a units when the pK_a values of (24) and (26) are compared with their non-methylated analogues.[19]

Hammett Correlations.—Hammett ρ values have been calculated for several series. The series, ρ value, correlation coefficient (r), and standard error (s), were as follows: (1)—(5), 2.60, 0.983, 0.2818; (6)—(11), 2.1, 0.961, 0.302; (13), (14), and (16)—(18), 2.84, 0.94, 0.60. The three Hammett plots are shown in Figure 2 together with the three u.v.-determined values for compounds (13), (14), and (15).

In previous work, in 60% v/v EtOH-H₂O we have obtained Hammett ρ values of 2.78 and 2.34 for the ionization of a series of diaryl- and dimethyl/aryl-sulphamides, respectively.[1] The values of 2.84 for the di-n-propyl series and of 2.60 for the piperidyl series in the present work are reasonable and in good agreement with the value of 2.34 for the dimethyl series.[1] These three series are examples of trisubstituted sulphamides.

A Taft ρ* could not be obtained for the series RNHSO₂NMe₂² using the basic equation log $K/K_0 = \rho^*\sigma^*$ as the points showed wide scatter. The somewhat lower ρ value (2.1) for the morpholinyl series can be attributed to more delocalization of charge by the morpholinyl ring than by the piperidyl system.

In the few instances where we had $-M$ substituents, *e.g.* compounds (23) and (31), we were unfortunately unable to make pK_a determinations due to insolubility of these compounds (see Table 2 footnotes). Inclusion of such compounds would have provided a means, particularly in our Hammett series, of probing the extent of conjugative interactions between such substituents and the anions. However, we feel that, in the case of $-M$ substituents, conjugative interaction in these systems is very considerable since in a related sulphamide series we have obtained superior Hammett plots by employing σ^- rather than σ for 4-nitro substituents.[1]

The Hammett ρ values obtained for sulphonanilide, YC₆H₄SO₂NHC₆H₄X, ionizations, where Y is constant within a series and X is varied, are about 2.6 in 60% w/w EtOH-H₂O (approximately 55.9% v/v).[20] These values are in good agreement with the Hammett ρ values that we have obtained for the sulphamide series. When X is fixed within a sulphonanilide series and Y is varied the ρ values, in 50% w/w EtOH-H₂O, fall to about 1.6.[14,21] It appears that sulphamide ionizations are similarly affected. Thus, a tentative ρ value of 1.68 can be calculated from correlation of the pK_a values of compounds (19)—(21).

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