The Acid Dissociation of Arenesulphonamides: σ_{Het} Constants for Thia- and Oxa-substituents in Five-membered *S*-Linked Heterocycles and Effects of Substituents in the *N*-Linked Aromatic Ring

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The acidity constants of 50 heteroarenesulphonamides in 50% w/w water–ethanol at 20 °C are reported. Values of σ constants for the heteroatoms at the α- and β-positions of the *S*-linked five-membered ring are derived and compared with those in the literature. Effects of substituents in the *N*-linked ring of heteroarenesulphonanilides are also discussed.

THE acid dissociation of benzenesulphonamides has been investigated extensively [1-4] and the effect of structure on the strengths of these weak organic acids has been evaluated in terms of the Hammett equation.

Following studies on the spectroscopic behaviour,[5] the conformation,[6] and the formation of heteroarene sulphonamides,[7-9] we now report their pK_a values in 50% w/w

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[1] A. V. Willi, *Helv. Chim. Acta*, 1956, **39**, 46.

[2] (*a*) G. Dauphin and A. Kergomard, *Bull. Soc. chim. France*, 1961, **3**, 486; G. Dauphin, A. Kergomard, and H. Veschambre, *ibid.*, 1957, **9**, (*b*) p. 3395; (*c*) p. 3404.

[3] M. Yoshioka, K. Hamamoto, and T. Kubota, *Bull. Chem. Soc. Japan*, 1962, **35**, 1724.

[4] T. A. Mastrukova, Yu. N. Sheinker, I. K. Kuznetsova, E. M. Peresleni, T. B. Sakharova, and M. I. Kabachnik, *Tetrahedron*, 1963, **19**, 357.

[5] A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Spectrochim. Acta*, 1974, **30A**, 611.

[6] G. C. Pappalardo, S. Gruttadauria, E. Maccarone, and G. Musumarra, *Canad. J. Chem.*, 1976, **54**, 1672.

[7] A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, (*a*) *J. Org. Chem.*, 1973, **38**, 2457; (*b*) *Ann. Chim.* (*Italy*), 1973, **63**, 281; *J. Org. Chem.*, 1974, **39**, (*c*) p. 1689; (*d*) p. 3595.

[8] E. Maccarone, G. Musumarra, and G. A. Tomaselli, (*a*) *Ann. Chim.* (*Italy*), 1973, **63**, 861; (*b*) *J. Org. Chem.*, 1974, **39**, 3286.

[9] A. Arcoria, V. Librando, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Tetrahedron*, in the press.

water–ethanol, which yield information on the effects of heteroatoms and other substituents on their acidity. By regarding the heteroatoms as substituents,[10] σ_{Het} constants for thia- and oxa-systems [11] can be obtained from equation (i), where ρ and pK_0 are, respectively,

$$\sigma_{\mathrm{Hgt}} = pK_0 - pK_a/\rho \qquad \text{(i)}$$

the slope and the intercept of the Hammett plot including data for the corresponding substituted benzene derivatives.

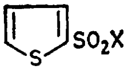
The disadvantages of this simple method of defining new σ values, especially for reaction series with small ρ values, have been pointed out recently,[12] and statistical analysis has been applied to the treatment of Hammett and related equations.[12,13] Statistical analysis of the pK_a values of *meta*- and *para*-benzenesulphonanilides substituted in either benzene nucleus in 50% aqueous ethanol,[13a] however, has confirmed that 'this set represents the range of validity of the classical Hammett equation' leading to the conclusion that the additivity relationship is, in this case, 'very good' and 'is not significantly improved' by using a general non-additive equation.

RESULTS AND DISCUSSION

The pK_a values for the examined heteroarenesulphonamides in 50% w/w water–ethanol at 20 °C are reported in Table 1, together with σ_{Het} values derived from equation (i) by using the appropriate ρ and pK_0 values.[2b,4]

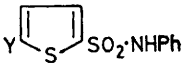
TABLE 1

pK_a Values of heteroarenesulphonamides in 50% (w/w) water–ethanol at 20 °C

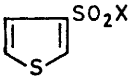


	pK_a †	n ‡	Ref.	$\sigma_{\alpha\text{-S}}$
(1) X = NH_2	10.76	2	*a*	0.40
(2) NHMe	12.20	2	*b*	0.30
(3) NHPh	9.41	4	*c*	0.35
(4) $NH{\cdot}C_6H_4Me$-2′	9.66	2	*d*	
(5) $NH{\cdot}C_6H_4Me$-3′	9.56	2	*c*	0.33
(6) $NH{\cdot}C_6H_4Me$-4′	9.72	2	*c*	0.34
(7) $NH{\cdot}C_6H_4{\cdot}OMe$-2′	9.93	2	*d*	
(8) $NH{\cdot}C_6H_4{\cdot}OMe$-3′	9.21	3	*e*	0.35
(9) $NH{\cdot}C_6H_4{\cdot}OMe$-4′	9.77	2	*c*	0.35
(10) $NH{\cdot}C_6H_4Cl$-2′	8.41	2	*d*	
(11) $NH{\cdot}C_6H_4Cl$-3′	8.51	2	*e*	0.32
(12) $NH{\cdot}C_6H_4Cl$-4′	8.74	2	*e*	0.34
(13) $NH{\cdot}C_6H_4{\cdot}NO_2$-2′	7.40	2	*d*	
(14) $NH{\cdot}C_6H_4{\cdot}NO_2$-3′	7.57	3	*d*	0.30
(15) $NH{\cdot}C_6H_4{\cdot}NO_2$-4′	6.76	2	*f*	0.34
(16) $NH{\cdot}C_6H_4Et$-2′	9.71	2	*d*	
(17) $NH{\cdot}C_6H_4Et$-4′	9.63	3	*d*	
(18) $NH{\cdot}C_6H_4Pr^i$-2′	9.81	2	*d*	
(19) $NH{\cdot}C_6H_4Pr^i$-4′	9.64	2	*d*	
(20) $NH{\cdot}C_6H_3Me_2$-2′,6′	10.31	2	*d*	
(21) $NH{\cdot}C_6H_3Et_2$-2′,6′	10.41	3	*d*	
(22) $NH{\cdot}C_6H_3Pr^i{}_2$-2′,6′	10.52	2	*d*	
(23) NH-(α-naphthyl)	8.95	2	*d*	
(24) NC-(β-naphthyl)	9.16	2	*d*	
(25) NH-(α-pyridyl)	8.71	2	*d*	0.33
(26) NH-(β-pyridyl)	7.71	2	*d*	
(27) NH-(γ-pyridyl)	8.54	2	*d*	
(28) $NH{\cdot}CH_2Ph$	11.93	2	*g*	0.35

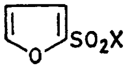
TABLE 1 (*Continued*)



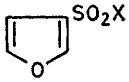
	pK_a †	n ‡	Ref.	pK_a (calc.)
(29) Y = Me	9.65	2	*h*	9.68
(30) Cl	8.84	2	*i*	9.03
(31) Br	8.84	2	*j*	9.03
(32) I	8.97	2	*j*	8.95
(33) NO_2	7.68	2	*h*	



				$\sigma_{\beta\text{-S}}$
(34) X = NH_2	11.20	2	*k*	0.09
(35) NMe	12.66	2	*g*	0.00
(36) NPh	9.83	3	*l*	0.09
(37) NHC_6H_4Me-3′	9.94	3	*l*	0.10
(38) $NH{\cdot}C_6H_4Me$-4′	10.13	2	*l*	0.08
(39) $NH{\cdot}C_6H_4{\cdot}OMe$-4′	10.20	2	*l*	0.09
(40) $NH{\cdot}C_6H_4Cl$-3′	8.90	2	*l*	0.08
(41) $NH{\cdot}C_6H_4Cl$-4′	9.14	2	*l*	0.08
(42) $NH{\cdot}C_6H_4{\cdot}NO_2$-3′	7.94	2	*l*	0.06
(43) $NH{\cdot}C_6H_4{\cdot}NO_2$-4′	7.23	2	*l*	0.03
(44) $NH{\cdot}CH_2Ph$	12.47	2	*g*	0.04



				$\sigma_{\alpha\text{-O}}$
(45) X = NH_2	10.39	2	*m*	0.67
(46) NHPh	9.02	2	*n*	0.59
(47) $NH{\cdot}C_6H_4Me$-4′	9.34	2	*n*	0.61
(48) $NH{\cdot}C_6H_4{\cdot}OMe$-4′	9.30	3	*n*	0.61
(49) $NH{\cdot}CH_2Ph$	11.54	2	*g*	0.57



				$\sigma_{\beta\text{-O}}$
(50) X = NHPh	9.53	2	*n*	0.27

† Maximum error ±0.03 pK_a units for all compounds except (2), (35), and (44) (±0.06). ‡ Number of determinations.

[a] H. D. Hartough, 'Thiophene and its Derivatives,' Interscience, New York, 1952, p. 426. [b] W. Steinkopf and T. Hopner, *Annalen*, 1933, **501**, 174. [c] A. P. Terent'ev and G. M. Kadatskii, *Zhur. obshchei Khim.*, 1952, **22**, 153 (*Chem. Abs.*, 1952, **46**, 11,178). [d] Ref. 5. [e] Ref. 7*a*. [f] S. Occhipinti, G. Scarlata, and M. Torre, *Boll. Sed. Acc. Gioenia Sci. Nat.* (*Catania*), 1973, **4**, 11, 181. [g] This work. [h] Ref. 8*a*. [i] R. H. Cundiff and R. R. Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1424; H. Y. Lew and C. R. Noller, *ibid.*, p. 5715. [j] A. P. Terent'ev and G. M. Kadatstkii, *Zhur. obschchei Khim.*, 1951, **21**, 1524 (*Chem. Abs.*, 1952, **46**, 2536). [k] I. Langer, *Ber.*, 1884, **17**, 1556; W. Steinkopf, W. H. Jacob and H. Penz, *Annalen*, 1934, **512**, 136. [l] Ref. 7*c*. [m] R. O'Cinneide, *Nature*, 1947, **160**, 260. [n] Ref. 7*d*.

Substituent Effects in the S-*Linked Ring.*—The acidity constants of substituted arenesulphonanilides and α-arylsulphonylaminopyridines in 50% w/w water–ethanol at 20 °C have been reported.[4] In this study the authors concluded that σ^0 values have to be utilized for their correlation, SO_2 acting as an insulating group.

A subsequent paper reporting the pK_a values for 196 substituted arenesulphonamides under the same con-

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[10] (*a*) H. H. Jaffé and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 220; (*b*) C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, Cambridge, 1973, p. 99; (*c*) P. Tomasik and C. D. Johnson, *Adv. Heterocyclic Chem.*, 1976, **20**, 1.

[11] E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J.C.S. Perkin II*, 1976, 906.

[12] (*a*) M. Sjöström and S. Wold, *Acta Chem. Scand.* (*B*), 1976, **30**, 167; (*b*) W. H. Davis, jun., and W. A. Pryor, *J. Chem. Educ.*, 1976, **53**, 285.

[13] (*a*) O. Exner and P. Janak, *Coll. Czech. Chem. Comm.*, 1975, **40**, 2510; (*b*) S. Clementi, F. Fringuelli, P. Linda, and G. Savelli, *Gazzetta*, 1975, **105**, 281.

ditions,[2b] however, points out that strongly electron-donating *para*-substituents exhibit σ values intermediate between σ and σ°. This is ascribed to conjugation between the aromatic ring and the sulphonyl group involving the unoccupied 3*d* orbital of the sulphur atom, whose acceptor character is confirmed by the SO_2 symmetric i.r. frequencies.

In the case of five-membered heterocycles, sulphur and oxygen atoms exhibit electron-withdrawing inductive effects and electron-donating resonance effects. The balance between these effects determines the σ_{Het} values for S or O in the α- and β-position listed in Table 1.

The $\sigma_{\alpha\text{-S}}$ value calculated from data for the substituted thiophen-2-sulphonamides[2b] (3), (5), (6), (8), (9), (11), (12), (14), and (15) is, within experimental error, constant, and equal to that obtained from 2-thienylsulphonylaminopyridine[4] (25); $\sigma_{\beta\text{-S}}$ calculated from data for the substituted thiophen-3-sulphonanilides (36)—(43) and $\sigma_{\alpha\text{-O}}$ from substituted furan-2-sulphonanilides (46)—(48) are also constant. Moreover, the values calculated from data for heteroarenesulphonamides are similar to those calculated from data for their *N*-methyl, *N*-phenyl, and *N*-benzyl derivatives. Table 2 lists σ values calculated in the present work together with those relative to the pK_a values of carboxylic acids,[14] to the alkaline hydrolysis of carboxylic esters,[15] and to the solvolytic rearrangement of β-arylethyl tosylates.[16] The reasons for the differences between these sets of values have not yet been clarified,* neither has the extent of the importance of hydrogen bonding in these compounds.[10c] Values of σ_β are in our case very close to those derived from the pK_a values of the appropriate carboxylic acids; σ_α values are significantly lower. Owing to the non-general validity of literature values, an interpretation of this trend can hardly be attempted.

TABLE 2

σ Values for heteroatoms in five-membered rings

	σ [a]	σ [b]				σ [c]	σ [d]
		H	*N*-Methyl	*N*-Phenyl	*N*-Benzyl		
α–S	0.67	0.40	0.30	0.35	0.35	0.03	0.00
α–O	1.04	0.67		0.59	0.57	0.32	0.33
β–S	0.11	0.09	0.00	0.09	0.04	0.04	
β–O	0.25			0.27		0.04	

[a] From the pK_a values of carboxylic acids (pK_0 = 4.20; ref. 14). [b] This work. [c] From the alkaline hydrolysis of carboxylic esters (ref. 15). [d] From the solvolytic rearrangement of β-arylethyl tosylates (ref. 16).

Compounds (29)—(33), in which a substituent is present in the thiophen ring, can be regarded as disubstituted benzene derivatives and, assuming the additivity of substituent effects, their pK_a values can be calculated.[11] These values (Table 1) are in excellent agreement with the experimental ones for 5-CH_3 (29) and 5-I (32) derivatives, but higher for 5-Cl (30) and 5-Br (31) derivatives. This trend has already been observed in the reactions of 5-substituted 2-thenoyl chlorides with aniline,[17] causing deviations in the Hammett plot. In the case of compound (33) the direct electronic interaction between the nitro- and the thia-substituents does not allow application of the additivity principle.

Substituent Effects in the N*-Linked Ring*.—The Hammett plot for the 3'- and 4'-substituted thiophen-2-sulphonanilides (3), (5), (6), (8), (9), (14), and (15) † gives the best correlation (*r* 0.999) with σ° values;[18a] $\rho' = 2.55$ ($s = 0.036$), p$K_0 = 9.38$ ($s = 0.041$). An excellent correlation (*r* 0.999) with σ° values is also found for the thiophen-3-sulphonanilide derivatives (36)—(43); † $\rho' = 2.53$ ($s = 0.042$), p$K_0 = 9.79$ ($s = 0.048$). Both ρ' values are very close to those calculated for different series of substituted benzenesulphonanilides[2c] and, as expected, indicate that the sensitivity is higher to substituents in the *N*-linked than in the *S*-linked phenyl ring.[2c]

The correlation with σ° (which differs significantly from σ only for strongly electron-donating substituents) however does not imply lack of conjugation. In fact the behaviour of the 4'-NO_2 substituent, which exhibits σ values intermediate between σ and σ^-, points to a certain degree of conjugation between the *N*-linked ring and the reaction centre, where a negative charge is formed in the conjugate base.

The acidic behaviour of 2'-substituted thiophen-2-sulphonanilides (4), (7), (10), (13), (16), and (18), which does not follow any sequence of '*ortho*' polar constants reported,[18b] can be compared with that of the corresponding *para*-derivatives (6), (9), (12), (15), (17), and (19). This comparison shows that Me, Et, Pr^i, and OMe *ortho*-substituents behave similarly to the corresponding *para*-substituents, while for 2'-Cl and 2'-NO_2 the derived 'apparent' σ values are respectively 0.38 and 0.78. The acidity constants of 2',6'-disubstituted compounds (20)—(22) are higher than expected from the additive Hammett equation, each *ortho*-methyl, -ethyl, and -isopropyl substituent exhibiting in this case an 'apparent' σ value of −0.18, −0.20, or −0.22, respectively.

The pK_a values of the naphthyl derivatives (23) and (24) are lower than that of compound (3), owing to the electron-withdrawing power of the 'benzo'-substituent, for which values of $\sigma_{2',3'}$ (0.17) and $\sigma_{3',4'}$ (0.09) can be evaluated (small values, as predicted theoretically[19]).

In the case of the pyridyl derivatives (25)—(27), the β-isomer is a stronger acid than the α- and γ-compounds. The calculated σ_m value for the 'aza'-substituent

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* A possible explanation for this variation may be found in the unusual enthalpy and entropy changes accompanying dissociation of the heterocyclic carboxylic acids.[15]

† A σ value of 1.02 was used, as calculated from 7 analogous series of *N*-arylbenzenesulphonamides.[2c]

[14] (*a*) A. R. Butler, *J. Chem. Soc.* (*B*), 1970, 867; (*b*) F. Fringuelli, G. Marino, and A. Taticchi, *J.C.S. Perkin II*, 1974, 1738; (*c*) G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 242.

[15] G. T. Bruce, A. R. Cooksey, and K. I. Morgan, *J.C.S. Perkin II*, 1975, 551, and references therein.

[16] D. S. Noyce and R. L. Castenson, *J. Amer. Chem. Soc.*, 1973, **95**, 1247.

[17] G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazzetta*, 1973, **103**, 319.

[18] J. Shorter, 'Correlation Analysis in Organic Chemistry,' Clarendon, Oxford, 1973, (*a*) p. 17; (*b*) p. 44.

[19] Ref. 10*b*, p. 114.

(0.65) is in excellent agreement with those reported;[10c] as (26) exists predominantly in the sulphonamido-form.[4,5,20] For (25) and (27), in which a considerable percentage of imino-form is present, $\sigma_{\alpha\text{-N}} = 0.26$ and $\sigma_{\gamma\text{-N}} = 0.33$ are found, the acidity being much lower than expected.

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol, i.r. spectra for KBr discs, and n.m.r. spectra for solutions in $CDCl_3$ at 60 MHz.

The preparation and the properties of most of the heteroarenesulphonamides have been described (see references in Table 1). Additional compounds used in this study were synthesized according to the same procedure,[5,7a] with methanol [(35)] or benzene [(28), (44), and (49)] as solvent.

N-*Benzylthiophen-2-sulphonamide* (28) formed prisms, m.p. 73—74° (Found: C, 51.85; H, 4.45; N, 5.6; S, 25.0. $C_{11}H_{11}NO_2S_2$ requires C, 52.15; H, 4.4; N, 5.55; S, 25.3%); $\lambda_{max.}$ 239 (log ε 3.97) and 250infl. nm (3.91); $\nu_{max.}$ 3 255 (NH str.), 1 330 (SO_2 asym. str.), and 1 140 cm^{-1} (SO_2 sym. str.); δ 4.17 (2 H, d, CH_2), 4.97br (1 H, s, NH), 7.04 (1 H, dd, H-4), 7.23 (5 H, s, ArH), and 7.48—7.67 (2 H, m, H-3 and -5); $M^{+\cdot}$ 253.

N-*Methylthiophen-3-sulphonamide* (35) afforded needles, m.p. 87° (Found: C, 33.9; H, 4.15; N, 7.9; S, 36.35. $C_5H_7NO_2S_2$ requires C, 33.9; H, 4.0; N, 7.9; S, 36.2%); $\lambda_{max.}$ 236.5 nm (log ε 3.82); $\nu_{max.}$ 3 270 (NH str.), 1 320 (SO_2 asym. str.), and 1 155 (SO_2 sym. str.); δ 2.66 (3 H, d, CH_3), 4.90br (1 H, s, NH), 7.25—7.60 (2 H, m, H-4 and -5), and 7.99 (1 H, dd, H_2); $M^{+\cdot}$ 177.

N-*Benzylthiophen-3-sulphonamide* (44) yielded needles, m.p. 77—78° (Found: C, 51.85; H, 4.4; N, 5.7; S, 25.25. $C_{11}H_{11}NO_2S_2$ requires C, 52.15; H, 4.4; N, 5.55; S, 25.3%); $\lambda_{max.}$ 238 nm (log ε 3.83); $\nu_{max.}$ 3 300 (NH str.), 1 315 (SO_2 asym. str.), and 1 155 (SO_2 sym. str.); δ 4.18 (2 H, d, CH_2), 5.10br (1 H, s, NH), 7.17—7.57 (7 H, m, ArH and H-4 and -5), and 7.98 (1 H, dd, H-2); $M^{+\cdot}$ 253.

N-*Benzylfuran-2-sulphonamide* (49) gave prisms, m.p. 76° (Found: C, 55.35; H, 4.75; N, 6.1; S, 13.35. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.65; N, 5.9; S, 13.5%); $\lambda_{max.}$ 228.5 nm (log ε 4.01); $\nu_{max.}$ 3 290 (NH str.), 1 330 (SO_2 asym. str.), and 1 150 cm^{-1} (SO_2 sym. str.); $M^{+\cdot}$ 237.

pK_a *Measurements*.—Measurements were made with a digital pH meter (Amel 333) equipped with an automatic burette; an Ingold electrode HA 401 was used for high alkalinity. The sulphonamide solution was *ca.* 1×10^{-3}M concentration could thus be assumed equal to activity. The solution (100 ml) was titrated in a thermostatted cell (20 ± 0.02 °C), under nitrogen, with 0.1N-sodium hydroxide. The electrode was standardized with buffer solutions before and after each titration. The volume of sodium hydroxide added was negligible with respect to the volume of the solution and the percentage of alcohol was practically constant during the titration. Distilled ethanol and doubly distilled water were used to prepare the 50% w/w water–ethanol. The sodium hydroxide solution was also prepared with doubly distilled water and kept out of contact with air. The pK_a values were obtained from the titration curves in the range 30—70% neutralization, by using the formula already reported.[2a]

The observed pH values were reduced by 0.18 units to take into account the change from water to 50% w/w water–ethanol.[2b] For high pK_a values (>9.5) the formula including a correction due to $[OH^-]$ was used;[2a] a value for $[H^+][OH^-]$ of 1×10^{-15} at 20 °C was taken for the examined aqueous ethanolic mixture.[2b]

The pK_a values of benzenesulphonamide and benzenesulphonanilide, determined to check the reproducibility of the method, were in excellent agreement (±0.01 pK_a units) with literature values.[2b]

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[20] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1961, 378.