Electrical Effects in Monosubstituted Thiazoles. pKa Values of Some 5- and 2-Substituted Thiazoles

By **Luciano Forlani** * and (in part) **Gabriele Breviglieri,** Istituto di Chimica Organica, viale Risorgimento 4, Bologna, Italy

Paolo De Maria, * Istituto di Chimica degli Intermedi, viale Risorgimento 4, Bologna, Italy

pK_a Values of a number of representative 2- and 5-substituted thiazoles were determined spectrophotometrically and/or potentiometrically in aqueous solution at 25 °C. The pK_a is very sensitive to changes of substituent, the full range of values observed covering *ca.* 10 logarithmic units. The substituent in position 2 appears to interact with the reaction centre through mesomeric as well as inductive effects; the latter is the dominant effect. Steric effects appear to be absent. The relative sensitivities to variation of the substituent in positions 2 and 5 of these thiazoles and of other ' aza ' substituted heterocyclic systems are briefly compared. The usefulness of an ' *ortho* ' polar effect derived from the pK_a of 2-' aza ' substituted heterocyclic bases is critically examined.

THE electrical effects of substituents bonded to heterocyclic systems which contain an ' aza-group ' (pyridine,[1,2] imidazole,[3] and related derivatives) have been extensively investigated. Considerable interest has been shown in substituents bonded in the α position with respect to the ' aza-group ' and attempts to derive an ' *ortho* ' polar effect from the pK_a values of these substrates have been carried out. McDaniel and Brown[1] first proposed such a generalisation, which was subsequently questioned by Charton.[2]

However investigations on penta-atomic heterocyclic

25 °C. The results, together with relevant experimental details, are collected in Table 1, which also includes some values taken from the literature. The range of substituents comprises both electron-releasing and -withdrawing substituents. Very large differences were observed by varying the substituent. The pK_a values range over *ca.* 10 logarithmic units.

In the case of 2-(NN-dimethylamino)thiazole (and 2-aminothiazole), both nitrogen atoms (annular and exocyclic) are possible protonation centres. We think that protonation occurs at the ring nitrogen atom because the u.v. spectral variation between protonated and unprotonated

TABLE 1

pK_a Values (H_2O; 25 °C) of some monosubstituted thiazoles

Substituent	pK_a	Method [a] (p.e.[b])	m [c]	λ_{max}.B [d]/nm (ε)	λ_{max}.B⁺H [d]/nm (ε)	λ_{det} [e]/nm
2-NO₂	−5.08	S (±0.1)	0.80	313 (5 214)	301 (6 530)	328, 290
2-SO₂Me	−2.82	S (±0.07)	0.92	256 (6 742)	260 (8 091)	266, 272
2-SO₂Ph	−2.60	S (±0.07)	0.97	266 (1 2109)	278 (12 750)	278, 292
2-SOPh	−1.75	S (±0.04)	0.94	258 (8 632)	270 (10 210)	270, 288
2-Cl	−0.75	S (±0.04)	1.04	243 (5 040)	253 (6 870)	256
2-Br	−0.86	S (±0.04)	1.1	246 (5 318)	259 (8 789)	268
2-OMe	1.57	P,S (±0.03)	1.0	234 (4 312)	239 (4 710)	246
2-NHAc	1.68	P,S (±0.05)	1.0	264 (8 930)	269 (10 258)	274
2-Ph	2.52	P (±0.04)				
2-NMe₂	5.27	P (±0.03)				
5-NO₂	−1.50	S (±0.05)	1.1	283 (7 211)	260 (7 359)	256, 288
5-SO₂Me	−1.00	S (±0.04)	1.0	230 (6 995)	235 (6 170)	222, 244
5-Cl	0.43	S (±0.03)	1.0	242 (4 596)	252 (4 580)	256, 234
5-Br	0.64	S (±0.03)	1.0	244 (4 863)	257 (5 050)	262
5-OMe	2.39	S (±0.04)	1.0	250 (3 388)	267 (3 764)	274

[a] S = Spectrophotometric, P = potentiometric. [b] Probable error. [c] Evaluated from least-squares analysis of log I *versus* $-H_0$ plots; m = slope and pK_a is value of H_0 for log I = 0. [d] B = Unprotonated base, B⁺H = protonated base. [e] Wavelength used in determinations.

The following pK_a values were obtained from ref. 5: thiazole, 2.51; 2-methylthiazole, 3.43; 2-ethylthiazole, 3.37; 2-t-butylthiazole, 3.15; 2-aminothiazole, 5.32; 5-methylthiazole, 3.12.

systems have been restricted to a few substituents only; we now present results on the basicity of some 2- and 5-substituted thiazoles, pertinent to the above investigation and with the aim of clarifying some problems arising from the reactivity[4] of thiazole derivatives, for which protonation of the ' aza-group ' is sometimes the rate-determining step.

RESULTS

The pK_a † values were obtained spectrophotometrically and/or potentiometrically, as appropriate, in water at

† As is customary we use the pK_a of the conjugated acid of the thiazole base as the measure of basicity.

species is quite similar to the variation observed for the other substituents. The same conclusions were obtained by Mizukami and Hirai[6] for the ionization of 4-amino-2-methylpyrimidine. 2-Aminothiazole could be involved in imino–amino tautomerism; however no significant difference between the pK_a values of 2-amino- and 2-(NN-dimethylamino)-thiazole was observed. Therefore our results support the general view[7] that 2-aminothiazole is essentially present in the amino form.

DISCUSSION

First we consider the problem of possible steric effects which can reasonably be expected from the closeness of the reaction centre and the 2-substituents. Upon

considering alkyl groups (2-methyl- and 2-t-butyl-thiazole), the enhanced size of the substituent does not lead to appreciable differences in the pK_a values. Furthermore a plot of pK_a for 5-substituted thiazoles against that for 2-substituted thiazoles is linear (r 0.990 5). The only significant deviation is that of the nitro group, which will be discussed later. A one parameter correlation implies the presence of one inter-action mechanism between the ' aza-group ' and the substituent.[8] As position 5 is not affected by steric requirements, the observed variations in position 2 arise from the electronic effects of the substituents only. This conclusion is in agreement with that obtained from other previously studied heterocyclic systems.

Usually when the substituents are in a position to conjugate with the reaction centre (as for 2-substituted thiazoles), it is accepted that the substituents interact by mesomeric effects which are considered to be more important than inductive effects. This is well estab-lished by the use of σ_p values (or $\sigma_p{}^+$, $\sigma_p{}^-$) in the Hammett equation.[9] However for 2-substituted thiazoles (as well as for 2-substituted pyridines or imidazoles) the best correlation between pK_a and σ values, is that obtained by using σ_m values (see Figure). σ_I, $\sigma°_m$, σ_p, and $\sigma_p{}^+$ give unacceptable correlations. The only deviations from linearity observed in the Figure are those for the NO_2, NH_2, and NMe_2 substituents, which are usually considered to have strong mesomeric properties. The use of σ_m values for the other groups indicates that the present system is more sensitive to inductive than mesomeric effects. This is related to the peculiar geometry of thiazoles and is in agreement with that observed for pyridine and imidazole systems, where the substituent and the reaction centre are bonded to the same carbon atom. In this situation the superimposi-tion of inductive and mesomeric effects gives a balance in which the former is stronger than the latter. In fact it is known that the distance between the reaction centre and substituent is very important in determining the degree of inductive effect involved in the reaction series.[10] The ρ values (reported in Table 2) for the systems considered are in agreement with our con-clusions.

If the substituent is bonded in position 5 of the thiazole ring, the use of σ_m values is largely justified and satis-factory and the ρ value (Table 2) is in keeping with the present discussion. Clearly position 5 of the thiazole ring is meta-like to the nitrogen atom in position 3.

The observed deviation for NO_2, NH_2, and NMe_2 can be attributed to mesomeric interactions, as the sub-stituent is prone to conjugation. However we have some doubts about the usefulness of multiparameter equations,[9] in explaining the deviation of only two sub-stituents as in the case under investigation. It is interesting to observe that the deviation of NO_2 empha-sizes the strong electron-withdrawing ability of this group when it is bonded to the thiazole ring. In the reaction of 5-substituted 2-halogenothiazoles with sodium thiophenoxide,[11] we have previously observed that a 5-

nitro group exerts a very strong electron-accepting effect and a σ^- value of 1.6 was calculated. Furthermore a nitro group is able to stabilize the negative charge of a Meishenehimer-like complex formed in the reaction of 2-methoxy-5-nitrothiazole with sodium methoxide.[12]
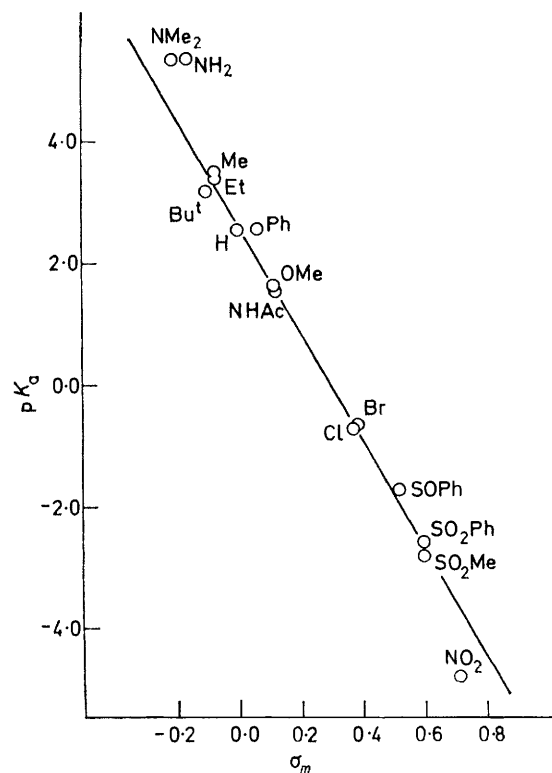
Plot of pK_a values of 2-substituted thiazoles *versus* σ_m values

The presence of mesomeric interaction by a 2-nitro-group also explains the deviation observed in the plot of pK_{a5} *versus* pK_{a2}, because this interaction is absent when the nitro group is in position 5.

TABLE 2

ρ Values obtained from basicity (pK_a values in H_2O at 25 °C) of some monosubstituted heterocycles and σ_m values

Substrate	No.[a]	ρ	Ref.
2-Substituted thiazole	15	−9.9 [b]	
2-Substituted thiazole	13	−8.8 [c]	
5-Substituted thiazole	7	−6.0 [d]	
2-Substituted pyridine	13	−11.8	2
2-Substituted imidazole	5	−11.1	3
2-Substituted 1-methylimidazole	3	−10.6	3
2-Substituted quinoline	7	−10.4	2
2-Substituted benzimidazole	7	−10.9	3
3(4)-Substituted pyridine	20	−5.70 [e]	1,3

[a] No. = number of substituents. [b] ±0.4 (as standard deviation), r 0.9888. [c] By exclusion of NO_2, NH_2, and NMe_2 groups; ±0.2 (as standard deviation), r 0.9963. [d] ±0.3 (as standard deviation), r 0.9935. [e] σ_m and σ_p values as appropriate.

The greater importance of the inductive than the mesomeric effect is not generally observed for benzene systems, because when the substituents are in positions 3 and 4, the inductive effect is largely reduced by the

distance from the reaction centre. Therefore the use of pK_a values of 2-substituted ' aza '-containing hetero-cycles for the estimation of ' *ortho* ' electronic effects in the benzoic acid series is incorrect. The substituent constant obtained for the 2-' aza '-substituted systems could be applied to reactions which occur at C(1) of a benzene ring bearing 2-substituents. Obviously in this case complications would arise from steric effects which are not present in the system studied here.

EXPERIMENTAL

Materials.—Thiazole derivatives were prepared and purified by the usual methods.

Dissociation Constant Determinations.—Although in a few cases both the spectrophotometric and potentiometric techniques were used for the same compound, normally the former was preferred for determining the pK_a of the weaker bases ($pK_a \leqslant 0.65$) while for the stronger bases ($pK_a \geqslant 1.5$) the latter was preferred.

(1) *Potentiometric measurements.* Glass electrodes and an ABU 11 autoburette in conjunction with a Radiometer PH M26 pH-meter were used for potentiometric titrations. The pH-meter was standardized with standard aqueous buffers [13] and the temperature was set at 25 ± 0.1 °C. Since the base is normally quite weak the assumption of $[B^+H] = [HCl]_{stoich}$ is not valid. Therefore the pK_a was estimated from $[H^+] = a_{H^+}/\gamma_{H^+}$, $[B^+H] = [HCl]_{stoich}$ $-[H^+]$, and $[B] = [B_0] - [B^+H]$, where $[HCl]_{stoich}$ is the concentration of hydrochloric acid added and $[B_0]$ the initial concentration of base. The pK_a can be calculated from equation (1). The activity coefficients were calculated

$$pK_a = pH + \log\gamma_{B^+H} + \log ([B^+H]/[B]) \qquad (1)$$

from the Davies equation,[14] with a Debye–Huckel function A of 0.511.

(2) *Spectrophotometric measurements.* The method adopted was essentially that proposed by Katritzky *et al.*[15] which has been recently shown [16] to afford reliable results for polysubstituted thiazoles. The absorbance of equivalent amounts of substrate in acids of various molarities was measured at an appropriate wavelength at 25 ± 0.2 °C with an Unicam SP 700 spectrophotometer. Appropriate blank solution was used in the reference cell in each case. The absorbance was recorded immediately after the addition of substrate.

Plots of absorbance against H_0 gave good sigmoidal curves. A major problem associated [17] with the determination of the dissociation constant of weak organic bases as

well as with their thermodynamic significance is the defini-tion of the acidity functions used. Our results support previous evidence [16] that the large majority of thiazoles [17] behave as Hammett bases as expressed by the values of m in Table 1. This is also evidence that the site of proton-ation is the ' aza ' nitrogen in all cases. In the case of 2-nitrothiazole only m differs significantly from unity. How-ever we did not attempt to treat the results [18] by anchoring the pK_a of 2-nitrothiazole to the common standard state [16] in dilute acid solutions. This is mainly due to the fact that we collected evidence that ' medium effect ' [17] on the fully protonated and deprotonated forms of this thiazole change m with changing wavelength. These medium effects cannot be allowed for by the correction used in the present method [15] and the deviation of m from unity for 2-nitro-thiazole could well be an artifact due to these medium effects. However the pK_a of 2-nitrothiazole should be strictly considered as a H_0 value at half protonation.

REFERENCES

[1] D. H. McDaniel and H. C. Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 3756.

[2] M. Charton, *J. Amer. Chem. Soc.*, 1964, **86**, 2033.

[3] M. Charton, *J. Org. Chem.*, 1965, **30**, 3346.

[4] M. Bosco, V. Liturri, L. Troisi, L. Forlani, and P. E. Todesco, *J.C.S. Perkin II*, 1974, 508.

[5] R. Phan-Tan-Luu, J. M. Surzur, J. Metzger, J. P. Aune, and C. Dupuy, *Bull. Soc. chim. France*, 1967, 3274.

[6] S. Mizukami and E. Hirai, *J. Org. Chem.*, 1966, **31**, 1199.

[7] J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, ' The Tautomerism of Heterocycles,' Academic Press, London, 1976.

[8] J. E. Leffler and E. Grunwald, ' Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, ch. 6.

[9] N. B. Chapman and J. Shorter, 'Advances in Linear Free Energy Relationships,' Plenum, London, 1972.

[10] C. K. Ingold, ' Structure and Mechanism in Organic Chem-istry,' Cornell University, New York, 1968.

[11] M. Bosco, L. Forlani, V. Liturri, P. Riccio, and P. E. Todesco, *J. Chem. Soc.* (*B*), 1971, 1373.

[12] G. Bartoli, O. Sciaccovelli, M. Bosco, L. Forlani, and P. E. Todesco, *J. Org. Chem.*, 1975, **40**, 1275.

[13] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' Butterworths, London, 1965.

[14] C. W. Davies, ' Ion Association,' Butterworths, London, 1962.

[15] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakin, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.

[16] A. R. Katritzky, C. Ogratis, H. O. Tarhan, H. M. Dou, and J. Metzger, *J.C.S. Perkin II*, 1975. 1614.

[17] E. M. Arnett, *Progr. Phys. Org. Chem.*, 1965, **1**, 233.

[18] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899.