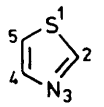
Electrical Effects in Substituted Thiazoles. pK_a Values of Some 5-Substituted 2-Aminothiazoles and 5-Substituted 2-*NN*-Dimethylaminothiazoles

By **Luciano Forlani,*** *Istituto di Chimica Organica, Università di Bologna, Viale Risorgimento 4, Bologna, Italy*
Paolo De Maria* and **Adamo Fini,** Istituto di Chimica degli Intermedi, Università di Bologna, Viale Risorgimento 4, Bologna, Italy

Comparison of the pK_a values of some 5-X-aminothiazoles with those of the corresponding 5-X-2-*NN*-dimethylaminothiazoles allows the assignment of the aromatic amino form to 2-aminothiazole derivatives. A Hammett plot of pK_a values against σ_{meta} substituent constants is linear as required if the protonation centre is the endocyclic nitrogen in all cases. Cross-conjugation between the amino groups in position 2 and the substituents in position 5 is present only when the nitro-group is the substituent. Conjugative interaction between the amino group and the ' aza ' group is also discussed.

In a recent paper [1] we reported the ionisation constants of monosubstituted 1,3-thiazoles, but only scanty data are available on 2-aminothiazoles. Stauss and his co-



workers [2] measured the pK_a values of 5-(and 4-)aryl-2-aminothiazoles, with *para*-substituents in the benzene ring. In this system the substituent effect is clearly depressed by the distance from the protonation centre; as a consequence the observed ρ values are not higher than unity in both cases.

More detailed information on the transmission of polar substituent effects on thiazole derivatives can be obtained when the substituent is directly bonded to the thiazole ring.[1,3] It is known that aminothiazoles can in principle exist in tautomeric amino or imino forms.[4] However it has been shown [5] that the aromatic amino form is predominant for the large majority of 2-aminothiazoles. With the aim of collecting more information on substituent effects from equilibrium measurements and of testing the presence of possible imino tautomers, we have determined thermodynamic pK_a values, in water at 25 °C, of representative 5-substituted 2-aminothiazoles and of some 2-*NN*-dimethylaminothiazoles.

RESULTS

The pK_a values obtained potentiometrically and/or spectrophotometrically are reported in Table 1 together with some relevant experimental details. As expected, large differences (>5 pK_a units) were observed for the various substituents which include strong electron-withdrawing and electron-releasing groups. In Table 1 the pK_a of 2-benzylamino- and 2-phenylamino-thiazole are also reported.

TABLE 1

pK_a Values of some 5-X-2-*NN*-(R,R')-aminothiazoles in water at 25 °C

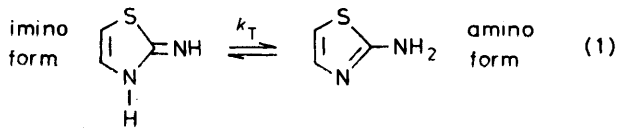
X	R	R'	pK_a (s.d.) [a]	pK_a (calc. [b])	Method	Method $\lambda_{det.}$/nm [d] and buffers
H	H	H	5.32 [c]			
Me	H	H	5.71 (±0.03)	5.74	P	
OMe	H	H	4.98 (±0.03)	4.60	P	
Ph	H	H	4.90 (±0.02)	4.96	SP	286, acetate, pH 4.75, 4.92, 5.92
SPh	H	H	4.16 (±0.02)	4.48	SP	254, acetate, pH 4.26, 4.76, 4.96
Cl	H	H	3.66 (±0.01)	3.10	P	
Br	H	H	3.61 (±0.04)	2.98	P	
CO_2Et	H	H	3.04 (±0.02)	2.92	SP	276, monochloroacetate, pH 3.02, 3.25, 3.42
SO_2Ph	H	H	1.79 (±0.02)	1.72	S	270
NO_2	H	H	0.61 (±0.03)	1.06	S	380
H	Me	Me	5.27 [c]			
Me	Me	Me	6.08 (±0.05)	5.69	SP	254—260, hydrogenphosphate pH 6.51, 6.96
Ph	Me	Me	4.89 (±0.02)	4.91	SP	294, 318, acetate, pH 4.64, 4.87, 5.05
Br	Me	Me	3.66 (±0.05)	2.93	S–SP	260, 265, monochloroacetate, pH 3.14, 3.27, 3.46
NO_2	Me	Me	0.48 (±0.03)	1.01	S	397
CO_2Et	Me	Me	2.77 (±0.03)	2.87	P	
H	H	CH_2Ph	5.15 (±0.05)		SP	250—264, 276—284, acetate, pH 4.64
H	H	Ph	4.33 (±0.02)		SP	275—290, acetate, pH 4.64

[a] Standard deviation. [b] The pK_a values were calculated from equation (2), where $\rho_2\sigma_2$ is the pK_a of 2-amino- (or 2-*NN*-dimethylamino-)thiazole and $\rho_{2,5}\ \sigma_{2,5} = 0$. [c] Data from ref. 1. [d] Wavelengths for determination.

DISCUSSION

The results reported in Table 1 show that the ionisation constants of 2-aminothiazoles are very similar to those observed for the parent 2-*NN*-dimethylaminothiazoles.

There is a small difference when the substituent is the nitro group. Although this difference is outside the limits of experimental error (ΔpK_a 0.13, *i.e.* a difference in pK_a values of *ca.* 30%), the present data strongly indicate that the predominant form for all the aminothiazoles here considered is the amino-aromatic tautomer. A similar conclusion was previously [6] arrived at for 2-aminothiazole itself, for which a tautomeric constant $K_T = 2 \times 10^4$ for process (1) was calculated. This value was estimated [6] by taking as a model for the imino-form, 2-imino-3-methylthiazole which has pK_a 9.6, much higher than that of 2-aminothiazole. However the introduction of a methyl group for a hydrogen on the endocyclic nitrogen could affect the observed pK_a value of the model compound. Also the pK_a values of 2-*N*-benzylamino- and 2-*N*-phenylamino-thiazole (see Table 1) indicate the absence of an imino form, as they are satifactorily correlated by a previously derived Hammett plot of the pK_a values of the 2-substituted thiazoles against substituent σ_{meta} values. Least squares treatment shows that the substituent effect in 5-X-2-aminothiazoles

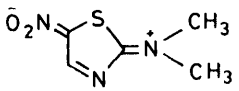


(1)

is satifactorily expressed by the σ_{meta} values of the substituents. An analogous correlation is shown by the pK_a values of 5-X-2-*NN*-dimethylaminothiazoles *versus* σ_{meta} values. The results are pK_a^0 5.42 ± 0.17, ρ −6.0 ± 0.5 (r 0.976) and pK_a^0 5.51 ± 0.26, ρ −6.6 ± 0.7 (r 0.977) for the 2-aminothiazoles and for the 2-*NN*-dimethylaminothiazoles, respectively. Errors are reported as standard deviations. The Student t test indicates that the correlations are significant at better than 99.9%.

In the 2-aminothiazoles there are two possible protonation centres, the amino and the ' aza ' groups. The use of σ_{meta} in the above Hammett plots gives an indication of the site of protonation of these bases.[7] In fact, in previous work [3,8] it was observed that the electronic interaction between reaction centres bonded to the carbon in position 2 (as well as the C-2 itself, when it is the reaction centre) and the substituent in position 5 can be conveniently expressed by σ_{para}. Between these two positions extra conjugation can also be observed. On the other hand the use of σ_{para} (or of other scales of substituent constants [1]) does not give acceptable correlations for the present series of pK_a values. This strongly supports the conclusion [1] that the ' aza ' group is a more basic centre than the amino group for a large number of substituted aminothiazoles. An analogous conclusion [9] was previously arrived at from the alkylation reaction (by alkyl halides).

The present ρ values are very close to that previously [1] calculated from the pK_a values of 5-substituted thiazoles (ρ −6.0). As a consequence a plot of the pK_a values from Table 1 *versus* the previous pK_a values [1] for 5-substituted thiazoles is linear and of unit slope (slope 1.04 ± 0.08 for the 2-aminothiazole series) as expected if the protonation site is the same endocyclic nitrogen for both thiazole series. The only deviant substituent is the nitro group as a consequence of cross conjugation with the amino group.[10] The importance of structure (A) was



(A)

ascertained by dynamic n.m.r. measurements.[11] Apart from this deviation, it seems reasonable to assume that the combined effects of the substituent in position 5 and the amino group in position 2 are additive. Therefore in equation (2) [12] where the subscripts 2 and 5 refer to

$$pK_{a(2,5)} = pK_a^0 + \rho_2\sigma_2 + \rho_5\sigma_5 + \rho_{2,5}\sigma_{2,5} \quad (2)$$

thiazole positions bearing substituents and ρ_2 and ρ_5 were as previously calculated [1] from monosubstituted thiazoles, the interaction term $\rho_{2,5}\sigma_{2,5}$ can be neglected.

When the pK_a values of 2-substituted, of 5-substituted, and of the present 2-amino-5-substituted thiazoles are treated according to equation (2) (neglecting the interaction term $\rho_{2,5}\sigma_{2,5}$) *two* separate and parallel straight lines of unit slope are obtained. These linear relationships can be expressed algebraically by equations (3) for monosubstituted thiazoles (r 0.988) and (4) for

$$pK_x - pK_a^0 = 0.47 \pm 0.16 + 1.12 \pm 0.05(\rho_2\sigma_2 + \rho_5\sigma_5) \quad (3)$$

$$pK_x' - pK_a^0 = 1.31 \pm 0.14 + 1.07 \pm 0.1(\rho_2\sigma_2 + \rho_5\sigma_5) \quad (4)$$

substituted aminothiazoles (r 0.942). The levels of significance of the correlations with equations (3) and (4) are better than 99.9% as demonstrated by the t test.

This indicates that the basicity of the aminothiazoles is higher than expected from the basicity of the other thiazoles.[1] The preceding discussion indicates that this difference is not due to the cross-conjugation term in equation (2). However we previously noted [1] that the amino and dimethylamino groups deviate from linearity in the Hammett plot of the pK_a values of the 2-substituted thiazoles *versus* the σ_{meta} values. 2-Aminothiazole and 2-*NN*-dimethylaminothiazole are in fact somewhat stronger bases than expected from their σ_{meta} values.[1] Tentatively, we attributed [1] this deviation to mesomeric interaction of the amino groups with the protonation centre. Now this behaviour is confirmed and extended to all the aminothiazoles considered here. It is also of interest that using experimental pK_a values for 2-amino- and 2-*NN*-dimethylamino-thiazole as $\rho_2\sigma_2$, equation (2) reasonably correlates our data for mono- and di-substituted thiazoles [as shown by pK_a(calc) in Table 1], with exclusion, of course, of the 5-nitro-2-aminothiazoles.

The extent of mesomeric interaction between the amino and the ' aza ' groups can be evaluated by application of the Taft equation [13] to 2-substituted

TABLE 2

Physical properties of some 5-X-2-*NN*-(R,R')-aminothiazoles

X	R	R'	M.p. (°C) [a] (solvent)	Lit.	$\lambda_{max.}$ [b] B	log ε	$\lambda_{max.}$ [c] BH+	(log ε)
Me	H	H	94—95 ($CHCl_3$)	95—96.5 [14]				
Ph	H	H	205—206 (EtOH–H_2O)	207.5—208.5 [15]	306	4.16	286	4.17
CO_2Et	H	H	161—162 (C_6H_6)	161—162 [16]	298	4.21	276	4.17
Br	H	H	95—96 ($CHCl_3$)	94—95 [17,18]				
Cl	H	H	111—112 ($CHCl_3$)	110—112 [17]				
NO_2	H	H	196—198 (MeOH)	195—196 [19]	380	4.09		
OCH_3	H	H	105—106 (C_6H_6)	105—106 [20]				
SPh	H	H	123—124 (EtOH)	123—124 [21]	276	4.06	254	4.09
SO_2Ph	H	H	225—226 (EtOH)	227—228 [22]	290	3.79	270	3.91
Me	Me	Me	86—88/15 [d]	Ref. 23 [e]	267	3.99	263	4.03
Ph	Me	Me	126—127 (light petroleum)	Ref. 23 [e]	318	3.87	294	3.86
CO_2Et	Me	Me	90—92/15 [d]	Ref. 16 [e]				
Br	Me	Me	35—36 ($CHCl_3$)	35—36 [17]	273	3.93	265	3.95
NO_2	Me	Me	161—162 (EtOH)	160—162 [24]	397	4.33	333	4.03
H	H	Ph	128—129 (CCl_4)	128—129 [25]	290		279	
H	H	CH_2Ph	131—132 (CCl_4)	131—132 [25,26]	262		260	

[a] M.p.s and b.p.s are uncorrected. [b] In nm for the unprotonated base. [c] In nm for the protonated base. [d] B.p. (°C)/p(mmHg). [e] M.p. of b.p. not reported.

thiazoles [1] [equation (5)]. By using only the pK_a values of substituents with σ_R near zero, ρ_I can be calculated (ρ_I -9.0 ± 0.4) which is, of course, very close to our

$$pK_a = pK_a^0 + \rho_I\sigma_I + \rho_R\sigma_R \qquad (5)$$

previous ρ_{meta} value [1] of -8.8. From this a ρ_R value of -4.4 can be obtained and ρ_R/ρ_I 0.5 results.

The relative importance of the electrical effects of the substituents in position 2 explains why the pK_a' values of 2-substituted thiazoles are generally satisfactorily correlated [1] with substituent σ_{meta} values.

EXPERIMENTAL

Materials.—Table 2 reports physical properties and some analytical data of the thiazole derivatives which were prepared by the usual methods. The n.m.r. spectral data are in agreement with the structures in all cases.

pK_a *Measurements.*—Depending upon the basicity of the thiazole, spectrophotometric or potentiomentric methods (referred as S and P in Table 1) were adopted as previously described.[1] In several instances, however, the thiazole base was not sufficiently soluble in water for reliable potentiometric titrations.[27] In these cases, the ionisation constants were determined spectrophotometrically by standard procedures [27] in the presence of an appropriate external buffer, whose pH value was potentiometrically measured. This method is identified as SP in Table 1. The activity coefficients of ionic species were calculated from the Davies [28] equation, and the activity coefficients of neutral species were assumed to be unity.

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