Tautomerism of Aminothiazoles. pK_{BH^+} Values of 2-Aminothiazoles and of Some Model Imines

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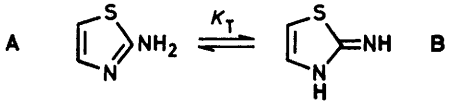
pK_{BH^+} Values of a number of 2-aminothiazoles, of their methiodides and of some fixed model imines have been measured in water at 25 °C. In favourable cases this allows the determination of the tautomeric constant K_T (=[amine]/[imine]). Comparison of the results shows that 2-aminothiazoles generally exist in the aminoaromatic form. 2-*p*-Tosylaminothiazole exists predominantly in the imino-form. 2-Aminothiazoles are generally protonated at the aza-nitrogen while the model imines are protonated at the exocyclic nitrogen. 2-*p*-Tosyliminothiazoles protonate at the aza-nitrogen as a consequence of the large substituent effect of the tosyl group.

In the amino–imino tautomerism of 2-aminoazoles, the aminoaromatic tautomer is generally the only detectable form.[1] The amino-form is also predominant in the 2-aminothiazoles.[2] The tautomeric equilibrium A ⇌ B

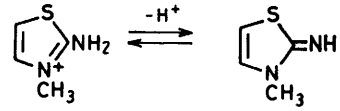


can be expected to shift towards B when electron-accepting substituents are bonded to the thiazole ring or to the exocyclic nitrogen. HMO calculations indicate[3] that this is the case and it has been shown that the imino-tautomer B is predominant in dimethyl sulphoxide for 2-*p*-tosylaminothiazole and sulphathiazole [2-*p*-aminophenylsulphonylimino)thiazoline].[4]

In order to collect further information on the prototropic problem of 2-aminothiazoles, we have determined pK_{BH^+} values of some substituted 2-aminothiazoles in water at 25 °C and compared these values with the pK_{BH^+} values of some fixed model imines.

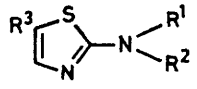
RESULTS

The 2-aminothiazoles (I)—(VIII) and 2-iminothiazolines (IX)—(XII) were considered. The pK_{BH^+} measurements are collected in Table 1, together with pK_{BH^+} values of some methiodide derivatives. Table 1 also reports the pK_{BH^+} values of 2-aminobenzothiazole (XIII), of its methiodide derivative, and of 3-methyl-2-iminobenzothiazole (XIV). As expected if the same

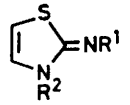


protonation equilibrium is involved, compounds (IX) and (XIV) show very similar pK_{BH^+} values to those of the corresponding methiodides of (I) and (XIII). It can therefore be concluded that the protonation site of the imino-form is the exocyclic nitrogen.

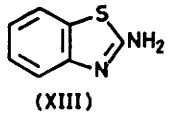
For sulphonamide (VIII) two pK_a values have been determined, $pK_{B'H}$ and the usual pK_{BH^+}. The former is



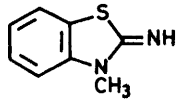
(I) $R^1=R^2=R^3=H$
(II) $R^1=R^2=H, R^3=CH_3$
(III) $R^1=R^3=H, R^2=CH_2Ph$
(IV) $R^1=R^3=H, R^2=Ph$
(V) $R^1=H, R^2=Ph, R^3=CH_3$
(VI) $R^1=H, R^2=Ph, R^3=NO_2$
(VII) $R^1=CH_2Ph, R^2=p\text{-}CH_3C_6H_4SO_2, R^3=H$
(VIII) $R^1=R^3=H, R^2=p\text{-}CH_3C_6H_4SO_2$



(IX) $R^1=H, R^2=CH_3$
(X) $R^1=p\text{-}CH_3C_6H_4SO_2, R^2=CH_3$
(XI) $R^1=H, R^2=2,4\text{-}(NO_2)_2C_6H_3$
(XII) $R^1=Bu^s, R^2=2,4\text{-}(NO_2)_2C_6H_3$



(XIII)



(XIV)

close to the values expected for the deprotonation of arenesulphonamides [5] and obviously cannot be observed when an alkyl group replaces hydrogen as in (VII).

TABLE 1

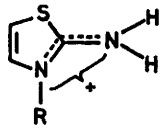
pK_{BH^+} values of some 2-aminothiazole derivatives

Compound	pK_{BH^+}(s.d.) [a]	Method [b]	$\lambda_{det.}$/nm and buffers
(I)	5.32 [c]		
(I)methiodide	9.65 [d]	P	
(II)	5.71 [c]		
(II)methiodide	9.95(0.05)	P	
(III)	5.15 [c]		
(III)methiodide	8.98(0.03)	P	
(IV)	4.33 [c]		
(IV)methiodide	6.30(0.02)	P	
(V)	4.57(0.03)	SP	284—296, acetate, pH 4.54
(VI)	−0.099(0.04)	S	410
(VII)	−0.53 [e]	S	290—300
(VIII)	−1.33(0.05)	S	260
	$pK_{B'H}$ 7.06(0.01)	SP	274—286, hydrogen-phosphate, pH 6.96
(IX)	9.50(0.05)	P	
(X)	−2.49 [f]	S	280—290
(XI)	7.00(7.03)	SP	390—420, hydrogen-phosphate, pH 6.96
(XII)	6.50 [g]	SP	355—400, 440—480, acetate, pH 5.49; hydrogen-phosphate, pH 6.86
(XIII)	4.23(0.03) [h]	P	
(XIII)methiodide	8.07(0.05)	P	
(XIV)	7.96(0.02)	P	

[a] Standard deviation. [b] P = potentiometric; S = spectrophotometric; SP = spectrophotometric in the presence of an external buffer. [c] Data from ref. 6a. [d] Data from ref. 7. [e] In MeOH (20% v/v). [f] In MeOH (2% v/v). [g] In MeOH (4.5% v/v). [h] Literature value 4.51.[8]

DISCUSSION

We have recently shown [6a] that the site of protonation of 2-aminothiazoles is the endocyclic nitrogen. On the other hand the fixed imino-tautomers are believed [7] to be protonated at the exocyclic nitrogen. Our present results show that the imino-derivatives here considered (see Table 1) are *ca.* 4 pK_{BH^+} units more basic



than the parent 2-aminothiazoles. This is consistent with previous assumptions [7] about this protonation site in view of considerable resonance stabilisation of the conjugate acids of these imino-derivatives. This same behaviour was observed for urea (and thiourea).[8] pK_{BH^+} Values for 3-(2,4-dinitrophenyl)-2-iminothiazoline (XI) and 3-(2,4-dinitrophenyl)-2-s-butyliminothiazoline (XII) provide further indication that in the imino-form the more basic centre is the exocyclic nitrogen. In fact these pK_{BH^+} values cannot be referred to an =N–H deprotonation equilibrium, which is impossible for the 2-s-butylimino-derivative, and are much higher values than those expected for 2,4-dinitroanilino-derivatives (pK_a of 2,4-dinitroaniline [9] in water at 25 °C is −4.27). The dinitrophenyl group is certainly bonded to the endocyclic nitrogen as determined by *X*-ray diffraction [10] and this group produces a considerable decrease in the basicity of the exocyclic nitrogen with respect to the methyl group ($pK_{BH^+(IX)} - pK_{HB^+(XI)} = 2.5$), but the pK_{BH^+} values of (XI) and (XII) are higher than those usually observed in the 2-aminothiazole series, where the protonation site is different, *e.g.* $pK_{BH^+(XI)} - pK_{BH^+(I)} = 1.7$.

From both pK_{BH^+} values of the amino- and of the fixed imino-forms assuming a common cation, K_T values can be calculated from equation (1). Our K_T values

$$K_T = K_{amino}/K_{imino} = [amino]/[imino] \quad (1)$$

(collected in Table 2) are probably slightly higher than the ' true values ' because of the feeble polar effect of the

TABLE 2

K_T Values (= [amino]/[imino]) of some 2-aminothiazole derivatives

Derivative	K_T
(I)	2.1×10^4 [a]
(II)	1.7×10^4
(III)	6.8×10^3
(IV)	9.3×10
(XIII)	6.9×10^3

[a] Literature value 2×10^4.[7]

methyl group which enhances the basicity of the model compared with the imino-form. Nevertheless the present K_T values are useful as they allow some conclusions to be drawn. Alkyl substitution in position 5 does not affect the K_T values and the aminoaromatic form remains the only significant tautomer. On the other hand K_T is slightly depressed when alkyl substitution occurs in the exocyclic nitrogen: the K_T value decreases to about a third on passing from 2-aminothiazole (I) to 2-benzylaminothiazole (III). A significant decrease in K_T [$K_{T(I)}/K_{T(IV)}$ *ca.* 200] is observed on introducing a phenyl group on the exocyclic nitrogen. In this case the two forms come close to having comparable stability even if the amino-form is always the predominant one. The K_T value (obtained by this same method) for 2-anilinopyridine is reported [11] to be very similar to that obtained by Angyal for 2-aminopyridine.[7] Apparently the five-membered ring of the thiazole moiety is more sensitive to phenyl substitution than the six-membered system of pyridine.

Substituents in position 5 of the 2-anilinothiazole scarcely affect the tautomeric equilibrium as the pK_{BH^+} values of 5-methyl- and 5-nitro-2-anilinothiazole parallel the corresponding values of the previously studied 5-substituted 2-aminothiazoles and 5-substituted 2-dimethylaminothiazoles.[6a] Our conclusion about the higher stability of the amino- with respect to the imino-form, even when strong electron-withdrawing groups

are present in the aminothiazole ring, apparently does not agree with recent HMO calculations on this same system.[3] However it is well known that the presence and nature of the solvent dramatically affects tautomeric equilibria in solutions.[1] Previously reported pK_{BH^+} values (in water) and ^1H n.m.r. spectral data (in [$^2H_6$]-DMSO) for aminothiazoles agree well with our present conclusion.

In the case of 2-aminobenzothiazole the annelation effect shifts the tautomeric equilibrium slightly (see Table 2) towards the imino-form, compared with 2-aminothiazole. However, the amino-form remains predominant as reported in the literature.[1,12]

Sulphathiazole is usually considered to exist mainly in the imino-form [13] and *X*-ray analysis supports this view. However $pK_{B'H}$ measured for 2-*p*-tosylaminothiazole is of the order expected for arenesulphonamides, even if, in the present instance, it cannot be related to the tautomeric equilibrium A $\rightleftharpoons$ B. In the sulphonamides considered, the presence of a strong electron-withdrawing group bonded to the exocyclic nitrogen affords complications. 2-(*N*-Benzyl-*N*-*p*-tosylamino)thiazole (VII) (a fixed amino-form) shows a pK_{BH^+} value which is satisfactorily correlated by the Hammett plot for the pK_{BH^+} values of 2-substituted thiazoles.[14] Therefore its protonation site is probably the endocyclic nitrogen. Although the presence of methanol in the solvent could slightly affect the results, the fixed imino-form (X) is *ca.* 100 times less basic than the fixed amino-form (VII). This probably means that the protonation equilibrium involves the endocyclic nitrogen, in this case as a consequence of the strong effect of the tosyl group on (X). 2-*p*-Tosylaminothiazole (VIII) is less basic than the parent 2-(*N*-benzyl-*N*-*p*-tosylamino)thiazole (VII) (ΔpK_{BH^+} 0.8). This difference is higher than that reasonably expected from the electronic effect of the benzyl group on an amino-structure [see for example compounds (I) and (III)]. On the other hand if compound (VIII) is mainly in the imino-form (as indicated by ^1H n.m.r. spectral data [4]) the pK_{BH^+} difference between (VIII) and (X) is not comprehensible in terms of a protonation occurring on the exocyclic nitrogen in both cases, but may be expected for a protonation on the endocyclic nitrogen whose basicity is depressed by steric hindrance by the methyl group. As a consequence, in this case amino- and imino-forms do not have a common cation as required for K_T evaluation by the Angyal method. Although the present discussion of 2-sulphonylaminothiazoles involves some approximations and assumptions, the imino-form of 2-*p*-tosylaminothiazole is probably the predominant tautomer.

EXPERIMENTAL

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

pK_{BH^+} *Measurements.*—Depending on the basicities and solubilities in water of the thiazole bases, potentiometric (P), spectrophotometric (S), or e.m.f. spectrophotometric (SP) methods have been used as previously described.[6a,14] Activity coefficients of ionic species were calculated from the Davies equation.[15] Methiodide derivatives were titrated potentiometrically with NaOH of appropriate molarity in carbon dioxide-free solutions. Compound (VII) is extremely insoluble in H_2O and was determined in the presence of 20% (v/v) methanol. Compounds (X) and (XII) also require the presence of small amounts of methanol for the same reason. The model compounds (IX) and (XI)—(XIV) were titrated potentiometrically with HCl in carbon dioxide-free solutions. pK_{BH^+} of compound (VIII) was determined by the Bunnett–Olsen method [16] (ϕ 0.45), which is known to give reliable results for a large range of compounds which do not behave as Hammett bases.[17]

The traditional procedure for log *I versus* H_0 plots gives for (VIII) $H_{0\ 1/2}$ −1.94 (*m* 0.64) and pK_{BH^+} −1.24.

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