Base-Catalyzed Hydrogen-Deuterium Exchange in some 5- and 6-Substituted Benzothiazoles. Activity of the Sulphur and Nitrogen Heteroatoms in the Transmission of the Substituent Effects

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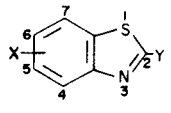
The rates of base-catalyzed hydrogen-deuterium exchange at C-2 in some 6-substituted benzothiazoles were studied and compared with the analogous values pertinent to some 5-substituted benzothiazoles, reported in a previous paper. The simple Hammett equation was found not to allow a good interpretation of the experimental data. However, a good agreement was obtained by the application of the Hammett-Jaffé equations. From these calculations, it was concluded that the sulphur and the nitrogen heteroatoms of the thiazole ring have, in these reactions, a very similar activity in the transmission of the substituent effects from the benzo ring at C-2 of the thiazole ring. Therefore, while in other reactions only the nitrogen heteroatom is active, in these reactions a considerable stabilization of the α-carbanion is clearly shown also by the sulphur heteroatom.

J. Heterocyclic Chem., **13**, 1021 (1976).

In a previous paper (1), the rates of base-catalyzed hydrogen-deuterium exchange at C-2 in some 5-substituted benzothiazoles and in thiazole[4,5-*c*]pyridine were studied.

The benzothiazole system **1** is very efficient in transmitting substituent effects from the benzo ring to the groups bonded in position 2 of the thiazole ring (2). For this reason, the transmission through the thiazole ring of the substituent effects in the benzothiazoles, and of the polar effects of the aza group in the thiazolopyridine, was assessed from these data.



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The substituents in position 5 (*meta* in respect to the nitrogen) were considered *meta* to groups present in position 2, and the substituents in position 6 (*para* in respect to the nitrogen) were considered *para* to groups bonded in position 2, according to observations that the effects are transmitted through the thiazole ring mainly by the nitrogen atom in position 3, while the sulphur in position 1 does not make a significant contribution. For a short discussion of this occurrence and the main pertinent references see the previous paper on this matter (1), and the discussion section of this paper.

In consideration of these facts, in the previous paper, the simple Hammett equation $\log k_s/k_H = \rho \sigma_m$ was used.

In the present paper the rates of base-catalyzed hydrogen-deuterium exchange at C-2 in some 6-substituted benzothiazoles are reported. From the comparison of these data with those of the analogous 5-substituted benzothiazoles, some new interesting information is obtained on the ability of the nitrogen and sulphur heteroatoms to transmit substituent effects through the thiazole ring for these exchange reactions.

Results and Discussion

We have measured the rates of base-catalyzed hydrogen-

deuterium exchange of thiazole at C-2, for some 6-X-substituted benzothiazoles (X = NH_2, CH_3, Cl and NO_2), under the same experimental conditions employed for the 5-substituted derivatives (1).

The second-order rate constants are shown in Table 1. For more comprehensive evidence in the evaluation and successive discussion of these data, the second-order rate constants for the 5-X-substituted benzothiazoles (X = H, CH_3, Cl and NO_2) of the previous paper are shown in the same Table.

Table 1

The second-order (10^4 k_s/ 1 mol^{-1} sec^{-1}) rate constants for base-catalyzed hydrogen-deuterium exchange of 5-X- and 6-X-substituted benzothiazoles (10^{-1} to 10^{-2} *M*) in deuteriomethanol with sodium methoxide (10^{-1} to 10^{-2} *M*) at 25°.

X	10^4 k_s/ 1 mol^{-1} sec^{-1}	log k_s	σ_m	σ_p
H (a)	1.21	-3.917	0.000	0.000
5-CH_3 (a)	0.70	-4.155	-0.069	-0.170
6-CH_3	0.65	-4.187		
5-Cl (a)	5.00	-3.301	0.373	0.227
6-Cl	6.19	-3.208		
5-NO_2 (a)	66.31	-2.178	0.710	0.778
6-NO_2	64.29	-2.192		
6-NH_2 (b)	0.177	-4.753	-0.160	-0.660

(a) These values were reported from the previous paper (1).
(b) The 5-aminobenzothiazole was not studied because this compound is very unstable (3).

By a careful examination of these data one observation is immediate: the second-order rate constants were very similar when the same substituent is present in position 5 or 6 of the benzo ring. This fact determines the failure of a simple Hammett equation $\log k_s/k_H = \rho\,\sigma$, using σ_m and σ_p respectively for the 5- and 6-substituted derivatives, according to previous assumptions.

For this reason we have applied the Hammett-Jaffé equations (4) **2** and **3**:

$$\log k_5/k_H = \rho_N\,\sigma_m + \rho_S\,\sigma_p$$

$$\log k_6/k_H = \rho_N\,\sigma_p + \rho_S\,\sigma_m$$

related to the second-order rate constants for the 5- (k_5) and 6-substituted benzothiazoles (k_6), respectively. In the same equations the ρ values for the sulphur and nitrogen thiazolic heteroatoms are expressed by ρ_S and ρ_N, respectively.

Combining the equations **2** and **3** one can obtain the linear correlations **4** and **5**, as proposed by Ricci and Vivarelli (5) in analogous cases.

$$\log (k_5 \cdot k_6) = (\rho_N + \rho_S)(\sigma_m + \sigma_p) + 2 \log k_H \qquad \mathbf{4}$$

$$\log k_5/k_6 = (\rho_N - \rho_S)(\sigma_m - \sigma_p) \qquad \mathbf{5}$$

Plotting log ($k_5 \cdot k_6$) and log k_5/k_6 values against $\sigma_m + \sigma_p$ and $\sigma_m - \sigma_p$ values respectively, one obtains $\rho_N + \rho_S = 2.3 \pm 0.03$ and $\rho_N - \rho_S = -0.33 \pm 0.24$, as shown in Figure 1.

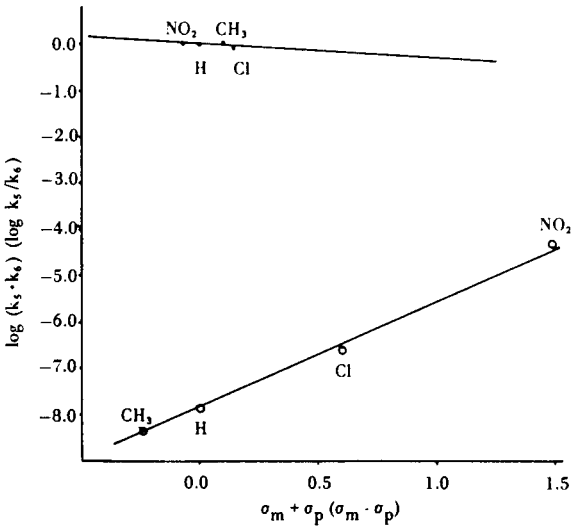

Figure 1. The slope of $(\sigma_m + \sigma_p)$ · log $(k_5 \cdot k_6)$ plot (•) is $\rho_N + \rho_S = 2.3 \pm 0.03$ and the slope of $(\sigma_m - \sigma_p)$ · log k_5/k_6 plot (•) is $\rho_N - \rho_S = -0.33 \pm 0.24$.

By a simple mathematical derivation, $\rho_N = 0.985 \pm 0.135$ and $\rho_S = 1.315 \pm 0.135$ were obtained. From the comparison of these ρ values, one can conclude that the sulphur and the nitrogen heteroatoms of the thiazole ring have a very similar activity in the transmission of the substituent effects from the benzo ring at C-2 of the thiazole ring. In fact the $\rho_N - \rho_S$ value is not too far from the standard error.

Analogous conclusion can be reached assuming $\rho_N = \rho_S = \rho$ in the equations **4** and **5**, from which one gets the equation **6**, where log k_5 = log k_6 = log k_s.

$$\log k_s/k_H = \rho\,(\sigma_m + \sigma_p) \qquad \mathbf{6}$$

Plotting log k_s against $\sigma_m + \sigma_p$ one obtains $\rho = \rho_N = \rho_S = 1.13 \pm 0.02$, as shown in Figure 2.

However, because the $\rho_N - \rho_S$ value in the plot of Figure 1 is clearly different from 0, beyond the standard error, one can consider the sulphur heteroatom a little more efficient than the nitrogen heteroatom in the transmission of the substituent electronic effects.

These conclusions were in considerable contrast with the results of some of our previous investigations on the

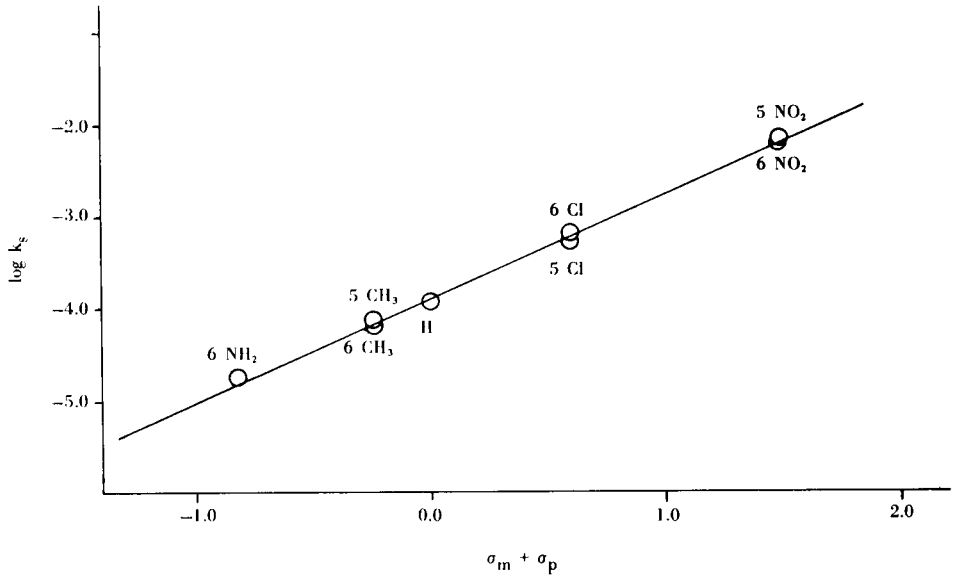

Figure 2. The slope of $(\sigma_m + \sigma_p)$ - log k_s plot is $\rho_N + \rho_S = \rho = 1.13 \pm 0.02$.

nucleophilic substitutions in 2-halogenobenzothiazoles (6,2), the acidity of some 2-carboxybenzothiazoles (7,2), and the oxidation of some 2-methylmercaptobenzothiazoles (8,2), in which no contribution by the sulphur heteroatom has been found, as confirmed also by Jaffé and Lloyd Jones (9).

The ρ_N, ρ_S and ρ values obtained using the Hammett-Jaffé equations and the simple Hammett equation, respectively, for the methoxydechlorination reaction of some 2-chlorobenzothiazoles, for the oxidation reaction by perbenzoic acid of some 2-methylmercaptobenzothiazoles, for the pK_a determination of some 2-carboxybenzothiazoles and for the base-catalyzed hydrogen-deuterium exchange in some benzothiazoles, are summarized in Table 2.

In the nucleophilic substitution at C-2 there is a direct interaction between the nucleophile and the π heteroaromatic electronic system, and the ability of the nitrogen heteroatom to assume the negative charge of the intermediate can explain the negligible ρ_S value. Analogous considerations cannot justify, however, the fact that the ρ_S value is much smaller than the ρ_N and very near 0 in the acidity of the 2-carboxybenzothiazoles and in the oxidation reaction of the 2-methylmercaptobenzothiazoles.

In the case of the base-catalyzed hydrogen-deuterium exchange reactions in the 5- and 6-substituted benzothiazoles, the considerable stabilization of the carbanion in the sp^2 orbital of the C-2 also by the sulphur in position 1, besides by the nitrogen in position 3, can be ascribed to the d-σ overlap, according to many previous papers on this

Table 2

The ρ_N, ρ_S and ρ values obtained from the methoxydechlorination reaction of 2-chlorobenzothiazoles, oxidation reaction of 2-methylmercaptobenzothiazoles, pK_a determination of 2-carboxybenzothiazoles and base-catalyzed hydrogen-deuterium exchange in benzothiazoles.

Reaction	Hammett-Jaffé equations		Hammett equation
	ρ_N	ρ_S	ρ
Methoxydechlorination of 2-chlorobenzothiazoles	1.96 ± 0.33	0.71 ± 0.58	2.46 ± 0.35
Oxidation of 2-methylmercaptobenzothiazoles	-0.44 ± 0.06	-0.09 ± 0.06	-0.51 ± 0.08
pK_a of 2-carboxybenzothiazoles	1.305 ± 0.06	0.025 ± 0.06	1.422 ± 0.056
Base-catalyzed hydrogen-deuterium	0.985 ±0.135	1.315 ± 0.135	- -

matter (10), or to polarization phenomena, in accordance with some recent theories on the activity of the sulphur atom (11). In fact, at present, the d-orbital conjugation is much questioned by Mangini, *et al.*, and several other authors (12).

Our results provide experimental evidence for the considerable contribution of the sulphur heteroatom in the transmission of the substituent effects, but from these data, however, we cannot conclude that the sulphur carries on its own activity by polarization rather than by d-orbital interaction.

Further investigations are in progress in our laboratories in an attempt to clarify the details of the sulphur heteroatom activity in these reactions.

EXPERIMENTAL

The ^1H nmr spectra were recorded on a JEOL JNM-C-60 HL spectrometer, using TMS as internal standard.

6-Nitrobenzothiazole, 6-Chlorobenzothiazole and 6-Methylbenzothiazole.

These compounds were prepared as reviewed by Todesco, *et al.*, (13).

6-Aminobenzothiazole.

This compound was prepared by reduction of the 6-nitrobenzothiazole as proposed by Spieler and Prijs (3) for the 5-nitrobenzothiazole.

Kinetic Measurements of hydrogen-deuterium exchange.

The experimental conditions were the same as those employed for the measurements of the base-catalyzed hydrogen-deuterium exchange in 5-substituted benzothiazoles of the previous paper (1). In this case only the mathematical and graphical treatments of the experimental data were different, as previously discussed.

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