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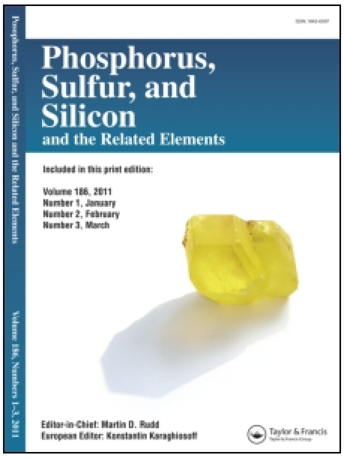

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BASE-CATALYZED HYDROGEN-DEUTERIUM EXCHANGE IN BENZO DERIVATIVES OF FIVE-MEMBERED AROMATIC HETEROCYCLES. PART VII. PRIMARY HYDROGEN ISOTOPE EFFECTS IN SOME 5- AND 6-SUBSTITUTED BENZOTHIAZOLES

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The rates of the base-catalyzed hydrogen-deuterium exchange at position 2, and the reverse, in some 5- and 6-substituted benzothiazoles are reported. The plots of log k_{sH}, and log k_{sD} against the $\sigma_m + \sigma_p$ values of the substituents, according to the Hammett–Jaffé equations, are slightly curved. The primary hydrogen isotope effect k_{sH}/k_{sD} varies between 0.7 and 2.3 and the plot of log k_{sH}/k_{sD} against the $\sigma_m + \sigma_p$ values of the substituents is a more pronounced curve, showing a maximum near to the $\sigma_m + \sigma_p$ value of -0.3. By these investigations the simple utilization of the primary hydrogen isotope effect in the prediction of reaction mechanisms seems extremely hazardous.

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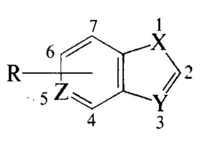
INTRODUCTION

By the study of the rates of base-catalyzed hydrogen-deuterium exchange at position 2 in some benzo derivatives of five-membered aromatic heterocycles, interesting conclusions were drawn and reported in our previous papers.[1–6]



X = O, S, Se.
Y = CH, N.
Z = CH, N.
R = H, 5-CH_3, 6-CH_3, 5-Cl, 6-Cl, 5-NO_2, 6-NO_2, 6-NH_2.

In particular, it was emphasized that in the benzothiazole derivatives, in these reactions, the sulphur and the nitrogen heteroatoms of the thiazole ring have a nearly similar activity in the transmission of the substituent effects from the benzo ring at the position 2 of the thiazole ring.[1,2,5]

Furthermore, by comparison of the rates of the base-catalyzed hydrogen-deuterium exchange at position 2 in 1-benzothiazole, benzoxazole, benzoselenazole, benzothiophene, benzofuran and benzoselenophene, it was concluded that the heteroatoms examined (nitrogen, oxygen, sulphur and selenium) were able to stabilize the α-carbanions in different and sometimes contradictory way.[3–6] The inconsistent behaviours observed were explained by assumption that, in these reactions, several effects were involved by the above-mentioned heteroatoms and that none of these decidely and constantly outweighs the others.

These assumptions were supported by the determination of the primary hydrogen isotope effects which resulted to be considerably different for the above-cited substrates.[6] Analogous occurrences has been usually ascribed to different rate-limiting steps in the reaction mechanisms. In fact, it is known that the magnitude of the isotope effect can be related in several cases, but certainly not always, to the mechanism of the reaction.[6,7]

In order to elucidate the limits and importance of the primary hydrogen isotope effect variation, as well as the possibility of a use in diagnosing

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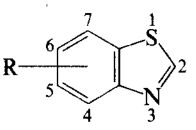
mechanisms on the basis of its magnitude, the isotope effects in some substituted benzothiazoles were studied and reported in this paper. The attention was focused on these last compounds because the benzothiazole manifested a primary hydrogen isotope effect (2.1) hypothetically susceptible of considerable increase for certain substituted derivatives, in the case in which the Hammett–Jaffé correlation were still respected.[2,5,6]

RESULTS AND DISCUSSION

The second-order rate constants of base-catalyzed hydrogen-deuterium exchange at position 2(k_{sH}), the same rate constants of the reverse exchange (k_{sD}), and the primary hydrogen isotope effects (k_{sH}/k_{sD}) for some 5- and/or 6-R-substituted benzothiazoles are shown in the following table.



R = H, 6-NO_2, 5-Cl, 5-CH_3, 6-CH_3, 6-NH_2, 6-$N(CH_3)_2$.

In accordance with our previous paper,[2] the Eqs. (1) and (2) are applied.

$$\log(k_{sH}/k_H) = \rho_H(\sigma_m + \sigma_p) \tag{1}$$

$$\log(k_{sD}/k_D) = \rho_D(\sigma_m + \sigma_p) \tag{2}$$

In these equations k_{sH} and k_{sD} represent the second-order rate constants of base-catalyzed hydrogen-deuterium and deuterium-hydrogen exchange, respectively, for the 5- and 6-substituted benzothiazole derivatives. The same rate constants for unsubstituted benzothiazole are represented with k_H and k_D, while ρ_H and ρ_D represent the ρ values relative to the hydrogen-deuterium and the reverse exhange.

Plotting the log k_{sH} and log $_{sD}$ values versus the $\sigma_m + \sigma_p$ values (see table), one can obtain, respectively, the behaviours shown in Figure 1 and Figure 2. In these figures, the full lines represent the best straight lines and the dotted lines represent the best quadratic curve, fitted by the method of least squares.

These behaviours confirm in part some of our previous assumptions.[2] In fact, in the base-catalyzed hydrogen-deuterium exchange the sulphur and the nitrogen heteroatoms of the thiazole ring manifest a very similar activity in the transmission of the substituent effects from the benzo ring at the position 2 of the thiazole ring. This occurrence is demonstrated by the good linear distribution ($r^2 = 0.9948$) of the log k_{sH} values against the $\sigma_m + \sigma_p$ values, either for 5- or for 6-substituted benzothiazoles, assuming $\rho_N = \rho_S$, (Figure 1) so the $\rho_H = 1.08 \pm 0.03$ value is in good agreement with the $\rho = 1.13 \pm 0.03$ value of previous paper.[2] In this case the best straight line is not so different from the best quadratic curve.

On the contrary, plotting the log k_{sD} values versus the $\sigma_m + \sigma_p$ values, the linear distribution ($r^2 = 0.9493$) becomes weaker, the curvature being greater (Figure 2). Notwithstanding this, one can tentatively determine a $\rho_D = 1.18 \pm 0.1$ value, that is not very different from the above-mentioned ρ_H value.

By a simple and qualitative examination of the data reported in Table I, one observation is immediate: the primary hydrogen isotope effect varies from nearly 0.7 to nearly 2.3 with the effects of the substituents present in the benzo ring, showing the greatest values for the compounds 4 and 5 and the smallest values for the compounds 1 and 7.

Plotting the log (k_{sH}/k_{sD}) values versus the $\sigma_m + \sigma_p$ values (Eq. 3, Figure 3) the correlation between the primary hydrogen isotope effect and the effects of the substituents present in the benzo ring ($\sigma_m + \sigma_p$) is obtained.

$$\log(k_{sH}/k_{sD}) = \log(k_H/k_D) + \sigma_m + \sigma_p) \times (\rho_H - \rho_D) \tag{3}$$

Also in this figure the full line represents the best straight line and the dotted line represents the best quadratic curve fitted by the method of least squares with a maximum near to the $\sigma_m + \sigma_p = -0.3$ value.

In accordance with the previous studies on this matter and the mechanism proposed for these reactions by several authors, different primary hydrogen isotope effects indicate different rate-limiting steps. In detail, the proton transfer may be preceded by an equilibrium due to back protonation and the rate of reprotonation may or may not be slower than the rate of replacement of hydrogen by deuterium, high (usually from 3 to 8) or low primary hydrogen isotope effect being observed respectively (see Scheme).[6,9]

$$\text{C—H} + \text{B} \rightleftarrows \text{C}^- \text{——HB} \longrightarrow$$
$$\text{C}^- \text{——DB} \rightleftarrows \text{CD} + \text{B}$$

SCHEME

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TABLE I

The second order (1 mol^{-1} sec^{-1}) rate constants for the base-catalyzed hydrogen-deuterium exchange at C-2 of some 5- and 6-R-substituted benzothiazoles (k_{sH}) and the reverse exchange (k_{sD}); the $k_{sH} \cdot k_{sD}$ values and the primary hydrogen isotope effects (k_{sH}/k_{sD}); the respective log values; the σ_m, σ_p and $\sigma_m + \sigma_p$ for each compound.[a]

Compound	R	$10^4\ k_{sH}$	$\log k_{sH}$	$10^4\ k_{sD}$	$\log k_{sD}$	$k_{sH} \cdot k_{sD}$	$\log(k_{sH} \cdot k_{sD})$	k_{sH}/k_{sD}	$\log(k_{sH}/k_{sD})$	σ_m[b]	σ_p[b]	$\sigma_m + \sigma_p$
1	6-NO_2	[c]64.29	−2.19	96.00	−2.02	6.17×10^{-5}	−4.21	0.67	−0.17	+0.71	+0.78	+1.49
2	5-Cl	[c]5.00	−3.30	3.73	−3.43	1.87×10^{-7}	−6.73	1.34	0.13	+0.37	+0.23	+0.60
3	H	[c]1.21	−3.92	[c]0.57	−4.24	6.90×10^{-9}	−8.16	2.12	0.33	0.00	0.00	0.00
4	6-CH_3	[c]0.65	−4.19	0.28	−4.55	1.82×10^{-9}	−8.74	2.32	0.37	−0.07	−0.17	−0.24
5	5-CH_3	[c]0.70	−4.15	0.31	−4.51	2.17×10^{-9}	−8.66	2.26	0.35	−0.07	−0.17	−0.24
6	6-NH_2	[c]0.177	−4.75	0.114	−4.94	2.02×10^{-10}	−9.69	1.55	0.19	−0.16	−0.66	−0.82
7	6-$N(CH_3)_2$	0.127	−4.90	0.121	−4.92	$1.54 + 10^{-10}$	−9.81	1.05	0.02	−0.21	−0.83	−1.04

[a] Substrate concentration 10^{-1} M; solvent deutereomethanol or methanol; sodium methoxide 10^{-1} to 1 M; temperature 25°C (±0.1).

[b] These values were reported from the Ref. 8.

[c] These values were reported from the previous papers.[1–5]

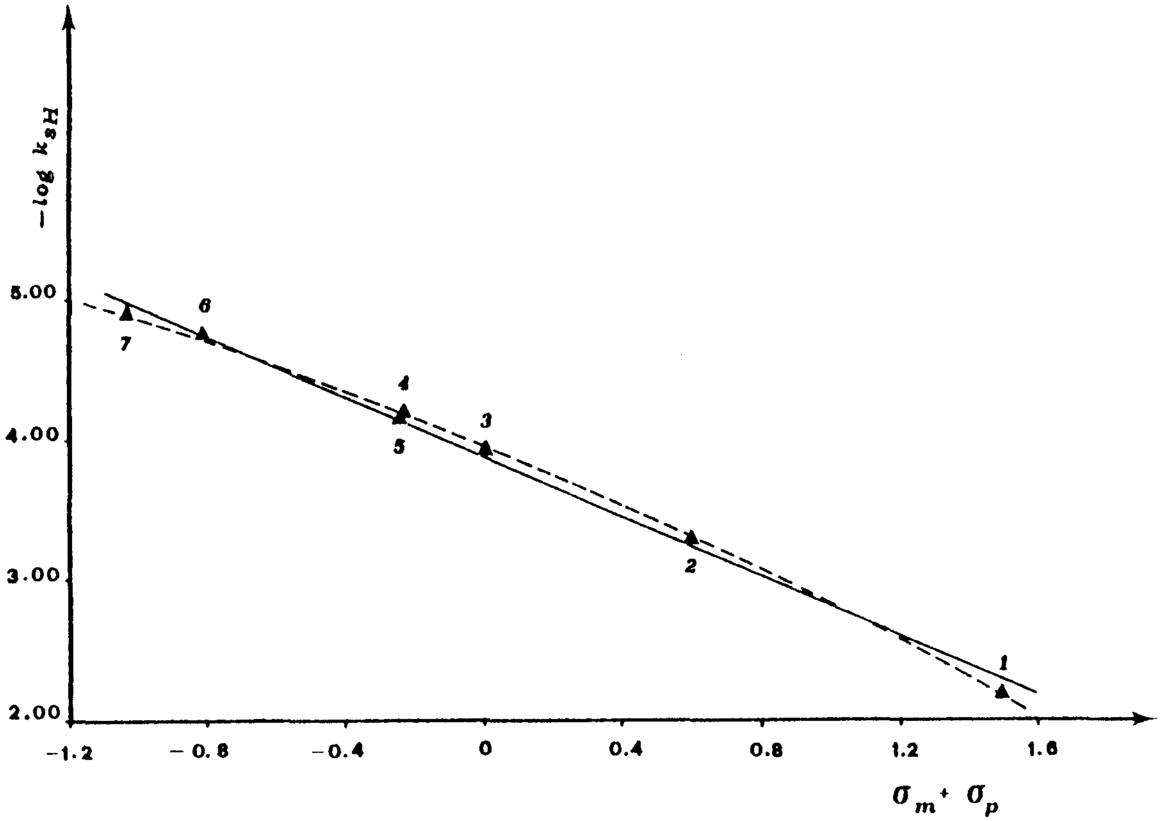

FIGURE 1 Plot of log k_{sH} versus $\sigma_m + \sigma_p$. The best straight line is log $k_{sH} = 1.0752(\sigma_m + \sigma_p) - 3.8759$ ($r^2 = 0.9948$); the slope is $\rho_H = 1.08 \pm 0.03$. The dotted line represents the best quadratic curve fitted by the method of least squares log $k_{sH} = 0.09025(\sigma_m + \sigma_p)^2 + 0.1035(\sigma_m + \sigma_p) - 3.93459$($r^2 = 0.9988$).

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In the present investigation, all the primary hydrogen isotope effects result low and less than 3, indicating that the same rate-limiting step should be operative in the base-catalyzed hydrogen-deuterium exchange mechanism of all the substrates examined.

On the other hand, the curvilinear distribution shown in Figure 3 is in contrast with the Eq. (3) in which the linear correlation between the primary hydrogen isotope effects and the substituent effects in the benzo ring ($\sigma_m + \sigma_p$) theoretically implies, for all the substrates, the possibility of a variation of the isotope effects with the substituent effects in continuous way and in a very large range. In fact, in the case in which the nearly linear increases manifested by the primary hydrogen isotope effects of the compounds 1–5 were continued also for the compounds 6 and 7, higher primary hydrogen isotope effects should be observed. In this respect, it is noteworthy that, plotting the log(k_{sH}/k_{sD}) values versus the $\sigma_m + \rho_p$ values (Figure 3), the deviation from the straight line for the compounds 6 and 7, ascribable to the slightly reduced primary hydrogen isotope effects, arises from the rate of deuterium-hydrogen exchange slightly faster than expected.

This occurrence is real and in agreement with analogous investigations on this matter,[7] in particular with the Marcus rate theory, which has been demonstrated for the proton transfer from the carbon acid and which should be a useful guide to the transition state structure.[10] If this is proved to be the case, the question is on the opportunity of a connection between the primary isotope effect of different classes of compounds; it appears clearly impossible, or at least extremely risky, to relate it with the mechanism of the reactions.

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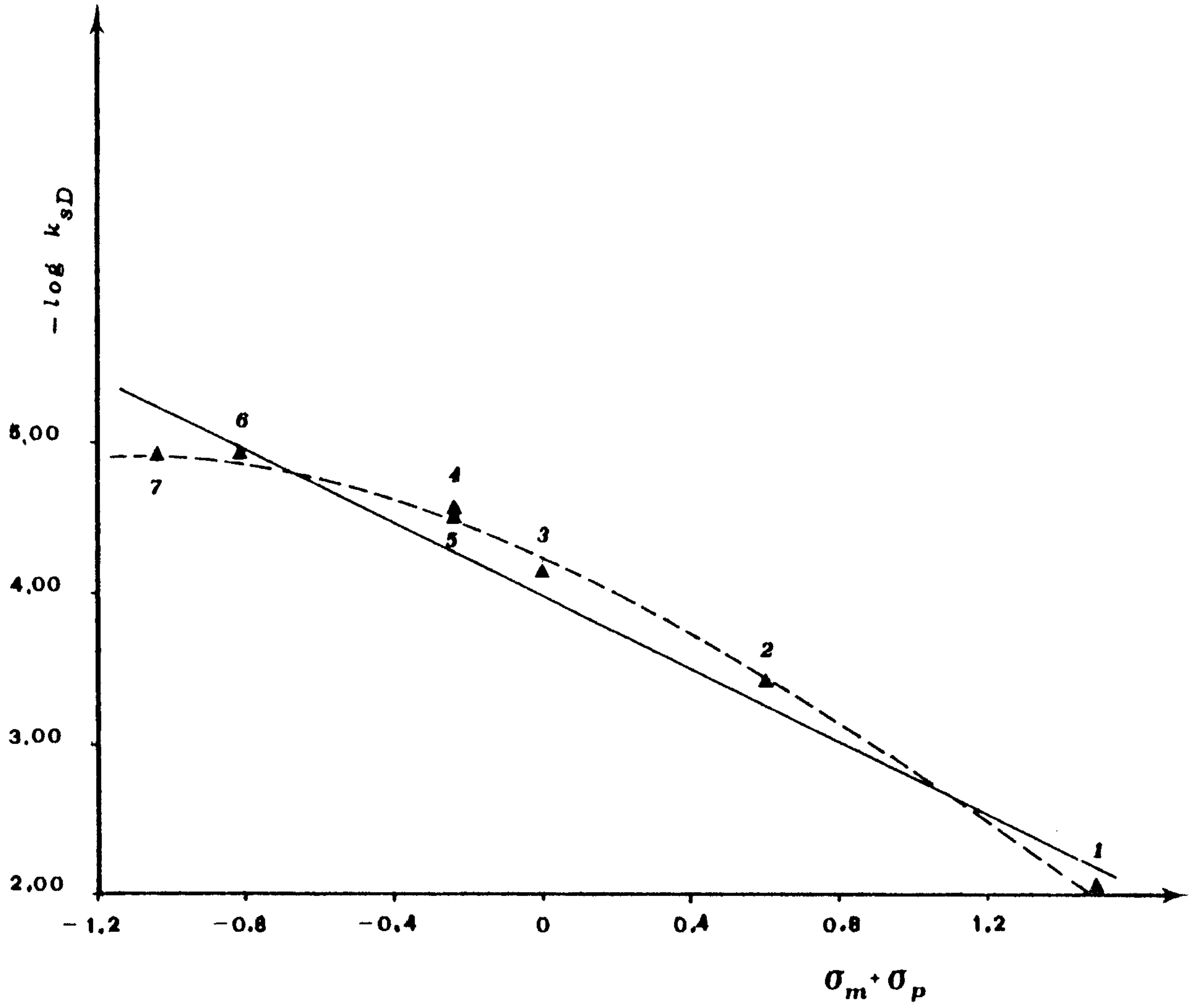

FIGURE 2 Plot of log k_{sD} versus $\sigma_m + \sigma_p$. The best straight line is log $k_{sD} = 1.1836(\sigma_m + \sigma_p) - 4.0449(r^2 = 0.9493)$; the slope is $\rho_D = 1.18 \pm 0.1$. The dotted line represents the best quadratic curve fitted by the method of least squares log $k_{sD} = 0.32393(\sigma_m + \sigma_p)^2 + 1.03995(\sigma_m + \sigma_p) - 4.25558(r^2 = 0.9924)$.

Furthermore, even in the same class of compounds the pronounced drop-off in the primary hydrogen isotope effect observed for the compounds 6 and 7 asks for a different rate-limiting step. The maximum found in the region of $\sigma_m + \sigma_p = -0.3$ is to be related, following Westheimer, with the maximum symmetry of the transition state structure.[11]

As a conclusion, while once again it seems extremely hazardous the simple utilization of the primary hydrogen isotope effect in the prediction of a reaction mechanism, more useful information can possibly be drawn by a careful comparison between the transition states with similar or equivalent structure, that is a comparative examination of the trends of best quadratic curve for different classes of compounds.

So a comparative study of the substituent effect in the benzo ring on the primary hydrogen isotope effect at position 2 in benzoxazole, benzoselenazole, benzothiophene, benzofuran and benzoselenophene could hopefully lead to rationalize the contradictory behaviours manifested by the heteroatoms examined.

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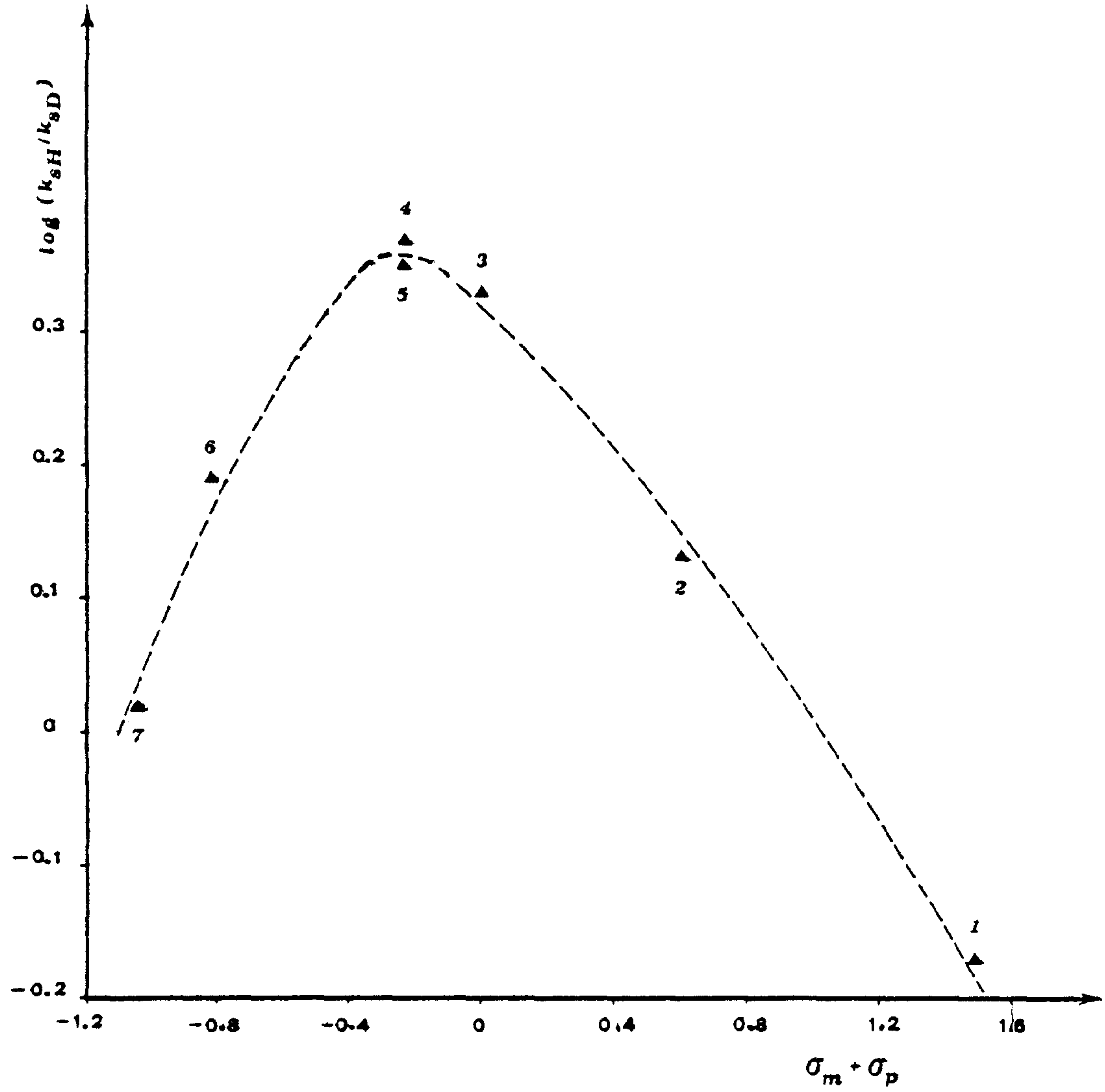

FIGURE 3 Plot of $\log(k_{sH}/k_{sD})$ versus $\sigma_m + \sigma_p$. The dotted line represents the best quadratic curve fitted by the method of least squares $\log(k_{sH}/k_{sD}) = -0.23587(\sigma_m + \sigma_p)^2 - 0.003697(\sigma_m + \sigma_p) + 0.32384(r^2 = 0.8071)$.

EXPERIMENTAL

The ^1H nmr spectra were recorded on a Perkin–Elmer R 12 B spectrometer, using TMS as internal standard.

6-Nitrobenzothiazole, 5-Chlorobenzothiazole, 6-Methylbenzothiazole, 5-Methylbenzothiazole and 6-Aminobenzothiazole were prepared as previously reported.[1,2]

1-Benzothiazole is commercial product, purified by standard methods for use in kinetic measurements of isotopic exchange.

6-Dimethylaminobenzothiazole was prepared by some modifications of the methods of Heller *et al.*, and Bogert *et al.*[12]

The 2-deuterated derivatives were prepared as previously reported.[6]

The experimental conditions for kinetic measurements of isotopic exchange were the same reported in detail in the previous papers.[1–6] In this connection, see also the table of this paper.

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