

Base-Catalyzed Hydrogen-Deuterium Exchange in Benzo Derivatives of
Five-membered Aromatic Heterocycles. Part III. A Comparative
and Systematic Study of the 1-Benzothiophene, Benzofuran,
Benzothiazole and Benzoxazole Systems

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The rates of base-catalyzed hydrogen-deuterium exchange at C-2 in 1-benzothiophene, benzofuran, benzothiazole and benzoxazole were studied. For benzothiophene and benzofuran the relative second-order rate constants of hydrogen-deuterium exchange were 4:1, while for benzothiazole and benzoxazole they were 1:20. These data can be explained by assuming that the sulphur heteroatom interacts electronically with the atom in position 3 of the five-membered ring. While, very probably, the d-orbital conjugation cannot depend much on the atom in position 3, the polarization phenomena can vary more with the atom in position 3. For this reason it was thought that the electronic activity of the sulphur heteroatom is due to polarization phenomena rather than d-orbital interaction.

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In our previous papers (1,2), the second-order rate constants of base-catalyzed hydrogen-deuterium exchange at C-2 of the thiazole ring in thiazolo[4,5-*c*]pyridine and in some 5- and 6-substituted benzothiazoles were studied. Careful examination of these rate constant values produced some interesting conclusions.

First, the reactivity of thiazolo[4,5-*c*]pyridine is practically the same as that of 5-nitrobenzothiazole, indicating in this case a nearly complete equivalence between an aza and a C-NO₂ group (1), in accordance with Mangini's assumption (3).

Second, the sulphur and the nitrogen heteroatoms of the thiazole ring have, in these reactions, similar activity in the transmission of the substituent effects from the benzo ring to the C-2 of the thiazole ring ($\rho_N = 0.985 \pm 0.135$ and $\rho_S = 1.315 \pm 0.135$). Therefore, while in other reactions only the nitrogen heteroatom is active, these reactions clearly show a considerable stabilization of the α -carbanion due to the sulphur heteroatom as well (2).

A third and general conclusion is that the study of the base-catalyzed hydrogen-deuterium exchange rate constants in these compounds gives much information concerning the electronic properties of the compounds and of the component heteroatoms. However, from our

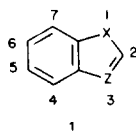
preliminary data it cannot be concluded that the activity of the sulphur heteroatom is due to polarization phenomena, in accordance with some recent theories (4), rather than by d-orbital interaction, according to many previous papers (5,6), which at present are being questioned by various authors (7).

Taking into consideration the results already obtained from our previous investigations and in an attempt to better clarify the details of the much debated activity of the sulphur heteroatom in these reactions, the rates of base-catalyzed hydrogen-deuterium exchange at C-2 in benzothiophene, benzofuran, benzothiazole and benzoxazole were studied and the results are reported in this preliminary paper.

Results and Discussion.

We have measured the rates of base-catalyzed hydrogen-deuterium exchange at C-2 in 1-benzothiophene, benzofuran and benzoxazole, under the same experimental conditions employed for the 5- and 6-substituted benzothiazoles, as reported in the previous papers (1,2).

The second-order rate constants of base-catalyzed hydrogen-deuterium exchange at C-2 in 1-benzothiophene (1a), benzofuran (1b), benzothiazole (1c) and benzoxazole (1d) are shown in the Table.



X = S, O.
Z = CH, N.

Table

The second-order ($k_s/1 \text{ mol}^{-1} \text{ sec}^{-1}$) rate constants for base-catalyzed hydrogen-deuterium exchange at C-2 in benzothiophene (**1a**), benzofuran (**1b**), benzothiazole (**1c**) and benzoxazole (**1d**) ($10^{-1} M$) in deuteriomethanol with sodium methoxide (10^{-1} to $1 M$) at 25° , and the ratios k_S/k_O of the second-order rate constants in two analogous compounds containing sulphur and oxygen as heteroatoms.

Compound	X	Z	$k_s/$ $1 \text{ mol}^{-1} \text{ sec}^{-1}$	k_S/k_O
1a	S	CH	2.29×10^{-7}	4
1b	O	CH	5.83×10^{-8}	
1c (a)	S	N	1.21×10^{-4}	
1d	O	N	2.41×10^{-3}	

(a) This value was reported from the previous paper (1).

From a comparison of the kinetic data, three conclusions can be drawn.

First, the second-order rate constants of hydrogen-deuterium exchange in the aza derivatives were considerably greater than those relative to the corresponding carbo derivatives. This predictable fact, based upon analogous cases (5), can be ascribed to the higher stabilization of the α -carbanion by the nitrogen heteroatom rather than by the $-\text{CH}=\text{}$ group.

Second, the relative second-order rate constants of hydrogen-deuterium exchange at C-2 in benzothiophene and benzofuran (ratio $k_S/k_O = 4$) were 4:1, in good agreement with what was found, under very different experimental conditions (ratio $k_S/k_O = 4$ in $0.57 M$ potassium ethoxide in deuterioethanol at 140°), by Zatssepina, *et al.*, (5,8). This occurrence was ascribed, by these and previous authors in analogous cases, to the ability of the sulphur atom to considerably stabilize the α -carbanions by d-orbital conjugation (5,6).

In the third conclusion, the relative second-order rate constants of hydrogen-deuterium exchange at C-2 in benzothiazole and benzoxazole (ratio $k_S/k_O = 5.0 \times 10^{-2}$) were 1:20. This unusual behaviour of a sulphur compound in respect to the analogous oxygen compound, in considerable contrast with many previous papers and theories (5,6) on the enhanced stabilization of the α -carbanions by the sulphur heteroatom through the d-orbital overlap, was found and discussed also by

Todesco, *et al.*, (9) in a previous preliminary investigation.

The rates of base-catalyzed hydrogen-deuterium exchange at C-2 in benzothiazole and benzoxazole were also investigated by Zatssepina, *et al.*, (8,10) in $0.57 M$ potassium ethoxide in deuterioethanol at 140° . Under these conditions, the ratio of the rate constants of hydrogen-deuterium exchange in the two compounds above-mentioned (k_S/k_O) was 1.6×10^{-1} ; therefore, the rate constant for benzoxazole is 6 times as great as that of benzothiazole. From these data and those pertinent to benzothiophene and benzofuran, by the Russian authors, it was concluded that the d-orbital interaction is always operative, in greater or in smaller amounts, for the sulphur heteroatom and outweighs the inductive effect of the more electronegative oxygen atom.

Our data, reported in the present and previous papers, together with those of Todesco, *et al.*, and those of Zatssepina, *et al.*, can also all be justified and explained by the assumption that the sulphur heteroatom interacts electronically with the atom present in position 3 of the five-membered ring.

Very probably, in our opinion, while the d-orbital conjugation cannot depend to such a large extent upon the atom in position 3, the polarization phenomena can vary more with the atom present in position 3. For this reason it was thought that the sulphur heteroatom, as a general rule, exhibits its electronic activity by polarization phenomena rather than by the d-orbital conjugation.

In fact one can hypothesize that in benzothiophene the greater polarizability by the sulphur heteroatom electrons, as shown by Streitwieser, *et al.*, (4) determines the greater stabilization of the relative α -carbanion, compared with that of benzofuran. In benzothiazole, on the contrary, the nitrogen heteroatom could produce a preliminary polarization of the sulphur heteroatom electrons unfavorable to the formation and subsequent stabilization of the relative α -carbanion, compared with that of benzoxazole.

For confirmation of this behaviour, investigations on base-catalyzed hydrogen-deuterium exchange in the 5- and 6-substituted derivatives of benzothiophene, benzofuran and benzoxazole are in progress in our laboratories, in order to determine exactly the activity of the sulphur, oxygen, nitrogen and carbon atoms in the transmission of the substituent effects from the benzo ring to the position 2 of the five-membered rings, as previously investigated for the benzothiazole system (1,2).

Obviously, from these data one can also measure the different abilities of the sulphur, oxygen, nitrogen and carbon atoms to stabilize the α -carbanion.

In the event that these data do not give clear and unequivocal information concerning the details of the electronic activities of these atoms, in particular those of the sulphur heteroatom, at present much debated, we will

investigate the mechanisms of the base-catalyzed hydrogen isotope exchange in their single steps, in order to determine, in each case, the rate-limiting steps.

In our opinion, studying the kinetic isotope effects, according to many previous papers on this matter (5,11), can possibly also completely elucidate the problems in question.

EXPERIMENTAL

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

Benzothiophene, benzofuran and benzoxazole were commercial products and were purified by standard methods for use in kinetic measurements of isotopic exchange.

Kinetic measurements of hydrogen-deuterium exchange. The experimental conditions were the same employed for the measurements of base-catalyzed hydrogen-deuterium exchange in the 5- and 6-substituted benzothiazoles (1,2). In this connection, see also the Table of this paper.

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