

Deuteriodeprotonation in some Borazarothienopyridines and Thienopyridines

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Deuteriodeprotonation of some substituted 4,5-borazarothieno[2,3-*c*]pyridines (I) and 7,6-borazarothieno[3,2-*c*]pyridines (II) has been studied by the nmr technique. Exchange occurred predominantly in the 3-position, and the effect of methyl substitution on rate is discussed. The rates of exchange in some derivatives of I and II were compared with those of the isoelectronic thieno[2,3-*c*]pyridines (III) and thieno[3,2-*c*]pyridines (IV). Similar rates were obtained, confirming the aromatic nature of I and II. The deuteriodeprotonation of 4-methyl-4,5-borazarothieno[2,3-*c*]pyridine (Ic), 7-methyl-7,6-borazarothieno[3,2-*c*]pyridine (IIc), 4-methylthieno[2,3-*c*]pyridine (IIIc), and 7-methylthieno[3,2-*c*]pyridine (IVc) were measured at different concentrations of deuteriosulfuric acid and different temperatures, showing that the protonated heterocycles are substrates in the deuteriodeprotonation reaction. Standard rates at pH 0 and 100° were calculated for these systems.

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In previous investigations, it has been demonstrated that thieno-fused 3,2-borazapyridines, such as 4,5-borazarothieno[2,3-*c*]pyridines (I) and 7,6-borazarothieno[3,2-*c*]pyridines (II) undergo electrophilic aromatic substitution reactions, such as nitration and bromination in strongly acidic media (1,2). The substrates under these conditions are most probably the protonated form (on the pyridinic nitrogen), and nitration occurs predominantly in the 3-position (1), while bromination occurs at the 3- and 2,3-positions (2). In the nitration of system I ($R'' = H$), 10-25% of the 2-nitro isomer was also formed, while II ($R'' = H$) only gave the 3-isomer (1). Introduction of a methyl group in the 4-position of II led to the formation of approximately equal amounts of the 2- and 3-nitro isomers, while introduction of methyl groups in other positions in the borazapyridine ring-part of both I and II only had small effects on the isomer distribution (2). In order to obtain more quantitative information on differences in the reactivity of the 2- and 3-positions in electrophilic substitution in systems I and II and on the effect of methyl substitution on the reactivities, we have

studied the rates of hydrogen-deuterium exchange under strongly acidic conditions by the nmr technique. Concentrations of deuteriosulfuric acid between 84.7 and 96.0% were used, and the exchange proceeded conveniently between 50-75°. The hydrogen-deuterium exchange for a few derivatives of I and II was also compared with

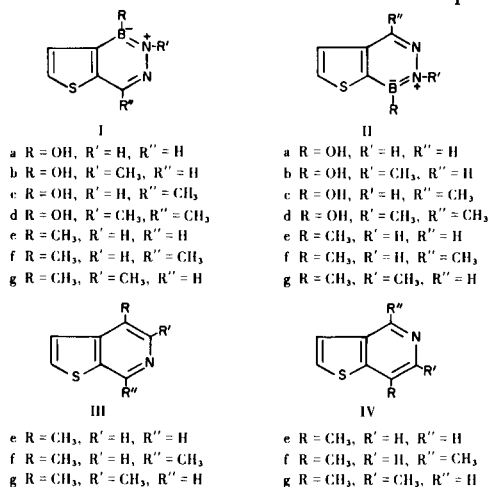


Table I

Pseudo-first Order Rate Constants for Deuteriodeprotonation of some Hydroxyborazarothienopyridines
(0.0005 molar solution in 0.50 ml. of 96.7% Deuteriosulfuric Acid)

Compound	57.0 °C		65.2 °C		72.9 °C	
	$k_2 \cdot 10^5$ sec. ⁻¹	$k_3 \cdot 10^5$ sec. ⁻¹	$k_2 \cdot 10^5$ sec. ⁻¹	$k_3 \cdot 10^5$ sec. ⁻¹	$k_2 \cdot 10^5$ sec. ⁻¹	$k_3 \cdot 10^5$ sec. ⁻¹
Ia (3)	0.43	4.27	1.21	7.67	3.10	17.5
Ib (4)	0.43	5.70	2.22	10.10	6.17	27.7
Ic (2)	0.58	3.80	1.10	5.70	3.33	15.2
Id (2)	1.03	4.80	2.21	8.83	6.25	17.3
IIa (4)	1.46	3.57	3.57	8.83	8.33	18.3
IIb (4)	1.38	6.17	3.28	13.00	8.17	28.8
IIc (2)	2.43	4.83	5.90	9.83	12.10	24.3
IId (2)	2.23	8.50	5.05	13.80	13.20	35.7

that of the isoelectronic thienopyridines (III, IV) with the same substitution pattern. The exchange was very clean, and no other products could be detected in the nmr spectra before deuteration was complete.

In Table I, the rates for some B-OH derivatives, or rather their anhydrides, are given, as it is known that these B-OH compounds rapidly form anhydrides in concentrated sulfuric acid (2). It can be seen that in the 4,5-borazarothieno[2,3-*c*]pyridine system, hydrogen exchange occurs more selectively than is the case with the 7,6-borazarothieno[3,2-*c*]pyridines. This is apparently due to the fact that while the reactivity of the 3-position is similar in both Ia and IIa, the reactivity of the 2-position in IIa is approximately three times greater than in Ia. Introduction of a methyl group on nitrogen increases the rate of hydrogen exchange both of the 2- and 3-positions of Ib compared to Ia, except at 57°, and Id compared to Ic. In the II-series, on the other hand, *N*-methyl substitution increases the rate of exchange in the 3-position by about 75%, but hardly affects the rate of the 2-position. Introduction of a methyl group in the 7-position of I has a small effect on the reactivity but interestingly, causes a slight decrease of the reactivity of the 3-position, which was hardly expected (*cf.* Ic with Ia and Id with Ib). Of greater interest is the introduction of a methyl group in the 4-position, as now also steric effects (*peri*-effects) could come into play. However, it is evident that such substitution increases the rate of hydrogen exchange of both the 2- and 3-positions (*cf.* IIc with IIa and IIId with IIb), but due to the greater increase of the reactivity of the 2-position leads to diminished selectivity (smaller k_3/k_2 ratio). It is interesting to note that in the nitration reaction the selectivity towards nitration is greater in IIa than in Ia (2) while the opposite is true for deuteration. It is possible that steric hindrance from the *peri*-substituent in the nitration is the reason for this. The effect of methyl groups in increasing the amount of 2-substitution is obvious both for deuteration and nitration for system I. For II, on the other hand, the effect of the 4-methyl group in increasing the proportion of 2-isomer is stronger for nitration than deuteration, probably indicating as mentioned above stronger steric effects in nitration. Good Arrhenius activation energies could not be obtained from the above-mentioned measurements. This could partly be due to anhydride formation or other factors, and the rates obtained give only qualitative information about the reactivity.

In order to avoid this complication and make possible comparison with the isoelectronic thienopyridines, a more detailed investigation of the deuterium exchange of some B-CH₃ derivatives was undertaken. The compounds studied were 4-methyl-4,5-borazarothieno[2,3-*c*]pyridine (Ie) (4), 4,7-dimethyl-4,5-borazarothieno[2,3-*c*]pyridine (If) (2), 4,5-dimethyl-4,5-borazarothieno[2,3-*c*]pyridine (Ig) (4),

7-methyl-7,6-borazarothieno[3,2-*c*]pyridine (IIe) (4), 4,7-dimethyl-7,6-borazarothieno[3,2-*c*]pyridine (IIIf) (2), 6,7-dimethyl-7,6-borazarothieno[3,2-*c*]pyridine (IIIg) (5), and the isoelectronic 4-methylthieno[2,3-*c*]pyridine (IIIe) (6), 4,5-dimethylthieno[2,3-*c*]pyridine (IIIf) (7), 7-methyl-

Table II

Pseudo-first Order Rate Constants for Deuterioprotonation of some B-Methylborazarothienopyridines (0.001 mole in 0.50 ml. of 96.6% Deuteriosulfuric Acid) at 55°

Compound	$k_2 \cdot 10^5$ sec. ⁻¹	$k_3 \cdot 10^5$ sec. ⁻¹
Ie (4)		4.27
If (2)		3.73
IIe (4)	0.47	2.16
IIIf (2)	1.40	5.50

thieno[3,2-*c*]pyridine (IVe) (6), and 6,7-dimethylthieno[3,2-*c*]pyridine (IVg) (7).

In Table II the results of deuterioprotonation of Ie, If, IIe, and IIIf at 55.0° in 96.6% deuteriosulfuric acid are given. The rates for the 3-position do not differ very much from those of the corresponding B-OH derivatives. However, in the [2,3-*c*]-series, the exchange in the 2-position could not be observed under these conditions, while in the [3,2-*c*]-series it appears to be somewhat slower than in the B-OH derivatives. The effect of methyl substitution in the 7-position (*cf.* Ie with If) on exchange in the 3-position is negligible, while methyl substitution in the 4-position of the [3,2-*c*]-system increases the rate of exchange by a factor 2-3 both in the 2- and 3-positions.

A first comparison between the rates of similarly substituted borazarothienopyridines and thienopyridines was made by studying Ig, IIg, IIIg, and IVg at temperatures between 33.9° and 54.0° in 96.8% deuteriosulfuric acid. The rates of deuterioprotonation of the 3-position are given in Table III. The accuracy of these measurements

Table III

Pseudo-first Order Rate Constants (k in sec.⁻¹) for Deuterioprotonation of 4,5-Dimethyl-4,5-borazarothieno[2,3-*c*]pyridine (Ig), 6,7-Dimethyl-7,6-borazarothieno[3,2-*c*]pyridine (IIg), 4,5-Dimethylthieno[2,3-*c*]pyridine (IIIg), and 6,7-Dimethylthieno[3,2-*c*]pyridine (IVg) (0.0005 mole in 0.50 ml. 96.8% Deuteriosulfuric Acid at different temperatures)

Compound	33.9 °C $k_3 \cdot 10^5$	39.5 °C $k_3 \cdot 10^5$	45.0 °C $k_3 \cdot 10^5$	50.0 °C $k_3 \cdot 10^5$	54.0 °C $k_3 \cdot 10^5$
Ig	4.50	8.00	15.0	26.5	42.8
IIg	3.33	6.33	10.3	21.5	24.5
IIIg	29.3	53.5	92.5	186	197
IVg	5.00	8.83	18.3	30.0	40.6

was not high enough to make determination of the thermodynamic functions meaningful. Under these conditions, no exchange of the 2-position was observed in IIIg and IVg. On the other hand, in both borazathienopyridines slow exchange could be observed in the 2-position. Rate constants of $5.8 \cdot 10^{-6} \text{ sec.}^{-1}$ and $18 \cdot 10^{-6} \text{ sec.}^{-1}$ were observed for Ig and IIg, respectively at 54.0° . It can be noted that the rates of the four systems are very similar except for IIIg, which reacts 5-8 times faster than the other three. The thienopyridines are somewhat more reactive than the corresponding borazathienopyridines, and in both systems, the [2,3-*c*]-fused compounds are more reactive than the corresponding [3,2-*c*]-fused compounds. The lower reactivity of the borazaro derivatives is in accordance with the fact that monocyclic 3,2-borazaro-pyridines are more deactivated towards electrophilic substitution than the analogous pyridines (5). The greatest difference between the borazathienopyridines and the thienopyridines lies in the higher reactivity of the 2-position of the former, which previously has been observed in the higher selectivity in the nitration and bromination of thienopyridines than in borazathienopyridines (5). Of course the similarity in reactivity between the borazathienopyridine and the thienopyridines gives evidence for the aromatic nature of the former.

In order to be able to compare the rates of deuterio-deprotonation of our substrates with other systems, the procedure recently developed by Katritzky and coworkers for obtaining standard rate constants (k_0) for acid-catalyzed exchange reactions at pH 0 and 100° (8) which requires the construction of rate profiles was applied to Ie, IIe, IIIe, and IVe. Their deuterio-deprotonation was measured in detail at 75° at different concentrations of deuterio-sulfuric acid and also at different temperatures in the interval between 54 and 75° . The logarithm of the pseudo-first order rate constants for exchange in the 3-position at different acidities is given in Table IV. Under these ex-

perimental conditions exchange in the 2-position was not observed. The % deuteriosulfuric acid values were corrected according to reference (8). The slopes and the intercepts of the rate profiles (plotting $\log k$ vs. $-D_0$) are obtained from a statistical analysis, the results of which are given in Table V. The $\log k_0$ values (standard rates)

Table V

Rate Profiles of Data of Table IV

Substrate	Slope	Intercept	Corr. Coeff.	$-\log k_0$
Ie	0.87	10.35	0.992	9.09
IIe	0.89	10.71	0.973	9.45
IIIe	0.87	10.20	0.978	8.94
IVe	0.84	10.66	0.977	9.40

were obtained by adding to the intercepts (which give $\log k$ at $H_0 = 0$ and $T = 75^\circ$) the quantity 1.26, *i.e.* assuming, as Katritzky *et al.* (8) an average ΔH^\ddagger of $30 \text{ kcal/mole}^{-1}$. The values obtained for the slopes clearly indicate that the reactions proceed on the protonated species in all cases. Protonation in Ie and IIe occurs on the "pyridinic" nitrogen, as the nmr spectra in sulfuric acid show an additional splitting of 7 Hz for the H-7 resonance of Ie and IIIe and for the resonance H-4 of IIe and IVe. These splittings are assigned to the coupling of these hydrogens with the proton at the neighboring nitrogen. According to these standard rates, all four compounds are much more reactive than benzene (where $\log k_0$ is -11.0 (9)) but less reactive than thiophene ($\log k_0$ is -2.4 at C-2 and -6.0 at C-3 (10)), as well as benzo[*b*]thiophene for which an estimated value of -4.7 was obtained for C-3 (11).

From the standard rates, it follows that the [2,3-*c*]-fused systems Ie and IIIe are 2-3 times more reactive than the corresponding [3,2-*c*]-fused systems IIe and IVe. This was already qualitatively indicated by deuterio-deprotonation measurements of thieno[2,3-*c*]pyridine and

Table IV

Pseudo-first Order Rate Constants (k in sec.^{-1}) for Deuterio-deprotonation at the 3-Position of 4-Methyl-4,5-borazathieno[2,3-*c*]pyridine (Ie), 7-Methyl-7,6-borazathieno[3,2-*c*]pyridine (IIe), 4-Methylthieno[2,3-*c*]pyridine (IIIe), and 7-Methylthieno[3,2-*c*]pyridine (IVe) in Deuteriosulfuric Acid/Deuterium Oxide at 75°C .

Deuteriosulfuric Acid (%)	$-D_0$ (75°)	$-\log k_{Ie}$	$-\log k_{IIe}$	$-\log k_{IIIe}$	$-\log k_{IVe}$
84.7	7.23	4.08	4.41	4.01	4.54
86.4	7.43	3.96	4.04	3.77	4.44
88.6	7.69	3.58	3.90	3.36	4.33
90.6	7.91	3.44	3.53	3.28	3.88
96.0	8.61	2.90	3.14	2.78	3.44

thieno[3,2-c]pyridine at 55° in 98.3% deuteriosulfuric acid (12). Large differences in the reactivity of the 3-position due to the mode of annelation of the six-membered pyridine ring onto the thiophene ring are not expected as in the Wheland intermediate no conjugative interaction with any position of the six-membered ring is possible. For electrophilic substitution in the 2-position, on the other hand, conjugative interaction with the six-membered ring is possible and it would be predicted that the [3,2-c]-isomer should be more reactive than the [2,3-c]-isomer, as in the latter case one of the resonance structures of the Wheland intermediate has a positive charge on the pyridinic nitrogen. This result was really obtained in a parallel study on unsubstituted thienopyridines (13). Moreover, in the isoelectronic borazaropyridines, as mentioned above, it was found that the 2-position of 7,6-borazarothieno[3,2-c]pyridine derivatives was more reactive than the corresponding position in 4,5-borazarothieno[2,3-c]pyridine. As is evident from Table V, the standard rate of the borazarothienopyridine Ie is very similar to the thienopyridine IIIe and that of IIe even more so to IVe, providing evidence for the aromatic nature of the borazaropyridine ring. The comparison with unpublished data on the corresponding unsubstituted thienopyridines (13) shows that in general, methyl substitution in the six-membered ring has only minor effects on the reaction rates. This has also been observed for pyrrolopyridines (14).

The rates of deuterioprotonation of Ie, IIe, IIIe, and IVe were also measured at different temperatures and one constant wt. % of deuteriosulfuric acid (Table VI), and values for ΔH^\ddagger and ΔS^\ddagger (97.5%) were calculated (Table VII). However, when the standardization procedure according to Katritzky *et al.* (8) is to be applied, the activation parameters (ΔH^\ddagger , ΔS^\ddagger) at constant D_0 are needed (8,15). The differences between these parameters and the corresponding quantities at constant wt. % of deuteriosulfuric acid are quite large, and the following relationships were developed (15), for the many cases when the rate profile is available at one temperature only and the variation of rate with temperature is given at constant %

Table VI

Variation of Rate Constants (k in sec.⁻¹)
with Temperature at a Given Acidity

(i) Experimental Rates at a Single % Deuteriosulfuric Acid (97.5)

Substrate	-log k 54 °C	61 °C	66 °C	75 °C
Ie	3.50	3.29	3.08	2.73
IIe	3.75	3.47	3.27	3.24
IIIe	3.40	3.22	2.99	2.90
IVe	4.05	3.83	3.57	3.38

(ii) Calculated Rates at a Single D_0 Value (-9.00)

Substrate	3.72	3.35	3.03	2.50
Ie	3.72	3.35	3.03	2.50
IIe	3.97	3.53	3.22	3.00
IIIe	3.62	3.28	2.94	2.67
IVe	4.26	3.89	3.62	3.15

deuteriosulfuric acid.

$$\Delta \bar{H}^\ddagger - \Delta H^\ddagger = 2.303 \text{ RmK}$$

$$\Delta \bar{S}^\ddagger - \Delta S^\ddagger = 2.303 \text{ RmK/T}$$

where m is the slope of the only rate profile available, K is the proportionality coefficient for the variation of D_0 with temperature, and T refers to the standard absolute temperature.

Two methods have been suggested to calculate $\Delta \bar{H}^\ddagger$ and $\Delta \bar{S}^\ddagger$ from ΔH^\ddagger and ΔS^\ddagger . One method requires the use of the two equations just mentioned. The other method (8) requires the recalculation of log k, at each temperature, at a D_0 value intermediate between those corresponding to 97.5% at the individual temperatures. Now 97.5% deuteriosulfuric acid corresponds to the following D_0 values: -9.25 at 54°, -9.07 at 61°, -8.94 at 66°, and -8.73 at 75°, the average value being -9.00. The recalculation of log k values at $D_0 = -9$ was performed from experimental values using the experimental slopes of the rate profiles at 75°, *i.e.* assuming that the slopes do not change with temperature. The activation parameters at constant D_0 were then computed from these new data.

Table VII

Activation Parameters at Constant wt. % Deuteriosulfuric Acid and at Constant D_0 :
 ΔH^\ddagger in kcal/mole⁻¹, ΔS^\ddagger in cal/mole⁻¹ k⁻¹

Substrate	ΔH^\ddagger (a)	ΔS^\ddagger (a)	$\Delta \bar{H}^\ddagger$ (b)	$\Delta \bar{S}^\ddagger$ (b)	$\Delta \bar{H}^\ddagger$ (c)	$\Delta \bar{S}^\ddagger$ (c)
Ie	18.7 ± 1.2	-17.7 ± 3.4	29.8 ± 1.1	15.3 ± 3.1	28.9	9.7
IIe	12.0 ± 3.6	-38.8 ± 10.9	23.6 ± 3.7	-4.4 ± 10.9	22.5	-10.8
IIIe	12.3 ± 2.4	-36.7 ± 7.0	23.4 ± 2.5	-3.5 ± 7.4	22.5	-9.3
IVe	16.3 ± 2.0	-27.4 ± 5.6	26.9 ± 0.3	4.0 ± 1.0	26.2	-0.9

(a) At 97.5% deuteriosulfuric acid. (b) At $D_0 = -9.0$. (c) At constant D_0 : calculated from equations in the text.

The difference obtained with these two methods was small, as is evident from Table VII.

As found previously (8), most of the variation occurs in the entropy term, indicating strong solvent interactions. The $\Delta\bar{H}^\ddagger$ value was near the assumed average value of 30 kcal/mole in two cases, in which the correlation coefficient for the Eyring equation was good.

EXPERIMENTAL

The methods of preparation of the borazarothenopyridines and thienopyridines are given in references 2-7. The B-OH derivatives were purified by repeated crystallization from aqueous ethanol. The other compounds were purified by sublimation before use. Deuteriosulfuric acid of commercial quality was used. Acid of different concentrations was obtained by adding weighed amounts of deuterium oxide. The exact acid concentration was determined by potentiometric titration at the Analytical Department of the Chemical Center.

The deuteriodeprotonations were carried out on a Varian A-60 spectrometer equipped with a temperature regulator. The temperature was regularly checked by using the chemical shifts for ethylene glycol (16). In experiments with longer half-life times than an hour, the tubes were kept in a thermostat between measurements. The variation of temperature was generally less than $\pm 0.15^\circ$.

A weighed amount of 0.0005 mole of the substrate was dissolved at -5.0° in 0.50 ml. of deuteriated sulfuric acid of known concentration. When the substrate had dissolved (after 3-5 minutes), the solution was transferred to an nmr tube with a tight-fitting plastic cap. The solution was thermostated and the spectrum was recorded at appropriate intervals. The rate of exchange was followed by measurement of the integrals of the disappearing signals. The B-methyl or C-methyl groups or the 4- and 7-hydrogen

resonances were used as references. The signals were integrated at least seven times. The first-order rate constants were then calculated by plotting the logarithm of the ratio of the integrals of the disappearing band and the reference against time in the usual way, using the least-squares method.

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