The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXXVIII.[1] Hydrogen Exchange of Isoxazoles and Isothiazoles

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Acid-catalysed deuteriodeprotonation rates are recorded for isoxazole, isothiazole, and some methyl derivatives. The rates are extrapolated to give rate constants at 100° and pH 0 which are compared with those for other heteroaromatic ring systems to provide quantitative estimates of relative reactivity. Quantitative effects of methyl groups provide evidence for the relative degree of bond-fixation, and indicate that the aromaticity increases in the series isoxazole, pyrazole, isothiazole.

We have continued our study of the acid-catalysed hydrogen exchange rates of the fundamental five-membered heteroaromatic rings in our attempts to obtain quantitative measures of their reactivity towards electrophiles. This paper deals with isoxazoles and isothiazoles and allows meaningful comparison of several fundamental systems.

Orientation of Hydrogen Exchange.—Deuteriation reactions were followed by n.m.r. spectroscopy: chemical shifts for the neutral species of isoxazoles [2] and isothiazoles [3] (reported in Table 1 together with pK_a values) agree with literature data. Isoxazole, isothiazole, and their 3- and 5-methyl derivatives all underwent exchange at the 4-position, as was shown by the disappearance of the 4-proton signal. Further heating of these compounds with D_2SO_4 of various concentrations showed no further change of the n.m.r. spectrum under moderate conditions; under forcing conditions the compounds decomposed. 4-Methylisoxazole underwent extensive decomposition on heating at 120° in 40% D_2SO_4; at lower temperatures the n.m.r. spectrum remained unchanged and no evidence for acid-catalysed hydrogen exchange was found.

EXPERIMENTAL

Spectroscopic and kinetic procedures were as previously reported.[4] Results are shown in Table 2.

Preparation of Compounds.—The following were prepared by the literature methods quoted: isoxazole, b.p. 92—94° (lit.,[5] b.p. 93—95°), 4-methylisoxazole (from 1,1,3,3-tetraethoxy-2-methylpropane [6]) b.p. 125—127° (lit.,[7] b.p. 126—128°, and 5-methylisothiazole, b.p. 44—46° at 18 mmHg (lit.,[8] b.p. 44—46° at 18 mmHg). 3- and 5-Methylisoxazoles were kindly given by Dr. A. J. Boulton; isothiazole and 3-methylisothiazole were commercial specimens (May and Baker).

TABLE 1

N.m.r. chemical shifts (τ; 60 MHz), coupling constants (Hz), and pK_a values for isoxazoles and isothiazoles

	Solvent	3-R	4-R	5-R	$J_{3,4}$	$J_{4,5}$	pK_a [a]
Isoxazole	CCl_4	1·77	3·68	1·52	1·0	1·8	−2·97 [b]
	30% D_2SO_4	1·22	3·30	1·35	1·4	2·0	
3-Methylisoxazole	$CDCl_3$	7·74	3·87	1·74		1·8	−1·62
	30% D_2SO_4	7·29	2·93	1·07		2·0	
5-Methylisoxazole	$CDCl_3$	1·96	4·06	7·58	1·0		
	30% D_2SO_4	0·87	3·00	7·25	1·4		−2·01
Isothiazole	$CDCl_3$	1·40	2·7	1·30	1·2	4·0	
	CCl_4	1·50	2·75	1·35	1·2	4·0	−0·52
	30% D_2SO_4	0·92	2·24	0·47	3·0	6·0	
3-Methylisothiazole	CCl_4	7·54	3·00	1·46		5·0	0·48
	30% D_2SO_4	7·28	2·44	0·67		6·0	
5-Methylisothazole	CCl_4	1·79	3·12	7·43	1·5	0·7 [c]	0·02
	30% D_2SO_4	1·92	3·31	8·00	2·4		

[a] At 25 °C. [b] A. G. Burton, Ph.D. Thesis, University of East Anglia, 1971. p. 68. [c] Coupling between 4-H and 5-R.

DISCUSSION

Mechanism of Reaction.—The rate profiles for the isoxazoles (Figure 1) indicate that in each case the reaction is proceeding on the free base. At acidities below the pK_a values for these compounds (which are at 100° in the region of −1 to −2, see Table 3) the rate increases with acidity, with rate profile slopes in the region of +0·5. At acidities greater than the pK_a, the rates are essentially invariant with acidity.

Similarly, the slightly negative rate profile slopes for the isothiazoles (Figure 2) indicate that these compounds

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[8] M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 1964, 446.

also undergo exchange as the free-base species. Reaction on the free base as a majority species was not observed since the pK_a values of the isothiazoles at the temperatures used fall in the pD region.

TABLE 2

Pseudo-first-order rate constants (k in s^{-1}) for deuteriodeprotonation

Isoxazole at 156°; exchange at the 4-position

D_2SO_4 (%)	$-D_0$ (156°)	$-\log k$
6·8	0·07	4·17
14·4	0·52	4·15
33·9	1·71	3·45
53·9	3·10	3·06
73·0	4·77	3·14
86·6	6·16	3·05

Isoxazole at 110°; exchange at the 4-position

	$-D_0$ (110°)	
9·3	0·27	6·03
35·4	1·96	5·30
39·0	2·22	5·24
46·1	2·74	5·13
50·0	3·04	4·73
57·0	3·60	4·46

3-Methylisoxazole at 80°; exchange at the 4-position

	$-D_0$ (80°)	
12·4	0·51	6·46
31·6	1·77	5·72
53·7	3·51	5·75
59·0	4·03	5·85
67·9	5·02	5·80

5-Methylisoxazole at 80°; exchange at the 4-position

	$-D_0$ (80°)	
8·3	0·24	5·00
40·7	2·47	4·48
59·5	4·07	4·21
73·3	5·71	4·32

Isothiazole at 166°; exchange at the 4-position

	$-D_0$ (166°)	
42·1	2·23	5·24
69·3	4·20	5·75
72·2	4·58	5·74
85·4	5·47	5·92

3-Methylisothiazole at 166°; exchange at the 4-position

	$-D_0$ (166°)	
28·0	1·22	4·86
43·7	2·35	4·96
56·0	3·20	4·96
72·5	4·60	5·49
85·4	5·47	5·50

5-Methylisothiazole at 143°; exchange at the 4-position

	$-D_0$ (143°)	
27·9	1·33	4·98
50·2	2·90	5·28
73·9	5·00	5·49
97·5	7·66	5·63

Standard Rates.—k_0 For rates at standard conditions (pH = 0 and T = 100°) were obtained by extrapolation from the rate profiles by our standard procedure[9,*] (Table 3). For the isoxazoles studied extrapolations were carried out independently (a) on that part of the rate profiles relating to exchange occurring on the free base as a majority species and (b) on the free base as minority species; in each case good agreement was obtained between the values of k_0 found. Values calculated from rate profiles determined at different temperatures also agreed well. Average values of k_0 are reported in the last column of Table 3. The variation of pK_a values of isoxazole and isothiazole with temperature has been assumed to follow equation (1), derived for pyridine pK_a values.[9]

$$pK_a(100°) = 0{\cdot}82pK_a(25°) + 0{\cdot}09 \quad (1)$$

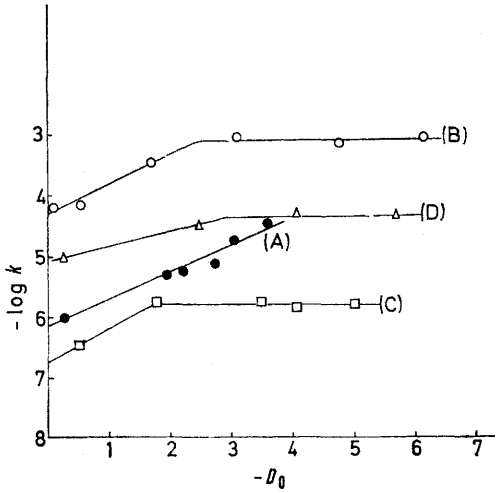


FIGURE 1 Rate profile for deuteriodeprotonation in D_2SO_4 of (A) isoxazole at 110°, (B) isoxazole at 156°, (C) 3-methylisoxazole at 80°, (D) 5-methylisoxazole at 80°

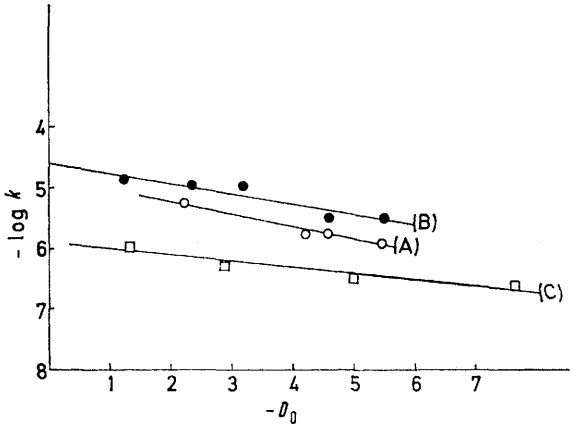


FIGURE 2 Rate profile for deuteriodeprotonation in D_2SO_4 of (A) isothiazole at 166°, (B) 3-methylisothiazole at 166°. (C) 5-methylisothiazole at 143°

* Attention should be drawn to the fact that the corrections of acid due to substrate protonation are more complicated than indicated by the equation given in ref. 9. This equation (i) applies only for corrections at pH > 0. For corrections at H_0 < 0, equation (ii), which treats H_2SO_4 as a monobasic acid, is to be used. In our paper,[9] the correct equation (ii) and not (i) was applied, but this was not made clear in the text.

wt% of acid = $(Ewz - 4904y)/(Ez - 49{\cdot}04y)$ for H_2SO_4 (i)
wt% of acid = $(Ewz - 8908y)/(Ez - 89{\cdot}08y)$ for H_2SO_4 (ii)

[9] A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1065.

Standardised k_0 values were also calculated for 3,5-dimethylisoxazole, 3,5-dimethylisothiazole and 2,3,5-trimethylisothiazolium cation, kinetic data for which were reported previously.[10]

Activation by Methyl Groups.—Increments in log k_0 for exchange at the 4-position caused by a 3- and/or a 5-methyl group in isoxazole and isothiazole are compared with the corresponding increments for 1-methylpyrazole [4] in Table 4.

Whereas the combined effect of a 3- and a 5-methyl group is similar in each ring system and whereas again in each ring system this combined effect is nearly the sum of the individual effects of the 3- and 5-methyl groups separately, the actual increments for a 3- and 5-methyl group vary significantly according to the heteroatom involved. The difference between the increments in log k_0 for a 3- and 5-methyl group, which should vary directly with bond fixation in the ground state, is larger for isoxazole (1·4) than for pyrazole (0·7) and for isothiazole (0·2). This indicates that the aromaticity increases in the same order and contributes the first quantitative evidence that the 1,2-azoles follow the same aromaticity order as furan < pyrrole < thiophen.[11]

The increments in log k_0 for exchange at the 4-position due to a 5-methyl group are related to the increases in rate caused by a 5-methyl group on trifluoroacetylation at the 2-position of furan (3·2), thiophen (2·6), and pyrrole (1·4).[12] The increments for hydrogen exchange of the azoles are somewhat smaller which reflects either a less selective reaction or different nucleophilicity of the parent diazoles, but the same trend is observed, emphasising the higher sensitivity to structural changes in the oxygen heterocycles.

TABLE 3

Standard rates at pH 0 and 100°

Compound	Ref.	T/°C	Position	Species charge	Range % D_2SO_4	Range $-D_0(T)$	Range $-\log k$(stoich)	d[log k(stoich)] / d $(-D_0)$	$-\log k$(stoich) at $D_0 = 0$	$-\log k$(stoich) at $D_0 = 0$, T = 100°	pK_a at 25° [a]	pK_a at 100° [b]	m	$-\log k_0$ Calculated	$-\log k_0$ average
		156	4	0(maj)	7—40	0·1—1·7	4·2—3·5	0·47	4·28	6·57				6·57	
Isoxazole	c	156	4	0(min)	54—87	3·1—6·2	3·1—3·1	0·00	3·08	5·37	−2·57	−2·01	0·80	6·98	7·6
		110	4	0(maj)	9—57	0·3—3·6	6·0—4·5	0·46	6·21	6·67				6·67	
3-Methylisoxazole	c	80	4	0(maj)	12—32	0·5—1·8	6·4—5·7	0·59	6·76	5·76				5·76	
		80	4	0(min)	32—68	1·8—5·0	5·7—5·8	0·00	5·78	4·78	−1·22	−0·91	0·76	5·47	5·6
5-Methylisoxazole	c	80	4	0(maj)	8—41	0·2—2·5	5·0—4·5	0·23	5·06	4·06				4·06	
			4	0(min)	60—73	4·1—5·7	4·2—4·3	0·00	4·27	3·27	−1·61	−1·23	0·82	4·28	4·2
3,5-Dimethylisoxazole	d	80	4	0	24—96	1·3—8·5	4·0—5·7	−0·24	3·51	2·51	−1·21	−0·90	1·05	3·46	
	d	50	4	0	45—72	3·0—6·0	5·5—5·9	−0·12	5·16	2·44	−1·21	−0·90	1·05	3·39	3·4
Isothiazole	c	166	4	0	42—72	2·2—4·6	5·2—5·9	−0·20	4·86	7·50	−0·12	−0·01	0·98	7·51	7·5
3-Methylisothiazole	c	166	4	0	17—73	0·7—4·6	4·9—5·5	−0·17	4·60	7·24	0·88	0·81	0·96	6·46	6·5
5-Methylisothiazole	c	143	4	0	28—98	1·3—7·7	5·0—5·6	−0·10	4·93	6·73	0·42	0·43	0·99	6·30	6·3
3,5-Dimethylisothiazole	d	128	4	0	36—65	1·9—4·2	5·0—5·8	−0·31	4·45	5·66	1·52	1·34	1·02	4·30	4·3
		128	4	+	78—96	5·6—7·6	6·0—4·8	0·52	8·89	10·10				10·10	10·1
2,3,5-Trimethylisothiazolium cation	d	128	4	+	64—95	4·1—7·5	6·7—4·8	0·65	8·94	10·15				10·15	10·2

[a] Corrected for deuteriated media (see ref. 9). [b] Variation with T calculated by equation (1) (see text). [c] This work. [d] Ref. 10.

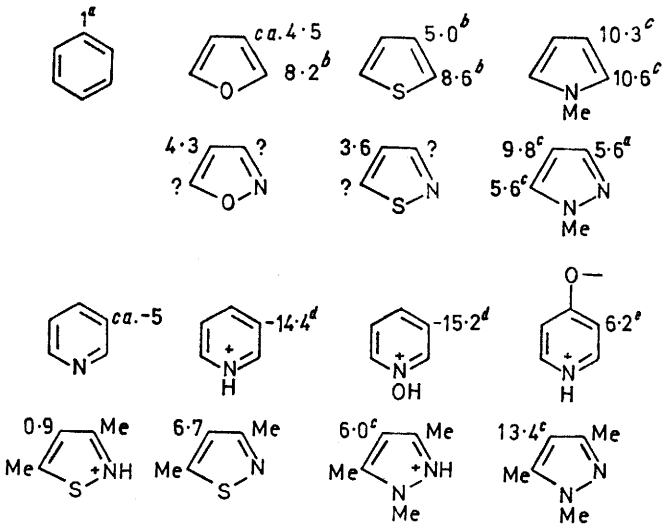
TABLE 4

Increments in log k_0 for methyl substitution in isoxazole and isothiazole

Extra methyl(s) (position)	Heteroatom O	S	N(Me) [a]
3	1·1	1·0	0·9
5	2·5	1·2	1·6
3,5	3·3	3·2	3·6

[a] Data from ref. 10.

Partial Rate Factors.—log(Partial rate factors) for isoxazole and isothiazole, calculated with respect to one position of benzene (log $k_0 = -11{\cdot}0$),[1] are reported in the Scheme, together with values for some other heterocyclic compounds.[4]



SCHEME

[a] Ref. 1. [b] Ref. 13. [c] Ref. 4. [d] Ref. 14. [e] Ref. 9.

The partial rate factors for the 1,2-diazoles cannot be explained by a simple additivity of the effects of the two

[10] A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2365.
[11] M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocyclic Chem.*, in the press.
[12] S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71.
[13] S. Clementi and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1077.
[14] S. Clementi, C. D. Johnson, and A. R. Katritzky, work in preparation.

individual heteroatoms, as already pointed out [4] for pyrazole. By comparison with furan, thiophen, and pyrrole, the electron-withdrawing effect of the 2-nitrogen atom appears to be quite small; the observed deactivations of 0·2, 1·4, and 0·5 log units respectively are far lower than that of *ca.* 5 log units expected on a simple basis with $\sigma^+_{m-N} = 0·7$.† For isoxazole and isothiazole, a reactivity at the 4-position lower than that of benzene is expected on the basis of simple additivity ($\sigma^+_{\beta-O}$ −0·44,[17] and $\sigma^+_{\beta-S} = -0·52$),[18] whereas the actual partial rate factors show reactivity enhanced some 10^4 times. This supports the claim [19] that the high reactivity towards electrophiles of five-membered heterocyclic rings is not dependent on high π electron density at the ring carbon atoms. 1-Methylpyrazole is by far the most reactive of the 1,2-diazoles, in agreement with the large activation due to an NMe group ($\sigma^+_{\beta-NMe} = -1·4$).[4] However, the reactivity order between isoxazole and isothiazole is the reverse of that found for the β-positions of furan and thiophen, indicating different interactions with the 2-nitrogen atom, possibly related to the aromaticity of these compounds.

The isothiazole conjugate acid (which possesses the same k_0 as the 2-methoisothiazolium cation) is some 10^6 times less reactive than the corresponding free base: this reactivity difference is similar to that found [4] for the 1-methylpyrazole series.

Comparison of the five- and six-membered rings (Scheme) discloses reactivities differing by 25 log units. However, in all cases where an electron donor and an electron-withdrawing group occur in the same compound, the activating effect of the donor group far outweighs the deactivation due to the acceptor group.

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† This value for σ^+_{m-N} is a rough average between our suggested figure (0·65),[15] and the σ^0 value recently reported (0·72),[16] which should be close to σ^+ as far as a *meta*-position is involved.

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