The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXXIV.[1] The Hydrogen-exchange Rates of Methylpyrazoles

By **Sergio Clementi, Paul P. Forsythe, C. David Johnson,*** and **Alan R. Katritzky,*** School of Chemical Sciences, University of East Anglia, Norwich

Acid-catalysed hydrogen-exchange rates are recorded for 1-methylpyrazole and for its 3-, 4-, and 5-mono- and 3,4-, 3,5-, and 4,5-dimethyl derivatives, together with those for the corresponding 2-methylpyrazolium cations. The rates have been extrapolated to give rate constants at 100° and pH 0: these are discussed with reference to the effect of the methyl groups and of the two cyclic pyrazole nitrogen atoms on electrophilic substitution rates.

We recently reported on the hydrogen-exchange rates of 1,3,5-trimethylpyrazole, 3,5-dimethylisoxazole, and 3,5-dimethylisothiazole.[2] We plan to use hydrogen-exchange rates as a general measure of the electrophilic reactivity of heteroaromatic compounds,[3] and we have therefore studied substituent effects on these rates in azoles. This paper concerns the effect of methyl substituents. Compounds were prepared by known or standard methods. The kinetics of deuteriation of pyrazole have previously been reported;[4] this work is discussed below.

TABLE 1

N.m.r. chemical shifts (τ) and coupling constants (Hz) for methylpyrazoles and methylpyrazolium cations (at 60 MHz)

Ring substituents	pK_a	Solvent[a]	R^1	R^2	R^3	R^4	R^5	J_{34}	J_{45}
1-Methyl	2·09 ± 0·05[b]	$CDCl_3$	6·13		2·51	3·78	2·63	2	2·5
		CCl_4	6·19		2·70	3·90	2·78	2	2·5
		30% D_2SO_4	5·80		1·77	3·12	1·84	3	3
1,2-Dimethyl		D_2O	5·90	6·00	1·90	3·20	1·90	3	3
1,3-Dimethyl	2·82 ± 0·03[b]	CCl_4	6·34		7·68	4·20	2·95		2·5
		30% D_2SO_4	5·95		7·60	3·45	2·04		3
1,5-Dimethyl	2·89 ± 0·05	CCl_4	6·39		2·85	4·16	7·84	2	
		30% D_2SO_4	6·02		2·01	3·40	7·60	3	
1,2,3-Trimethyl		D_2O	5·95	6·05	7·65	3·50	2·10		3
1,4-Dimethyl	2·48 ± 0·05	$CDCl_3$	6·27		2·75	7·98	2·93		
		CCl_4	6·30		2·91	8·00	3·00		
		30% D_2SO_4	5·97		2·01	7·85	2·01		
1,2,4-Trimethyl		D_2O	5·96	6·05	2·21	7·83	2·21		
1,3,4-Trimethyl	3·28 ± 0·04	CCl_4	6·34		7·95	8·10	3·14		
		30% D_2SO_4	6·02		7·64	7·96	2·08		
1,4,5-Trimethyl	3·12 ± 0·04	CCl_4	6·40		3·07	8·10	7·92		
		30% D_2SO_4	6·07		2·18	7·97	7·68		
1,2,3,4-Tetramethyl		D_2O	6·04	6·15	7·68	8·02	2·07		

[a] Solutions were *ca.* 10%. [b] J. Elguero, E. Gonzales, and R. Jacquier, *Bull. Soc. chim. France*, 1968, 5009.

Orientation of Hydrogen-exchange Reactions.—The position of hydrogen exchange was deduced from the n.m.r. spectra (Table 1). Chemical shifts in Table 1 were assigned by comparison with published data by Elguero, Jacquier *et al.*,[5,6] and other workers,[7] with which the results of Table 1 are entirely compatible.

1-Methylpyrazole on heating in D_2SO_4 underwent

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[1] Part XXXIII, S. Clementi and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1077.

[2] A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2365.

[3] A. R. Katritzky, lecture delivered at Cork Mechanisms Conference, Kinsale, Co. Cork, Ireland, 1971.

[4] E. Chung Wu and J. D. Vaughan, *J. Org. Chem.*, 1970, **35**, 1146.

[5] J. Elguero, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. chim. France*, 1966, 3727.

[6] J. Elguero, R. Jacquier, and D. Tizane, *Bull. Soc. chim. France*, 1969, 1687.

[7] See *e.g.* T. J. Batterham and C. Bigum, *Org. Magnetic Resonance*, 1969, **1**, 431; M. Kamiya, *Bull. Chem. Soc. Japan*, 1970, **43**, 3344.

initial exchange at the 4-position, followed by simultaneous deuteriation at the 3- and 5-positions, as shown by the changes in the n.m.r. spectrum. However, the 1,2-dimethylpyrazolium cation underwent exchange only at the 4-position.

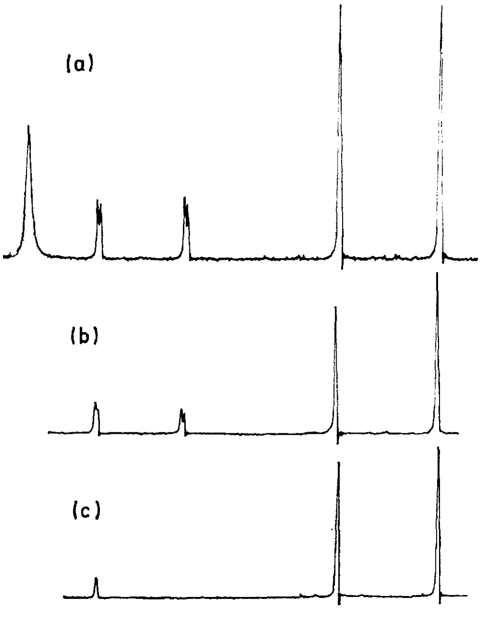

FIGURE 1 1,3-Dimethylpyrazole; n.m.r. spectra in D_2SO_4 (60%) (a) without heating, (b) after 6 h at 80°, (c) after 24 h at 181°

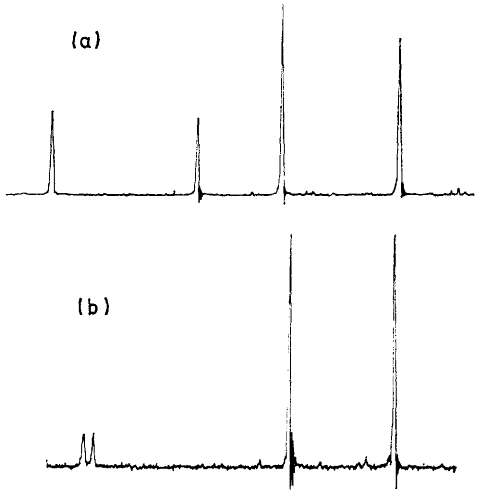

FIGURE 2 1,4-Dimethylpyrazole; n.m.r. spectra (a) in CCl_4, (b) after 48 h at 142° in D_2SO_4 (60%) followed by extraction into CCl_4 showing *ca.* 50% exchange at both 3- and 5-positions

1,3-Dimethylpyrazole on heating in D_2SO_4 exchanged first the 4- and then the 5-position proton as demonstrated by the disappearance of the 4-proton signal (with simultaneous change in the coupling pattern in the 5-position signal) followed by disappearance of the 5-signal (see Figure 1). Similarly, 1,5-dimethylpyrazole was shown to undergo successive reaction at the 4- and 3-positions. The 1,2,3-trimethylpyrazolium cation, by contrast, was found to undergo exchange at the 4-position only.

Exchange of 1,4-dimethylpyrazole took place simultaneously at the 3- and 5-positions; at all the acidities studied the rates at the 3- and 5-position did not differ by more than 10% (see Figure 2). The 1,2,4-trimethylpyrazolium cation did not exchange on being heated with D_2SO_4. Both 1,3,4- and 1,4,5-trimethylpyrazole underwent smooth exchange at the single free ring position, *i.e.* at the 5- and 3-positions respectively. Again the corresponding cation, 1,2,3,4-tetramethylpyrazolium, did not exchange.

EXPERIMENTAL

Compounds.—The following were prepared by the literature methods quoted: 1-methylpyrazole prepared as for pyrazole,[8] b.p. 120—122° (lit.,[9] 126—127°), 1,4-dimethylpyrazole (from 1,1,3,3-tetraethoxy-2-methylpropane [10]), b.p. 146—148° (lit.,[9] b.p. 146—147°).

1,2-*Dimethylpyrazolium Toluene*-p-*sulphonate.*—1-Methylpyrazole (1·5 g), methyl toluene-*p*-sulphonate (4·0 g), and THF (40 ml) were heated under reflux for 24 h. The *product* separated from the cooled solution; it was crystallised from ethanol as plates (2·5 g, 55%), m.p. 160—162° (Found: C, 55·4; H, 10·1; N, 6·0. $C_{12}H_{16}N_2O_3S$ requires C, 55·7; H, 10·0; N, 5·7%).

1,2,4-*Trimethylpyrazolium Toluene*-p-*sulphonate.*—1,4-Dimethylpyrazole (1·0 g) and methyl toluene-*p*-sulphonate (3·0 g) were heated under reflux in dry THF (30 ml) for 24 h. After cooling to 0°, the *sulphonate* was filtered off; it was crystallised from ethanol as plates (2·2 g, 75%), m.p. 154—155° (Found: C, 54·9; H, 6·4; N, 9·8. $C_{13}H_{18}N_2O_3$ requires C, 55·3; H, 6·4; N, 9·9%).

1,3- *and* 1,5-*Dimethylpyrazoles.*—The method of Burness [11] gave the mixed isomers, b.p. range 141—150° at 760 mmHg (lit.,[11] b.p. 141—150°). A Nester–Faust spinning band column was used to separate the isomers: [12] 1,3-, b.p. 72° at 45 mmHg, n_D^{20} 1·4653 (lit.,[9] n_D^{20} 1·4690) and 1,5-dimethylpyrazole, b.p. 56° at 35 mmHg, n_D^{20} 1·4789 (lit.,[9] n_D^{20} 1·4790). The compounds were homogeneous as shown by g.l.c. on a Carbowax column.

1,2,3-*Trimethylpyrazolium Toluene*-p-*sulphonate.*—The unseparated mixture of 1,3- and 1,5-dimethylpyrazole (2·6 g), methyl toluene-*p*-sulphonate (6·0 g), and THF (40 ml) were heated under reflux for 24 h. The product separated and was crystallised from ethanol to give the *sulphonate* (4·8 g, 58%), as plates, m.p. 169—170° (Found: C, 54·8; H, 6·4; N, 10·1. $C_{13}H_{18}N_2O_3$ requires C, 55·3; H, 6·4; N, 10·1%).

1,3,4- *and* 1,4,5-*Trimethylpyrazole.*—The mixed isomers were prepared by a literature method,[13] b.p. range 72—84° at 25 mmHg, and separated by the Nester–Faust spinning band column to give 1,3,4-, b.p. 70° at 20 mmHg (lit.,[14] b.p. 160° at 760 mmHg) and 1,4,5-trimethylpyrazole, b.p. 71°

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[8] R. G. Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 3994.

[9] V. F. Bystrov, I. I. Grandberg, and G. I. Sharova, *Zhur. obshchei Khim.*, 1965, **35**, 293.

[10] V. T. Klimko and A. P. Skoldinov, *Zhur. obshchei Khim.*, 1959, **29**, 4027.

[11] D. M. Burness, *J. Org. Chem.*, 1956, **21**, 97.

[12] For full details see P. P. Forsythe, Ph.D. Thesis, University of East Anglia, 1972.

[13] K. von Auwers and E. Cauer, *J. prakt. Chem.*, 1930, **126**, 198.

[14] D. Dal Monte, A. Mangini, and R. Passerini, *Gazzetta*, 1956, **86**, 797.

at 18 mmHg (lit.,[14] b.p. 176° at 760 mmHg). The compounds were homogeneous by g.l.c. on a Carbowax column, oven temperature 160°.

1,2,3,4-*Tetramethylpyrazolium Toluene*-p-*sulphonate*.—1,3,4-Trimethylpyrazole (1·0 g) gave, as before the *sulphonate* as plates (1·90 g, 70%), m.p. 120—122° (from ethanol) (Found: C, 56·5; H, 6·8; N, 9·5. $C_{14}H_{20}N_2O_3$ requires C, 56·7; H, 6·8; N, 9·5%).

Kinetic Procedures.—For most compounds the kinetics were followed as previously recorded.[2] For 1,4-dimethylpyrazole, aliquot portions were heated with D_2SO_4 for predetermined times; the reaction mixture was then treated until basic with Na_2CO_3 and extracted with CCl_4; the n.m.r. spectrum in CCl_4 was then determined, using the 4-methyl peak as standard. The complete kinetic data are shown in Table 2.

For spectroscopic techniques, see ref. 2. pK_a Values

Table 2

Pseudo first order rate constants (k/s^{-1}) for deuteriodeprotonation ($-D_0$ refers to the reaction temperature)

D_2SO_4 (%)	$-D_0$	$-\log k$
(i) 1-Methylpyrazole at 90°; exchange at the 4-position		
55·4	3·50	4·58
68·5	4·97	4·80
80·0	6·40	5·00
87·6	7·28	4·84
94·0	8·04	4·60
97·0	8·45	4·25
(ii) 1-Methylpyrazole at 70°; exchange at the 4-position		
49·5	3·21	5·18
53·8	3·59	5·13
56·0	3·81	5·32
56·8	3·89	5·19
64·6	4·72	5·50
68·0	5·17	5·45
72·8	5·79	5·61
74·6	6·03	5·63
75·6	6·16	5·54
85·4	7·41	5·84
85·5	7·42	5·75
88·0	7·72	5·72
94·4	8·51	5·34
(iii) 1,2-Dimethylpyrazolium cation at 70°; exchange at the 4-position		
74·0	5·96	6·52
80·6	6·82	6·12
86·0	7·48	5·71
92·0	8·19	5·41
(iv) 1-Methylpyrazole at 212°; exchange at the 3- and 5-positions		
56·0	3·00	4·28
56·6	3·04	4·24
72·3	4·21	4·34
82·0	5·11	4·89
94·0	6·25	5·00
(v) 1-Methylpyrazole at 181°; exchange at the 3- and 5-positions		
38·2	1·92	5·05
54·5	3·03	5·32
64·8	3·75	5·54
68·0	4·04	5·56
74·6	4·68	5·90
75·6	4·77	5·94
(vi) 1,3-Dimethylpyrazole at 80°; exchange at the 4-position		
14·5	0·63	3·77
31·0	1·73	3·89
40·4	2·42	3·96
69·0	5·16	4·33
96·0	8·51	2·72
(vii) 1,3-Dimethylpyrazole at 70°; exchange at the 4-position		
47·0	3·02	5·05
53·4	3·55	4·93
55·6	3·76	4·94
58·0	4·01	4·96
64·0	4·64	5·19
69·8	5·40	4·99
71·2	5·59	4·87
74·8	6·06	4·40
77·8	6·45	4·59
87·0	7·59	3·89
92·0	8·19	3·44
93·0	8·33	3·40
94·0	8·46	3·38
(viii) 1,3-Dimethylpyrazole at 59°; exchange at the 4-position		
57·0	4·02	5·51
58·8	4·20	5·57
68·4	5·37	5·59
77·2	6·57	5·03
89·8	8·17	4·20
(ix) 1,2,3-Trimethylpyrazolium cation at 70°; exchange at the 4-position		
57·6	3·97	6·26
72·8	5·80	4·64
83·0	7·12	3·79
85·6	7·42	3·71
(x) 1,3-Dimethylpyrazole at 181°; exchange at the 5-position		
55·0	3·05	5·62
58·1	3·27	5·76
69·8	4·22	5·98
77·8	5·00	6·22
78·0	5·02	6·20
(xi) 1,3-Dimethylpyrazole at 164°; exchange at the 5-position		
29·6	1·40	5·64
58·8	3·42	6·11
68·4	4·21	6·33
(xii) 1,5-Dimethylpyrazole at 80°; exchange at the 4-position		
28·0	1·52	3·73
46·2	2·89	4·01
53·6	3·50	4·13
69·7	5·25	4·44
78·2	6·33	4·41
84·8	7·14	4·04
96·2	8·53	3·19
(xiii) 1,5-Dimethylpyrazole at 59°; exchange at the 4-position		
57·2	4·03	5·22
60·0	4·33	5·35
69·0	5·45	5·50
80·0	6·95	5·13
89·1	8·08	4·55
94·0	8·70	4·32
(xiv) 1,5-Dimethylpyrazole at 212°; exchange at the 3-position		
70·3	4·01	4·64
84·2	5·31	4·79
(xv) 1,5-Dimethylpyrazole at 181°; exchange at the 3-position		
54·8	3·03	5·56
57·0	3·20	5·63
69·1	4·16	5·95
(xvi) 1,4-Dimethylpyrazole at 164°; exchange at the 3- and 5-positions		
46·1	2·52	4·50
57·6	3·33	4·75
58·0	3·36	4·90
64·8	3·87	4·82
65·0	3·89	4·96
69·8	4·36	5·13
80·7	5·48	5·39
85·6	5·95	5·66

TABLE 2 (*Continued*)

D_2SO_4 (%)	$-D_0$	$-\log k$
(xvii) 1,4-Dimethylpyrazole at 142°; exchange at the 3- and 5-positions		
12·0	0·39	5·24
21·0	0·94	5·50
42·0	2·31	5·63
73·5	4·95	6·47
(xviii) 1,3,4-Trimethylpyrazole at 164°; exchange at the 5-position		
45·3	2·47	4·60
53·1	3·00	4·67
80·6	5·47	5·21
(xix) 1,4,5-Trimethylpyrazole at 142°; exchange at the 3-position		
10·5	0·22	5·16
41·6	2·28	5·72
53·0	3·10	6·00
(xx) 1,4,5-Trimethylpyrazole at 164°; exchange at the 3-position		
43·3	2·33	4·72
53·8	3·05	4·90
57·6	3·33	5·03
68·5	4·22	5·23
84·3	5·84	5·71

were measured as recommended by Albert and Serjeant [15] by the spectrophotometric method (Table 1).

DISCUSSION AND RESULTS

Exchange at the 4-*Position*.—For all the pyrazoles with an unsubstituted 4-position, exchange occurred preferentially at this position. The rate profiles for the exchange at the 4-position of 1-methyl- (Figure 3), 1,3-dimethyl- (Figure 4), 1,5-dimethyl- (Figure 4), and 1,3,5-trimethylpyrazole [2] all show a mechanistic change-over mainly near D_0 −5 to −6 with rates reaching a minimum at this acidity. This indicates that all these pyrazoles are undergoing exchange as the free bases at lower acidities and as the conjugate acids at higher acidities. This conclusion is supported in each case by the rate profiles of the corresponding methyl cations, 1,2-dimethyl- (Figure 3) and 1,2,3-trimethylpyrazolium cation (Figure 4), which are closely similar (both in shape, and in absolute rate) to the parent compounds in higher acidities but which do not show the rate minimum near D_0 −5 to −6.

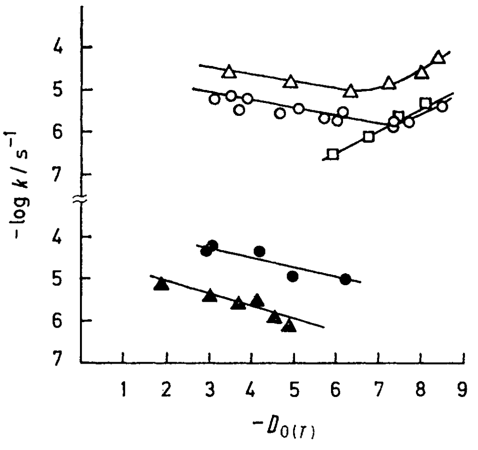

FIGURE 3 Rate profiles for hydrogen exchange of the 4-proton of 1-methylpyrazole at 70 (○) and 90° (△), of the 1,2-dimethylpyrazolium cation at 70° (□), and of the 3- and 5-protons of 1-methylpyrazole at 181 (▲) and 212° (●)

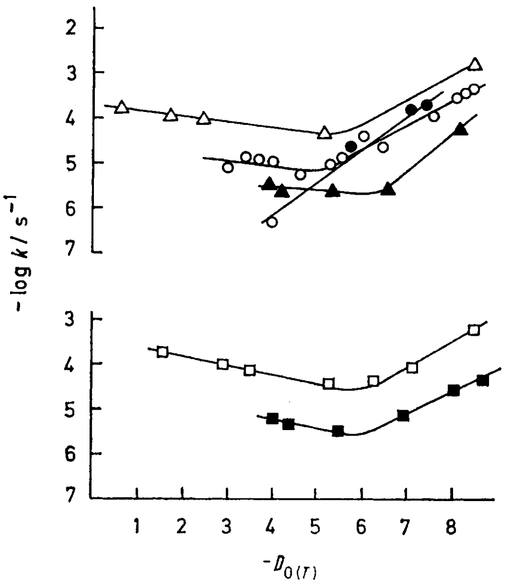

FIGURE 4 Rate profiles for hydrogen exchange of the 4-proton of 1,3-dimethylpyrazole at 59 (▲), 70 (○), and 80° (△), of the 1,2,3-trimethylpyrazolium cation at 70° (●); and for the 4-proton of 1,5-dimethylpyrazole at 59 (■) and 80° (□)

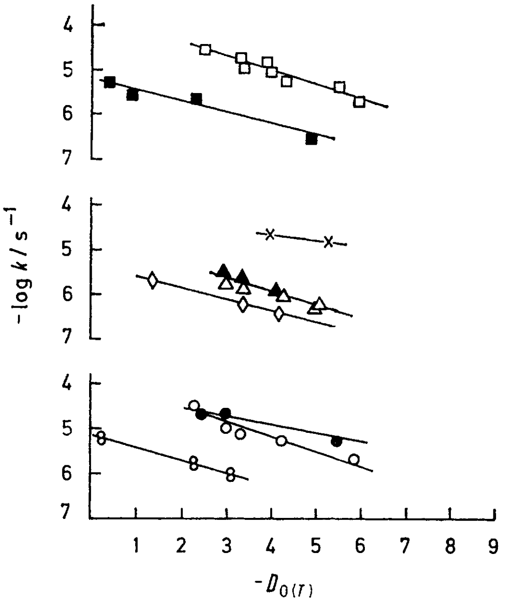

FIGURE 5 Rate profiles for hydrogen exchange of the 3- and 5-protons of 1,4-dimethylpyrazole at 142 (■) and 164° (□); for hydrogen exchange of the 5-proton of 1,3-dimethylpyrazole at 164 (◇) and 181° (△); for hydrogen exchange of the 3-proton of 1,5-dimethylpyrazole at 181 (▲) and 212° (×); for hydrogen exchange of the 5-proton of 1,3,4-trimethylpyrazole at 164° (●); and for hydrogen exchange of the 3-proton of 1,4,5-trimethylpyrazole at 142 (8) and 164° (○)

Exchange at the 3- *and* 5-*Positions*.—At high tem-

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[15] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962, p. 69.

peratures all the pyrazoles with free 3- and/or 5-positions undergo exchange at these positions. The rate profile for exchange (simultaneously) at the 3- and 5-positions of 1-methyl- (Figure 3) and 1,4-dimethylpyrazole (Figure 5), at the 3-position of 1,5-dimethyl- (Figure 5) and 1,4,5-trimethylpyrazole (Figure 5), and at the 5-position of 1,3-dimethyl- (Figure 5) and 1,3,4-trimethylpyrazole (Figure 5) all show rates declining gradually with increasing acidity, good evidence that all these reactions occur on the free base species, with no mechanistic changeover. This conclusion is confirmed by the lack of reaction under similar conditions of any of the corresponding 2-methylpyrazolium cations (1,2-dimethyl-, 1,2,3-trimethyl-, 1,2,4-trimethyl-, and 1,2,3,4-tetramethylpyrazolium cation) at the 3- or 5-positions.

TABLE 3

Standard rates at pH = 0 and 100°

Substituents	Ref.	Temp. (°C)	Position(s)	Species charge	Range % D_2SO_4	Range $-D_0$	Range −log *k*(stoich)	$\frac{d[\log k(\text{stoich})]}{d(-D_0)}$ Slope	−log *k* (stoich) at $D_0 = 0$	−log *k* (stoich) [a] at $D_0 = 0$ and 100°	pK_a 25° [b]	pK_a 100°	−log k_0	
1-Methyl	*c*	70	4	+	85—94	7·4—8·5	5·8—5·3	0·42	8·92	7·38			7·38	7·6
		90	4	+	88—97	7·3—8·5	4·8—4·2	0·48	8·37	7·89			7·89	
		70	4	0	49—76	3·2—6·2	4·7—5·5	−0·16	4·64	3·10	2·49	2·13	0·97	1·2
		90	4	0	55—80	3·6—6·4	4·6—5·0	−0·15	4·05	3·57	2·49	2·13	1·44	
		181	3, 5	0	38—76	1·9—4·8	5·1—5·9	−0·31	4·41	7·55	2·49	2·13	5·42	5·4
		212	3, 5	0	56—94	3·0—6·3	4·2—6·0	−0·25	3·48	7·54	2·49	2·13	5·41	
1,2-Dimethyl (cation)	*c*	70	4	+	74—92	6·0—8·2	6·5—5·4	0·51	9·55	8·02			8·02	8·0
1,3-Dimethyl	*c*	59	4	+	68—90	5·4—8·2	5·6—4·2	0·50	8·28	6·11			6·11	6·1
		70	4	+	70—94	5·4—8·5	5·0—3·4	0·52	7·78	6·24			6·24	
		80	4	+	69—96	5·2—8·5	4·3—2·7	0·48	6·81	5·81			5·81	
		59	4	0	57—68	4·0—5·4	5·5—5·6	−0·04	5·36	3·19	3·22	2·73	0·46	0·3
		70	4	0	47—64	3·0—4·6	5·1—4·9	−0·09	4·66	3·12	3·22	2·73	0·39	
		80	4	0	15—69	0·6—5·2	3·8—4·3	−0·12	3·68	2·68	3·22	2·73	−0·05	
		164	5	0	30—68	1·4—4·2	5·6—6·3	−0·24	5·30	7·87	3·22	2·73	5·14	5·2
		181	5	0	55—78	3·1—5·0	5·6—6·2	−0·28	4·79	7·93	3·22	2·73	5·20	
1,5-Dimethyl	*c*	59	4	+	80—94	7·0—8·7	5·1—4·3	0·47	8·38	6·21			6·21	6·6
		80	4	+	78—96	6·3—8·5	4·4—3·2	0·56	7·99	6·99			6·99	
		59	4	0	57—69	4·0—5·5	5·2—5·5	−0·18	4·53	2·36	3·29	2·79	−0·43	−0·4
		80	4	0	28—70	1·5—5·3	3·7—4·4	−0·19	3·45	2·45	3·29	2·79	−0·34	
		181	3	0	55—69	3·0—4·2	5·6—6·0	−0·34	5·71	8·85	3·29	2·79	6·06	6·0
		212	3	0	70—84	4·1—5·3	4·6—4·8	−0·12	4·72	8·78	3·29	2·79	5·99	
1,2,3(5)-Trimethyl (cation)	*c*	70	4	+	58—86	4·0—7·4	6·3—3·7	0·75	9·15	7·61			7·61	7·6
1,3,5-Trimethyl	*d*	35	4	+	64—83	5·1—7·8	5·6—4·1	0·59	8·72	5·01			5·01	5·0
		35	4	0	56—64	4·1—5·1	5·5—5·6	−0·05	5·35	1·64	4·52	3·80	−2·16	−2·4
		50	4	0	16—62	0·8—4·7	4·0—4·8	−0·20	3·92	1·20	4·52	3·80	−2·60	
1,2,3,5-Tetramethyl (cation)	*d*	35	4	+	63—83	4·9—7·8	5·7—3·6	0·69	9·07	5·36			5·36	5·4
1,4-Dimethyl	*c*	142	3, 5	0	12—74	0·4—5·0	5·2—6·5	−0·26	5·16	6·94	2·88	2·45	4·49	4·2
		164	3, 5	0	46—86	2·5—6·0	4·5—5·7	−0·32	3·71	6·28	2·88	2·45	3·83	
1,4,5-Trimethyl	*c*	142	3	0	11—53	0·2—3·1	5·2—6·0	−0·29	5·09	6·87	3·52	2·98	3·89	3·8
		164	3	0	43—84	2·3—5·8	4·7—5·7	−0·28	4·06	6·63	3·52	2·98	3·65	
1,3,4-Trimethyl	*c*	164	5	0	45—81	2·5—5·5	4·6—5·2	−0·21	4·07	6·64	3·68	3·11	3·53	3·5

[a] Using $\Delta H^\ddagger = 30$ kcal mol^{-1}. [b] Corrected for deuteriated media (see ref. 16). [c] This work. [d] Ref. 2.

Activation Parameters and Extrapolated Rate Constants.—'Corrected' activation parameters were calculated from the kinetic data in Table 2 by the standard procedure.[16] Most of the real variations probably occur in $\Delta S^\ddagger$, although $\Delta H^\ddagger$ values cover a range of over 20 kcal mol^{-1} (average value being 31 kcal mol^{-1}); this scattering is probably due to errors arising from the changeover point restricting the range of experimental determinations.

For reasons previously given,[16] we have extrapolated all rate constants to the standard conditions of pH = 0 and 100° (Table 3), using the standard procedure.[16] These calculations were performed taking $\Delta H^\ddagger = 30$ kcal mol^{-1} as previously suggested,[16] with which value the average reported above is in good agreement. Temperature dependence of pK_a values was taken equal to pyridines.*

The Quantitative Effect of Methyl Groups on Exchange Rates.—The incremental values of Table 4 show that whereas methyl groups invariably increase reaction rates, the quantitative effect depends on the position undergoing exchange, the relative orientation of the methyl group, and the species undergoing reaction. The incremental log k_0 values were obtained from extrapolated rates at $D_0 = -4$ and 100° for free base reactions and $D_0 = -8$ and 100° for conjugate acids. Values of log k_0 increments derived from standard rates (figures in parentheses in Table 4), are less reliable because of the larger extrapolations.

TABLE 4

Increments in log k_0 for methyl substitution in 1-methylpyrazole

Extra methyl(s)	Effect on 1-methyl reactive position (charge)		Effect on 1,2-dimethyl cation	
	4(0)[a,b]	4(+)[c,b]	3,5(0)[a,b]	4(+)[c,b]
3	1·3(0·9)	1·9(1·5)	0·4(0·2)	2·3(0·4)
4			1·3(1·2)	
5	1·5(1·6)	1·5(1·0)	0·4(−0·6)	2·3(0·4)
3,4			2·2(1·9)	
4,5			1·7(1·6)	
3,5	3·8(3·6)	3·7(2·6)		4·1(2·6)

[a] Calculated from extrapolated rates at $D_0 = -4$ and 100°. [b] Figures in brackets are calculated from standard rates at $D_0 = 0$ and 100°. [c] Calculated from extrapolated rates at $D_0 = -8$ and 100°.

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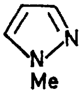
* Attention should be drawn to the fact that the corrections of acid due to substrate protonation are more complicated than indicated by the equation given in ref. 16. This equation (i) applies only for corrections at pD > 0. For corrections at $D_0 < 0$, equation (ii), which treats D_2SO_4 as a monobasic acid, is to be used. In our paper, the correct equation (ii) and not (i) was applied, but this was not made clear in the text.

$$\text{wt\% of acid} = (Ewz - 5004y)/(Ez - 50{\cdot}04y) \text{ for } D_2SO_4 \qquad \text{(i)}$$

$$\text{wt\% of acid} = (Ewz - 10{,}008y)/(Ez - 100{\cdot}08y) \text{ for } D_2SO_4 \qquad \text{(ii)}$$

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

Based on the bond fixation implicit in structure (1), a 5-methyl group should have more influence than a 3-methyl group for exchange in the 4-position as the neutral species. That no significant difference between 3- and 5-methyl groups is found points to considerable bond delocalisation and aromaticity in pyrazoles. The activating effects of 3- and/or 5-methyl groups for exchange in the 4-position of the conjugate acids and of 1,2-dimethylpyrazolium cations are similar to, or slightly greater than, those found for the free bases. The effects of the methyl groups on exchange of the 4-proton in the 3,5-dimethyl species are nearly additive.


(1)

As already mentioned, exchange at the 3- and 5-positions could not be followed separately in 1-methyl- or in 1,4-dimethyl-pyrazole because the rates are too similar; this again indicates the lack of any substantial bond fixation influence by which the 4-methyl group would be expected to accelerate the rate for the 5-position more than that for the 3-position. Comparison of the somewhat more rapid rate of the 1,3,4-, as compared with the 1,4,5-trimethyl analogue, possibly reflects some bond fixation, but the effect is marginally significant.

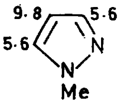
Methyl groups in the 3- or 5-positions have little effect on the rate of exchange at the 5- or 3-positions respectively; this is expected because of the *meta*-relationship of such methyl groups to the reactive centre.

Comparison with Previous Electrophilic Substitution Reactions of Pyrazoles.—Numerous examples exist of electrophilic substitution reactions at the 4-position of pyrazoles.[17] Such reactions at the 3- or 5-positions are rarer: halogenation at this position has however long been known[17] and more recently nitration.[18,19] The kinetics of bromination of pyrazole and its 1-methyl and 3,5-dimethyl derivatives[20] and of the nitration of pyrazole[21] and of 1,3,5-trimethylpyrazole[2] have been reported.

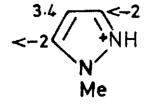
All the deuterio-derivatives of pyrazole have been reported;[22] they were prepared by base-catalysed exchange. The kinetics of deuteriation of pyrazole were studied by Wu and Vaughan[4] who concluded that reaction at the 4-position occurred by acid catalysis on the free base or the anion and that exchange at the 3-,5-positions occurred by base catalysis on the cation. Extrapolation of these data for exchange at the 4-position of the neutral species yields $\log k_0 = -1{\cdot}8$ at 100° and pH 0, using $\Delta H^{\ddagger} = 30$ kcal mol^{-1} as in the present work: the earlier authors reported $\Delta H^{\ddagger} = 22$ kcal mol^{-1} which would give $\log k_0 = -0{\cdot}8$. Considering the long extrapolations involved this must be considered to be in excellent agreement with the result now reported (see Table 3) of $\log k_0 = -1{\cdot}2$ for 1-methylpyrazole for exchange at the 4-position of the neutral species.

Partial Rate Factors and Comparison with Other Heterocycles.—log (Partial rate factors) (calculated using $\log k_0$ for benzene as $-11{\cdot}0$)[23] are indicated in the structures for 1-methylpyrazole (2), the 1-methylpyrazolium cation (3), and 1-methylpyrrole (4).[24]

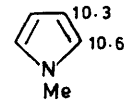
The large activating effect when an NMe group replaces a CH=CH function in the benzene system is clear from (4). With ρ for hydrogen exchange at standard conditions[1] as $-7{\cdot}5$, the values quoted (4) give $\sigma^+_{\mathrm{NMe}} \simeq -1{\cdot}4$ for exchange at both the α- and β-positions.*



(2)



(3)



(4)

For the neutral pyrazole species the electron-withdrawing effect of the 2-nitrogen atom has but little effect at the 4-position (*meta*), and even at the 3- and 5-positions (*ortho* and *para*) electron withdrawal by =N– is far outweighed by the electron-donor effect of –NMe–. The figures quoted for (2) and (3) indicate considerable interaction between the two nitrogen atoms. For cation (3), the partial rate factor at the 4-position allows calculation of $\Sigma\sigma^+$ for the composite heterocyclic group (–NMe·N$^+$H=) as $\{[-7{\cdot}6-(-11{\cdot}0)]/-7{\cdot}5\} = -0{\cdot}4$. In the absence of interaction the expected $\Sigma\sigma^+$ is $+0{\cdot}5$, since $\sigma^+_{\beta\text{-NMe}} = -1{\cdot}4$ and $\sigma^+_{m\text{-NH}^+} = +1{\cdot}9$.[25] Strong interaction between heteroatoms in diazoles is expected on theoretical grounds and our preliminary results demonstrate similar strong interactions between donor and acceptor groups in pyridines and diazines:[25] we plan a comprehensive discussion of such data.

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* σ^+_{NMe} For *N*-methylpyrrole was previously reported as *ca.* $-1{\cdot}9$ from solvolysis data (see G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 235). The value of $-1{\cdot}4$ may be affected by the different conditions to which the data of ref. 24 relate. Thus the value of $-1{\cdot}9$ may be more reliable (*cf.* A. El-Anani, S. Clementi, A. Katritzky, and L. Yakhontov, *J.C.S. Perkin II*, 1973, 1072).

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