Kinetics and Mechanism of Nitration of 3-Methyl-1,2-benzisoxazole

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The kinetics of nitration of 3-methyl-1,2-benzisoxazole and the corresponding 2-methyl quaternary salt are used to elucidate the species which undergo nitration.

THE kinetics and mechanism of electrophilic substitution of heteroaromatic compounds have been extensively studied by Katritzky and his co-workers; in particular monocyclic compounds have been examined.[1] Polycyclic heteroaromatic compounds have been less extensively studied.[2] The nitration of 3-methyl-1,2-benzisoxazole (1) in sulphuric acid is reported to yield smoothly the 5-nitro-derivative (2),[3] but no mechanistic and kinetic information is given. The present paper records our kinetic results on nitration of compound (1) and cation (3). The parent heterocycle (1) and the nitro-derivative (2) were converted into the metho-salts (3) and (4), respectively, by reaction with trimethyloxonium tetrafluoroborate.

EXPERIMENTAL

Materials.—Compound (1) (27%) was prepared by the literature method[4] as a liquid, b.p. 80—81° at 1 mmHg,

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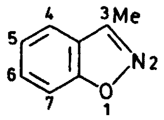
[1] G. Bianchi, A. G. Burton, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 1950, and the other papers in this series.

[2] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, 'Nitration and Aromatic Reactivity,' Cambridge University Press, Cambridge, 1971, p. 206.

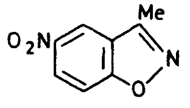
[3] H. Lindemann and H. Thiele, *Annalen*, 1926, **449**, 63.

[4] G. Casini, F. Gualtieri, and M. L. Stein, *J. Heterocyclic Chem.*, 1969, **2**, 279, and references cited therein.

after separation by column chromatography [silica gel H; Merck; ethyl acetate–cyclohexane (1 : 4) as eluant] from the isomer 2-methylbenzoxazole.



(1)



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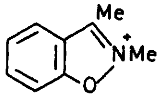
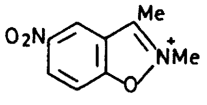


(3)



(4)

3-Methyl-5-nitro-1,2-benzisoxazole.— 3-Methyl-1,2-benzisoxazole (1.0 g) was dissolved in concentrated H_2SO_4 (20 ml; 98% C. Erba RP). Concentrated HNO_3 (1 ml; C. Erba RP) was added dropwise to the cooled solution which was stirred for 0.5 h. The mixture was poured into ice to give the nitro-derivative (2) (1 g, 75%) as needles from ethanol, m.p. 128—129 °C (lit.,[3,5a,b] 128, 129, and 134 °C, respectively) (Found: C, 53.9; H, 3.8; N, 15.4. Calc. for $C_8H_6N_2O_3$: C, 53.95; H, 3.4; N, 15.75%); δ ($CDCl_3$) 2.68 (3 H, s, Me), 7.67 (1 H, q, ArH), 8.47 (1 H, q, ArH), and 8.60 (1 H, q, ArH).

2,3-Dimethyl-1,2-benzisoxazolium Tetrafluoroborate.—3-Methyl-1,2-benzisoxazole (1.3 g) and trimethyloxonium tetrafluoroborate (4.0 g) in 15 ml of nitromethane were left for 48 hours at room temperature. Evaporation of the solvent under reduced pressure gave an oily residue which was dissolved in acetone (10 ml) and then precipitated on addition of dry ethyl ether as *needles* (1.7 g, 76.14%), m.p. 140—142 °C (Found: C, 45.8; H, 4.5; N, 6.3. $C_9H_{10}NO,BF_4$ requires C, 46.0; H, 4.3; N, 5.95%); δ $[(CD_3)_2CO]$ 3.18 (3 H, s, Me), 4.60 (3 H, s, Me), and 7.60—8.50 (4 H, m, ArH).

2,3-Dimethyl-5-nitro-1,2-benzisoxazolium Tetrafluoroborate.—3-Methyl-5-nitro-1,2-benzisoxazole (0.18 g) treated as above with excess of trimethyloxonium tetrafluoroborate, gave *2,3-dimethyl-5-nitro-1,2-benzisoxazolium tetrafluoroborate* (0.21 g, 73%) as crystals, m.p. 148—150 °C (Found: N, 10.3. $C_9H_9N_2O_3,BF_4$ requires N, 10.0%); δ $[(CD_3)_2CO]$ 3.30 (3 H, s, Me), 4.70 (3 H, s, Me), 8.30 (1 H, d, ArH), 9.00 (1 H, q, ArH), and 9.35 (1 H, s, ArH).

Kinetic Determinations.—Nitric and sulphuric acid were AnalaR grade. The kinetics were followed under second-order conditions at near room temperature using a u.v. technique. 3-Methyl-1,2-benzisoxazole and 2,3-dimethyl-1,2-benzisoxazolium tetrafluoroborate were dissolved in sulphuric acid of the appropriate strength in a volumetric flask. A solution of nitric acid in sulphuric acid of the same strength as above was prepared in another volumetric flask. Both flasks were thermostatted, and the reaction started by mixing and vigorously shaking the contents of the two flasks. Portions were withdrawn at intervals and diluted with water to a suitable volume for measurements of the optical density. The concentration, x_t, of nitrated product formed after time t was obtained from equation (1).

$$x_t = a(\mathrm{OD}_t - \mathrm{OD}_0)/(\mathrm{OD}_\infty - \mathrm{OD}_0) \qquad (1)$$

$$k_2 = \frac{2.303}{t(b-a)} \log_{10} \frac{a(c - x_t)}{b(a - x_t)} \qquad (2)$$

Second-order rate constants were calculated from equation (2) by plotting $\log_{10}[a\,(b - x_t)/b\,(a - x_t)]$ against t. In these equations a is the initial concentration of the substrate, b the concentration of nitric acid, and OD_0, OD_t, and OD_∞ the optical densities at the beginning of the run, after time t, and after complete reaction.

The concentrations of the sulphuric acid solutions (Table 2) were corrected for water added with nitric acid, but not for water formed by ionisation of nitric acid. Attention was paid to ensure that the concentration of the sulphuric acid in the reaction volumetric flask did not change during the reaction because of the moisture from the air. In several instances the concentration of the sulphuric acid was re-checked at the end of the run.

Basicity Measurements.—pK_a Values, recorded in Table 1, were measured by the spectrophotometric method.[6] The values of H_0 were taken from those of Johnson *et al.*[7]

RESULTS AND DISCUSSION

Protonation Behaviour.—3-Methyl-1,2-benzisoxazole undergoes a protonation process which approximates to Hammett-base behaviour. It seems of interest to compare the pK_a (conjugate acid), —2.69, with those of other related compounds: 1,2-benzisoxazole, —4.7[8] or —4.2;[9] 5-methyl-1,2-benzisoxazole, —4.03;[9] 3-methyl-5-phenylisoxazole, —2.45.[10] A methyl group at position 3 or 5 raises the pK_a in the 1,2-benzisoxazole series, while the parent 1,2-benzisoxazole is a weaker base than the corresponding non-condensed compounds (*e.g.*, 3-methyl-5-phenylisoxazole). A similar trend has been reported for the isoxazole series.[10,11]

Identification of Species Undergoing Nitration.—Kinetic results for nitration of compound (1) and the metho-salt (3) at *ca.* 25° are given in Table 2 and the rate profile plots of log k_2(obs) against $-H_0$ are shown in the Figure. The rate profile slope in the 91—94% H_2SO_4 region (H_0 —9 to —9.6), $d[\log k_2(\mathrm{obs})]/dH_0$, is 0.97, while the slope of 0.32 at higher acidity shows that there is a changeover in mechanism with the reaction involving the conjugate acid of (1). The results for the model compound of the conjugate acid, the metho-salt (3), confirm this conclusion: the slope of the rate profile is 0.34 and the rates are closely similar.

At lower acidities, in the 78—84% H_2SO_4 region (H_0 —7 to —8), a plot of log k_2(obs) for (1) against (H_R + log a_{H_2O}) yields a good straight line, whose

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[5] (*a*) J. Meisenheimer, P. Zimmermann, and U. von Kummer, *Annalen*, 1926, **446**, 205; (*b*) H. Lindemann and S. Romanoff, *J. prakt. Chem.*, 1929, **122**, 214.

[6] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, Naeem Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.

[7] C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.

[8] M. L. Casey, D. S. Kemp, K. G. Paul, and D. D. Cox, *J. Org. Chem.*, 1973, **38**, 2294.

[9] N. Stabile, Ph.D. Thesis, University of Pavia, 1973.

[10] S. D. Sokolov, L. A. Kazitsyna, and I. K. Guseva, *J. Org. Chem.* (*U.S.S.R.*), 1966, **2**, 733.

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

TABLE 1

Absorption maxima and pK_a data for substituted 1,2-benzisoxazoles and 1,2-benzisoxazolium tetrafluoroborates

	$\lambda_{max.}$/nm (log ε) [a]			Basicity			
Compound	Neutral species	Cationic species	λ [c]/nm	λ [d]/nm	$H_0{}^{\frac{1}{2}}$	m [e]	pK_a
(1)	236 (3.86), 281 (3.33)	254 (4.10), 291 (3.61)	283	254	3.36	0.80	−2.69 ± 0.15
(2)	226 (4.32), 283 (3.79)	239 (4.83), 282 (4.06)					
(3)		258 (4.16), 300 (3.57) [b]	243				
(4)		243 (4.44)					

[a] Measured in water. [b] Measured in 98% H_2SO_4. [c] λ for study of nitration kinetics. [d] λ for pK_a. [e] Slope of plot of log $_{10}$ [BH^+]/[B] against H_0.

uncorrected slope is 0.87, which becomes 1.21 when the rate constants are corrected for the free base form (Table 2). At these acidities the rate of nitration of the model (3) is very much lower.

TABLE 2

Nitration of 3-methyl-1,2-benzisoxazole and 2,3-dimethyl-1,2-benzisoxazolium tetrafluoroborate at 25.0 and 25.2° respectively

(i) 3-Methyl-1,2-benzisoxazole

H_2SO_4 (%)	$-H_0$ (25°)	$-(H_R + \log a_{H_2O})$	$-\log k_2$(obs)/ l mol^{-1} s^{-1}	$\log k_2$(fb) [a] l mol^{-1} s^{-1}
78.03	7.13	15.65	3.58 ± 0.02	−0.37
79.95	7.46	16.40	2.90 ± 0.01	0.58
82.13	7.80	17.20	2.13 ± 0.01	1.63
83.95	8.13	18.00	1.56 ± 0.02	2.49
86.10	8.42		1.20 ± 0.01	
86.91	8.56		1.14 ± 0.01	
87.90	8.70		1.03 ± 0.03	
88.97	8.85		1.00 ± 0.01	
90.01	9.01		1.07 ± 0.00	
92.02	9.34		1.27 ± 0.01	
94.01	9.66		1.69 ± 0.05	
95.88	9.98		1.91 ± 0.04	
97.55	10.36		1.93 ± 0.03	

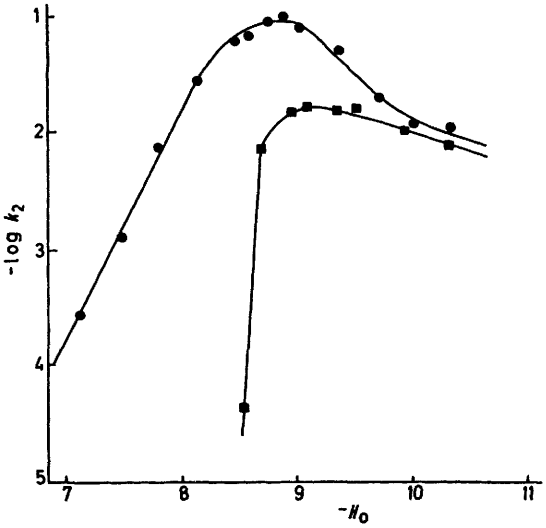
(ii) 2,3-Dimethyl-1,2-benzisoxazolium tetrafluoroborate

H_2SO_4 (%)	$-H_0$ (25°)	$-\log k_2$ (obs)/ l mol^{-1} s^{-1}
86.91	8.56	4.35 ± 0.09
87.90	8.70	2.13 ± 0.03
89.49	8.95	1.81 ± 0.01
90.33	9.08	1.78 ± 0.01
92.08	9.35	1.81 ± 0.02
93.04	9.51	1.78 ± 0.04
95.72	9.93	1.97 ± 0.00
97.55	10.36	2.12 ± 0.03

[a] $\log k_2\,(\text{fb}) = \log k_2\,(\text{obs}) + m(H_0{}^{\frac{1}{2}} - H_0)$.

Our results, compared with those of other authors,[12] allow us to conclude that 3-methyl-1,2-benzisoxazole is nitrated as a free base over the 80—90% H_2SO_4 region, while it is the conjugate acid which is nitrated at higher acidities.

Kinetic results at different temperatures and for two H_2SO_4 solutions, 82.12 and 97.55% respectively, were used to calculate the Arrhenius parameters in Table 3.



Rate profiles for nitration at 25.0° of 3-methyl-1,2-benzisoxazole (●) and 2,3-dimethyl-1,2-benzisoxazolinium tetrafluoroborate (■)

Selectivity of Nitration of 3-*Methyl*-1,2-*benzisoxazole*.—3-Methyl-1,2-benzisoxazole, as does the parent 1,2-benzisoxazole, undergoes nitration at position 5 and no other isomers could be detected in the reaction mixture by t.l.c. and n.m.r. analysis.

TABLE 3

Temperature dependence of rates of nitration of 3-methyl-1,2-benzisoxazole; activation parameters

H_2SO_4 (%)	Temp. (°C)	$\log k_2$ (obs.)/ l mol^{-1} s^{-1}	E_a/ kcal mol^{-1}	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/ kcal mol^{-1}	log$A$
81.12	25.2	−2.99 ± 0.11	15.1 ± 0.9	14.48 ± 0.9	−23.6 ± 0.3	21.5 ± 0.2	8.1 ± 0.9
	30.0	−2.84 ± 0.05					
	35.0	−2.61 ± 0.06					
	40.0	−2.48 ± 0.08					
97.55	25.0	−1.93 ± 0.08	6.94 ± 0.8	6.35 ± 0.8	−46.0 ± 0.3	20.0 ± 0.2	6.9 ± 0.8
	30.0.	−1.86 ± 0.06					
	35.0	−1.78 ± 0.06					
	40.0	−1.69 ± 0.05					

According to the perturbation approach, electrophilic aromatic substitution is charge and orbital controlled.[13] In contrast to the experimental results, MO calculations carried out for 1,2-benzisoxazole indicate

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[12] A. G. Burton, A. R. Katritzky, M. Konya, and H. O. Tarhan, *J.C.S. Perkin II*, 1974, 389; A. R. Katritzky, M. Konya, H. O. Tarhan, and A. G. Burton, *ibid.*, 1975, 1627.

[13] R. H. Hudson, *Angew. Chem. Internat. Edn.*, 1973, **12**, 36.

that the highest charge density is at position 7, while C-5 has a lower charge density.[14] Allowing for a close similarity between the electronic structures of 1,2-benzisoxazole and the 3-methyl derivative, it follows that nitration of both heterocyclic compounds is not charge controlled. It seems therefore reasonable to assume that in the case of 1,2-benzisoxazole and the 3-methyl derivative the orbital term prevails over the coulombic term and that the frontier orbital coefficients at position 5 are larger than at position 7.

We thank Professor A. R. Katritzky for helpful suggestions and C.N.R., Rome, for financial aid.

[6/364 *Received, 23rd February,* 1976]

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