Kinetics, Stoicheiometry, and Mechanism in the Bromination of Aromatic Heterocycles. Part 5.[1] Aqueous Bromination of Benzimidazole, 1-Methylbenzimidazole, and 2-Methylbenzimidazole

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The method of halogenation by instalments with coulo-chrono-potentiometric monitoring has been used to obtain reactivity profiles for reactions of benzimidazoles with bromine (aqueous solution, 298 K). Values of bimolecular rate constants for attack by Br_2 on molecular substrates, calculated using literature values of acidity constants, were:

Substrate	Site	k°_{bi}/dm^3 mol^{-1} s^{-1}
Benzimidazole	5	935 ± 1%
5-Bromobenzimidazole	7	40 ± 10%
1-Methylbenzimidazole	5	879 ± 1%
2-Methylbenzimidazole	5	6 300 ± 1%

Reactivities of azoles and benzazoles are correlated with site charge densities calculated by VESCF/BJ, CNDO/2, and CNDO/S molecular orbital methods.

THE authors of a recent review[2] remark that '. . . it is true of the azoles that, despite the large amount of information available about their reactions, there is little that can readily be related to theoretical studies of aromatic reactivity. . . . Where the two step mechanism does operate the first step is not necessarily rate determining, so that comparison with theoretical calculations is invalidated. Additionally where the mechanism is of the appropriate kind there is the minor problem of deciding whether the results relate to azole molecules themselves or to their anions or cations. . . . Generally, experiment and theory make only the most tenuous of contacts in the field of aromatic reactivity amongst the azoles. The primary need is for more quantitative mechanistic studies.'

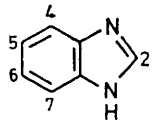
In our studies of the reactions of aqueous bromine with four members of the azole series, pyrazole,[3a] imidazole,[3b] indazole,[3c] and imidazo[1,2-*a*]pyridine we have confronted many of the problems indicated above. We now have good evidence, from rate laws and isotope effects, that the bimolecular processes leading to formation of the Wheland intermediates are rate determining.

[1] Part 4, B. E. Boulton and B. A. W. Coller, *Austral. J. Chem.*, 1974, **27**, 2349.

[2] K. Schofield, M. R. Grimmett, and B. R. T. Greene, 'Hetero-aromatic Nitrogen Compounds—The Azoles,' Cambridge University Press, Cambridge, 1976, pp. 181—183.

[3] B. E. Boulton and B. A. W. Coller, *Austral. J. Chem.* (*a*) 1971, **24**, 1413; (*b*) 1974, **27**, 2331; (*c*) *ibid.*, p. 2343.

By study of dependence of reactivities on the acidities of the aqueous media we found that the neutral molecule is the species which reacts with molecular bromine in each case. Choice of water as solvent, at 25 °C, enabled use of established equilibrium constants to evaluate absolute values of bimolecular rate constants. By



(I)

product analysis these were partitioned between alternative sites of attack. We found [3a,b] that *N*-methylation is a satisfactory method for removing ambiguity between tautomerically equivalent reaction sites. Other workers have carried out related studies with phenols,[4] anilines and aminopyridines,[5] thiophen,[6] alkoxybenzenes,[4] and benzene.[7] In this paper we describe extension of our studies to benzimidazoles.

Reactions of electrophilic reagents with benzimidazoles lead to a variety of substituent orientations depending on the reagents, proportions, and media used. When benzimidazole (I), or 1-methylbenzimidazole, is treated with nitric acid in concentrated sulphuric acid, wherein the reactive species is most likely to be the protonated form, the first formed product is the 5(6)-nitrobenzimidazole.[8] This is further converted into 5,6- and some 5,7(4,6)-dinitrobenzimidazole.[8c] The kinetics of mononitration of 2-methyl- and of 1,2-dimethyl-benzimidazole in 70—80% sulphuric acid [9] correspond to a kinetically significant transition state formed from nitronium ion and the conjugate acid of benzimidazole. In chloroform, reaction between bromine and benzimidazole is reversible and does not lead to bromodeprotonation at carbon.[10a] In glacial acetic acid, bromine converts 2-methylbenzimidazole to the 5(6)-bromo- and 5,7(4,6)-dibromo-substitution products and an orange polybromo-derivative.[10b] With 2-trifluoromethylbenzimidazole in aqueous acetic acid the 5(6)-position is first attacked by bromine.[10c] Excess of bromine leads to a mixture of 4,5,6,7-tetrabromo- and 4,5,6(5,6,7)-tribromo-derivatives. Ridd [10d] reports Smith's finding that benzimidazole, without a blocking group in the 2-position, is converted to 5(6)-bromobenzimidazole. Further substitution was not investigated. The reaction of iodine with benzimidazole in aqueous sodium hydroxide yields *N*-iodobenzimidazole [11a,b] rather than the 2-iodo-derivative.[11b,c] The above observations lead us to conclude that in the conjugate acid of benzimidazole the 5(6)-position is the most reactive toward electrophiles and suggest that the same site is also the most reactive in the neutral molecule. From experience with other azoles [1,3] we expected the reaction of bromine with benzimidazole in buffered aqueous solutions to involve preferential attack on the neutral molecule. Since the pairs of positions 5(6) and 4(7) are tautomerically equivalent in the parent molecular system, we have supplemented our studies of reactivity profiles and product analyses with similar measurements on 1-methylbenzimidazole to eliminate the ambiguities. In addition, we have investigated the effect of a methyl group in the 2-position.

EXPERIMENTAL

All inorganic reagents were of analytical reagent quality. Stocks of potassium bromide and sodium acetate were dried at 110 °C before use. Acetic acid stocks were prepared by dilution of AnalaR grade glacial acetic acid (B.D.H. Ltd.) and standardised by titration.

Materials.—Benzimidazole, obtained from B.D.H. Ltd., was purified by the method of Wagner and Millett [12] to needles, m.p. 171—171.5 °C. 5(6)-Bromobenzimidazole was prepared by a modification of the procedure used by Phillips.[13] Thus 1,2-diamino-4-bromobenzene [13c] (1.36 g) and formic acid (98%; 5.1 g) was dissolved in hydrochloric acid (73 cm^3, 4 mol dm^{-3}) and heated under reflux for 40 min. The solution was cooled, neutralised with aqueous ammonia (1 : 1), and left for two days. The buff precipitate was collected and recrystallised three times from water to obtain the crystalline solid (0.8 g, 61%), m.p. 130—131 °C (lit.,[13d] 130 °C). 5,7(4,6)-Dibromobenzimidazole was prepared from 1,2-diamino-3,5-dibromobenzene [10b,13c] using the procedure described above for obtaining 5(6)-bromobenzimidazole. We treated the crude yellow product with decolouring charcoal to obtain a solid, m.p. 223—225 °C (lit.,[14] 225 °C). 1-Methylbenzimidazole was prepared by the standard procedure of Pozharskii and Simonov.[15] The crude product was recrystallised three times from petroleum spirit to obtain needles, m.p. 61—62 °C (lit.,[15] 61—62 °C). 5-Bromo-1-methylbenzimidazole was prepared from crude

[4] (*a*) R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 1961, 63; (*b*) G. S. Kozak and Q. Fernando, *J. Phys. Chem.*, 1963, **67**, 811; (*c*) G. O'Dom and Q. Fernando, *Analyt. Chem.*, 1966, **38**, 844.

[5] (*a*) R. P. Bell and E. N. Ramsden, *J. Chem. Soc.*, 1958, 161; (*b*) R. P. Bell and P. De Maria, *J. Chem. Soc.* (*B*), 1969, 1057; (*c*) J. E. Dubois, P. Alcais, and G. Barbier, *Bull. Soc. chim, France*, 1968, 605; (*d*) J. E. Dubois, R. Uzan, and P. Alcais. *ibid.*, pp. 611, 617; (*e*) J. E. Dubois and R. Uzan, *ibid.*, p. 3534; (*f*) P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem Soc.* (*B*), 1970, 117.

[6] A. R. Butler and J. B. Hendry, *J. Chem. Soc.* (*B*), 1970, 170.

[7] E. Berliner and F. Gaskin, *J. Org. Chem.*, 1967, **32**, 1660.

[8] (*a*) O. Fischer and W. Hess, *Ber.*, 1903, **36**, 2968; (*b*) G. M. van der Ward, *Rec. Trav. chim.*, 1948, **67**, 45; (*c*) G. E. Ficken and D. J. Fry, *J. Chem. Soc.*, 1963, 736.

[9] V. Sterba, J. Arient, and F. Novratil, *Coll. Czech. Chem. Comm.*, 1966, **31**, 113.

[10] (*a*) P. Linda, *Tetrahedron*, 1969, **25**, 3297; (*b*) S. D. Dandegaonker, *J. Indian Chem. Soc.*, 1965, **42**, 777; (*c*) E. L. Samuel, *Austral. J. Chem.*, 1972, **25**, 2725; (*d*) B. V. Smith, quoted by J. H. Ridd in 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, vol. 1, p. 109.

[11] (*a*) D. Harrison, J. T. Ralph, and A. C. B. Smith, *J. Chem. Soc.*, 1963, 2930; (*b*) A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 1968, 2nd edn., p. 222; (*c*) H. Pauly and K. Gunderman, *Ber.*, 1908, **41**, 3999.

[12] E. C. Wagner and W. H. Millett, *Org. Synth.*, 1943, Coll. Vol. 2, 65.

[13] (*a*) M. A. Phillips, *J. Chem. Soc.*, 1931, 1143; (*b*) L. A. Cescon and A. R. Day, *J. Org. Chem.*, 1962, **27**, 581; (*c*) S. H. Dandegaonker and D. Shastri, *Monatsh.*, 1965, **96**, 614; (*d*) D. J. Rabiger and M. M. Joullie, *J. Chem. Soc.*, 1964, 915.

[14] (*a*) W. Basczyncki and S. Niementowski, *Bull. Acad. Sci. Cracow*, 1902, 421 (*Chem. Zentr.*, 1902, II, 940); (*b*) S. Niementowski, *Ber.*, 1892, **25**, 860.

[15] A. F. Pozharskii and A. H. Simonov, *Zhur. obshchei Khim.*, 1963, **33**, 179.

2-amino-4-bromo-*N*-methylaniline resulting from reduction of 4-bromo-*N*-methyl-2-nitroaniline.[13c] The raw material (1.9 g), formic acid (5.1 g; 98%), and hydrochloric acid (73 cm^3, 4 mol dm^{-3}) were heated under reflux for 1 h then cooled and neutralised with aqueous ammonia (1 : 1). The precipitate which separated was five times recrystallised from aqueous ethanol to obtain *crystals*, m.p. 123—125 °C (Found: C, 45.3; H, 3.4; N, 13.3; Br, 38.0. $C_8H_6BrN_2$ requires C, 45.5; H, 3.3; N, 13.3; Br, 37.9%). 2-Methylbenzimidazole (Koch–Light Ltd.) was recrystallised twice from water to obtain needles, m.p. 173—174 °C. *5(6)-Bromo-2-methylbenzimidazole* was prepared by the same procedure as was 5(6)-bromobenzimidazole except that acetic acid was used in place of formic acid and the product was recrystallised from aqueous ethanol to obtain a solid, m.p. 215—217 °C (lit.,[16] 215 °C). 5,7(4,6)-Dibromo-2-methylbenzimidazole was synthesised in the same way as 5,7(4,6)-dibromobenzimidazole with acetic acid instead of formic acid. Recrystallisation from aqueous ethanol gave crystals, m.p. 212—215 °C (lit.,[10b] 212—213 °C).

Kinetic Measurements.—We measured the kinetics of bromination of the benzimidazoles in aqueous media at 25.00 ± 0.02 °C by potentiometric monitoring of the decay of bromine in the periods between generation of instalments of bromine by electrolysis as previously described.[3a] This procedure gave us a set of first order bromine decay coefficients, which were divided by the initial concentrations of substrate, and plotted against the corresponding known degrees of bromination to obtain ' reactivity profiles '. Stoicheiometries were estimated by extrapolation to the degree of bromination at zero reactivity. Second-order rate coefficients k_2 for reactions between bromine and substrates in the given media, were determined by extrapolation to the reactivity at zero degree of bromination. Values of k_2 for further reactions of intermediate products were estimated by analogue and digital computer simulations of reactivity profiles and in one case, by direct study using prepared samples of a postulated intermediate.

Product Analyses.—Benzimidazole (0.236 g, 2 mmol) in aqueous solution (50 cm^3) at 25 °C containing excess of potassium bromide and acetate buffer at pH 5.5, was treated with an equal amount of bromine generated by electrolysis at a platinum electrode (20 mA for 5 h). The solution was then extracted with chloroform (5 × 20 cm^3) and again after adding NaOH to pH 7. The combined extracts were dried with $MgSO_4$ and evaporated under vacuum to yield a buff solid. This was shown, by t.l.c. (silica gel with 90% chloroform–10% methanol) and g.l.c. (5% OV-1 on Chromosorb W, 100—200 mesh), to contain one minor, one major, and one trace component with R_F and retention times of the first two matching those of benzimidazole (0.30, 1.5 min) and 5(6)-bromobenzimidazole (0.33, 3.1 min), respectively. The mass spectrum of the crude extract included weak molecular ion peaks *m/e* 274/6/8, corresponding to a dibromo-substituted benzimidazole. The crude product was three times recrystallised from water to obtain a solid, m.p. 130—131 °C, which had mixed m.p., i.r., and ^1H n.m.r. spectra identical with those of authentic 5(6)-bromobenzimidazole.

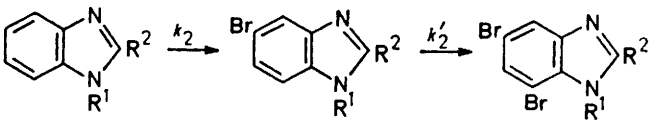
In the same medium, benzimidazole (0.236 g, 2 mmol) was treated with twice the stoicheiometric amount of bromine generated by electrolysis (20 mA for 10 h). A yellow solid was left after evaporation of the combined chloroform extracts. Analysis by t.l.c. and g.l.c. showed two minor and one major component with R_F and retention times matching those of benzimidazole, 5(6)-bromobenzimidazole, and 5,7(4,6)-dibromobenzimidazole (0.36, 4.6 min), respectively. The crude mixture was five times recrystallised from 50% aqueous ethanol to obtain a solid, m.p. 222—225 °C, with mixed melting point and i.r. spectrum identical with those of authentic 5,7(4,6)-dibromobenzimidazole.

Brominations and product analyses of 2-methylbenzimidazole, with one and two stoicheiometric amounts of bromine, were conducted as described for benzimidazole. The crude extracts were purified by repeated recrystallisation from aqueous ethanol and the principal products identified by comparison of i.r. spectra, m.p.s, and g.l.c. retention times with those of authentic specimens. With one equiv. of Br_2 the product was almost exclusively 5(6)-bromo-2-methylbenzimidazole and with two equiv. 5,6(4,7)-dibromo-2-methylbenzimidazole was obtained.

Reaction of 1-methylbenzimidazole with 1 equiv. of Br_2 was conducted as for benzimidazole, except that pH was not adjusted before extraction with chloroform. The crude extract, when recrystallised from aqueous ethanol, gave a solid, m.p. 123—125 °C, corresponding to 5-bromo-1-methylbenzimidazole, and did not depress the m.p. of an authentic sample of the latter.

RESULTS AND DISCUSSION

Identities of Products and Intermediates.—With benzimidazole and with 2-methylbenzimidazole the first



SCHEME Preferred orientation and sequence of brominations of benzimidazoles

formed product of aqueous bromination is the 5(6)-bromo-derivative, which is converted by further bromination into 5,7(4,6)-dibromobenzimidazole. With 1-methylbenzimidazole in which the ambiguity of tautomerism is eliminated, reaction with bromine occurs first at the 5-position and subsequently at the 7-position. It appears that the steric or electronic effects of the bromine atom in the 5-position of the parent system are sufficient to exclude a second bromination at the tautomerically equivalent 6-position and similarly at the 4-position. The second bromine enters *meta* to the first position of attack, in the manner to be expected if tautomerism did not take place.

Reactivities and Shapes of Profiles.—The reactivities k_2 have been divided by initial concentrations of the benzimidazoles to obtain the reactivity profiles in Figure 1. In each case reaction approaches completion when two mole of bromine have been consumed per mole of substrate. The values at zero degree of bromination are the second-order rate coefficients for bromination of the substrate in the medium used. The strongly elbowed shapes of the profiles indicate that the products of monobromination are much less reactive than their precursors. The lines drawn in Figure 1 were obtained by computer simulation assuming two-step reactions as

[16] J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1960, 1363.

in the Scheme. The best estimates of k_2/dm^3 mol^{-1} s^{-1} are given in Table 1.

simple linear form corresponding to a first-order dependence on substrate concentration in a reaction with unit

TABLE 1

Second-order rate coefficients for bromination of benzimidazoles (Bzim) in an aqueous medium * at pH 5.430 † and 25 °C

Bzim	k_2 [a] / dm^3 mol^{-1} s^{-1}	k_2' [b] / dm^3 mol^{-1} s^{-1}	pK_a(BzimH$^+$)	k_{bi} [g] / dm^3 mol^{-1} s^{-1}
Unsubstituted	53	4.0	5.532 [c]	855
1-Methyl	44	1.9	5.57 [d]	746
2-Methyl	124	32	6.190 [e]	5 964
5(6)-Bromo	4.4 [a]		4.66 [f]	37

* [KBr] 0.364 mol dm^{-3}, [NaAc] 0.0909 mol dm^{-3}, [HAc] 0.0192 mol dm^{-3}. † pK_a(CH$_3$COOH) 4.756, activity coefficients taken as unity.

[a] Evaluated by extrapolation of reactivity profiles to zero reaction. [b] Evaluated by computer simulation of reactivity profile shape. [c] Taken from ref. 17. Other literature values at 25 °C are: 5.55 [18a] and 5.48.[18b] Values reported for 20 °C are 5.53 [19a] and 5.68.[19b] [d] From ref. 19. [e] From ref. 17*a*. Ref. 19 also gives 6.19. [f] From ref. 20. Ref. 13*d* gives 4.89. [g] Estimated taking all activity coefficients as unity.

TABLE 2

Variation with [KBr] of rate coefficients for aqueous brominations of benzimidazoles at 25 °C. [NaOAc] 0.090 9 mol dm^{-3}, [HOAc] 0.019 2 mol dm^{-3}

	Benzimidazole [a]		1-Methylbenzimidazole [b]		2-Methylbenzimidazole [b]	
[KBr] / mol dm^{-3}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}
0.909	23.7	875	20.9	811	48.9	5 380
0.727	30.0	899	26.3	829	64.4	5 750
0.545	40.6	935	35.7	864	84.5	5 800
0.364	58.9	951	52.8	896	132	6 350
0.182	106	975	94.4	913	232	6 360
0.0909	170					

[a] Ionic strength 1.000 mol dm^{-3}, made up with KNO$_3$. [b] Ionic strength 1.182 mol dm^{-3}, made up with KNO$_3$ [c] Estimated as in Table 1.

TABLE 3

Variation with [NaOAc] of rate coefficients for aqueous brominations of benzimidazoles at 25 °C. [KBr] 0.364 mol dm^{-3}, [HOAc] 0.018 0 mol dm^{-3}

	Benzimidazole [a]		1-Methylbenzimidazole [b]		2-Methylbenzimidazole [b]	
[NaOAc] / mol dm^{-3}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [c] / dm^3 mol^{-1} s^{-1}
0.1814	99.4	1 130	80.2	943	279	7 360
0.0849	58.9	953	52.8	898	132	6 369
0.362	30.3	858	29.2	884	63.4	6 566
0.0213	20.3	876	18.0	836	36.6	6 259
0.0145	13.8	829	16.0	1 038	24.5	6 072

[a] Ionic strength 1.000 mol dm^{-3}, made up with KNO$_3$. [b] Ionic strength 1.182 mol dm^{-3}, made up with KNO$_3$. [c] Estimated as in Table 1.

TABLE 4

Variation with [NaOAc] of rate coefficients for bromination of benzimidazoles (aqueous; 25 °C). [KBr] 0.364 mol dm^{-3}, [HOAc] = 0.198 [NaOAc]. Ionic strength I = [KBr] + [NaOAc]

	Benzimidazole		1-Methylbenzimidazole		2-Methylbenzimidazole	
[NaOAc] / mol dm^{-3}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [a] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [a] / dm^3 mol^{-1} s^{-1}	k_2 / dm^3 mol^{-1} s^{-1}	k_{bi} [a] / dm^3 mol^{-1} s^{-1}
0.909	62	966	48	785	136	6 190
0.727	62	966			130	5 920
0.546	60	935			129	5 870
0.364	60	935	47	768	129	5 870
0.182	59	919			128	5 830
0.091	58	903	48	785	129	5 870

[a] Estimated as in Table 1.

The reactivity profile for separately prepared 5(6)-bromobenzimidazole, which could be measured to *ca.* 1 : 0.4 Br_2 before solid began to precipitate, had the stoicheiometry (1.0 ± 0.1). Under the conditions of Figure 1 k_2/dm^3 mol^{-1} s^{-1} = 4.4 ± 0.4, providing independent evidence for the belief that the value, 4.0,

[17] (*a*) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162; (*b*) D. D. Perrin, *J. Chem. Soc.*, 1965, 5590.

[18] (*a*) H. Walba and R. W. Isensee, *J. Org. Chem.*, 1961, **26**, 2789; (*b*) M. T. Davies, P. Mammalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420.

[19] (*a*) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240; (*b*) C. J. Hawkins and D. D. Perrin, *ibid.*, 1962, 1351.

[20] (*a*) H. Walba, D. L. Stiggall, and S. M. Coutts, *J. Org. Chem.*, 1967, **32**, 1954; (*b*) H. Walba, and R. Ruiz-Velasco, *ibid.*, 1969, **34**, 3315.

obtained for the second kinetic parameter in fitting the reactivity profile for benzimidazole by computer simulation, corresponds to further reaction of 5(6)-bromobenzimidazole.

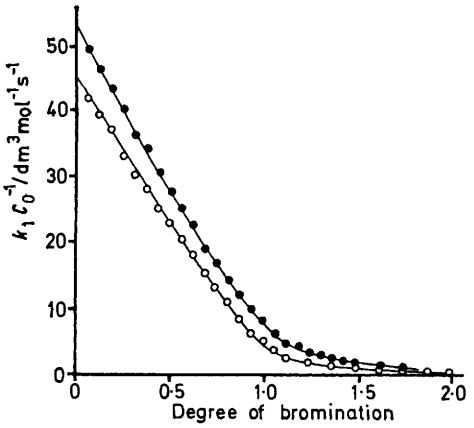


FIGURE 1 Reactivity profiles for bromination of benzimidazole (●) and 1-methylbenzimidazole (○): medium at 25 °C, [KBr] 0.364 mol dm^{-3}, [NaOAc] 0.0909 mol dm^{-3}, [HOAc] 0.0192 mol dm^{-3}. Curves were drawn by computer simulation to best fit according to the Scheme

In Tables 2—4 are listed values of k_2 for various [Br^-], [H^+], and [CH_3COO^-], respectively. These *in situ* reactivities varied inversely with increasing [Br^-], and with increasing [H^+], while being almost unaffected by increases in the concentration of the buffer base, CH_3COO^-. This is consistent with substitution occurring by way of the bimolecular rate-determining step (1) with

$$S + Br_2 \xrightarrow{k_{bi}} SBr^+ + Br^- \quad (1)$$

the subsequent step (2) being fast, so that general base catalysis was not apparent.

$$SBr^+ + Base \longrightarrow SH_{-1}Br + HBase^+ \quad (2)$$

The concentrations of the reactants for (1) are determined by the equilibria (3) and (4). They lead to k_2

$$Br_3^- \rightleftharpoons Br_2 + Br^- \quad (3)$$
$$SH^+ \rightleftharpoons S + H^+ \quad (4)$$

being less than the bimolecular rate coefficient in accordance with (5) with [Bromine] = [Br_3^-] + [Br_2] and

$$\text{rate} = k_2[\text{Bromine}][\text{Substrate}] = k_{bi}[Br_2][S] \quad (5)$$

[Substrate] = [SH^+] + [S]. Estimates of k_{bi} included in Tables 2—4 were obtained by means of equation (6), which was derived by assigning unity for all activity coefficients, where $K = K(3) = 0.059\,3$ [21] in aqueous

$$k_{bi} = k_2(1 + [Br_3^-]/[Br_2])(1 + [SH^+]/[S]) \simeq k_2(1 + [Br^-]/K)(1 + [H^+]/K_a) \quad (6)$$

solution at 25 °C and $K_a = K(4)$, with pK_a values given in Table 1.

Hydrogen ion concentrations were obtained from the approximate expression (7) with K_a {CH_3COOH (aqueous; 25 °C)} = 1.754×10^{-5}.

$$[H^+] \simeq K_a\{CH_3COOH\}[CH_3COOH]/[CH_3COO^-] \quad (7)$$

The approximate estimates of k_{bi} are nearly constant. Variations are of the magnitude to be expected with solutions of such high ionic strength which do not have a single swamping electrolyte.

Bimolecular Rate Constants.—Standard values for the bimolecular rate coefficients were evaluated by conducting experiments at several values of ionic strength by progressively reducing the concentration of KBr and performing linear extrapolations of logarithms of estimated values of k_{bi} to zero ionic strength, as shown in Figure 2.

Bimolecular constants can be compared in terms of molecular structure. It is clear that the 5-position in benzimidazole, standing in the benzene ring in the same relation to the secondary nitrogen as the *para*-position in aniline, has by far the greatest reactivity toward molecular bromine. The 7-position, which is *ortho* to the secondary nitrogen appears to be the next most reactive site with *ca.* 20 times lesser reactivity, while the 2-position in the five-membered ring had no perceptible reactivity under our conditions of study.

Our estimates of bimolecular rate constants for reactions of bromine with azoles are collected in Table 5. Indazole [3c] is similar to benzimidazole in having the 5-position the most reactive and the 7-position *ca.* 10-fold

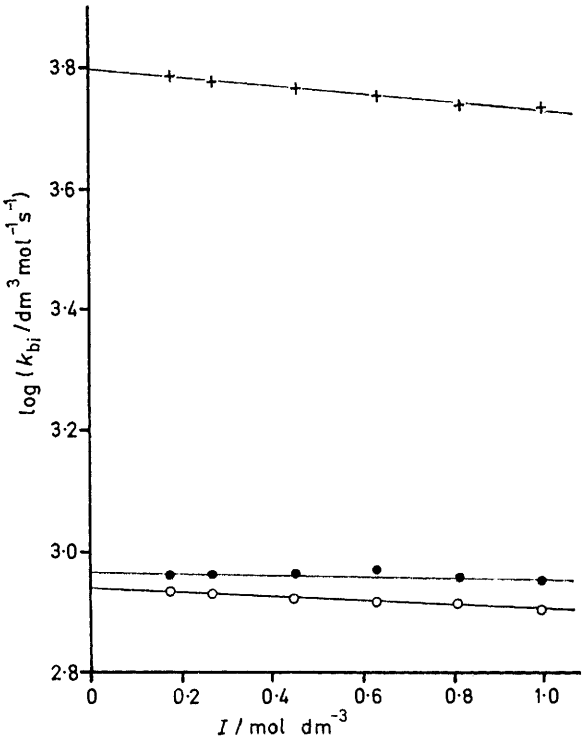


FIGURE 2 Variation with ionic strength of bimolecular rate coefficients for bromination of benzimidazole (●), 1-methylbenzimidazole (○), and 2-methylbenzimidazole (+): aqueous solution at 25 °C, [NaOAc] 0.0909 mol dm^{-3}, [HOAc] 0.0180 mol dm^{-3}, ionic strength I [KBr] + [NaOAc]

[21] D. B. Scaife and H. J. V. Tyrell, *J. Chem. Soc.*, 1958, 386.

less. However, the 3-position in the five-membered ring was intermediate in reactivity between these two benzenoid sites. With pyrazole,[3a] aqueous bromination occurred selectively at the 4-position and we can infer that the reactivity of the 3-(5-)position is not greater than *ca.* 4 000 $dm^3 mol^{-1} s^{-1}$, 1% of that of the 4-position.

TABLE 5

Rate constants for bimolecular reactions of bromine with specific sites in azoles aqueous; 25 °C

Substrate	Site	$k°_{bi}$/$dm^3 mol^{-1} s^{-1}$
*Benzim*idazole	5	935 [a]
	7	*ca.* 40 [c]
	2	<4 [d]
5(6)-Bromobenzimidazole	7	40 [b]
1-Methylbenzimidazole	5	879 [a]
2-Methylbenzimidazole	5	6 300 [a]
Imidazole [3b]	2	200 000
Imidazole [3b]	4	400 000
Imidazole [3b]	5	500 000
Indazole [3c]	3	2 800
Indazole [3c]	5	4 200
Indazole [3c]	7	400
Pyrazole [3a]	4	380 000
Benzene [7]		$6 \times 1.39 \times 10^{-5}$

[a] ±1%, assuming no error in pK_a and K values adopted in these calculations. [b] ±10%; calculated from estimated k_{bi} using the same ratio to $k°_{bi}$ as found with benzimidazole under the conditions of Table 1. [c] Order of magnitude estimate using measured value for 5(6)-bromobenzimidazole. [d] Upper limit based on uncertainty of unit stoicheiometry with 5(6)-bromobenzimidazole being *ca.* 10%.

The 5-bromo-derivative of benzimidazole is >20 times less reactive than benzimidazole. On the basis of the reactivities of specific sites in imidazole and bromoimidazoles we take the reactivity of this derivative as an order of magnitude estimate for the 7-position in benzimidazole.

The reactivity of 1-methylbenzimidazole is little different from that of benzimidazole. Thus it is again demonstrated that the effect of a methyl substituent acting through secondary nitrogen is small.[3] The present case is the first we have found in which there is deactivation towards bromination when a methyl group is introduced. From the 2-position, a methyl group, acting across or around the two rings of benzimidazole, activates the 5-position *ca.* 7-fold.

Reactivities and Individual Atom Charges.—In Table 6 are listed the reactivities towards aqueous bromine of the sites in the simple azoles and benzazoles together with nett charges calculated by VESCF/BJ,[22] CNDO/2,[23a,24] and CNDO/S [23b,24] methods. These semi-empirical molecular orbital methods have been very successful in accounting for dipole moments of azoles and other heteroaromatics and may be expected to give reasonable estimates of charges associated with individual sites of attack. The VESCF method is similar in principle to the CNDO approach but has been applied with explicit treatment only of π-electrons and non-bonded pairs while allowing for dependence of orbital ionization potentials on the nett charges of the atoms.

TABLE 6

Reactivities toward bromine and $10^3 \times$ site charges computed by molecular orbital methods

Site no.	1	2	3	4	5	6	7
Pyrazole							
log ($k°$/$dm^3 mol^{-1} s^{-1}$)			<4.0	5.58	<4.0		
Q(VESCF/BJ)	+225	−139	−15	−66	−35		
Q(CNDO/2)	+60	−130	+80	−80	+70		
Imidazole							
log ($k°$/$dm^3 mol^{-1} s^{-1}$)		5.30		5.60	5.70		
Q(VESCF/BJ)	+250	−1	−150	−48	−51		
Q(CNDO/2)	+40	+140	−190	+30	+0		
Indazole							
log ($k°$/$dm^3 mol^{-1} s^{-1}$)			3.45	<?	3.62	<?	2.60
Q(VESCF/BJ)	+230	−97	−27	−3	−16	−8	−29
Q(CNDO/2)	+13	−100	+60	+17	−37	+17	−46
Q(CNDO/S)	+35	−163	+85	+18	−33	+19	−28
Benzimidazole							
log ($k°$/$dm^3 mol^{-1} s^{-1}$)		<1.0		<1.0	2.91	<1.0	*ca.* 2.0
Q(VESCF/BJ)	+228	0	−121	−5	−16	−11	−30
Q(CNDO/2)	−21	+174	−225	−15	−24	−6	−35
Q(CNDO/S)	−13	+170	−237	−0	−15	−12	−15

Thus we conclude that the effect of annelation on the reactivity of the 3-position is not greatly deactivating and may even be activating. With imidazole,[3b] all three carbon atoms are susceptible to bromodeprotonation and we can deduce that the presence of the added benzo-group in benzimidazole deactivates the 2-position by a factor >5 000.

Since the reactivities of the azoles are within a few orders of magnitude of the expected translation plus rotational diffusion limit,[25] *ca.* 10^9—10^{10} $dm^3 mol^{-1} s^{-1}$, we can expect electric charges to make major contributions to the control of orientation of bromonium transfer. For pyrazole the sequence of negative charges computed by VESCF/BJ and CNDO/2, 4 > 5 > 3, are

[22] (*a*) R. D. Brown and B. A. W. Coller, *Theor. Chim. Acta*, 1967, **7**, 259; (*b*) R. D. Brown, B. A. W. Coller, and J. E. Kent, *ibid.*, 1968, **10**, 435.

[23] (*a*) J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970, p. 75; (*b*) J. Del Bene and H. H. Jaffe, *J. Chem. Phys.*, 1968, **48**, 1807, 4050; 1968, **49**, 1221; 1969, **50**, 1226.

[24] A. Escande, J. Lapasset, R. Faure, E-J. Vincent, and J. Elguero, *Tetrahedron*, 1974, **30**, 2903.

[25] G. B. Burfoot, E. F. Caldin, and H. Goodman, *J.C.S. Faraday I*, 1974, 105.

in qualitative agreement with the observed preference for bromodeprotonation at C-4. With imidazole the VESCF/BJ and CNDO/2 sequences of charges, $5 > 4 > 2$ agrees with the observed sequence of reactivities. However the CNDO/2 method yields charges on carbon atoms in imidazole which are very much less negative than the charge at the 4-position in pyrazole which experiment indicates to be of similar reactivity. The high reactivity found for the 2-position is unexpected according to charges calculated by either method.

According to VESCF/BJ,[22] CNDO/2, and CNDO/S,[24] annelation of the azoles leads to transfer of 40—80 me from the heterocyclic ring to the four sites of the benzo-group. These negative charges tend to be concentrated at positions 5 and 7 in the benzazoles corresponding to *para* and *ortho* in aniline derivatives. Thus it is no surprise to find that bromine attacks these positions in the benzazoles and that their reactivities are intermediate between those of aniline and benzene (Table 5). The predominance of attack at the 5-position in preference to 7 can be understood if the large positive charge on the nearby secondary nitrogen has a significant electrostatic repulsive effect on the developing positive charge as Br_2 attacks the 7-position. The reactivity of aniline itself is close to the upper limit of bimolecular rate coefficients imposed by translational and rotational diffusion in the approach of the attacking electrophile to the reactive sites.

Comparison of site charges gives qualitative understanding of the effects of annelation on reactivities in the azole rings. According to VESCF/BJ, the charge at the 2-position in imidazole is hardly altered while the nett charge in the five-membered ring goes up to $+0.062$. Experimentally we observe considerable deactivation of the 2-position by annelation. In pyrazole the charge associated with the 3-position becomes markedly more negative, going from -0.015 to -0.027, and changing in such a way as to oppose the deactivating effect of overall movement of electron density from the five-membered ring to the benzo-group. Experimental evidence, recounted above, indicates little, if any, deactivation in this system. According to CNDO/2 the deactivating effect of transfer of negative charge from the five-membered ring is reinforced in benzimidazole by marked withdrawal of electron density from the 2-position while in indazole the effect again seems to be mitigated by marked accumulation of electron density at the 2-position. The pattern of CNDO/S site charges for indazole, $5 > 7 > 4 > 6$, can be used to explain observed relative reactivities in the benzo-group without invoking repulsion by the charge on the nearby nitrogen atom. Similarly, for benzimidazole the CNDO/S sequence, $5 \approx 7 > 6 > 4$, is more nearly compatible with the observed reactivities, $5 > 7 > 6$, 4, 2. It is noted that the 3-position of indazole lies between positions 5 and 7 in reactivity while the MO calculations give this site the least negative (most positive) charge of all carbon centres for bromodeprotonation in the system. Further comment is reserved until the theoretical basis for comparing reactivities in five- with those in six-membered rings has been developed to a more quantitative level.

In this series we have met some of the needs identified by Schofield *et al.*[2] by demonstrating that the kinetically significant step in aqueous bromodeprotonation of the diazoles using bromine is the concerted bimolecular bromonium transfer from Br_2 to molecular substrate. Absolute values of bimolecular rate constants for attack on identified sites provide the quantitative information on reactivities which is needed for further development and testing of formulations of theories of reactivity in solutions. The upper limits of the reactivities of molecular diazoles towards Br_2 in aqueous solution seem to be determined by translational plus rotational diffusion.[25] The reactivities of the typical diazoles are within three to six orders of magnitude of these limits and we infer that the transition state in bromonium transfer occurs relatively early on the way to formation of the σ-complex.[26]

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[7/1386 *Received*, 1*st August*, 1977]

[26] P. B. De La Mare, ' Electrophilic Halogenation,' Cambridge University Press, Cambridge, 1976, p. 141.