Studies on Benzimidazoles. Part VII.[1] Kinetics and Mechanism of the Reaction of Thiophenoxydehalogenation of *NN'*-Disubstituted 2-Chlorobenzimidazolium Perchlorates

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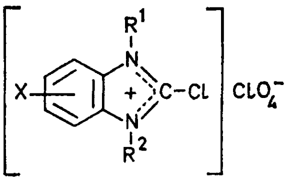
The kinetic behaviour of the title reaction was investigated as a function of pH, solvent and lithium perchlorate concentration. The results are mechanistically interpreted. The cleavage of the hydrogen–sulphur bond of the thiol and the formation of the linkage between sulphur and carbon in the position 2 of the benzoheterocyclic system are involved in the rate-determining step. The reactivity of the organic cation separated from its counterion is similar to that of the corresponding ion pair.

RECENTLY[2] the reactivity of 2-halogenobenzimidazoles with thiophenols in basic, neutral, and acidic media was studied. It was observed[1] that the reactivity of 2-chlorobenzimidazolium perchlorates (I) with thiophenol is modified by substituents in the benzene ring of the cation as expected for a nucleophilic aromatic substitution,[3] whereas anomalous variations are induced by substituents in the thiol ring which cause acceleration in all cases although the effect of electron-withdrawing substituents is more marked. This fact is unexpected on the basis of the simple nucleophilic character of the sulphur of the thiol derivative[4] and suggests that other factors are operating.



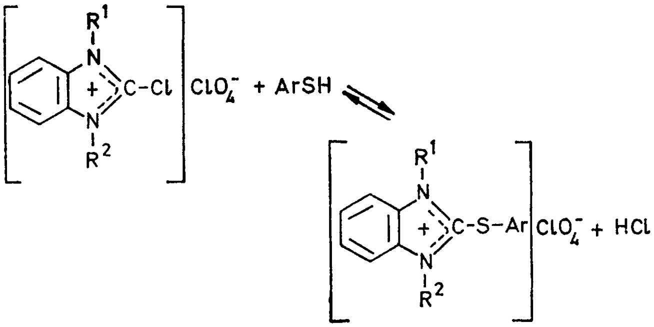
(I)

a; X = H, $R^1 = R^2 = Me$
b; X = H, $R^1 = Me$, $R^2 = Ph$
c; X = H, $R^1 = Me$, $R^2 = p\text{-}Cl\text{-}C_6H_4$

In order to elucidate the mechanism of such a reaction we studied the reactivity of some *NN'*-disubstituted 2-chlorobenzimidazolium perchlorate derivatives (Ia)—(Ic) with thiophenol.

RESULTS

The reactions of *NN'*-disubstituted 2-chlorobenzimidazolium perchlorates (Ia)—(Ic) with thiophenol were carried out at 40° in 80% (v/v) aqueous methanol in the presence of perchloric acid. In such conditions the reactions lead to the corresponding 2-phenylthio-derivatives [equation (1)] and follow second-order kinetics beyond 90% conversion. The reactivity of the system does not change substantially with the substituent R^2, although a rate enhancement was observed in the case of $R^1 = Me$, $R^2 = Ph$ or $p\text{-}Cl\text{-}C_6H_4$ compared to the *NN'*-dimethyl-substituted derivative (Table 1). This trend is analogous to that found for the reactions of methoxydechlorination of benzimidazoles (free bases). The rate coefficients for 2-chloro-*N*-phenyl- and 2-chloro-*N*-(*p*-chlorophenyl)-benzimidazoles with methoxide ion in methanol at 40° were $1 \cdot 82 \times 10^{-5}$ and $7 \cdot 11 \times 10^{-5}$ l mol^{-1} s^{-1} respectively.



(1)

The reactivity of our salts is sensitive to the addition of different amounts of perchloric acid: strong inhibition was

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[1] Part VI, A. Ricci, G. Seconi, and P. Vivarelli, *J. Chem. Soc.* (*B*), 1970, 254.

[2] A. Ricci and P. Vivarelli, *J. Chem. Soc.* (*B*), 1968, 1280.

[3] J. F. Bunnett and R. A. Zahler, *Chem. Rev.*, 1951, **49**, 273; J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1; J. F. Bunnett, *Ann. Rev. Phys. Chem.*, 1963, **14**, 271; G. Illuminati, *Adv. Heterocyclic Chem.*, 1964, **3**, 345.

[4] A. Ricci, M. Foà, P. E. Todesco, and P. Vivarelli, *Gazzetta*, 1965, **95**, 465.

observed for 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia) as shown in Table 2. Also listed are the acidities of the reaction solutions as measured by the ionization of 4-nitroaniline (equivalent to H_0). In such conditions the undissociated form of thiophenol is favoured. In fact from the pK_a of thiophenol [5] and from the value of H_0 corresponding to the lowest perchloric acid concentration used (see Table 2), it follows that only one part in *ca.* 4 × 10^6 of the stoicheiometric thiophenol is present as ArS^-.

TABLE 1

Specific rate coefficients for the reaction of $NR^1,N'R^2$ disubstituted 2-chlorobenzimidazolium perchlorates (0·8—1·4 × 10^{-2}M) with thiophenol (0·7—2·7 × 10^{-2}M) in MeOH–H_2O 80/20 (v/v) in the presence of perchloric acid (4·8 × 10^{-2}M) at 40° ± 0·01°

R^1, R^2	Me,Me	Me,Ph	Me,*p*-Cl-C_6H_4
10^2k/l mol^{-1} s^{-1}	10·7	20·9	43·4

TABLE 2

Acidity function (H_0) and influence of perchloric acid on the reaction of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (0·7—1·1 × 10^{-2}M) with thiophenol (3·2—4·1 × 10^{-2}M). Solvent MeOH–H_2O 80/20 (v/v) at 40° ± 0·01°

10^2[HClO$_4$]/mol l^{-1}	2·04	4·80	9·90	17·8	49·8
H_0	2·76	2·31	2·03	1·72	1·11
10^2k/l mol^{-1} s^{-1}	27·5	10·7	5·25	2·69	0·39

Table 3 shows the influence of the solvent on the same reaction. The behaviour of solvents as bases can be treated in terms of the Brönsted relation using the literature values of pK_a for the alcohols employed.

2-Chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia) is highly dissociated in MeOH–H_2O 80/20 (v/v) at 40° as previously reported.[6] From the value of the dissociation equilibrium constant it is possible to evaluate the degree of association of (Ia) as a function of the added perchlorate ion (Table 4). It can be seen that a small amount of perchlorate ion strongly influences this equilibrium, whereas greater concentrations affect it to a lesser extent. To obtain information on the reactivity of the unassociated organic cation relative to that of the ion pair, we measured the rates of reaction of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia) with thiophenol with various amounts of lithium perchlorate (Table 5 and the Figure). This variation has been studied at two different concentrations of perchloric acid and allowance has been made for the influence of the added salt on the acidity of the medium (see Table 5).

TABLE 3

Solvent effect on rate coefficient for the reaction of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (0·6—1·2 × 10^{-2}M) with thiophenol (0·8—2·7 × 10^{-2}M) at 40° ± 0·01°

Solvent	E [a]	M [a]	NP [a]	B [a]
[HClO$_4$]/mol l^{-1}	0·49	0·49	0·49	0·50
10^3k/l mol^{-1} s^{-1}	3·82	3·89	5·75	9·48
pK_a (in water)	14·8 [b]	15·1 [c]	16·1 [c]	16·8 [d]

Solvent	IP [a]	N [a]	D [a]
[HClO$_4$]/mol l^{-1}	0·50		
10^3k/l mol^{-1} s^{-1}	9·50	No reaction	No reaction
pK_a (in water)	17·1 [c]		

[a] E = 2-Methoxyethanol–H_2O 80/20 (v/v); M = MeOH–H_2O 80/20 (v/v); NP = propan-1-ol–H_2O 80/20 (v/v); B = t-butyl alcohol–H_2O 80/20 (v/v); IP = propan-2-ol–H_2O 80/20 (v/v); N = nitromethane; D = 1,2-dichloroethane. [b] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795. [c] J. Murto and M. L. Murto, *Acta Chem. Scand.*, 1966, **20**, 297. [d] M. Martin, *J. Chim. phys.*, 1962, **59**, 736.

TABLE 4

Variations of the ion-pair association of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate in the presence of variable amounts of perchlorate ion. Solvent MeOH–H_2O 80/20 (v/v) at 40° ± 0·01°

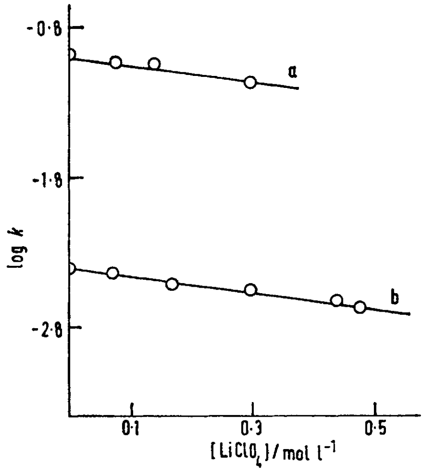
[ClO$_4^-$]/g ion l^{-1}		0·05	0·10	0·30	0·50	0·76	1·10
Association (%) *	22·1	48·3	59·4	74·0	79·0	82·5	85·2

* This was calculated according to the usual methods (S. Glasstone, ' An Introduction to Electrochemistry,' D. Van Nostrand Co., New York, 1962, 10th edn., p. 158.

TABLE 5

Effect of lithium perchlorate on the reaction of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (0·8—1·4 × 10^{-2}M) with thiophenol (1·0—5·3 × 10^{-2}M) in the presence of perchloric acid. Solvent MeOH–H_2O 80/20 (v/v) at 40° ± 0·01°

			[HClO$_4$] = 0·5M			
[LiClO$_4$]/mol l^{-1}		0·07	0·17	0·30	0·44	0·48
H_0	1·11	1·06	1·01	0·93	0·88	0·86
10^3k/l mol^{-1} s^{-1}	3·89	3·55	3·02	2·75	2·34	2·09
		[HClO$_4$] = 0·049M				
[LiClO$_4$]/mol l^{-1}		0·08	0·14	0·30		
H_0	2·25	2·17	2·15	2·14		
10^3k/l mol^{-1} s^{-1}	104	91·2	87·1	67·6		



Rate of reaction of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate with thiophenol *vs.* lithium perchlorate concentration in the presence of perchloric acid. (a) [HClO$_4$] = 0·049 M. (b) [HClO$_4$] = 0·5 M. *k* in l mol^{-1} s^{-1}

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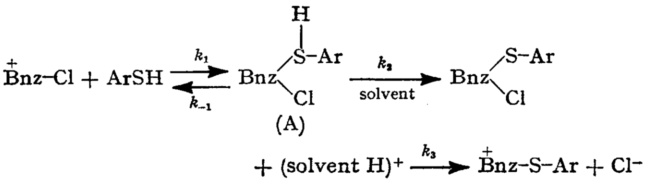
[5] G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, 1934, **17**, 1176.

[6] A. Ricci, G. Seconi, and P. Vivarelli, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 153.

DISCUSSION

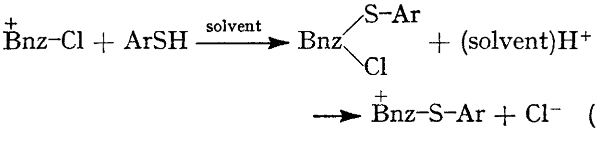
The results show that the reaction between 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia) and thiophenol is slowed down strongly by the addition of variable amounts of perchloric acid and is solvent sensitive. The influence of added perchloric acid is not to be ascribed to dissociated thiophenol which is present in different amounts according to the concentration of the perchloric acid. In fact, at the lowest perchloric acid concentration used, the rate of reaction between the equilibrium concentration of ArS^- and the heterocyclic cation, evaluated on the assumption that this reaction is a diffusion-controlled process, is *ca.* $1{\cdot}4 \times 10^{-3}$ l mol^{-1} s^{-1}. This value is *ca.* 200 times smaller than the experimental rate coefficient (see Table 2). Therefore the observed reactivity cannot be due to the small equilibrium concentration of thiophenoxy-anion. It follows that the rate decrease with increasing acid concentration should indicate that a proton transfer is involved in the rate-determining step. Accordingly the reaction rate is accelerated by more basic solvents. Indeed the solvent effect may be rationalized in terms of a basic catalysis which obeys the Brönsted relation. In less basic solvents like 1,2-dichloroethane and nitromethane,[7] there is no reaction even in the absence of perchloric acid. Moreover the influence of lithium perchlorate, more than a salt effect on the reaction, may be explained on the basis of its effect on the activity of the proton (see Table 5).

The above facts may be rationalized as shown in the Scheme ($\overset{+}{\text{Bnz}}$–Cl and $\overset{+}{\text{Bnz}}$–S–Ar are 2-chloro- and 2-phenylthio-benzimidazolium derivatives respectively)



SCHEME

where, for the sake of simplicity, the reaction is represented as a series of consecutive steps. In particular it may well be the case that the attack of the undissociated thiophenol (k_1) on the 2-carbon and the proton removal from the intermediate (k_2) occurs in a synchronous single step [equation (2)].



$$\overset{+}{\text{Bnz}}\text{–Cl} + \text{ArSH} \xrightarrow{\text{solvent}} \text{Bnz}\begin{matrix}\text{S–Ar}\\ \text{Cl}\end{matrix} + (\text{solvent})\text{H}^+ \longrightarrow \overset{+}{\text{Bnz}}\text{–S–Ar} + \text{Cl}^- \quad (2)$$

The release of Cl^- from the neutral adduct (k_3 in the Scheme) is assumed always to be a fast process by analogy with previous observations.[2] The adduct also represents the undissociated form of the benzimidazolium chloride which as a salt of a strong base must be largely dissociated and, in any case, equilibrates quickly to the ions. Applying the steady-state treatment in respect to (A) of the Scheme, and assuming $k_{-1} \gg k_2$ the kinetic expression becomes equation (3) which accounts for the observed second-order kinetics if $k_{obs} = k_1/k_{-1} \times k_2$. According to this interpretation the 'anomalous' effect of the substituents in the phenyl ring of thiophenol appears less surprising if we consider that these substituents exert opposite effects on the k_1/k_{-1} and k_2 values.

$$v = k_1/k_{-1} \times k_2[\overset{+}{\text{Bnz}}\text{–Cl}][\text{ArSH}] \qquad (3)$$

Thus, the reactivity observed is a function both of the nucleophilicity and acidity of the sulphur species. Such a Scheme also accounts for the modifications of the reactivity induced by increasing medium acidity and by the behaviour of the solvents as bases. In fact a stronger medium acidity prevents the cleavage of the hydrogen–sulphur bond, thus depressing the k_2 value and lowering the reactivity of the system. The opposite tendency is found in the more basic solvents.

When a methyl group of 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia) is replaced by an electron-withdrawing group (Ib: Ph; Ic: *p*-Cl–C_6H_4) the sulphur–carbon bond formation is favoured thus enhancing the value of k_1/k_{-1} and the reactivity of the system in agreement with the proposed mechanism.

Finally the above results show that the reaction rate examined is independent of the relative concentrations of the ion pair of benzimidazolium perchlorate and of the free heterocyclic cation. In fact the retarding effect of lithium perchlorate does not change with the perchloric acid concentrations (Figure) which affect the dissociation equilibrium of the organic salt to a different degree (Table 4). This observation indicates that the reactivity of both the associated and unassociated organic salt is practically the same.

EXPERIMENTAL

Materials.— 2-Chloro-*N*-methyl-*N'*-phenylbenzimidazolium perchlorate (Ib) and 2-chloro-*N'*-(*p*-chlorophenyl)-*N*-methylbenzimidazolium perchlorate (Ic) were obtained by the methylation with dimethyl sulphate of 2-chloro-*N*-phenylbenzimidazole[2] and 2-chloro-*N*-(*p*-chlorophenyl)benzimidazole, respectively, and the subsequent reaction with perchloric acid according to the method described[6] for 2-chloro-*NN'*-dimethylbenzimidazolium perchlorate (Ia). 2-*Chloro*-N-*methyl*-N'-*phenylbenzimidazolium perchlorate* (Ib) had m.p. 213—214° (decomp.) (from acetonitrile–anhydrous diethyl ether) (Found: C, 48·9; H, 3·5; Cl, 20·9; N, 8·2. $C_{14}H_{12}Cl_2N_2O_4$ requires: C, 48·8; H, 3·5; Cl, 20·6; N, 8·15%). 2-*Chloro*-N'-(p-*chlorophenyl*)-N-*methylbenzimidazolium perchlorate* (Ic) had m.p. 201—202° (from acetonitrile–anhydrous diethyl ether) (Found: C, 44·7; H, 2·95; Cl, 28·3; N, 7·45. $C_{14}H_{11}Cl_3N_2O_4$ requires: C, 44·4; H, 2·95; Cl, 28·1; N, 7·4%).

2-*Chloro*-N-(p-*chloro*)*phenylbenzimidazole*. This was obtained by reaction of *N*-(*p*-chlorophenyl)benzimidazolin-2-one with phosphoryl trichloride in the presence of hydrochloric acid as previously described for the preparation of

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[7] G. W. Wheland and J. Farr, *J. Amer. Chem. Soc.*, 1943, **65**, 1433.

2-chloro-*N*-phenylbenzimidazole [2] and had m.p. 132—133° (from ligroin) (Found: C, 59·0; H, 3·1; Cl, 26·9; N, 10·8. $C_{13}H_8Cl_2N_2$ requires: C, 59·5; H, 3·05; Cl, 26·9; N, 10·7%).

N-(p-*Chloro*)*phenylbenzimidazolin*-2-*one*. This was prepared by cyclization of 2-amino-4′-chlorodiphenylamine [8] (0·1 mol) with urea (0·11 mol) at 175—180° during 1 h. The reaction mixture was extracted with boiling 10% aqueous sodium hydroxide. The expected product, m.p. 222—224°, separates upon acidification with hydrochloric acid.

Commercial thiophenol was purified according to the usual methods.[9] Perchloric acid (70%) and lithium perchlorate were AnalaR products.

Reaction Products.—The reaction products were separated in the case of the reaction of 2-chloro-*NN*′-dimethylbenzimidazolium perchlorate with thiophenol under similar conditions to those of the kinetic experiments.[1] The methoxydehalogenation product was isolated in the case of the reaction between 2-chloro-*N*-phenylbenzimidazole (0·01 mol) and sodium methoxide (0·1 mol) in the same conditions as those used in the kinetic runs. After evaporation of the solvent we obtained 2-*methoxy*-N-*phenylbenzimidazole*, b.p. 129—130°/2 mmHg (Found: C, 75·4; H, 5·45; N, 12·4. $C_{14}H_{12}N_2O$ requires: C, 74·95; H, 5·4; N, 12·5%).

Solvents.—Methanol, propan-1-ol, propan-2-ol, and 2-methoxyethanol were purified by literature methods [10] and t-butyl alcohol was distilled from potassium.[11] Nitromethane and 1,2-dichloroethane (AnalaR reagents) were purified according to described procedures.[10,12] In the kinetic runs twice-distilled water was used.

Kinetics.—The experiments and the calculations of the reaction rate coefficients were performed according to methods previously employed.[1] Reported data are values averaged from 2 or 3 runs with different initial reactant concentrations. The experimental error is *ca.* ±2%. The rate of reaction between the equilibrium concentration of ArS^- with the benzimidazolium cation has been evaluated by a literature method.[13]

Determination of H_0 Values.—H_0 values were determined at 40° with 4-nitroaniline as indicator [14] ($pK_a = 0·89$) according to standard methods.[15] U.v. determinations were made with a Beckman DU spectrophotometer using thermostatted cells.

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[12] A. I. Vogel, ' Practical Organic Chemistry,' 3rd edn., Longmans, Green and Co., London, 1956, p. 177.

[13] M. W. Austin and J. H. Ridd, *J. Chem. Soc.*, 1963, 4204.

[14] A. I. Biggs, *J. Chem. Soc.*, 1961, 2572.

[15] Ch. Kalidas and S. R. Palit, *J. Chem. Soc.*, 1961, 3998.