Reactivity of 7-Halogeno-4-nitrobenzofurazans towards Thiophenols. A Kinetic Investigation

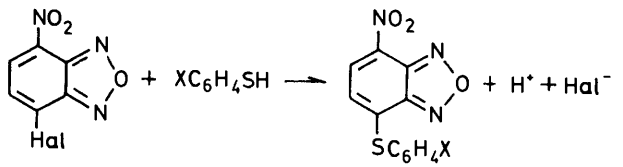
By **Mauro Domenico del Rosso, Leonardo Di Nunno,* Saverio Florio,** and (in part) **Antonio Amorese,** Istituto di Chimica Organica, Università, via Amendola 173, 70126 Bari, Italy

The reactions of 7-chloro- and 7-bromo-4-nitrobenzofurazan with thiophenols in methanol afford the products of arylthiodehalogenation together with the corresponding hydrogen halide. Kinetic analysis indicates a remarkable auto-inhibition which has been interpreted on the basis of two competitive mechanisms, one due to the ionized and the other to the un-ionized thiophenol. The substituent effect in the thiophenol for the two mechanisms is discussed.

As previously reported, 5-chloro- and 7-chloro-4-nitrobenzofurazan react with thiophenol in methanol yielding 5-phenylthio- and 7-phenylthio-4-nitrobenzofurazan, respectively.[1] A similar reaction with 'un-ionized' thiophenols is known for other activated substrates, namely halogeno-quinolines,[2] -benzimidazoles,[3] and -thiazoles.[4] While reactions of the latter compounds with thiophenols have been extensively investigated, kinetic data have not been reported for the corresponding reactions of halogenonitrobenzofurazans. A kinetic investigation has now been made using 7-chloro- and 7-bromo-4-nitrobenzofurazan and a number of substituted thiophenols in methanol.

RESULTS

7-Chloro-4-nitrobenzofurazan reacts with 'un-ionized' thiophenols XC_6H_4SH (X = H, 4-Me, 4-OMe, 4-Br, or 3-Cl) in methanol according to Scheme 1. The reasons, however,



SCHEME 1

do not follow normal second-order kinetics, marked auto-inhibition being observed for all thiophenols. This auto-inhibition may be attributed to the acid produced during the reaction. In fact, whereas the addition of the product of substitution does not produce any effect, the addition of methanesulphonic acid reduces the reactivity and, for suitable concentrations (*i.e.* in excess over the acid produced during the reaction), regularizes the kinetics. In Table 1 second-order constants for the reactions of 7-chloro-4-nitrobenzofurazan with the above mentioned thiophenols at various concentrations of methanesulphonic acid are reported. In all cases, the reactivity progressively decreases upon increasing the concentration of methanesulphonic acid. The plot of the observed second-order rate constants against $1/[H^+]$ ($[H^+]$ being the concentration of methanesulphonic acid in the range 0.01—0.1M) was a straight line for all thiophenols obeying equation (1). The values of A and B are collected in Table 2.

$$k_{obs.} = A/[H^+] + B \quad (1)$$

Similar behaviour was also observed for 7-bromo-4-nitrobenzofurazan. The addition of methanesulphonic acid alone, even in the highest concentrations used in our experiments (0.1M) did not appreciably modify the u.v. spectrum of 7-chloro-4-nitrobenzofurazan in methanol. This is consistent with the very low basicity of the substrate (*e.g.* the reported pK_a for benzofurazan is −8.4;[5] in comparison, pK_a values for quinoline, benzimidazole and thiazole have been reported to be 4.95, 5.53, and 2.5, respectively).[4,6]

Finally, some reactions were carried out with 7-chloro-4-nitrobenzofurazan and sodium thiophenoxide in methanol. Because of the greater electron density on sulphur in ArS^- than in ArSH, reactivities were very high (some kinetic measurements were made with a stopped-flow apparatus). In these conditions, however, the reactions were not clean

TABLE 1

Observed second-order kinetic constants $k_{obs.}$ (l mol^{-1} s^{-1}) in the reactions of 7-chloro-4-nitrobenzofurazan with XC_6H_4SH in methanol at 25° and in the presence of $MeSO_3H$

X = H	$[MeSO_3H]$/M	0.0233	0.0303	0.0454	0.0588	0.106	0.244	
	10^5k	1.5	1.5	1.0	1.0	0.68	0.69	
X = 4-Me	$[MeSO_3H]$/M	0.0244	0.0320	0.0394	0.0522	0.0752	0.127	
	10^5k	2.3	1.9	1.9	1.8	1.7	1.3	
X = 4-OMe	$[MeSO_3H]$/M	0.0198	0.0218	0.0244	0.0336	0.0427	0.0532	
	10^5k	3.3	2.8	2.9	2.4	2.2	2.0	
X = 4-Br	$[MeSO_3H]$/M	0.0218	0.0244	0.0275	0.0336	0.0394	0.0532	0.0769
	10^5k	6.5	6.1	5.8	5.1	4.5	4.3	3.5
X = 3-Cl	$[MeSO_3H]$/M	0.0198	0.0218	0.0244	0.0275	0.0298	0.0505	
	10^5k	6.0	5.4	5.2	4.8	4.8	4.1	

TABLE 2

Values of A and B [from equation (1)] for the reactions of 7-chloro-4-nitrobenzofurazan with XC_6H_4SH in methanol at 25°. Data in parentheses refer to 7-bromo-4-nitrobenzofurazan at the same temperature

X	10^7A/s^{-1}	10^5B/l mol^{-1} s^{-1}
H	2.3 ± 0.3	0.57 ± 0.08 (0.5 ± 0.1)
4-Me	2.5 ± 0.4 (2.7 ± 0.3)	1.2 ± 0.1 (0.7 ± 0.02)
4-OMe	3.6 ± 0.4	1.3 ± 0.15
4-Br	8.7 ± 0.5 (16 ± 2)	2.5 ± 0.15 (1.4 ± 0.1)
3-Cl	5.8 ± 0.6	2.9 ± 0.2

[the product of thiophenoxydehalogenation was obtained together with considerable amounts of other unidentified products (t.l.c.)] and therefore were not further investigated.

DISCUSSION

The first observation we made is the auto-inhibition due to the hydrogen halide formed during the reaction. None of the previously studied substrates [2-4] showed this phenomenon. The decrease of the reactivity clearly cannot be attributed to protonation of the substrate, which was not observed (u.v. experiments). Besides, such protonation, if operative, would have the opposite effect since the activation of the substrate towards nucleophilic attack would presumably be increased.[7] Thus, the observed decrease in reactivity must be related to a change involving the thiophenol, which is present in both un-ionized and ionized (thiophenoxide) forms, the latter mainly arising from the acid–base interaction of the undissociated thiophenol with the solvent (a similar interaction with the substrate may once again be neglected because of its very low basicity).

Since thiophenoxide ion, as expected (and experimentally found, see Results section), is much more reactive than the undissociated thiophenol, a decrease in overall reactivity during the reaction, due to the release of hydrogen halide, is then quite reasonable. Accordingly, the initial addition of methanesulphonic acid also reduces the reactivity and, when in excess over the hydrogen halide released during the reaction, keeping

$$ArSH + MeOH \underset{k_{-1}}{\overset{k_1(fast)}{\rightleftharpoons}} ArS^- + MeOH_2^+;\ K_{ion} = k_1/k_{-1} \quad (a)$$

$$ArS^- + Substrate \xrightarrow[(slow)]{k_2} products$$

$$ArSH + Substrate \xrightarrow{k_3} products \quad (b)$$

SCHEME 2

the ratio $[ArS^-]:[ArSH]$ practically constant, produces normal kinetics. The overall reaction is depicted in Scheme 2.

From Scheme (2) equation (2) is derived and hence the

$$V_{tot} = V_a + V_b = (k_2K_{ion}/[MeOH_2^+] + k_3)[ArSH][Substrate] \quad (2)$$

observed second-order rate constant is given by equation (3) {*i.e.* the dependence on the acid concentration is that experimentally found [equation (1)]}. On the basis of

$$k_{obs.} = \frac{k_2K_{ion}}{[MeOH_2^+]} + k_3 \quad (3)$$

equations (1) and (3), using the values of A and B in Table 2 as well as the known values of pK_a in methanol of the thiophenols,[8] k_2 and k_3 have been calculated for each thiophenol (Table 3).

The logarithms of the rate constants k_2 are linearly correlated (r 0.98) with the σ values of the substituents in the thiophenol (ρ −1.8). This is consistent with a mechanism of the S_NAr type as previously postulated for the reaction of the same substrate with methoxide ion in methanol.[9]

On the other hand, so far as the reaction with the undissociated thiophenols is concerned (k_3), the substituent effect is irregular. The reactivity was enhanced both by electron-donating and -withdrawing substituents, in a way similar to that found for halogenobenzimidazoles,[3]

TABLE 3

Second-order kinetic constants (l mol^{-1} s^{-1}) k_2 and k_3 (Scheme 2) for the reactions of 7-chloro-4-nitrobenzofurazan with XC_6H_4SH in methanol at 25°; pK_a of XC_6H_4SH in methanol are also reported. Data for k_2 and k_3 in parentheses refer to 7-bromo-4-nitrobenzofurazan at the same temperature

X	k_2	10^5k_3	pK_a of XC_6H_4SH [a] in methanol
H	87.4	0.57 (0.5)	8.58
4-Me	177 (190)	1.2 (0.7)	8.85
4-OMe	336	1.3	8.97
4-Br	53.6 (99)	2.5 (1.4)	7.79 [b]
3-Cl	18.3	2.9	7.50

[a] Data from ref. 8*a*. [b] Estimated to be not very different from the pK_a value of 4-ClC_6H_4SH (Hammett equation). See also the reported value at 20 °C (pK_a 7.82).[8b]

and halogenothiazoles.[4] In the latter cases this was rationalized on the basis of a mechanism of reaction involving preliminary acid–base interaction between the substrate and ArSH (Scheme 3). In Scheme 3 the

$$ArSH + Substrate \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} Substrate{\cdot}H^+ + ArS^-;\ k_a/k_{-a} = K_a$$

$$Substrate{\cdot}H^+ \xrightarrow{k_b} products;\ (k_{-a} \gg k_b)$$

SCHEME 3

product k_bK_a is the measured second-order rate constant and hence, as k_b and K_a are influenced in opposite ways by any change in the substituent, the effect on the reactivity is irregular. This explanation is reasonable for the above substrates because of their appreciable basicity.

In the case of halogenonitrobenzofurazans, on the contrary, a significant acid–base preliminary interaction between ArSH and the substrate can be ruled out, as discussed above. Thus a different explanation is required. Some mechanisms of reaction which account for our findings are reported below.

In the mechanism reported in Scheme 4, nucleophilic

$$ArSH + MeOH \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} ArSH \cdots OHMe;\ K_{HB} = k_4/k_{-4}$$

$$ArSH \cdots OHMe \xrightarrow{k_5 Substrate} Products$$

SCHEME 4

attack of sulphur [once again corresponding to a mechanism of the S_NAr type, class A in Bunnett's classification,[10] in the light of the observed kinetic element effect (see Table 3)] is thought to operate not through the 'free' thiophenol, but once again through a more reactive form that in this case would arise by a hydrogen-bond interaction between the thiophenol and the solvent. Such interactions, together with the ionization depicted

in Scheme 2 [equation (a)], have been previously reported [2] and would be essential for the reaction. Accordingly, in solvents where insufficient interactions of the type described are possible (*e.g.* in toluene), no reactivity was observed with appropriately activated substrates (*N*-methyl-4-chloroquinolinium ion) and thiophenol, while the same reaction was possible in methanol.[2]

In the light of Scheme 4, the observed rate is given by equation (4) which, by assuming $k_{-4} \gg k_5$, becomes (5)

$$\text{rate} = k_4k_5[\text{ArSH}][\text{Substrate}]/(k_{-4} + k_5) \quad (4)$$

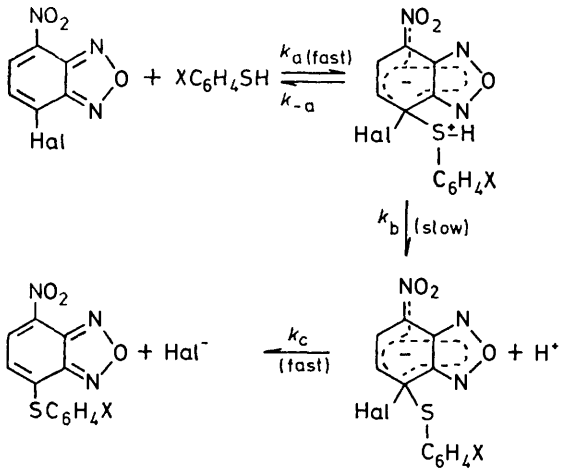
$$\text{rate} = K_{\text{HB}}k_5[\text{ArSH}][\text{Substrate}] \quad (5)$$

where K_{HB}, the equilibrium constant for the hydrogen bond interaction, is k_4/k_{-4}. Thus the measured kinetic constant is given by equation (6). This again involves

$$k_3 = K_{\text{HB}}k_5 \quad (6)$$

two simultaneous phenomena with opposing electronic requirements (the hydrogen bond interaction and the nucleophilic attack of sulphur on the site of reaction), and produces the observed irregular substituent effect.

In this connection it can be seen that a similar irregular substituent effect could also be deduced by inspection of the A values listed in Table 2 which correspond to the reaction of the ionized thiophenol. This is due to the fact that they are, as k_3, the product of the pre-equilibrium thermodynamic constant (ionization of thiophenol) for the kinetic constant of subsequent nucleophilic attack (*i.e.* $A = k_2K_{\text{ion}}$). When k_2 values are calculated, in fact, the substituent effect becomes regular, as expected. An alternative mechanism of reaction in accord with the observed irregular substituent effect is reported in Scheme 5. This involves proton abstraction from



SCHEME 5

positive sulphur as the rate-determining step. A similar occurrence has been reported for the reactions of activated aromatic substrates with amines.[11] In the case of the much more acidic thiophenols, however, it seems rather unlikely.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected.

Materials.—Methanol for kinetic experiments was a good commercial product (Hoechst), further purified by standard procedures. Methanesulphonic acid (Fluka) was further purified by distillation *in vacuo*.

7-Chloro-4-nitrobenzofurazan, m.p. 96.5—97°,[12] and 7-bromo-4-nitrobenzofurazan, m.p. 96—97°,[13] were synthesized as previously reported. Thiophenol,[14] 4-methylthiophenol,[15] 4-methoxythiophenol,[16] 3-chlorothiophenol,[17] and 4-bromothiophenol [18] were prepared and purified by standard methods.

Products.—7-Phenylthio-4-nitrobenzofurazan had m.p. 157—158° (lit.,[1] 157°) (Found: C, 51.8; H, 2.45; N, 15.25; S, 11.6. Calc. for $C_{12}H_7N_3O_3S$: C, 52.75; H, 2.6; N, 15.4; S, 11.75%), 7-(4-methylphenylthio)-4-nitrobenzofurazan, m.p. 147—148° (lit.,[19] 145—147°) (Found: C, 55.05; H, 3.5; N, 14.25; S, 11.25. Calc. for $C_{13}H_9N_3O_3S$: C. 54.35; H, 3.15; N, 14.6; S, 11.15%), 7-(*4-methoxyphenylthio*)-*4-nitrobenzofurazan*, m.p. 141—142° (Found: C, 51.6; H, 3.1, N, 13.7; S, 10.75. $C_{13}H_9N_3O_4S$ requires C, 51.5; H, 2.95; N, 13.85; S, 10.55%), 7-(*4-bromophenylthio*)-*4-nitrobenzofurazan*, m.p. 171—172° (Found: C, 40.8; H, 2.0; Br, 22.65; N, 11.45; S, 9.15. $C_{12}H_6BrN_3O_3S$ requires C, 40.9; H, 1.7; Br, 22.7; N, 11.95; S, 9.1%), 7-(3-*chlorophenylthio*)-*4-nitrobenzofurazan*, m.p. 115—116° (Found: C, 47.2; H, 1.8; Cl, 11.5; N, 13.85; S, 10.4. $C_{12}H_6ClN_3O_3S$ requires C, 46.85; H, 1.95; Cl, 11.5; N, 13.65; S, 10.4%).

Rate Measurements.—Kinetic experiments were carried out in methanol in a thermostatted apparatus (25°), using variable concentrations of methanesulphonic acid (see Table 1) and in excess of the arenethiol over the substrate (pseudo-first-order conditions). The reactions were followed titrimetrically, by measuring the halide ion (Volhard), after quenching by dilution in water followed by extraction of the arenethiol in excess with chloroform. From the pseudo-first-order constants, second-order kinetic constants (k_{obs}) were obtained by dividing by the concentration of ArSH. The second-order rate constants were then treated on the basis of the equations (1) and (3), affording the kinetic constants k_2 and k_3 (Table 3). The experimental error for the second-order rate constants ($k_{\text{obs.}}$) is ±3%. For constants A and B (obtained graphically as above reported), the error is somewhat higher and variable, depending on the slope and on the intercept in each case (see Table 2).

We thank the C.N.R., Rome, for the financial support. We also thank Professors P. E. Todesco, University of Bologna, and C. J. M. Stirling, University College of North Wales, Bangor, for helpful discussions.

[9/178 *Received*, 6*th February*, 1979]

REFERENCES

[1] P. B. Ghosh and M. W. Whitehouse, *J. Medicin. Chem.*, 1968, **11**, 305; P. B. Ghosh, *J. Chem. Soc.* (*B*), 1968, 334.
[2] G. Illuminati, P. Linda, and G. Marino, *J. Amer. Chem. Soc.*, 1967, **89**, 3521.
[3] A. Ricci and P. Vivarelli, *J. Chem. Soc.* (*B*), 1968, 1280
[4] M. Bosco, V. Liturri, L. Troisi, L. Forlani, and P. E. Todesco, *J.C.S. Perkin II*, 1974, 508.
[5] A. J. Boulton and P. B. Ghosh, *Adv. Heterocyclic Chem.*, 1969, **10**, 1.
[6] A. Albert in A. R. Katritzky, ' Physical Methods in Heterocyclic Chemistry,' Academic Press, New York, 1963, vol. I, pp. 1—108.
[7] J. Miller, ' Aromatic Nucleophilic Substitution,' Elsevier, London, 1968, p. 239.
[8] (*a*) G. Guanti, G. Garbarino, C. Dell'Erba, and G. Leandri,

Gazzetta, 1975, **105**, 849; (*b*) R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1962, 1062.
[9] D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *Chimica e Industria*, 1971, **53**, 940.
[10] J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020; J. F. Bunnett and R. H. Garst, *ibid.*, 1965, **87**, 3879.
[11] Z. Rappoport and J. F. Bunnett, *Acta Chem. Scand.*, 1974, **28B**, 478; C. F. Bernasconi and C. L. Gehriger, *J. Amer. Chem. Soc.*, 1974, **96**, 1092.
[12] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1966, 1004.
[13] L. Di Nunno, S. Florio, and P. E. Todesco, *J.C.S. Perkin II*, 1975, 1469.
[14] R. Adams and C. S. Marvel, *Org. Synth.*, Coll. Vol. I, 1947, 504.
[15] H. Decker and T. U. Fellemberg, *Annalen*, 1907, **356**, 326.
[16] R. Leuckart, *J. prakt. Chem.*, 1890, **41**, 189.
[17] G. Daccomo, *J. Chem. Soc.*, 1892, **62**, 306.
[18] Hubner, Alsberg, *Annalen*, 1870, **156**, 327.
[19] J. G. Belton, *Proc. Royal Irish Acad.* (*B*), 1974, **74**, 185.