Kinetics of Piperidino- and Benzenethiolate-dehalogenation of Some 4-Substituted 2,3-Dihalogeno-5-nitrothiophens in Methanol

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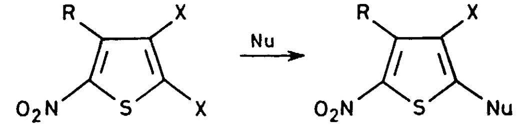
The reactivity of 2,3-dihalogeno-4-R-5-nitrothiophens [R = H (I) and Me (II); halogen = Cl (b) and I (c)] with piperidine and sodium benzenethiolate has been studied in methanol at various temperatures. The results obtained together with previous data concerning 2,3-dibromo-4-R-5-nitrothiophens [R = H (I) and Me (II)] and 2-halogeno-5-nitrothiophens [(IV); halogen = Br (a), Cl (b), and I (c)] have shown that the activating effect of the 3-halogen substituent is largely affected by the nature of both halogen and nucleophile, and furnished further examples of weak activation by a *meta*-methyl group.

It is customary to consider the methyl group as an electron-repelling substituent relative to hydrogen. Such a $+I$ effect generally lowers the mobility of a leaving nitro-activated halogen in S_NAr reactions.[1]

A study[2] of piperidino– and benzenethiolate–debromination of 2,3-dibromo-5-nitrothiophen (Ia) and 2,3-dibromo-4-methyl-5-nitrothiophen (IIa), in methanol, brought to light an unusual example of rate enhancement by a methyl group located in a '*meta*'-position with respect to the reaction centre. This peculiar behaviour was tentatively related to the Reinheimer and Bunnett (R–B) effect[3] of the 3-bromine on the 2-bromine 'augmented' by the 4-methyl group.



(I) R = H
(II) R = Me
a: X = Br; b: X = Cl; c: X = I

(III)

We now report kinetic data for the reactions of compounds (Ib and c) and (IIb and c) with piperidine and benzenethiolate in methanol.

This study was designed to ascertain whether the weak activation by the *meta*-methyl group is dependent on the halogen both as leaving group and *ortho*-substituent, in which case the role played by the polarizability effects would be demonstrated.

RESULTS AND DISCUSSION

Products.—Compounds (I) and (II), on treatment with either piperidine or sodium benzenethiolate, gave the corresponding substitution products (III) in high yield, as shown by t.l.c. and u.v.–visible spectral analysis. The relevant physical data are shown in Table 1.

Kinetic Data.—Rate constants and activation parameters for piperidino- and benzenethiolate-substitution of compounds (I) and (II) are reported in Tables 2 and 3, where are also shown the corresponding data for 2-X-5-nitrothiophens (IVa—c), previously obtained.[4]

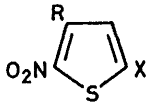
Reactivity of Dihalogeno- versus *Monohalogeno-substituted Compounds.*—A comparison of kinetic constants for piperidino-substitutions of compounds (I) with those for the corresponding reactions of compounds (IV) (k_I/k_{IV} ratios in Table 2) shows that the accelerating effect of the 3-X substituent increases in the order I < Br < Cl, *i.e.* with decreasing size of the '*ortho*'-halogen atom. Assuming, as a rough approximation, that the three halogens exert the same total electronic effect, this reactivity sequence would point out a steric hindrance to the approach of nucleophile (piperidine) which increases with increasing the van der Waals radius of halogen atom.

TABLE 1

Physical and spectroscopic data for 2-Nu-3-X-4-R-5-nitrothiophens (III) [a]

X	R	Nu	M.p. (°C)	$\lambda_{max.}$/nm [b]	log ϵ [b]
Cl	H	NC_5H_{10} [c]	58	434	4.17
Cl	Me	NC_5H_{10}	120	432	4.19
I	H	NC_5H_{10}	97	424	4.08
I	Me	NC_5H_{10}	104	419	4.07
Cl	H	SPh [c]	98	388	3.95
Cl	Me	SPh	110	386	4.00
I	H	SPh	110	392	3.95
I	Me	SPh	119	392	4.00

[a] All compounds (III) were crystallized from methanol. The piperidino-derivatives are red–orange and the sulphides yellow. [b] In methanol. [c] E. Profft and G. Solf, *J. prakt. Chem.*, 1964, **24**, 38.



(IV) R = H
(V) R = alkyl
a; X = Br
b; X = Cl
c; X = I

A different trend of reactivity ratios is observed in benzenethiolate-substitutions (Table 3). In this case, it is possible to distinguish clearly the role played by the polarizability effects which, increasing in the order Cl <

TABLE 2

Kinetic data and activation parameters for piperidino-substitutions of compounds (Ia—c), (IIa—c), and (IVa—c) in methanol

Compound	10^5 k/l mol^{-1} s^{-1} [a] (T/°C)	$\Delta H^\ddagger$ [b]/ kcal mol^{-1}	$-\Delta S^\ddagger$ [c]/ cal mol^{-1} K^{-1}	k_I/k_{II} [d]	k_I/k_{IV} [d]
(Ia) [e]	7.72(20.10), 17.4(30.00), 36.9(40.39)	13.5	31		
(IIa) [e]	10.9(20.10), 25.9(30.00), 52.4(40.00)	13.8	29	0.70	
(IVa) [f]	1.63(20.01), 3.89(30.01), 9.37(40.03)	15.3	28		4.8
(Ib)	15.8(20.00), 35.3(30.10), 72.1(39.95)	13.3	30		
(IIb)	21.5(20.00), 47.0(30.10), 94.8(40.00)	12.9	31	0.74	
(IVb) [f]	2.55(19.98), 5.85(30.05), 13.9(40.00)	14.8	29		6.3
(Ic)	0.630(19.95), 1.48(30.04), 3.44(40.02)	14.8	32		
(IIc)	0.900(19.92), 2.06(30.00), 4.47(40.00)	14.0	34	0.69	
(IVc) [f]	0.245(19.97), 0.644(30.01), 1.60(39.95)	16.6	28		2.6

[a] The rate constants are accurate to within ±3%. [b] At 20 °C; the maximum error is 0.5 kcal mol^{-1}; 1 cal = 4.184 J. [c] At 20 °C. [d] Values calculated at 20 °C from activation parameters. [e] See ref. 2. [f] See ref. 4.

Br < I, oppose primary steric effects and cause the observed k_I/k_{IV} ratios.

The 'adjusted' rate ratios $(k_I/k_{IV})_S/(k_I/k_{IV})_N$,[3] which reflect only differences in the inherent nucleophilic reactivity of benzenethiolate (S) and piperidine (N) and differences in local interactions (steric and London forces) of *ortho*-halogens with reagents, are, respectively, for Br, Cl, and I, 9.4, 6.5, and 5.0. These values indicate that the London forces play a role significantly more important than primary steric effects with all three halogens.

TABLE 3

Kinetic data and activation parameters for benzenethiolate-substitutions of compounds (Ia—c), (IIa—c), and (IVa—c), in methanol

Compound	k/l mol^{-1} s^{-1} [a] (T/°C)	ΔH [b]/ kcal mol^{-1}	$-\Delta S^\ddagger$ [c]/ cal mol^{-1} K^{-1}	k_I/k_{II} [d]	k_I/k_{IV} [d]
(Ia) [e]	1.19(0.15), 2.63(9.80), 6.23(20.00)	12.7	11.6		
(IIa) [e]	1.77(0.16), 3.63(9.80), 7.66(20.00)	11.2	16.4	0.81	
(IVa) [f]	0.0573(10.06), 0.136(20.02), 0.321(30.00)	14.2	13.9		45
(Ib)	2.47(10.1), 5.15(20.00), 10.2(30.10)	11.5	16.0		
(IIb)	4.28(10.1), 9.09(20.02), 17.0(30.05)	11.2	15.9	0.58	
(IVb) [f]	0.0512(10.06), 0.126(20.02), 0.291(30.00)	14.2	14.0		41
(Ic)	1.15(19.95), 2.44(30.05), 5.14(40.02)	13.0	13.8		
(IIc)	1.99(19.95), 4.09(30.02), 7.75(40.02)	11.8	17.0	0.57	
(IVc) [f]	0.0344(10.06), 0.0873(20.02), 0.202(30.00)	14.5	13.7		13

[a-f] As Table 2.

The meta-*Methyl Group Activation.*—The introduction of a methyl group in position 4 of (I) causes an increase of reactivity for all three dihalogeno-substituted compounds with both nucleophiles (k_I/k_{II} ratios in Tables 2 and 3). Some possible explanations of this acceleration are as follows. (i) The London forces effect depends, inversely, on the distance between 3-halogen and reaction centre:[5] since the 4-methyl group exerts a buttressing action on the 3-halogen, the previous distance diminishes and an 'enhanced' Reinheimer–Bunnett effect results. (ii) The 4-methyl group causes the adjacent 3-carbon–halogen bond to be forced out of the plane of the aromatic ring. In this situation, the 3-halogen atom should exert only its inductive effect with respect to the reaction centre. Alternatively or simultaneously, the outer sphere electrons of the 3-halogen should become more polarizable, giving rise to the observed enhancement of the R–B effect.

Rather unexpectedly, one observes practically the same k_I/k_{II} ratio for all three pairs of dihalogeno-substituted compounds whatever the nucleophile. This observation is hardly reconcilable with hypothesis (i): in fact, the enhancement of polarizability effects should strongly depend both on the inherent polarizability of the halogen atom (see k_I/k_{IV} ratios in Table 3) and on the 'interaction distance' between the 4-methyl group and the 3-halogen which in turn is critically related to its van der Waals radius.

The explanation proposed under (ii) would appear more reasonable; the three halogens show, indeed, very similar σ_m values.*

Thus, this matter appeared to us to be settled. However, as it sometimes happens, we met another case of activation by a *meta*-methyl group which put again under discussion the previous explanation. Studying the reactions, with piperidine and sodium benzenethiolate in methanol, of some 3-alkyl-5-bromo-2-nitrothiophens (Va) we observed, indeed, that even if there is ***no halogen*** in the 3-position, the *meta*-alkyl group determines a weak acceleration with respect to the parent compound (IVb).[7]

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (Ib),[8] (Ic),[9] methanol,[10] piperidine,[11] and benzenethiol,[10] were prepared and/or purified according to the methods reported. The other compounds were prepared as below and gave correct elemental analyses.

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* Because of their composition (inductive and conjugative contributions) σ_m values [6] can be considered a good measure of the electronic effects of halogens in our case.

2,3-*Dichloro*-4-*methyl*-5-*nitrothiophen* (IIb).—Nitric acid (*d* 1.5; 5 ml) in acetic anhydride (6 ml), cooled at −20 °C, was slowly added with stirring to a solution of 2,3-dichloro-4-methylthiophen[12] (4.2 g) in acetic anhydride (6 ml) at 20 °C. After stirring for 15 min, the mixture was poured onto crushed ice. The oil which separated was extracted with ether: the ethereal extracts were washed with aqueous sodium hydrogencarbonate and water and dried (Na_2SO_4), and the ether was distilled off. The residue was chromatographed on a column of silica gel with light petroleum as eluant. The 2,3-*dichloro*-4-*methyl*-5-*nitrothiophen* was crystallized from light petroleum, m.p. 34—35 °C.

2,3-*Di-iodo*-4-*methyl*-5-*nitrothiophen* (IIc).—3-Methyl-2-nitrothiophen[13] (1.4 g) was heated under reflux for 24 h in a solution of mercury(II) acetate [mercury(II) oxide (8.6 g) in acetic acid (50 ml)]. After being kept at room temperature overnight the product of mercuriation was filtered off and washed with water, ethanol, and ether. The product of mercuriation was treated at 50—60 °C for 0.5 h with iodine (6 g) in a solution of potassium iodide (12 g) in water (90 ml). After being cooled the mixture was decolourised with $Na_2S_2O_3$, filtered, and extracted with ether. The ethereal extracts were washed with water, dried (Na_2SO_4), and the ether distilled off. The yellow di-iodo-compound was purified by chromatography on a column of silica gel (eluant light petroleum) and by recrystallization from ligroin–benzene, m.p. 159—160 °C.

2-N-*Piperidyl*-3-X-5-*nitrothiophens and* 3-X-4-R-5-*Nitro-2-thienyl Sulphides* (III).—These were prepared and purified according to the general methods reported, respectively, in refs. 11 and 14.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[10, 11] The concentrations used were 10^{-4}—10^{-3}M-substrate, 0.2—1M piperidine, and 10^{-4}M-benzenethiol (in the presence of an excess of sodium methoxide). The wavelengths and log ε used are indicated in Table 1.

We are indebted to Professor N. B. Chapman for his constructive criticism. D. S. thanks the C.N.R. for support.

[1/1460 *Received*, 18*th September*, 1981]

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