

Nucleophilic Substitutions in Five-membered Rings. Primary Steric Effects in Thiophen Derivatives

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In order to study primary steric effects (p.s.e.) in nucleophilic substitutions of five-membered rings, the rate of piperidino and benzenethiolate substitution of some 2-L-5-nitrothiophens (Ia—d) and 2-L-3-methyl-5-nitrothiophens (IIa—d) have been measured in methanol. The rate ratios ($k_{\text{H}}/k_{\text{Me}}$) obtained show an absence of p.s.e. in piperidino substitutions when the leaving group is halogen but not when L = SO₂Ph. Benzenethiolate substitution data show the presence of a large Reinheimer–Bunnett effect.

AROMATIC nucleophilic substitutions of benzene derivatives are greatly affected by primary steric effects (p.s.e.).¹ The electronic effect exerted by an alkyl group *ortho* to the site of substitution, which can be estimated to cause a 2–6 fold decrease in rate,² is exceeded by its p.s.e. especially if a bulky nucleophile is used.

The p.s.e. decreases from piperidine³ to aniline,^{3a} sodium methoxide,^{3a,c} iodide,⁴ and benzenethiolate.^{3c,5} With sodium benzenethiolate, the p.s.e. is exceeded by the Reinheimer–Bunnett effect.^{3c} This factor manifests itself in a tendency for nucleophilic reagents of high polarizability, such as benzenethiolate ion, to be especially

¹ J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968, pp. 95, 350.

² N. B. Chapman and J. Shorter, 'Advances in Linear Free Energy Relationships,' Plenum Press, London, 1972, p. 103 and references therein.

reactive with substrates having large halogen atoms (or other polarizable groups) at or near the site of substitution. The physical principle underlying this factor is believed to be the operation, in the transition state, of London forces between regions of high polarizability in the reagent and in the substrate.

The data collected for benzene derivatives refer to halogen (F, Cl, and Br) as leaving group and changes in

³ (a) B. Capon and N. B. Chapman, *J. Chem. Soc.*, 1957, 600; (b) P. Van Beck, J. O. M. Van Langen, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1956, **75**, 1137; (c) J. D. Reinheimer and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1959, **81**, 315; (d) N. E. Sbarbati, *J. Org. Chem.*, 1965, **30**, 3365.

⁴ P. J. C. Fierens and A. Halleux, *Bull. soc. chim. Belges*, 1955, **64**, 696.

⁵ (a) A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brioux, *J. Chem. Soc. (B)*, 1966, 963; (b) P. Beltrame and P. Carniti, *Gazzetta*, 1973, **103**, 723.

$k_{\text{H}}/k_{\text{Me}}$ can be expected as the steric requirements of the replaced group are varied.

The large p.s.e. present in derivatives of a six-membered ring can decrease for those of a five-membered ring because of the more favourable geometry of the latter. As we have previously pointed out⁶ the interactions between two adjacent groups in the thiophen ring are smaller than in the benzene ring because the distance between them is increased by 0.15–0.20 Å. In order to study p.s.e. in the thiophen ring we have measured the reactivity of compounds (Ia–d) and (IIa–d) with piperidine and sodium benzenethiolate.

Under the same experimental conditions (IIc) reacted with piperidine giving the expected product (V), but sodium benzenethiolate did not give the corresponding sulphide (VI). Research is in progress to provide an explanation for this anomalous behaviour.

Kinetic Data.—To obtain information on the influence of the steric requirements of the replaced group on the p.s.e. we have compared the reactivity towards nucleophiles (piperidine and sodium benzenethiolate) of some 2-L-5-nitrothiophens (Ia–d) with that of the corresponding 2-L-3-methyl-5-nitrothiophens (IIa–d). The steric influence of the 3-methyl group on the reaction

TABLE I

Kinetic data and thermodynamic parameters for substitution of piperidine into compounds (Ia–d) and (IIa–d) in methanol

Compound	$10^5 k/l \text{ mol}^{-1} \text{ s}^{-1} \text{ } ^a (T/^\circ\text{C})$			$\Delta H^\ddagger/\text{kcal mol}^{-1} \text{ } ^b$	$-\Delta S^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1} \text{ } ^c$	$k_{\text{H}}/k_{\text{Me}} \text{ } ^d$ at 20°
(Ia) ^e	2.55 (19.98)	5.85 (30.05)	13.9 (40.00)	14.8	28.9	3.0
(IIa) ^f	0.820 (19.95)	2.02 (29.95)	4.39 (39.95)	14.7	31.5	
(Ib) ^g	1.63 (20.01)	3.89 (30.01)	9.37 (40.03)	15.3	28.1	3.9
(IIb) ^f	0.410 (19.95)	1.06 (30.00)	1.92 (37.75)	15.2	31.3	
(Ic) ^e	0.245 (19.97)	0.644 (30.01)	1.60 (39.95)	16.6	27.6	3.8
(IIc) ^f	0.0630 (20.04)	0.166 (29.92)	0.380 (40.03)	15.8	32.8	
(Id) ^e	0.655 (19.98)	1.46 (30.30)	3.06 (40.05)	13.4	36.5	17
(IId) ^f	0.0364 (20.04)	0.0836 (30.10)	0.145 (40.09)	12.0	46.8	

^a The rate constants are accurate to within $\pm 3\%$. ^b At 20°, the probable error is 0.5 kcal mol⁻¹. ^c At 20°. ^d Values recalculated from thermodynamic parameters. The maximum error is $\pm 6\%$. ^e At λ_{max} , 448 nm (log ϵ 4.50). ^f At λ_{max} , 440 nm (log ϵ 4.16). ^g Data from D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim. (Italy)*, 1965, **55**, 1260.

TABLE 2

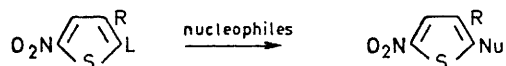
Kinetic data and thermodynamic parameters for substitution of sodium benzenethiolate into compounds (Ia–d) and (IIa, b, and d) in methanol

Compound	$k/l \text{ mol}^{-1} \text{ s}^{-1} \text{ } ^a (T/^\circ\text{C})$			$\Delta H^\ddagger/\text{kcal mol}^{-1} \text{ } ^b$	$-\Delta S^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1} \text{ } ^c$	$k_{\text{H}}/k_{\text{Me}} \text{ } ^d$ at 20°
(Ia) ^e	0.0512 (10.06)	0.126 (20.02)	0.291 (30.00)	14.2	14.0	0.38
(IIa) ^f	0.333 (19.95)	0.707 (30.00)	1.27 (37.75)	13.0	16.3	
(Ib) ^e	0.0573 (10.06)	0.136 (20.02)	0.321 (30.00)	14.2	13.9	0.40
(IIb) ^f	0.343 (19.96)	0.730 (29.95)	1.65 (40.80)	13.2	15.5	
(Ic) ^e	0.0344 (10.06)	0.0878 (20.02)	0.202 (30.00)	14.5	13.7	
(Id) ^e	3.59 (0.00)	7.23 (10.00)	13.9 (20.02)	10.1	18.6	1.3
(IId) ^f	5.11 (10.03)	10.4 (20.03)	19.2 (30.02)	10.7	17.4	

^a The rate constants are accurate to within $\pm 3\%$. ^b At 20°, the probable error is 0.5 kcal mol⁻¹. ^c At 20°. ^d Values recalculated from thermodynamic parameters. The maximum error is $\pm 6\%$. ^e Data from ref. 11. ^f At λ_{max} , 383 nm (log ϵ 3.85).

RESULTS AND DISCUSSION

Products of Reaction.—Compounds (Ia–d) and (IIa, b, and d) on treatment with either piperidine or sodium



- | | |
|---------------------------|---|
| (I) R = H | (III) R = H, Nu = NC ₅ H ₁₀ |
| (II) R = Me | (IV) R = H, Nu = SPh |
| a; L = Cl | (V) R = Me, Nu = NC ₅ H ₁₀ |
| b; L = Br | (VI) R = Me, Nu = SPh |
| c; L = I | |
| d; L = SO ₂ Ph | |

benzenethiolate gave the corresponding substitution products (III)–(VI) in high yield (t.l.c. and u.v. analyses).

* Using the Hammett relationship in the study of piperidinobromination of a series of 2-bromo-3-X-5-nitrothiophens in methanol, we have observed⁷ that the datum for X = Me lies on the observed straight line ($\rho = +4.02$, $r = 0.998$, $n = 7$).

centre in the transition state for nucleophilic substitutions of compounds (IIa–d) gives rise to a situation similar to that observed for benzene derivatives.^{3c,5b} Rate constants and thermodynamic parameters for the reactions studied are reported in Tables 1 and 2.

Reactivity with Piperidine.—By comparing the reactivity (see Table 1) of compounds (I) and (II), we have calculated $k_{\text{H}}/k_{\text{Me}}$ as ca. 4 for (Ib) and (IIb). This datum when compared to that obtained for compounds in the benzene series^{3b} ($k_{\text{H}}/k_{\text{Me}}$ ca. 45) emphasizes the absence of p.s.e. in the piperidinobromination in the thiophen series. The small decrease in reactivity caused by the 3-methyl group can be related to the electron-repelling power of an *o*-methyl group and not to its p.s.e.* The $k_{\text{H}}/k_{\text{Me}}$ values calculated for the other two halogens are

⁶ (a) D. Spinelli, C. Dell'Erba, and G. Guanti, *J. Heterocyclic Chem.*, 1968, **5**, 323; (b) D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, 1974, 1632.

⁷ D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, in the press.

quite similar to that calculated for bromine ($L = \text{Cl}$, $k_{\text{H}}/k_{\text{Me}}$ ca. 3; $L = \text{I}$, $k_{\text{H}}/k_{\text{Me}}$ ca. 4) thus indicating that the piperidinodehalogenations studied by us are free from p.s.e.s.

An interesting fact has been observed when $L = \text{SO}_2\text{Ph}$. In this case we have measured a high $k_{\text{H}}/k_{\text{Me}}$ (17) showing a significant p.s.e. and confirming the peculiar behaviour^{6b} of this group. In fact, because of the large steric requirements of SO_2Ph , p.s.e.s also operate in piperidino substitution at C-2 in a five-membered ring.

Reactions with Sodium Benzenethiolate.—The results obtained in the study of the reactions of compounds (Ia, b, and d) and (IIa, b, and d) with sodium benzenethiolate (see Table 2) indicate that in these cases a Reinheimer-Bunnett effect^{3c} operates. In fact the presence of a methyl group adjacent to the reaction centre causes a slight, but significant increase in the reactivity ($k_{\text{H}}/k_{\text{Me}}$ ca. 0.4) with halogen ($L = \text{Cl}$ and Br) as leaving group. Moreover with the bulky phenylsulphonyl leaving group the retarding effect of *o*-methyl is very low ($k_{\text{H}}/k_{\text{Me}}$ ca. 1.3), *i.e.* less (see above and ref. 2) than that expected on the basis of the electron-repelling effect of this substituent. The reactivity pattern of compounds (Ia, b, and d) relative to (IIa, b, and d) in the reactions with sodium benzenethiolate arises from a balancing of different factors: (i) the small decrease caused by the electron-repelling effect of the methyl group, (ii) the important accelerating Reinheimer-Bunnett effect, and (iii) the steric interactions between the leaving and entering groups and the methyl group. As we have previously seen, the last factor is more important when $L = \text{SO}_2\text{Ph}$ and seems to be responsible for the inversion of the reactivity ($k_{\text{Id}}/k_{\text{IIId}} > 1$) compared with the situation observed with halogen as leaving group ($k_{\text{Ia,b}}/k_{\text{IIa,b}} < 1$).

Adjusted Rate Ratios.—The different behaviour of compounds (Ia—d) and (IIa—d) with the nucleophiles becomes more evident when the rate ratios (see Table 3) are considered. Such ratios^{3c} are taken to make allowance for substituent electronic effects; in fact they reflect only differences in the inherent nucleophilic reactivity of reagents and differences in local interaction (steric and London forces) of *ortho*-substituents (H or Me) with reagents. The higher $k_{\text{S}}/k_{\text{N}}$ for compounds (IIa, b, and d) with respect to (Ia—d) depends on the opposite effects exerted by the methyl group in the two reactions with piperidine and benzenethiolate. To evaluate the sensitivity of the leaving groups to the effects exerted by nucleophiles and their kinetic polarizabilities, we have calculated the adjusted rate ratios (see Table 3) which represent^{3c} only differences between benzenethiolate and piperidine with respect to local interactions with *ortho*-substituents (H or Me).

⁸ C. D. Hurd and K. L. Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965.

⁹ W. S. Babasinian, *J. Amer. Chem. Soc.*, 1935, **57**, 1763.

¹⁰ I. J. Rinkes, *Rec. Trav. chim.*, 1934, **53**, 643.

¹¹ G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1971, **8**, 537.

The highest ratio is that for the phenylsulphonyl group and the values for halogens follow their known polarizabilities.

TABLE 3

Rate ratios^a and adjusted rate ratios^a for reactions of compounds (Ia—d) and (IIa—d) at 20°

L	$k_{\text{S}}/k_{\text{N}}^b$		$(k_{\text{S}}/k_{\text{N}})_{\text{II}} / (k_{\text{S}}/k_{\text{N}})_{\text{I}}$
	R = H	R = Me	
Cl	5.0×10^3	4.0×10^4	8.0
Br	8.6×10^3	8.2×10^4	9.5
I	3.5×10^4		
SO_2Ph	2.1×10^6	2.8×10^7	13

^a See ref. 3c for the chemical meaning of these ratios. ^b Rate ratios between reactivity towards sodium benzenethiolate (k_{S}) and piperidine (k_{N}).

Conclusions.—All the data obtained indicate that the piperidinodehalogenation reactions in the thiophen series do not suffer p.s.e.s ($k_{\text{H}}/k_{\text{Me}}$ ca. 3—4), in contrast to the results obtained with benzene derivatives, because of the more favourable geometry of the five-membered ring. There is a p.s.e. ($k_{\text{Ia}}/k_{\text{IIa}}$ ca. 17) only with a large leaving group with high steric requirements. The reactivity data for sodium benzenethiolate shows that a large Reinheimer-Bunnett effect is operating.

EXPERIMENTAL

Synthesis and Purification of Compounds.—2-Chloro-5-nitrothiophen (Ia),⁸ 2-bromo-5-nitrothiophen (Ib),⁹ 2-iodo-5-nitrothiophen (Ic),¹⁰ 5-nitro-2-thienyl phenyl sulphone (Id),¹¹ 2-bromo-3-methyl-5-nitrothiophen (IIb),⁷ 2-*N*-piperidyl-5-nitrothiophen (III),¹² 5-nitro-2-thienyl phenyl sulphide (IV),¹³ 2-*N*-piperidyl-3-methyl-5-nitrothiophen (V),⁷ methanol,¹³ piperidine,¹² and benzenethiol¹³ were prepared and/or purified according to the methods reported. The other compounds were prepared as below and gave correct spectra (*i.r.* and/or *n.m.r.*) in accordance with the proposed structures.

2-Chloro-3-methyl-5-nitrothiophen (IIa). Compound (IIa) was prepared by the method for (IIb)⁷ from 2-chloro-3-methylthiophen,¹⁴ m.p. 44° (from light petroleum) (Found: Cl, 19.8; N, 8.0; S, 18.0. $\text{C}_5\text{H}_4\text{ClNO}_2\text{S}$ requires Cl, 20.0; N, 7.9; S, 18.1%).

2-Iodo-3-methyl-5-nitrothiophen (IIc). 3-Methyl-5-nitrothiophen-2-carboxylic acid (1.87 g, 10^{-2} mol)¹⁵ was heated under reflux for 2 h in a solution of mercuric acetate [mercuric oxide (4.3 g) in acetic acid (25 ml) and water (25 ml)]. After being kept at room temperature overnight the product of mercuriation was filtered off and washed with water, ethanol, and ether. On dilution with water the filtrate gave more product. The product of mercuriation (4.02 g) was treated at 50—60° for 0.5 h with iodine (2.55 g) in a solution of potassium iodide (5.94 g) in water (45 ml). After being cooled the mixture was decolourised with $\text{Na}_2\text{S}_2\text{O}_3$, filtered, and extracted with ether. The ethereal extracts were washed with water, dried (Na_2SO_4), and the ether distilled off. The *iodo-compound* was purified by recrystallization from ligroin in the presence of charcoal, m.p.

¹² D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim. (Italy)*, 1962, **52**, 1156.

¹³ D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim. (Italy)*, 1965, **55**, 1252.

¹⁴ E. Campaigne and W. M. LeSuer, *J. Amer. Chem. Soc.*, 1948, **70**, 415.

¹⁵ I. J. Rinkes, *Rec. Trav. chim.*, 1933, **52**, 1052.

34—35° (Found: I, 47.0; N, 5.2; S, 12.0. $C_5H_4INO_2S$ requires I, 47.2; N, 5.2; S, 11.9%).

5-Nitro-3-methyl-2-thienyl phenyl sulphone (II_d). *Compound* (II_d) was obtained by heating a solution in acetic acid of 5-nitro-3-methyl-2-thienyl phenyl sulphide (VI) under reflux with a large excess of hydrogen peroxide, m.p. 125° (from methanol) (Found: N, 4.8; S, 22.5. $C_{11}H_9NO_4S_2$ requires N, 4.9; S, 22.6%).

5-Nitro-3-methyl-2-thienyl phenyl sulphide (VI). *Compound* (VI) was prepared from 2-chloro-3-methyl-5-nitrothiophen (II_a) by the method for (IV),¹³ m.p. 65° (from light

petroleum) (Found: N, 5.5; S, 25.8. $C_{11}H_9NO_2S_2$ requires N, 5.6; S, 25.5%).

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.^{12,13} The concentrations used were 10^{-3} -substrate, 2×10^{-2} -piperidine, and 10^{-3} M-benzenethiol (in the presence of an excess of sodium methoxide). The wavelength and log ϵ at the maximum used are reported in the Tables.

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