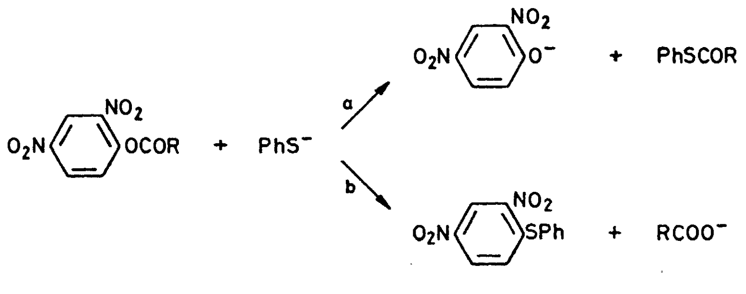
Polar Effects in Nucleophilic Substitutions at Aromatic and Carbonyl Carbon Atoms. Kinetics of the Reactions of Substituted Arenethiolates with 2,4-Dinitrophenyl Acetate and Benzoate

By **Giuseppe Guanti,* Carlo Dell'Erba, Francesca Pero,** and **Giorgio Cevasco,** Istituto di Chimica Organica dell'Università, C.N.R. Centro di Studio sui Diariloidi e loro Applicazioni, Palazzo delle Scienze, Corso Europa, 16132 Genova, Italy

2,4-Dinitrophenyl acetate (DNPA) and benzoate (DNPB) are cleaved by sodium benzenethiolate in 95% aqueous ethanol with scission of both the C_{CO}–O and the C_{Ar}–O bond. Substituent effects in the nucleophile have been studied by measurement of the nucleophilic reactivity of a series of substituted arenethiolates toward these two substrates. For both esters the percentages of C_{CO}–O bond scission decrease with increasing nucleophilicity of the arenethiolate. The overall rate constants, k_{tot}, were dissected into k_{CO} and k_{Ar} corresponding to the cleavage of C_{CO}–O and C_{Ar}–O bonds respectively. Both k_{CO} and k_{Ar} increase with increasing nucleophilicity of the arenethiolate. Logarithmic plots of k_{CO} and k_{Ar} against the acidity constants K_a of the corresponding *meta*-substituted arenethiols are rectilinear for both esters and give β_{CO} 0.44 and β_{Ar} 0.69 for DNPA, β_{CO} 0.53 and β_{Ar} 0.65 for DNPB. Proton basicity, carbon basicity, and nucleophilicity of the arenethiolate anions have been compared.

In accord with our interest in the chemistry of thioesters,[1] whose importance in enzyme-catalysed reactions is well known,[2] we chose to investigate the reaction of nitrophenyl esters of carboxylic acids with benzenethiolate. We found[3] that competition may arise between two electrophilic centres in the same ester substrate when sodium benzenethiolate reacts with dinitrophenyl esters of acetic and benzoic acid. We have underlined the importance of this result because there are only a few examples of aryl–oxygen fission for aryl esters of carboxylic acids.[4]

The reactions of sodium benzenethiolate with 2,4-dinitrophenyl benzoate (DNPB) and acetate (DNPA) are represented in the Scheme.



R = Me or Ph

SCHEME

Nucleophilic attack by benzenethiolate may occur at the carbonyl carbon (route a) with C_{CO}–O scission or at the dinitrophenyl carbon (route b) with C_{Ar}–O scission. In 95% aqueous ethanol DNPB is cleaved in the latter manner in *ca.* 84%, and DNPA in *ca.* 52%.

In this work the polar effect of substituents in the benzene ring of the arenethiol on the rate constants and on the proportion of the two modes of fission was examined by a systematic kinetic study of the reactions of a series of nine arenethiols with DNPA and DNPB. Study of the two ester substrates permits direct comparison of the effects of substituents in the nucleophile on both nucleophilic aromatic substitution and carbonyl displacement reactions. Although a large number of rate constants are available for both kinds of reaction,[5] our results reveal important similarities and differences in the response of the two centres, the aryl and the carbonyl carbon atom, to changes in nucleophile structure under a single set of experimental conditions. The effects on the rates caused by structural changes of the acyl group of the ester when the substrate was changed from DNPA to DNPB have also been evaluated.

RESULTS AND DISCUSSION

The reactions of the substituted sodium arenethiolates with the two ester substrates, DNPA and DNPB, were carried out in 95% aqueous ethanol at 22 °C. The reactions could be followed easily by monitoring the increase of optical density at *ca.* 340 nm, due to the formation of 2,4-dinitrophenol (DNP) and of 2,4-

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[4] A. Kirkien-Konasiewicz and A. Maccoll, *J. Chem. Soc.*, 1964, 1267; H. Suhr, *Chem. Ber.*, 1964, **97**, 3268.

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dinitrophenyl (substituted phenyl) sulphide, where the absorption by the starting ester and by the other cleavage products (*S*-aryl thiobenzoate and benzoic acid or *S*-aryl thioacetate and acetic acid) is negligible. The overall second-order rate constants thus obtained, k_{tot}, were then dissected into k_{CO} (rate of the C_{CO}–O bond cleavage) and k_{Ar} (rate of the C_{Ar}–O bond cleavage) through determination of the amounts of DNP and diaryl sulphide formed in the reaction, as described previously.[3]

Kinetic measurements establishing the reaction order, the reliability of the kinetic assay, the absence of solvolytic side reactions, and the solvent and ionic strength effects have been reported previously,[3] together with product isolation experiments. Additional control tests with a larger concentration range of reactants are described in the Experimental section.

TABLE 1

Reactions of DNPB with substituted arenethiolates in 95% aqueous ethanol at 22 °C. [DNPB] = 10^{-5}M; $[ArSH]_{total} = 3.2 \times 10^{-3}$M; $[ArSH]_{free} = 3 \times 10^{-3}$M; $[ArS^-] = 2 \times 10^{-4}$M

Substituent	k_{tot}[a]/ l mol^{-1} s^{-1}	%C_{CO}–O[b] scission	k_{CO}[a]/ l mol^{-1} s^{-1}	k_{Ar}[a]/ l mol^{-1} s^{-1}	pK_a[c]
1 *m*-Cl	16.4	19.8	3.2	13.2	8.09
2 *m*-Br	16.5	19.7	3.3	13.2	8.20
3 *m*-F	17.9	19.7	3.5	14.4	8.34[d]
4 *p*-Cl	32.5	18.5	6.0	26.5	8.41
5 *p*-F	74.6	17.2	12.8	61.8	8.88
6 *m*-OMe	69.6	16.2	11.3	58.3	9.14
7 H[e]	74.1	15.8	11.7	62.4	9.28
8 *m*-Me	122.6	14.0	17.2	105.4	9.52
9 *p*-Me	215.4	13.0	28.0	187.4	9.60

[a] k_{tot}, k_{CO}, and k_{Ar} are, respectively, second-order rate constants for the sum of C_{CO}–O and C_{Ar}–O cleavage, and for C_{CO}–O and C_{Ar}–O cleavage separately. [b] The figures listed are percentages of C_{CO}–O scission; subtraction from 100% gives the percentage of C_{Ar}–O scission. [c] Values taken from ref. 9. [d] Value taken from ref. 1. [e] Values taken from ref. 3.

TABLE 2

Reactions of DNPA with substituted arenethiolates in 95% aqueous ethanol at 22 °C. [DNPA] = 10^{-5}M; $[ArSH]_{total} = 3.2 \times 10^{-3}$M; $[ArSH]_{free} = 3 \times 10^{-3}$M; $[ArS^-] = 2 \times 10^{-4}$M

Substituent	k_{tot}[a]/ l mol^{-1} s^{-1}	%C_{CO}–O[b] scission	k_{CO}[a]/ l mol^{-1} s^{-1}	k_{Ar}[a]/ l mol^{-1} s^{-1}
1 *m*-Cl	16.6	61.9	10.3	6.3
2 *m*-Br	16.9	61.5	10.4	6.5
3 *m*-F	18.3	61.5	11.3	7.0
4 *p*-Cl	29.2	56.5	16.5	12.7
5 p-F	65.1	49.3	32.1	33.0
6 *m*-OMe	58.1	48.6	28.2	29.9
7 H[c]	66.1	48.3	31.9	34.2
8 *m*-Me	97.9	41.6	40.7	57.2
9 *p*-Me	160.7	36.6	58.8	101.9

[a] See footnote *a*, Table 1. [b] See footnote *b*, Table 1. [c] See footnote *e*, Table 1.

Tables 1 and 2 summarize the rate constants and the modes of scission for the reactions of DNPB and DNPA, respectively, with nine aryl-substituted sodium arenethiolates. Features of both sets of results are that electron-donating substituents in the nucleophile increase the reaction rate for both C_{CO}–O and C_{Ar}–O scission, whereas electron-withdrawing substituents have the opposite effect. Our results also show that C_{Ar}–O bond cleavage is more susceptible to changes of nucleophile than C_{CO}–O bond cleavage. In fact the extent of C_{CO}–O scission decreases with increasing pK_a values of the arenethiols, and there is a corresponding rise in the extent of C_{Ar}–O scission for both substrates. Upon proceeding from *m*-chloro- to *p*-methyl-benzenethiol the percentage of C_{CO}–O bond cleavage changes from *ca.* 20 to only 13% for DNPB and from *ca.* 62 to *ca.* 37% for DNPA.

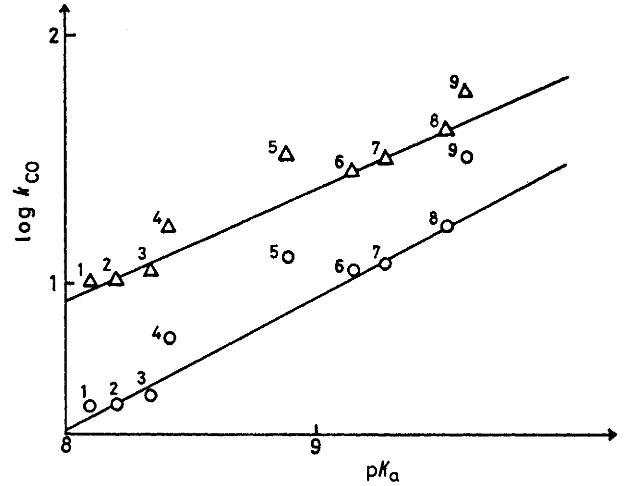

FIGURE 1 Logarithmic plot of the rate constants for carbonyl carbon attack (log k_{CO}) in the reaction of DNPA (triangles) and DNPB (open circles) with substituted arenethiolates in 95% aqueous ethanol at 22 °C *versus* the pK_a of the corresponding arenethiol. The slope calculated from values for *meta*-substituents is 0.44 (*r* 0.996, *s* 0.026 2) for DNPA and 0.53 (*r* 0.994, *s* 0.040 5) for DNPB. Numbering of substituents corresponds to that in Tables 1 and 2

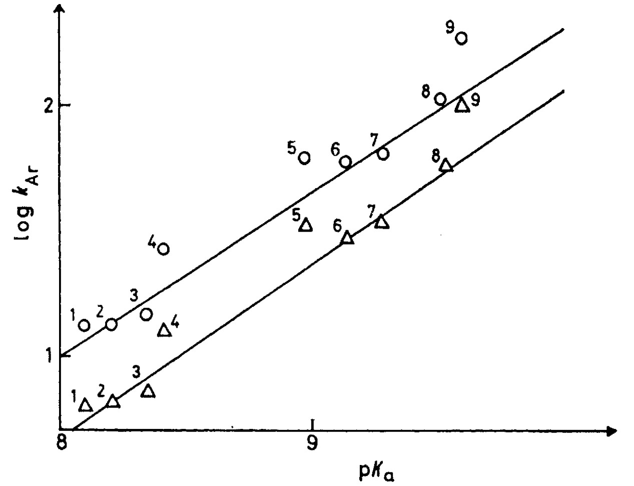

FIGURE 2 Logarithmic plot of the rate constants for aryl carbon attack (log k_{Ar}) in the reaction of DNPA (triangles) and DNPB (open circles) with substituted arenethiolates in 95% aqueous ethanol at 22 °C *versus* the pK_a of the corresponding arenethiol. The slope calculated from values for *meta*-substituents is 0.69 (*r* 0.995, *s* 0.049 3) for DNPA and 0.65 (*r* 0.994, *s* 0.051 7) for DNPB. Numbering of substituents corresponds to that in Tables 1 and 2

As is customary, we have correlated rate data by means of the Brönsted equation. Figures 1 and 2 show the logarithmic plots of the rate constants k_{CO} and k_{Ar}

respectively, against the apparent acid dissociation constants in ethanol (pK_a) of the corresponding arenethiols for their reactions with DNPB and DNPA. From the least-squares regression lines for the *meta*-substituents $\beta_{CO} = 0.53$ (*r* 0.994, *s* 0.040 5) for attack at the carbonyl carbon and $\beta_{Ar} = 0.65$ (*r* 0.994, *s* 0.051 7) for attack at the aromatic carbon of DNPB; $\beta_{CO} = 0.44$ (*r* 0.996, *s* 0.026 2) for attack at the carbonyl carbon and $\beta_{Ar} = 0.69$ (*r* 0.995, *s* 0.049 3) for attack at the aromatic carbon of DNPA. The β values we found show that (a) sensitivity to the basicity of the arenethiolate ions is higher for attack on aromatic than on carbonyl carbon, this difference being more manifest for the reaction with DNPA than with DNPB and (b) β_{Ar} is essentially the same for attack on the aromatic carbon of both esters.

Speculation about these β values may be advanced, in spite of the inherent limitations and dangers of using such relationships in interpreting mechanism, as has been pointed out.[6] In the reaction of *p*-nitrophenyl acetate (PNPA) with substituted arenethiols, where attack occurs only on carbonyl carbon, we observed β 0.61 [1] in 95% aqueous ethanol at 22 °C. A comparison of this β value with β_{CO} for DNPA (0.44) implies, in the light of general concepts, that a greater degree of bond formation occurs when PNPA is the substrate than for DNPA. This small decrease in β with increase of the leaving group ability of the phenol portion of the ester is perhaps consistent with a small decrease in selectivity with increasing reactivity which might be expected from the considerations discussed by Hammond and others.[7]

Similar behaviour has often been observed and a number of theoretical inferences have been drawn.[7] Nevertheless, the automatic identification of increased reactivity with decreased selectivity has been demonstrated in several cases [6] to be misleading. The situation is intricate and suggests caution in reaching conclusions.

Comparison of the β_{Ar} values from the present study with that found by Crampton [6c] for the reactions of substituted sodium arenethiolates with 1-chloro-2,4-dinitrobenzene in 95% (v/v) ethanol–water at 25 °C, *viz.* 0.65, implies that a similar degree of bond formation occurs in these reactions. The nucleophilic displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by benzenethiolate is known to proceed by the two-step intermediate complex mechanism,[5a,8] with the first step rate determining. Since displacements by benzenethiolate of chloride ion from 1-chloro-2,4-dinitrobenzene and of benzoate and acetate ions from DNPB and DNPA, respectively, occur at comparable rates in spite of the different electronic and steric characteristics of these groups, it is probable that bond-breaking has not made significant progress in the rate-determining transition state for attack at the aromatic carbon of DNPB and DNPA.

Figures 1 and 2 show that the points corresponding to electron-donating substituents such as *p*-methyl and *p*-halogeno deviate from linearity, *i.e.* the arenethiolates with these *para*-substituents have a nucleophilicity higher than expected on the basis of their proton basicity. This behaviour has been previously [1] observed for arenethiolates bearing *para*-substituents capable of releasing electrons mesomerically and different interpretations have been proposed.

To see whether more satisfactory correlations could be obtained, the rate constants from Tables 1 and 2 were plotted logarithmically against the carbon basicities (log K_{TNB}) of the arenethiolates determined by Crampton.[9] Excellent straight lines are obtained for all the substituents by plotting log k_{CO} and log k_{Ar} against log K_{TNB}: this confirms [1] that in different types of reactions the nucleophilic reactivities of the substituted arenethiolates are better correlated with their carbon rather than with their proton basicities. We obtained the following slope values: for DNPB, S_{CO} 0.40 (*r* 0.997, *s* 0.021 4), S_{Ar} 0.62 (*r* 0.995, *s* 0.048 8); for DNPB, S_{CO} 0.48 (*r* 0.993, *s* 0.042 1), S_{Ar} 0.59 (*r* 0.993, *s* 0.054 5). A similar treatment for PNPA gave a slope of 0.54.[1]

EXPERIMENTAL

Materials.—Reagent grade (RPE ACS Carlo Erba) 95% aqueous ethanol was purified by distillation of the azeotrope. DNPA, m.p. 71—72° (lit.,[10] 72°), and DNPB, m.p. 132—133° (lit.,[11] 132—133°), were prepared following described methods and were recrystallized from ligroin (b.p. 80—100°) and benzene, respectively. Arenethiols were either commercial specimens or were synthesized as before [1] from the corresponding anilines *via* the xanthate esters. The arenethiols were carefully distilled or recrystallized immediately before use, all the m.p.s or b.p.s agreeing with literature values. DNP was a recrystallized [m.p. 113—114° (lit.,[12] 114°) (from ethanol)] commercial specimen. 2,4-Dinitrophenyl (substituted phenyl) sulphides were prepared from 1-chloro-2,4-dinitrobenzene and substituted sodium arenethiolates in ethanol [6c] and recrystallized several times to constant m.p. 2,4-*Dinitrophenyl* m-*fluorophenyl sulphide* had m.p. 95—96° [from ligroin (b.p. 80—100°)] (Found: C, 48.9; H, 2.4; S, 10.8. $C_{12}H_7FN_2O_4S$ requires C, 49.0; H, 2.4; S, 10.9%).

The following *S*-aryl thioesters were obtained by condensation of the corresponding arenethiol with acetyl or benzoyl chloride according to known procedures: phenyl thioacetate,[13] *m*-chlorophenyl thioacetate,[14] *p*-chlorophenyl thioacetate,[14] *m*-cresyl thioacetate,[14] *p*-cresyl thioacetate,[14]

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TABLE 3

Invariance of second-order rate constants k_{tot} with conditions for the reaction of *m*-chlorobenzenethiolate with DNPB in 95% aqueous ethanol at 22 °C [a]

I/M	10^3[ArSH]$_{total}$/M	10^3[ArSH]$_{free}$/M	10^4[ArS$^-$]/M	k_{tot}[b]/l mol^{-1} s^{-1}	%C_{CO}–O[c]/scission	k_{CO}[b]/l mol^{-1} s^{-1}	k_{Ar}[b]/l mol^{-1} s^{-1}
0.000 2	3.2	3	2	16.4	19.8	3.2	13.2
0.000 2	60.2	60	2	16.6	19.9	3.3	13.3
0.002	62	60	20	15.5	19.7	3.1	12.4
0.002 [d]	60.2	60	2	15.6	19.8	3.1	12.5

[a] [DNPB] = 10^{-5}M throughout the runs. [b] See footnote *a*, Table 1. [c] See footnote *b*, Table 1. [d] Ionic strength maintained at 0.002M with lithium chloride.

m-methoxyphenyl thioacetate,[15] m-*bromophenyl thioacetate*, b.p. 146—148° at 11 mmHg (Found: C, 41.5; H, 3.1; S, 13.7. C_8H_7BrOS requires C, 41.55; H, 3.05; S, 13.85%), m-*fluorophenyl thioacetate*, b.p. 73—74° at 2 mmHg (Found: C, 56.4; H, 4.1; S, 18.9. C_8H_7FOS requires C, 56.45; H, 4.15; S, 18.85%), p-*fluorophenyl thioacetate*, b.p. 108—110° at 12 mmHg (Found: C, 56.3; H, 4.2; S, 18.8%), phenyl thiobenzoate,[16] *p*-chlorophenyl thiobenzoate,[17] *m*-fluorophenyl thiobenzoate,[18] *p*-fluorophenyl thiobenzoate,[18] *p*-cresyl thiobenzoate,[19] m-*chlorophenyl thiobenzoate*, m.p. 72—73° (from ethanol) (Found: C, 62.7; H, 3.7; S, 12.8. $C_{13}H_9ClOS$ requires C, 62.75; H, 3.65; S, 12.9%), m-*bromophenyl thiobenzoate*, m.p. 87—88° [from ligroin (b.p. 80—100°)] (Found: C, 53.3; H, 3.0; S, 10.9. $C_{13}H_9BrOS$ requires C, 53.25; H, 3.1; S, 10.95%), m-*cresyl thiobenzoate*, m.p. 46—47° (from ethanol) (Found: C, 73.5; H, 5.4; S, 14.0. $C_{14}H_{12}OS$ requires C, 73.65; H, 5.3; S, 14.05%), m-*methoxyphenyl thiobenzoate*, m.p. 67—68° [from ligroin (b.p. 80—100°)] (Found: C, 68.9; H, 4.9; S, 13.2. $C_{14}H_{12}O_2S$ requires C, 68.85; H, 4.95; S, 13.1%).

Kinetics.—The kinetic measurements were performed in a temperature controlled (22 ± 0.1 °C) cell compartment of a Gilford 2400-S spectrophotometer. The u.v. absorption due to the formation of both DNP and 2,4-dinitrophenyl (substituted phenyl) sulphide was followed near the isosbestic point. The spectrophotometric procedure previously [1] described was used and runs were set up under pseudo-first-order conditions. Good linear first-order plots, good infinity values, and good reproducibility between runs were obtained. The second-order rate constants, k_{tot}, calculated by dividing the first-order rate coefficients by the thiolate concentration, were, within experimental error, independent of the concentration of base and of the excess concentration of thiol present. This is illustrated in Table 3 for the reaction of DNPB with *m*-chlorobenzenethiol, a convenient reactant from the standpoint of its rate. The molar concentration of the thiolate was varied over a range of 10, and that of thiol over 20. The decrease of *ca.* 7% in k_{tot} with a 10-fold increase in thiolate concentration was expected on the basis of the effect of variation of ionic strength; [3] nevertheless it was confirmed by kinetic runs with ionic strength adjusted to the required value by addition of lithium chloride.

In order, therefore, to obtain a homogeneous set of data for all the substituted arenethiols, we have considered it convenient to choose the following reaction concentrations: substrate 10^{-5}M, free thiol 30 × 10^{-4}M, base 2 × 10^{-4}M. The excess of thiol over base was sufficient to ensure complete conversion of ethoxide and hydroxide ions into thiolate.

The overall rate constants k_{tot} were split into k_{CO} and k_{Ar} following the procedure of the previous [1] investigation. The values of the second-order rate constants are the average values obtained from no less than three separate experiments, the mean deviation being ±4%.

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