# Kinetic Studies of the Reactions of Some Phenyl Aryl Sulfides with Aliphatic Amines in Dimethyl Sulfoxide; the Mechanism of Base Catalysis

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The reactions of n-butylamine, pyrrolidine and piperidine with 4'-R-phenyl 2,4,6-trinitrophenyl sulfides (R = H, Me, Br, NO_2), 4a–d, result in the rapid formation of σ-adducts by attack at the unsubstituted 3-position; rate and equilibrium data are reported and substituent effects examined. Attack by amine at the 1-position of 4a–d, phenyl 2,4-dinitronaphthyl sulfide 9, and phenyl 2,6-dinitro-4-trifluoromethyl sulfide 11, results in displacement of the phenylthio group. The substitutions by butylamine show a first order dependence on the amine concentration indicating that nucleophilic attack is rate determining. However the substitutions by pyrrolidine are subject to general base catalysis and it is argued that here the rate limiting step is deprotonation of the initially formed zwitterionic intermediate.

Compelling evidence for the S_NAr mechanism of aromatic substitution comes from the observation of general base catalysis in reactions involving amine nucleophiles [1,2] (Scheme 1).
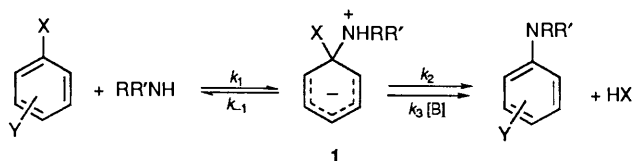
Scheme 1

However the mechanism of base catalysis is still the subject of interest and discussion.[3–9] One possibility is that proton transfer from the zwitterionic intermediate, 1, to base is rate limiting. Alternatively this proton transfer may occur in a rapid equilibrium to give an anionic intermediate from which the leaving group is lost in a general acid catalysed step. This latter pathway, the SB–GA mechanism, has gained wide acceptance for reactions occurring in dimethyl sulfoxide (DMSO) solvent. This follows an elegant study by Orvik and Bunnett of the reactions of 1-ethoxy-2,4-dinitronaphthalene with aliphatic amines;[10] they were able to observe in separate steps the formation of intermediates of structure 2 and their acid catalysed conversion into substitution products.
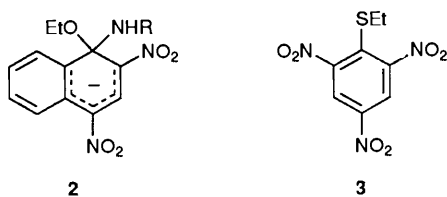
Related intermediates have been observed during the reactions of several other ring-activated alkyl aryl ethers with amines[11–17] and there is no doubt that here the SB–GA mechanism applies.

We recently[18] studied the reactions of ethyl 2,4,6-trinitrophenyl sulfide, 3, with n-butylamine and with pyrrolidine in DMSO where substitution occurs without the accumulation of intermediates on the reaction pathway. With n-butylamine a first order dependence on amine was observed indicating that nucleophilic attack, k_1, was rate determining. With pyrrolidine a squared dependence on amine was observed. We argued that base catalysis here was likely to involve rate-limiting proton

transfer from the zwitterionic intermediate. Our justification for this was the failure to observe an intermediate, the lower kinetic barrier expected for loss of an alkylthio- relative to an alkoxy-group,[19] and the unlikelihood of general acid catalysis involving proton transfer to a sulfur atom. Sekiguchi and co-workers have recently produced evidence that base catalysis in the substitution reaction of n-butylamine with 1-pyrrolidino-2,4-dinitronaphthalene also involves rate-limiting deprotonation of the zwitterionic intermediate.[20]

Here we report kinetic and equilibrium studies of the reaction of a series of phenyl aryl sulfides with n-butylamine, pyrrolidine and piperidine in DMSO. We were particularly interested to compare the results for phenyl 2,4,6-trinitrophenyl sulfide with those for ethyl 2,4,6-trinitrophenyl sulfide in order to examine the effect of changing the leaving-group. Results are also given for reactions of phenylthio-derivatives of 2,4-dinitronaphthalene and 2,6-dinitro-4-trifluoromethylbenzene. In all cases we find that in reaction with n-butylamine the rate-determining step is nucleophilic attack, k_1. With pyrrolidine (and piperidine where observations were made) substitution is base catalysed and it is argued that this is the result of rate-limiting proton-transfer from the initially formed zwitterionic intermediates.

Results

4'-Substituted Phenyl 2,4,6-Trinitrophenyl Sulfides.—UV–VIS measurements of substrates 4a–d (ca. 10^{-5} mol dm^{-3}) in DMSO containing amines (0.004–0.05 mol dm^{-3}) showed the presence of two well separated processes which are interpreted[18] by Scheme 2. In each case a rapid reversible equilibrium was observed leading to the 3-adduct (5) with λ_{max} 455–465 (ε 2 × 10^4 dm^3 mol^{-1} cm^{-1}) and 520–530 nm (shoulder). A second much slower process was observed resulting in formation of the N-substituted picramide derivatives, 8. The final spectra were identical to those of the independently prepared products, 8, in solutions of the same amine concentration. It is known[21] that the reaction products are themselves in rapid equilibrium with anions derived from them by amine addition at the 3-position and/or loss of a side-chain proton. There was no evidence for the accumulation of spectroscopically observable concentrations of intermediates such as 7 during these reactions. In the case of piperidine the second reaction was inconveniently slow for kinetic measurements.

We assume in our kinetic analysis that zwitterionic forms
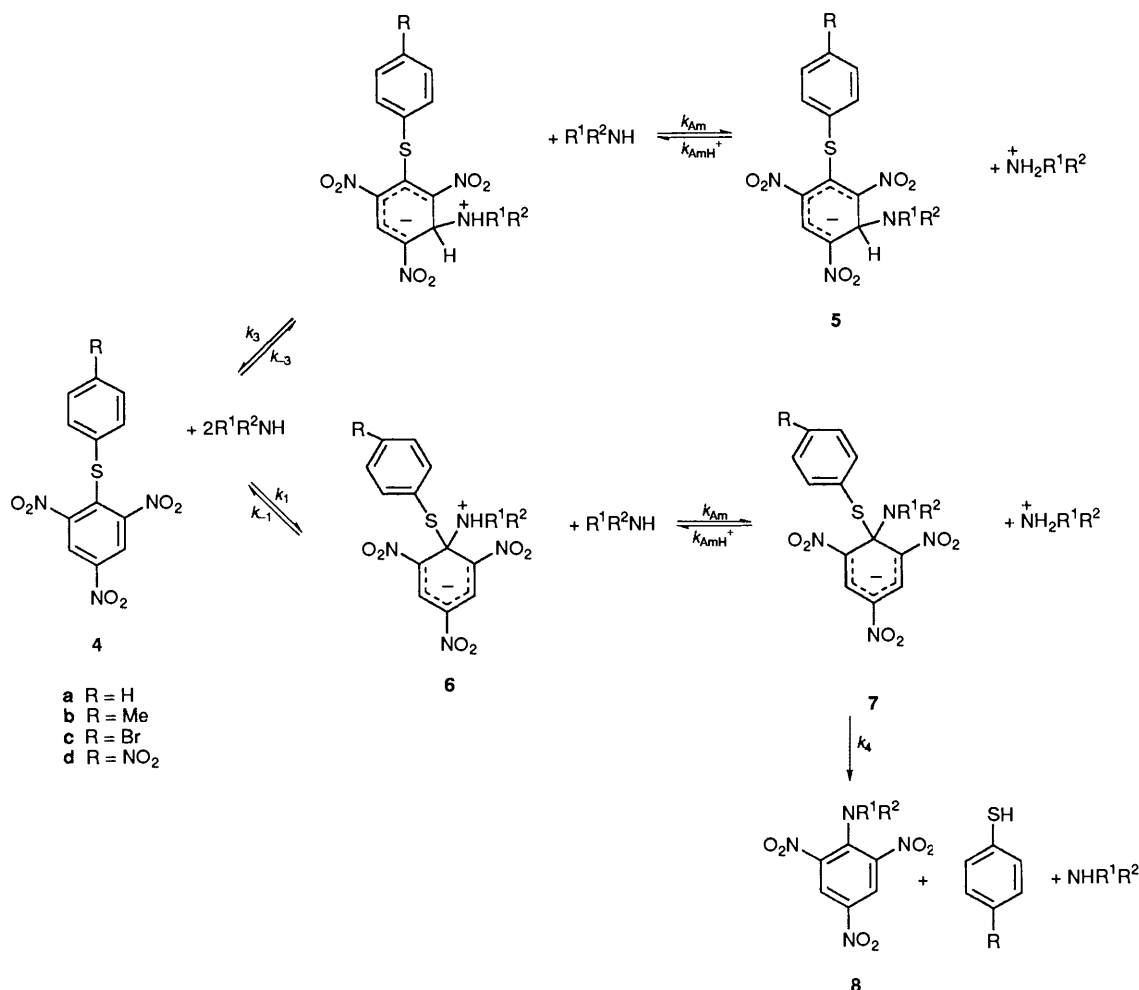
Scheme 2

a R = H
b R = Me
c R = Br
d R = NO$_2$

may be treated as steady-state intermediates.* Then the general rate expression for reaction at the 3-position to produce adducts **5** is eqn. (1).

$$k_{\text{fast}} = \frac{k_3 k_{\text{Am}}[\text{Am}]^2 + k_{-3} k_{\text{AmH}^+}[\text{AmH}^+]}{k_{-3} + k_{\text{Am}}[\text{Am}]} \quad (1)$$

The overall equilibrium constant, $K_{c,3}$, for conversion of substrate to adduct **5** is defined by eqn. (2), and is related to rate constants by eqn. (3).

$$K_{c,3} = \frac{[\mathbf{5}][\text{AmH}^+]}{[\mathbf{4}][\text{Am}]^2} \quad (2)$$

$$K_{c,3} = \frac{k_3}{k_{-3}} \times \frac{k_{\text{Am}}}{k_{\text{AmH}^+}} \quad (3)$$

We will assume, at present, that leaving group expulsion (the

* In Scheme 2 and elsewhere we use the symbol k_{Am} to represent the rate constant for proton transfer from zwitterionic intermediates to amine and the symbol k_{AmH^+} for the reverse reaction. There is strong evidence[13,22] that the values of these rate constants decrease with increasing steric crowding at the reaction centre. Thus it is expected that for a given amine the values of k_{Am} and k_{AmH^+} for reactions involving attack at the 1-position will be orders of magnitude lower than corresponding values for attack at the 3-position.
† Supplementary publication no. 56995. For details of the deposition scheme see the journal's 'Instructions for Authors (1994)', issue 1, 1994.

k_4 step in Scheme 2) is not rate-limiting. In that case, taking account of the rapid reversible reaction at the 3-position, the rate expression for product formation is eqn. (4).

$$k_{\text{slow}} = \frac{k_1 k_{\text{Am}}[\text{Am}]^2}{(k_{-1} + k_{\text{Am}}[\text{Am}])} \times \left(1 + K_{c,3} \frac{[\text{Am}]^2}{[\text{AmH}^+]}\right)^{-1} \quad (4)$$

It is convenient to define a modified rate constant, k'_{slow}, by eqn. (5), so that eqn. (4) may be written as eqn. (6).

$$k'_{\text{slow}} = k_{\text{slow}}\left(1 + K_{c,3} \frac{[\text{Am}]^2}{[\text{AmH}^+]}\right) \quad (5)$$

$$k'_{\text{slow}} = \frac{k_1 k_{\text{Am}}[\text{Am}]^2}{k_{-1} + k_{\text{Am}}[\text{Am}]} \quad (6)$$

There is also the possibility of the direct uncatalysed conversion of **6** to **8**. However our results indicate that this pathway does not contribute significantly to the overall substitution reaction.

Data for reaction of phenyl 2,4,6-trinitrophenyl sulfide **4a** are presented in Tables 1–3. Similar data for **4b–d** are reported as supplementary information in Tables 8–16.†

The results for reaction with n-butylamine, in Table 1, show that in the absence of added salt values of k_{fast} increase linearly with amine concentration. This indicates that the condition $k_{\text{Am}}[\text{Am}] \gg k_{-3}$ applies so that eqn. (1) reduces to eqn. (7). The values in Table 1 accord with this equation with k_3 1500 dm^3

mol^{-1} s^{-1} and $k_{-3}k_{AmH^+}/k_{Am}$ 45 s^{-1}. Combination of these values leads *via* eqn. (3) to a value for $K_{c,3}$ of 33 dm^3 mol^{-1}.

$$k_{fast} = k_3[Am] + \frac{k_{-3}k_{AmH^+}}{k_{Am}} \times \frac{[AmH^+]}{[Am]} \quad (7)$$

Table 1 Kinetic data[a] for reaction of **4a** with n-butylamine in DMSO at 25 °C

[BuNH$_2$]/ mol dm^{-3}	[Bu$\overset{+}{N}$H$_3$ClO$_4^-$]/ mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[b]	k_{slow}/s^{-1}	k_{calc}[c]
0.01	—	14.5	15	—	
0.02	—	31	30	—	
0.03	—	46	45	—	
0.04	—	61	60	—	
0.05	—	72	75	—	
0.01	0.01	57	60	0.26	0.25
0.02	0.01	54	53	0.25	0.28
0.03	0.01	60	60	0.25	0.25
0.04	0.01	71	71	0.21	0.21
0.05	0.01	85	84	0.18	0.18

[a] All measurements made by stopped-flow spectrophotometry at 540 nm. [b] Calculated from eqn. (7) with k_3 1500 dm^3 mol^{-1} s^{-1}, $k_{-3}k_{AmH^+}/k_{Am}$ 45 s^{-1}. [c] Calculated as

$$k_1[Am] \times \left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)^{-1}$$

with k_1 33 dm^3 mol^{-1} s^{-1} and $K_{c,3}$ 33 dm^3 mol^{-1}.

Values for k_{slow}, the rate constant for attack at the 1-position are also in Table 1. Values of k'_{slow} were calculated from eqn. (5) and are linear in amine concentration. This indicates that the condition $k_{Am}[Am] \gg k_{-1}$ applies, so that eqn. (6) reduces to eqn. (8). Values of k_{slow} calculated with k_1 33 dm^3 mol^{-1} s^{-1} are in excellent agreement with experimental values.

$$k'_{slow} = k_1[Am] \quad (8)$$

Data for reaction of **4a** with pyrrolidine are in Table 2. In the formation of the 3-adduct, **5**, the proton transfer step is partially rate-limiting and values calculated for k_{fast} with k_3 1.25 × 10⁴ dm^3 mol^{-1} s^{-1}, k_{Am}/k_{-3} 22.4 dm^3 mol^{-1} and k_{AmH^+} 2.6 × 10³ dm^3 mol^{-1} s^{-1} gave a good fit with experimental data. These values lead, using eqn. (3) to a value for $K_{c,3}$ of 108 dm^3 mol^{-1}. Values of k'_{slow}, relating to the displacement of the phenylthio group, show a squared dependence on the pyrrolidine concentration. This indicates that in eqn. (6) $k_{-1} \gg k_{Am}[Am]$, so that $k'_{slow} = K_1k_{Am}[Am]^2$. This is compatible with the proton transfer process being the rate determining step in the substitution reaction.

Kinetic and equilibrium results for the rapid reaction with piperidine producing the 3-adduct **5a**, $NR^1R^2 = NC_5H_{10}$ are in Table 3. Values of k_{fast}, in the absence of added piperidinium ions, show a squared dependence on the piperidine concentration. This indicates that $k_{-3} \gg k_{Am}[Am]$, showing that proton transfer is rate-limiting in the formation of **5a**. With this

Table 2 Kinetic data for the reaction[a] of **4a** with pyrrolidine in DMSO at 25 °C

| [Pyrrolidine]/ mol dm^{-3}	[Pyrrolidinium perchlorate]/mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[b]	$\dfrac{k_{slow}/}{10^{-2} s^{-1}}$	$\dfrac{k'_{slow}[c]/}{10^{-2} s^{-1}}$	$\dfrac{k'_{slow}}{[Am]^2}/dm^6$ mol^{-2} s^{-1}
0.006	—	8.8	8.9	—		
0.008	—	15	15	—		
0.010	—	22.5	23	—		
0.015	—	48	47	—		
0.020	—	76	77	—		
0.030	—	152	151	—		
0.006	0.01	32	32	—		
0.008	0.01	36	37	0.94	1.59	250
0.010	0.01	44	44	1.22	2.54	250
0.015	0.01	67	67	—	—	
0.02	0.01	96	95			
0.03	0.01	—		2.15	23.0	260
0.04	0.01	—		2.1	38	240
0.05	0.01	—		2.1	59	240

[a] All measurements at 540 nm, the fast reaction was measured by stopped-flow spectrophotometry and the slow reaction with the Lambda 2 spectrometer. [b] Calculated from eqn. (1) with k_3 1.25 × 10⁴ dm^{-1} mol^{-1} s^{-1}, k_{Am}/k_{-3} 22.6 dm^3 mol^{-1}, k_{AmH^+} 2.6 × 10³ dm^3 mol^{-1} s^{-1}. [c] Calculated from eqn. (5) with $K_{c,3}$ 108 dm^3 mol^{-1}.

Table 3 Kinetic and equilibrium data[a] for reaction of **4a** with piperidine in DMSO at 25 °C

[Piperidine]/ mol dm^{-3}	[Piperidinium chloride]/mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[b]	A (540 nm)	$\dfrac{K_{c,3}[c]/dm^3}{mol^{-1}}$
0.01	—	2.1	1.9		
0.02	—	7.4	7.6		
0.025	—	11	12		
0.03	—	16	17		
0.04	—	28	30		
0.05	—	50	48	0.053	
0.008	0.01	6.3	5.2	0.014	56
0.01	0.01	6.6	6.0	0.017	47
0.02	0.01	12	12	—	—
0.03	0.01	22	21	0.044	54
0.04	0.01	34	34	0.047	49
0.05	0.01	53	52	0.048	39

[a] All measurements at 540 nm by stopped-flow spectrophotometry. [b] Calculated from eqn. (9) with k_3k_{Am}/k_{-3} 1.9 × 10⁴ dm^6 mol^{-2} s^{-1} and k_{AmH} 400 dm^3 mol^{-1} s^{-1}. [c] Calculated, eqn. (2), as $\dfrac{A}{(0.053 - A)}\dfrac{[AmH^+]}{[Am]^2}$.
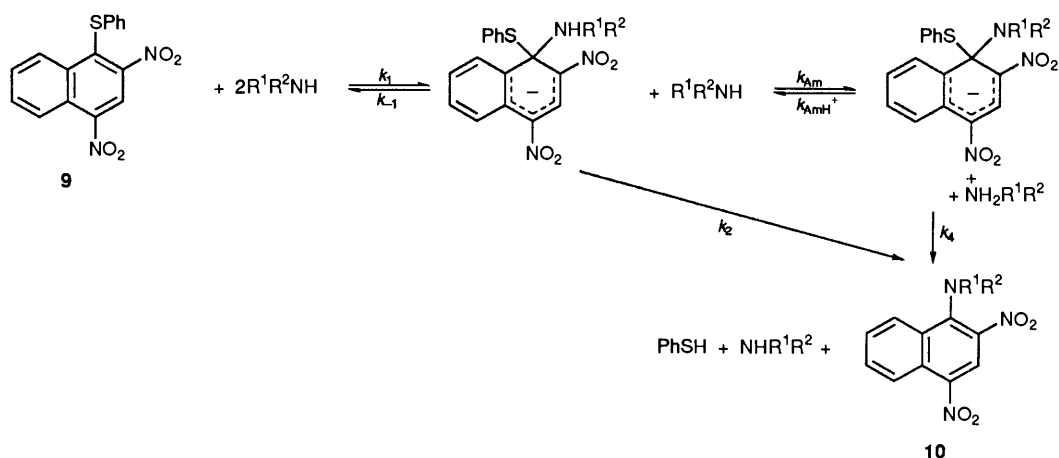
Scheme 3

condition, eqn. (1) simplifies to give eqn. (9). Values calculated with $k_3 k_{Am}/k_{-3}$ 1.9×10^4 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 400 dm^3

$$k_{fast} = \frac{k_3 k_{Am}}{k_{-3}} [Am]^2 + k_{AmH^+}[AmH^+] \qquad (9)$$

mol^{-1} s^{-1} give good agreement with experimental data. Combination of these values using eqn. (3) gave $K_{c,3}$ 48 dm^3 mol^{-1}, in acceptable agreement with values obtained from absorbance data.

Phenyl 2,4-Dinitronaphthyl Sulfide **9**.—Spectrophotometric measurements were made with **9** (*ca.* 10^{-5} mol dm^{-3}) in DMSO containing amines (0.01–0.15 mol dm^{-3}). In some cases amine salt (0.01 mol dm^{-3}) or 1,4-diazabicyclo[2.2.2]octane (DABCO; 0.025–0.10 mol dm^{-3}) were present. In all cases a single rate process was observed resulting in the quantitative formation of the substitution product, **10**. The UV–VIS spectra at completion of the measured process were in all cases identical to those of authentic samples of **10** dissolved in the reaction medium. In agreement with previous work[23] it was observed that the reaction products undergo further slow reactions with amines. Our results are discussed in relation to Scheme 3.

In the reaction with n-butylamine, the values of the first order rate constant, k_{obs}, increased linearly with amine concentration (Table 17, supplementary information) indicating that nucleophilic attack is rate limiting and giving a value for k_1 of 0.46 dm^3 mol^{-1} s^{-1}. The situation with pyrrolidine as the nucleophile is more complex. A plot, not shown, of k_{obs}/[pyrrolidine] *versus* pyrrolidine concentration goes through the origin and curves with decreasing slope as the pyrrolidine concentration is increased. That the plot goes through the origin indicates that the uncatalysed pathway, k_2 in Scheme 3, is unimportant. The curvature of the plot indicates that the proton transfer step, k_{Am}, is partially rate limiting so that eqn. (10) applies. Rate constants

$$k_{obs} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad (10)$$

were unaffected by the presence of 0.01 mol dm^{-3} pyrrolidinium perchlorate. However accelerations were produced by added DABCO when eqn. (11) will apply.

$$k_{obs} = \frac{k_1[Am](k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_{Am}[Am] + k_{DABCO}[DABCO]} \qquad (11)$$

Data are in Table 4 and give a good fit with eqns. (10) and (11)

with $k_1 k_{Am}/k_{-1}$ 30 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-1} 5 dm^3 mol^{-1} and k_{DABCO}/k_{-1} 1.2 dm^3 mol^{-1}. These values allow the calculation of a value for k_1 of 6 dm^3 mol^{-1} s^{-1}.

We note that if the hypothesis were made that formation of the anionic intermediate is a rapid equilibrium and that the k_4 step (involving general acid catalysed expulsion of the phenyl-thio group) is rate determining, then eqn. (12) is obtained.

$$k_{obs} = \frac{k_1 k_{Am} k_4 [Am]^2}{k_{-1}(k_4 + k_{AmH^+})} \qquad (12)$$

This would require a linear dependence of k_{obs}/[pyrrolidine] on pyrrolidine concentration rather than the curvature which is observed.

Values for the rate constant for reaction of **9** with piperidine to give **10** (NR^{1}R^2 = NC$_5$H$_{10}$) increase with the square of the amine concentration (Table 18, supplementary information). In terms of eqn. (10) this indicates that $k_{-1} \gg k_{Am}[Am]$. The value for $k_1 k_{Am}/k_{-1}$ is 0.40 dm^6 mol^{-2} s^{-1}. The observed kinetics indicate that the proton transfer step, k_{Am}, is rate limiting in the substitution process.

Phenyl 2,6-Dinitro-4-trifluoromethylphenyl Sulfide **11**.—The processes occurring here and the nomenclature used is analogous to that shown in Scheme 3. With n-butylamine a single rate process was observed giving the substituted product, *N*-n-butyl-2,6-dinitro-4-trifluoromethylaniline, which in the presence of excess amine was in equilibrium with its anion, **12**, with λ_{max} 440 nm, ε 1.8×10^4 dm^3 mol^{-1} cm^{-1}. The observed rate constant increased linearly with n-butylamine concentration indicating that nucleophilic attack was rate determining and giving k_1 0.48 dm^3 mol^{-1} s^{-1}. (Data given in Table 19, supplementary information.)

11   **12**   **13**
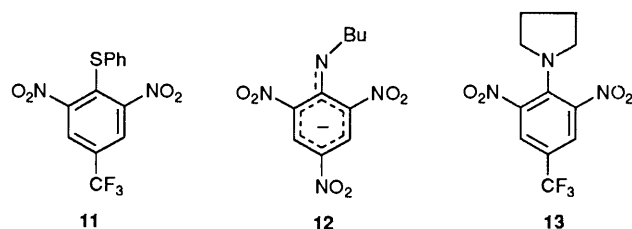
Reaction of **11** with pyrrolidine resulted in a rapid reaction giving the 3-pyrrolidino adduct (λ_{max} 360 and 521 nm). This reaction was suppressed by making measurements in the presence of 0.1 mol dm^{-3} pyrrolidinium perchlorate. Here the reaction product was **13**. It was noted that at high pyrrolidine

Table 4 Kinetic results[a] for the reaction of phenyl 2,4-dinitronaphthyl sulfide, **9**, with pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/ mol dm^{-3}	[Pyrrolidinium chloride]/mol dm^{-3}	[DABCO]/ mol dm^{-3}	k_{obs}/s^{-1}	k_{calc}[b]
0.01	—	—	0.0031	0.0029
0.015	—	—	0.0067	0.0063
0.02	—	—	0.012	0.011
0.04	—	—	0.042	0.040
0.06	—	—	0.090	0.083
0.08	—	—	0.14	0.14
0.10	—	—	0.21	0.20
0.15	—	—	0.40	0.39
0.05	0.01	—	0.060	0.060
0.075	0.01	—	0.12	0.12
0.10	0.01	—	0.21	0.20
0.025	—	—	0.017	0.017
0.025	—	0.025	0.021	0.020
0.025	—	0.050	0.024	0.023
0.025	—	0.075	0.027	0.027
0.025	—	0.10	0.030	0.030

[a] Measurements made at 440 nm with 2×10^{-5} mol dm^{-3} parent. [b] Calculated from eqn. (11) with k_1 6 dm^3 mol^{-1} s^{-1}, k_{Am}/k_{-1} 5 dm^3 mol^{-1} and k_{DABCO}/k_{-1} 1.2 dm^3 mol^{-1}.

Table 5 Summary of kinetic and equilibrium data in DMSO at 25 °C

	3[a]	4a	4b	4c	4d	9	11
Reaction with n-butylamine							
$K_{c,3}$[c]	11	33	17	57	270	—	—
k_3[d]	780	1 500	1 400	2 000	2 500	—	—
$k_{-3}k_{AmH^+}/k_{Am}$[e]	11	45	17	57	270	—	—
k_1[d]	8	33	28	36	43	0.46	0.48
Reaction with pyrrolidine							
$K_{c,3}$[c]	63	108	77	160	1 140	—	—
k_3[d]	8 100	12 500	10 800	19 000	26 000	—	—
k_{Am}/k_{-3}[c]	44	22	25	25	31	—	—
k_{AmH^+}[b,d]	5 700	2 600	3 500	2 900	700	—	—
$K_1 k_{Am}$[f]	60	250	210	400	200	30	0.18
Reaction with piperidine							
$K_{c,3}$[c]	38	48	43	110	510	—	—
k_{AmH^+}[b,d]	500	400	340	230	90	—	—
$k_3 k_{Am}/k_{-3}$[f]	15 300	19 000	14 600	26 000	46 000	—	—
$K_1 k_{Am}$[f]	—	—	—	—	—	0.4	—

[a] Data from ref. 18. [b] Refers to attack that the 3-position. [c] dm^3 mol^{-1}. [d] dm^3 mol^{-1} s^{-1}. [e] s^{-1}. [f] dm^6 mol^{-2} s^{-1}.

concentrations **13** was in rapid equilibrium with its 3-pyr-rolidino adduct. Kinetic data for the conversion of **11** to **13** showed that k_{obs} depended linearly on the square of the pyrrolidine concentration (Table 20, supplementary inform-ation). This indicates that proton transfer is rate limiting in the substitution process with $k_1 k_{Am}/k_{-1}$ 0.18 dm^6 mol^{-1} s^{-1}.

Discussion

Kinetic and equilibrium data are collected in Table 5 which also contains results[18] for ethyl 2,4,6-trinitrophenyl sulfide, **3**. For the phenyl 2,4,6-trinitrophenyl sulfides **4a–d**, as with **3**,[18] the most rapid reaction results in σ-adduct formation at the 3-position to give **5a–d**. For each individual substrate values of $K_{c,3}$ decrease in the order pyrrolidine > piperidine > n-butyl-amine reflecting the basicity order of the amines. Similarly values of k_3 for nucleophilic attack are about an order of magnitude greater for reaction of pyrrolidine than for n-butylamine. It is known that secondary amines have greater steric requirements than primary amines[9,11,12,20,23] but our results indicate that for attack at an unsubstituted ring position there is little steric hindrance to nucleophilic attack. A Hammett plot of the values of $K_{c,3}$ for **4a–d**, Fig. 1, has slope, p, of 1.2. In

view of the remoteness of the substituents from the reaction centre this value is surprisingly large and indicates that the phenylthio-groups play a significant role in delocalising negative charge in the adduct. For comparison[24] the p value for the related process of hydroxide addition at the 3-position is 0.98. Values of $K_{c,3}$ and k_3 are lower for **3** than for **4** reflecting the poorer electron withdrawing ability of the SEt group relative to the SPh group. The data in Table 5 show that values of k_3 increase with increasing electron withdrawal by the 1-substituent while values of k_{AmH^+} decrease. It is seen that values of k_{Am}/k_{-3}, where available, show little variation with substrate structure.

It is noteworthy that, as observed in related systems,[13,18,25,26] the rate determining step in the formation of the 3-adducts, **5a–d**, changes from nucleophilic attack (the k_3 step) with n-butylamine as the nucleophile, to proton transfer (the k_{Am} step) with piperidine. With pyrrolidine proton transfer is partially rate limiting. Which step is rate determining will depend on the value of the ratio $k_{Am}[Am]/k_{-3}$. As the value becomes smaller (< 1) then proton transfer will become rate determining. There is evidence that the major factor here is the change in value of k_{Am} with the changing nature of the amine. Thus literature data for σ-adduct formation at an unsubstituted position of
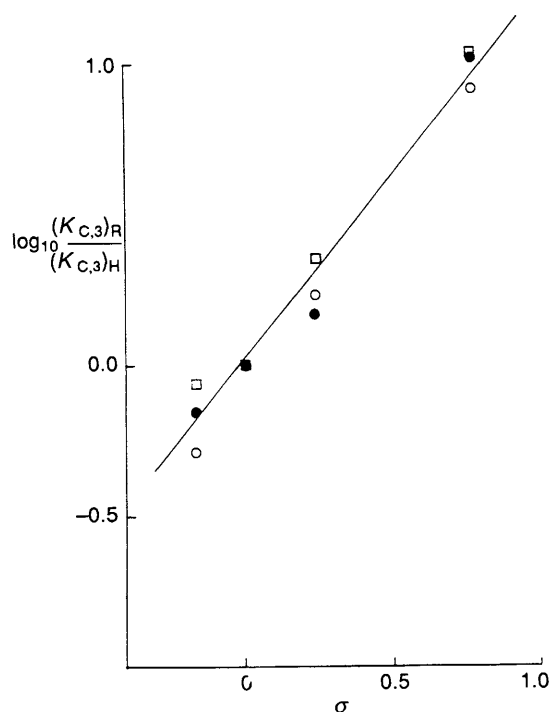
Fig. 1 Hammett plot for $K_{c,3}$ values in the formation of adducts 5a–d: (○) adducts with n-butylamine; (●) adducts with pyrrolidine; (□) adducts with piperidine

Table 6 Summary of data for reaction at the 1-position with pyrrolidine

	$K_1 k_{Am}/dm^6$ $mol^{-2} s^{-1}$	$k_1{}^a/dm^3$ $mol^{-1} s^{-1}$	$k_{Am}/k_{-1}{}^b/$ $mol\, dm^{-3}$
3	60	(80)	(0.8)
4a	250	(330)	(0.8)
4b	210	(280)	(0.8)
4c	400	(360)	(1.1)
4d	200	(430)	(0.5)
9	30	6	5
11	0.18	(5)	(0.04)

^{a} Values in parentheses were calculated assuming a ratio of 10 for k_1(pyrrolidine)/k_1(n-butylamine). ^{b} Calculated as $K_1 k_{Am}/k_1$.

1,3,5-trinitrobenzene show that the value of k_{Am} decreases from 3×10^7 dm^3 mol^{-1} s^{-1} for n-butylamine, to 1.5×10^6 dm^3 mol^{-1} s^{-1} with pyrrolidine and 1.4×10^5 dm^3 mol^{-1} s^{-1} with piperidine.[25,26] It has been argued previously[25,27] that in trinitro-activated substrates the ratio of k_{Am}/k_{AmH^+} will have a value of ca. 500, reflecting the higher acidity of zwitterionic adducts than of the corresponding ammonium ions, and that this value does not vary greatly with the nature of the amine. It follows that in the proton transfer equilibrium leading to adducts 5a–d values of both k_{Am} and k_{AmH^+} will decrease in the order n-butylamine > pyrrolidine > piperidine. The data in Table 5 confirm that values of k_{AmH^+} are larger by a factor of ca. ten for pyrrolidine than for piperidine. The argument is that although the proton transfer step leading to adducts 5 is thermodynamically favoured, values of rate constants are very much lower than those expected for diffusion controlled reaction. This reflects steric hindrance to approach of the reagents which becomes increasingly severe as the amine is changed from n-butylamine to pyrrolidine to piperidine. The preceding refers to adducts formed by attack at unsubstituted ring-positions, there is evidence that steric hindrance to proton transfer becomes even more severe when adducts involving attack at substituted ring-positions are involved.[13,22] For example the value of k_{Am} in the formation of 14 from n-butyl-

amine and 2,4,6-trinitrobenzyl chloride has the value 2.7×10^4 dm^3 mol^{-1} s^{-1} which is three orders of magnitude smaller than the corresponding value when reaction occurs at an unsubstituted position.


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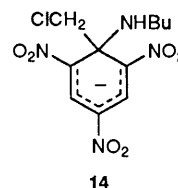
Reaction at the 1-Position.—With 4a–d attack at the 1-position was observed as a slow reaction following equilibration of the substrates with the 3-adducts, 5a–d. In the case of 9 and 11, where 3-adducts are less thermodynamically stable, attack at the 1-position was the only process observed. In all cases substitution of the phenylthio-group by amines to give the corresponding amino-derivatives occurred without the appearance, in spectroscopically observable concentrations, of intermediates on the reaction pathway.

With n-butylamine as the nucleophile, the substitution reactions were accurately first-order in amine concentration showing that nucleophilic attack, the k_1 step, is rate determining. In terms of Scheme 1, $k_2 + k_3[B] \gg k_{-1}$ so that the zwitterion is rapidly converted to products. This is likely to be a consequence, in terms of the mechanisms of Schemes 2 and 3, of relatively high values for k_{Am} (the rate constant for proton transfer) in the case of butylamine and low values of k_{-1}. The latter values may depend on the steric interactions in zwitterionic intermediates, such as 6; these interactions are expected to be lower for primary than for secondary amines. The values obtained for k_1 for 4a–d show relatively little dependence on the nature of the 4'-substituent (a Hammett plot has slope, ρ, of ca. 0.2) indicating the perhaps surprisingly small electronic effect of the substituent.

The substitutions by pyrrolidine are base catalysed. The assumption that this is the result of rate-limiting proton transfer from zwitterionic intermediates to amine, the k_{Am} step in Schemes 2 and 3, leads to the values of $K_1 k_{Am}$ given in Table 6. For 4a–d these values show only a small dependence on the nature of the 4'-substituent. The value of k_{Am} will be expected to be constant for 4a–d since the proton-transfer is in the thermodynamically preferred direction so that steric factors (constant in this series) will affect the value more than electronic factors. The inference is that K_1 values also show little dependence on the 4'-substituent. This is perhaps surprising but fits in with the observation that k_1 values for reaction with n-butylamine are largely invariant and also with the literature results for substituent effects on hydroxide attack.[24] The relatively small decrease in the value of $K_1 k_{Am}$ (from 250 to 60 dm^6 mol^{-2} s^{-1}) on changing the 1-substituent from SPh to SEt is compatible with this interpretation. The value of K_1 will be expected to decrease slightly due to the change in electronic effect, while the value of k_{Am} will be largely unchanged.

The alternative explanation of base catalysis is that the SB–GA mechanism applies. Here conversion to the anionic intermediate, 7 in Scheme 2, is a rapid equilibrium (with equilibrium constant $K_{c,1}$) and the general acid catalysed expulsion of the SPh group (k_4) is rate determining. If this were the case then the values given for $K_1 k_{Am}$ would in fact represent $k_4 K_{c,1}$. Since the latter term includes k_4, involving loss of the SR group, then a strong dependence on the nature of the SR group would be expected. Thus good correlations have been observed[3] between leaving group ability and acid strength; for example[28] phenoxide departure is 10^6 times faster than

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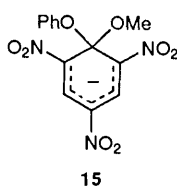
methoxide departure from the adduct **15**. It is known [29] that the p value for ionisation of substituted thiophenols is 3.0, while thiophenol is more acidic then ethanethiol by four orders of magnitude.[30] Hence a strong correlation between k_4 values and the electronic effects of the 4'-substituent in **4a–d** would be expected, and the value of k_4 should decrease dramatically on changing the leaving group from SPh to SEt. The case may be overstated in that the transition state, **16**, for the k_4 step will

16
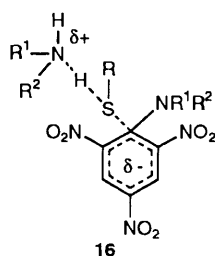
involve proton transfer to sulfur together with C–S bond breaking. Nevertheless the value of k_4 would be expected to show substantial dependence on the nature of the leaving group. The failure to observe such dependence argues against the SB–GA mechanism here. As noted previously in this paper the base dependence of the substitution reaction of **9** with pyrrolidine is in better accord with the rate limiting step being proton transfer rather than leaving group expulsion.

In Table 6 are summarised data for substitution reactions involving pyrrolidine. In general the experimentally observable quantity is $K_1 k_{Am}$, although with **9** values of k_1 and the ratio k_{Am}/k_{-1} could also be calculated. It is of interest to compare values of the latter ratio for different substrates. Values of k_1 for reaction with n-butylamine are known and in general values of rate constants for nucleophilic attack by pyrrolidine are larger by a factor of ca. 10. This is true for attack at the unsubstituted 3-position (Table 5) and also for attack at the 1-position in **9** where k_1(pyrrolidine)/k_1(n-butylamine) = 6/0.46. If the assumption is made that for the remaining substrates pyrrolidine is more reactive than n-butylamine by a factor of 10, the values in Table 6 are obtained. These show that for **3** and **4a–d** the value of k_{Am}/k_{-1} is roughly constant. This reflects the similar steric situation at the 1-position leading to similar values of k_{Am} and the similar ring-activation leading to similar k_{-1} values. For **11**, a lower value of k_{Am}/k_{-1} is obtained. The steric situation at the 1-position is similar to that in **3** and **4**, with nitro-groups at the 2- and 6-positions, so that the value of k_{Am} is likely to be unchanged. However the reduced ring-activation in **11**, with a CF_3 group at the 4-position, is likely to result in an enhanced value of k_{-1}. With **9** the highest value of k_{Am}/k_{-1} is observed. The value of k_{-1} is likely to be larger for **9** than for **4** since the ring-activation in the 2,4-dinitronaphthyl system will be less than the picryl group.[3] However the steric hindrance to proton transfer will be considerably less in **9** than in **4** with the removal of the 6-nitro group. Hence the dominant factor influencing the increase in value of k_{Am}/k_{-1} will be the larger value of k_{Am} for **9** than for **4**.

It is worth noting that for **9** rate constants for substitution are unchanged by the presence of added pyrrolidinium ions, and the reaction is catalysed by DABCO. These observations indicate

general base catalysis so that a mechanism involving rapid equilibration of substrate with its anionic adduct followed by slow, but uncatalysed, loss of PhS is not tenable. Our results show that DABCO is a less efficient catalyst than pyrrolidine, $k_{pyrrolidine}/k_{DABCO} = 4$ and this is in accord with data [20,25,26] from related systems involving rate limiting proton transfer where values of k_{Amine}/k_{DABCO} are in the range 3–5.

Reactions with piperidine were generally inconveniently slow for kinetic measurements or yielded products other than those expected for substitution at the 1-position. However reaction with **9** proceeded smoothly; and values of k_{obs} [eqn. (10)] showed a squared dependence on piperidine. This is consistent with rate determining proton transfer with a value of $K_1 k_{Am}$ of 0.40 dm^6 mol^{-2} s^{-1}. This value is 75 times smaller than that obtained for reaction with pyrrolidine. This factor is readily accounted for by a reduction of ca. 2–5 in the value of K_1 for the less nucleophilic piperidine [11,12,26] and by a reduction of ca. 10–20 in the value of k_{Am} for the sterically more demanding piperidine.[22,25]

Conclusions

Our results for the substitution process are readily interpretable assuming that base catalysis is the result of rate-limiting proton transfer from zwitterionic intermediates. That base catalysis is observed with pyrrolidine and piperidine but not with n-butylamine is largely a consequence of the decreasing values expected for k_{Am} in the series $k_{butylamine} > k_{pyrrolidine} > k_{piperidine}$. We have shown that the alternative SB–GA mechanism is unlikely here since the expected changes in reactivity with the nature of the leaving group are not observed. Although the SB–GA mechanism is established for reactions involving alkoxy-leaving groups there are further arguments, noted below, against its operation with SR leaving groups in the present systems.

Rate determining acid catalysed expulsion of the leaving group requires that $k_{AmH^+} > k_4$ for the processes shown in Schemes 2 and 3. There is strong evidence that this requirement is unlikely to be fulfilled with thiolate leaving groups. Thus it is known that the intrinsic barriers, in the Marcus sense, for reactions of sulfur bases with aromatic systems may be considerably lower than those for corresponding reactions of oxygen bases.[19] This implies that the rate constants for thiolate expulsions will be higher than those for alkoxide expulsion. In fact the rate constant for the uncatalysed expulsion of thiophenoxide from the adduct, **17**, has been shown [29] to have a

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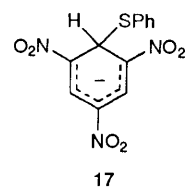
value in excess of 10^3 s^{-1}. In order for expulsion of SPh to be acid catalysed it would be necessary that $k_4 \gg 10^3$ dm^3 mol^{-1} s^{-1}. The values in Table 5 show that for reaction of pyrrolidine at unsubstituted ring positions $k_{AmH^-} \sim 10^3$ dm^3 mol^{-1} s^{-1}. The greater steric crowding when attack occurs at the 1-position should considerably decrease the value of k_{AmH^-}, so that $k_{AmH^-} < 10^3$ dm^3 mol^{-1} s^{-1}. Hence for reaction at the 1-position $k_4 \gg k_{AmH^+}$.

Further, acid catalysed expulsion of the leaving group, represented by the transition state, **16**, is unlikely in view of the pK_a values of the groups involved. In water the pK_a values of the pyrrolidinium ion and of thiophenol are 11.2 and 6.5 respectively [30] and this difference is unlikely to be reduced on

Table 7 Spectroscopic data for phenyl aryl sulfides

	δ			
Structure	Nitro-substituted ring (multiplicity)	Ring (multiplicity)	Other	$\lambda_{max}{}^a$/nm
4a	9.04 (s)	7.39 (m)		373
4b	9.00 (s)	7.28 (d)	2.31	380
		7.19 (d)		
4c	9.05 (s)	7.58 (d)		374
		7.34 (d)		
4d	9.21 (s)	8.20 (d)		315
		7.61 (d)		
9	8.93	7.25 (m)		343
	8.61 (d), 8.40 (d)			
	7.97 (t), 7.87 (t)			
11	8.73 ^{b} (q)	7.36 (m)		350

^{a} In DMSO. ^{b} Coupling of 0.7 Hz is observed with the CF_3 group.

transfer to DMSO. Hence **15** would represent a proton transfer which is strongly unfavourable in a thermodynamic sense, so that there should be no driving force for it to occur.

Experimental

Phenyl 2,4,6-trinitrophenyl sulfide, **4a**, and its 4′-substituted derivatives, **4b–d**, were prepared by reaction of picryl chloride with thiophenol or the appropriate 4-substituted thiophenol in warm ethanol in the presence of sodium acetate. Recrystallisation from ethanol yielded products whose m.p.s were in good agreement with literature data[31–33] with the exception of **4d**, m.p. 154 °C (lit., 257 °C). Compounds **9** and **11** were prepared by analogous reactions of the corresponding chloro-compounds with thiophenol.[34] In all cases spectroscopic data, collected in Table 7, were in agreement with the proposed structures. Reaction products (**8** and **10**; $NR^1R^2 = NHBut$, NC_5H_{10}, NC_4H_8) and **13** were available from previous work[18,21] or were prepared by reaction of the appropriate amine with the chloro-aromatic compound in methanol. Solvent amines and amine salts were prepared and/or purified as described previously.[18]

^1H NMR spectra were recorded using Varian-200XL or Bruker 250 MHz instruments with [$^2H_6$]DMSO as solvent. UV–VIS spectra and kinetic measurements were made with Beckman Lambda 2, or Hi-Tech SF 3L stopped-flow spectrophotometers at 25 °C. Reported rate coefficients are the means of several determinations and are precise to ±5%. Rate constants were measured under first-order conditions. Hence for reactions with buffers (amine plus amine salt) the buffer components were in large excess of the substrate concentration ($1-5 \times 10^{-5}$ mol dm^{-3}). For reactions with amines in the absence of added amine salts a sufficient excess of amine was used to achieve >95% conversion into adduct at equilibrium. Under these conditions,[18] eqn. (13) applies and was used to calculate rate constants.

$$\ln\left[\frac{A_\infty}{A_\infty - A}\right] = k_{obs}t \tag{13}$$

References

1 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 275.
2 C. F. Bernasconi, *M.T.P. Int. Rev. Sci.: Org. Chem. Ser. One*, Butterworths, London, 1973, Vol. 3, p. 33.
3 F. Terrier, *Nucleophilic Aromatic Displacement*, VCH, New York, 1991.
4 C. F. Bernasconi, *Acc. Chem. Res.*, 1978, **11**, 147.
5 T. A. Emokpae, J. Hirst and P. U. Uwakwe, *J. Chem. Soc., Perkin Trans. 2*, 1990, 2191.
6 J. Hirst, G. Hussain and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1986, 397.
7 I. Onyido and J. Hirst, *J. Phys. Org. Chem.*, 1991, **4**, 367.
8 T. A. Emokpae, P. U. Uwakwe and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1993, 125.
9 J. F. Bunnett and A. V. Cartano, *J. Am. Chem. Soc.*, 1981, **103**, 4861.
10 J. A. Orvik and J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 2417.
11 J. F. Bunnett, S. Sekiguchi and L. A. Smith, *J. Am. Chem. Soc.*, 1981, **103**, 4865.
12 H. Fujinuma, M. Hosokawa, T. Suzuki, M. Sato and S. Sekiguchi, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1969.
13 M. R. Crampton and P. J. Routledge, *J. Chem. Soc., Perkin Trans. 2*, 1984, 573.
14 Y. Hasegawa, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1314.
15 Y. Hasegawa, *J. Chem. Soc., Perkin Trans. 2*, 1984, 547.
16 Y. Hasegawa, *J. Org. Chem.*, 1985, **50**, 649.
17 Y. Hasegawa, *J. Chem. Soc., Perkin Trans. 2*, 1985, 87.
18 R. Chamberlin and M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2*, 1993, 75.
19 M. R. Crampton and J. A. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1989, 925.
20 S. Sekiguchi, M. Hosokawa, T. Suzuki and M. Sato, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1111.
21 R. Chamberlin and M. R. Crampton, *J. Chem. Res.*, 1993, (*S*), 106; (*M*), 811.
22 M. R. Crampton, P. J. Routledge and P. Golding, *J. Chem. Soc., Perkin Trans. 2*, 1984, 329.
23 S. Sekiguchi and J. F. Bunnett, *J. Am. Chem. Soc.*, 1981, **103**, 4871.
24 R. Chamberlin, M. R. Crampton and R. L. Knight, *J. Chem. Res.*, 1993, (*S*), 444; (*M*), 2986.
25 M. R. Crampton and B. Gibson, *J. Chem. Soc., Perkin Trans. 2*, 1981, 533.
26 M. R. Crampton and C. Greenhalgh, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1175.
27 C. F. Bernasconi, M. C. Muller and P. Schmid, *J. Org. Chem.*, 1979, **44**, 3189.
28 C. F. Bernasconi and M. C. Muller, *J. Am. Chem. Soc.*, 1978, **100**, 5530.
29 M. R. Crampton, *J. Chem. Soc. B*, 1968, 1208.
30 M. R. Crampton, in *The Chemistry of the Thiol Group*, ed. S. Patai, Wiley-Interscience, New York, 1974, 379.
31 G. Leandri and A. Tundo, *Ann. Chim.*, 1954, **44**, 479, 487.
32 W. A. Gey, E. R. Dalbey and R. W. van Dolah, *J. Am. Chem. Soc.*, 1956, **78**, 1803.
33 R. Passerini, *Boll. Sci. Fac. Chim. Ind. Univ. Bologna*, 1950, **8**, 122.
34 G. Leandri and L. Maioli, *Ann. Chim.*, 1955, **45**, 3, 9.