Kinetic and Equilibrium Studies of σ-Adduct Formation and Nucleophilic Substitution in the Reactions of Ethyl Thiopicrate with Aliphatic Amines in Dimethyl Sulfoxide

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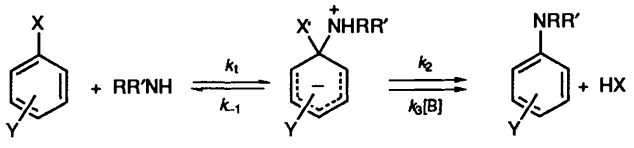
Kinetic and equilibrium results are reported for the reaction of ethyl thiopicrate with butylamine, pyrrolidine and piperidine in dimethyl sulfoxide. The most rapid reaction involves attack at the unsubstituted 3-position to give anionic σ-adducts. The rate-limiting step in this process changes from nucleophilic attack by amine with butylamine to proton transfer from the zwitterionic intermediate with piperidine; pyrrolidine shows intermediate behaviour. Attack by amine at the 1-position results in displacement of the ethylthio group, although intermediates are not observed during this process. It is suggested that base catalysis observed in the reaction with pyrrolidine may result from rate-limiting proton transfer from the zwitterionic intermediate. ^{1}H NMR measurements using 0.1 mol dm^{-3} solutions of substrate show that the displaced ethanethiolate ion may attack ring-carbon atoms of either unreacted substrate or substitution products.

There is current interest in the study of nucleophilic reactivity [1-3] and it has been shown that nucleophiles may be usefully compared in terms of the intrinsic barriers to their reactions.[4] This approach has been used in reactions with protons,[5] with alkenes[6] and with aromatic compounds.[7] In the latter case kinetic studies of σ-adduct formation by nucleophilic addition at unsubstituted ring-positions indicate much lower intrinsic barriers for reaction of sulfur bases than for oxygen bases.[8]

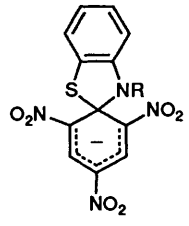
When nucleophilic attack occurs at a substituted ring-position then substitution may result and the accepted mechanism[9] for reaction with amine nucleophiles is shown in Scheme 1. The



Scheme 1

base-catalysed pathway may involve rate-limiting proton transfer from the zwitterionic intermediate to base, or general acid catalysis (by BH^+) of leaving group expulsion from an anionic intermediate in rapid equilibrium with the zwitterion. The latter pathway, the SB-GA mechanism, has been shown to be generally applicable to reactions involving displacement of alkoxy groups by amines in dimethyl sulfoxide (DMSO). Thus Orvik and Bunnett[9] were able to observe in separate steps the formation of anionic intermediates and their acid-catalysed conversion to substitution products. There have however been few kinetic studies of intermolecular displacements of thiolate groups by amines. Bunnett and Bernasconi[10] found that the reaction of 2,4-dinitrophenyl sulfide with piperidine, although not catalysed by piperidine itself, showed mild catalysis by hydroxide, suggesting that conversion of the zwitterionic intermediate to products was rate determining. This is, perhaps, surprising in view of the low energy barrier expected for loss of the thiolate group.[8] Several examples have been reported[3,11] of Smiles rearrangements involving intramolecular displacements of thiolate groups by amines, and the anionic spiro-adducts **1** and **2**, R = Me, Ph have been characterised spectroscopically.[12,13]

Here we report results of kinetic and NMR measurements for reaction of ethyl thiopicrate (ETP) with aliphatic amines in DMSO, and compare them with results for ethyl picrate



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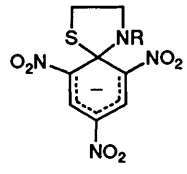

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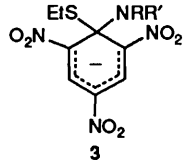
obtained previously.[14] We chose butylamine as an example of a primary amine, and pyrrolidine and piperidine as secondary amines. There is evidence[15,16] for steric and stereochemical problems involving substitutions with piperidine, so that there is a high energy barrier when the piperidino group is twisted either into or from the ring-plane in *ortho*-substituted benzene derivatives.

The kinetic measurements were made with low concentrations (2×10^{-5} mol dm^{-3}) of substrate, and are in accord with rapid attack by amine at an unsubstituted ring-position to give anionic σ-adducts. An interesting feature here is that the rate determining step changes from nucleophilic attack with butylamine to proton transfer with piperidine, with proton transfer being partially rate limiting with pyrrolidine. Attack at the 1-position, with butylamine and pyrrolidine results in substitution of the ethanethiolate group, although adducts of the type **3** are not observable kinetically or spectroscopically. Our results here suggest, in contrast to alkoxy group displacements, that base catalysis reflects rate-limiting proton transfer from the zwitterionic intermediate rather than acid catalysis of leaving group departure.



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NMR measurements were made with relatively high concentrations (0.1 mol dm^{-3}) of substrate and provide evidence that the displaced ethanethiolate group may attack the ring of either unreacted substrate or substitution products.

Table 1 ^{1}H NMR shifts (δ) for neutral species and anionic adducts

Structure	Ring	Ethylthio[a] CH_2	Ethylthio[a] CH_3	NRR′
ETP	9.11	2.93	1.12	—
5 NRR′ = NC_5H_{10}	8.85			3.05, 1.58
5 NRR′ = NC_4H_8	8.84			3.27, 1.95
5 NRR′ = NHBu	8.94			8.80 (NH), 3.03, 1.63, 1.30, 0.86
4 NRR′ = NC_5H_{10}	5.68, 8.45	2.9	1.1	
14 NRR′ = NC_5H_{10}	5.55, 8.45			Not measured
14 NRR′ = NC_4H_8	5.89, 8.35			3.38, 1.92
14 NRR′ = NHBu	5.60, 8.36			(2.6, 2.3),[b] 1.6, 1.2, 0.8
13 NRR′ = NC_5H_{10}	6.09, 8.31	2.6	1.1	Not measured
13 NRR′ = NC_4H_8	6.07, 8.27	2.46	1.14	(3.7, 3.3),[b] 1.92
13 NRR′ = NHBu	6.00, 8.35	2.47	1.12	(2.7, 2.5),[b] 1.6, 1.3, 0.9
11	5.99, 8.31			
10	8.36			
12	8.13	2.83, 3.16	1.07, 1.26	

[a] Coupling J = 7 Hz observed between methylene and methyl hydrogens. [b] Non-equivalent methylene hydrogens, α to nitrogen.

Experimental

Ethyl thiopicrate (1-ethylthio-2,4,6-trinitrobenzene) was prepared[17] by reaction of ethanethiolate ions with picryl chloride in ethanol, m.p. 45 °C (lit.,[17] 45 °C). *N*-Substituted-2,4,6-trinitroanilines were prepared[16] by reaction of the appropriate amine with picryl chloride in methanol. Solvent, amines and amine salts were prepared and purified as previously described.[14,18]

A preparative experiment was carried out involving the reaction of ethyl thiopicrate (0.5 g) in DMSO with a fourfold molar excess of piperidine. The mixture was allowed to stand for 4 h and was then poured onto crushed ice. The yellow-orange precipitate was collected.

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 mean of several separate determinations and are precise to within ±5%. ^{1}H NMR spectra were recorded using a Bruker 250 MHz instrument or a Varian 400 MHz instrument (VXR-400S) with [$^2H_6$]DMSO as solvent. The concentration of parent nitro-compound was 0.1 mol dm^{-3}. Spectra were recorded immediately (within 2 min) of the addition of amines and subsequent changes in the spectrum were monitored. Data for neutral species and anionic adducts are in Table 1. In agreement with previous work[19,20] it was found that adducts formed by addition of ethanethiolate ions at the unsubstituted 3-position of 1-substituted-2,4,6-trinitrobenzenes gave bands at *ca.* δ 6.05 and 8.30 due to ring-hydrogens. The corresponding bands of 3-adducts formed by amine attack were found[21] at *ca.* δ 5.6 and 8.4. The latter bands were broad indicating relatively rapid interconversion of parent molecules and adducts. Because of this separate bands were not identified due to the added amine groups. The methylene hydrogens of ethylthio-groups attached to sp^2-hybridised ring-atoms gave bands at δ 2.9, while those at sp^3 hybridised carbon were shifted upfield to δ 2.5. An interesting feature of the spectrum of the adduct **13**, NRR′ = NC_4H_8 is the observation of two bands at δ 3.3 and 3.7 due to ring-hydrogens α to nitrogen. The non-equivalence of these hydrogens results from the asymmetry introduced by nucleophilic attack at the 3-position and indicates that rotation about the nitrogen to ring-carbon bond in the adduct is slow. Related asymmetry was observed in the methylene groups α to nitrogen in the adducts **13** and **14**, NRR′ = NHBu which gave two multiplets.

Results

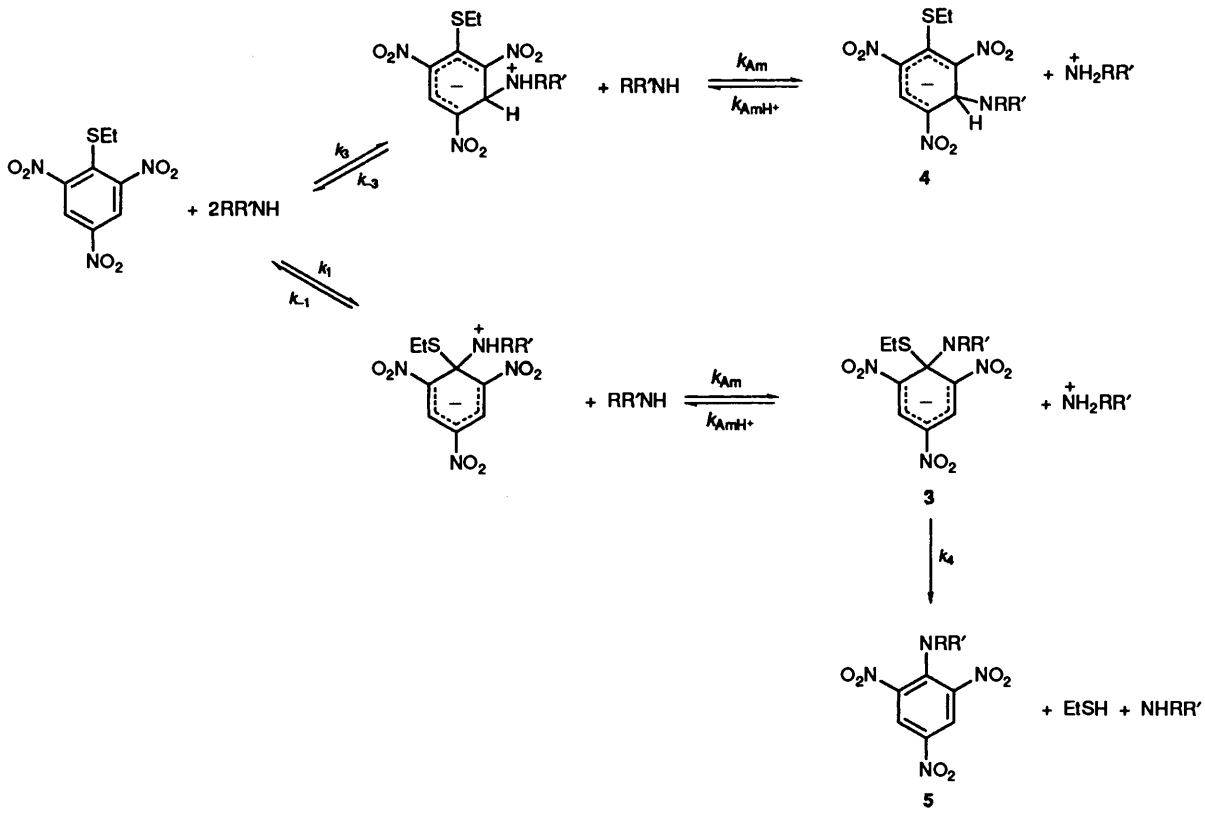
UV–VIS measurements of ETP (*ca.* 10^{-5} mol dm^{-3}) in DMSO containing amines (0.006–0.05 mol dm^{-3}) showed the presence of two well separated processes which are interpreted by Scheme 2. With each amine a very rapid reaction was observed leading to species with λ_{max} 450–460 nm (ε 2 × 10^4 dm^3 mol^{-1} cm^{-1}) and 510–520 nm (shoulder). In the case of piperidine there is NMR evidence that this species is the adduct **4**, NRR′ = NC_5H_{10}. With butylamine and pyrrolidine the initially formed adducts were too transient for NMR measurements. However it is known[1,14,22] that nucleophilic attack at unsubstituted positions of 1-substituted-2,4,6-trinitrobenzenes is considerably faster than at the 1-position. Hence, here too, we attribute the initial process to attack at the 3-position.

The spectra obtained at the completion of the second, slower process indicate that displacement of the ethylthio group has occurred to give *N*-substituted picramide derivatives, **5**. The final spectra obtained with butylamine and with pyrrolidine are identical with those of *N*-butylamino-2,4,6-trinitrobenzene and *N*-pyrrolidino-2,4,6-trinitrobenzene respectively in solutions of the same amine concentrations (see Fig. 1). Independent measurements show that, in fact, the reaction products are in rapid equilibrium with anions derived from them by amine addition and/or loss of a side-chain proton. There was no evidence for the accumulation of spectroscopically observable concentrations of intermediates such as **3** during these reactions. In the case of piperidine the second reaction was inconveniently slow for kinetic measurements.

Kinetic Analysis.—Rate constants for reaction were measured under first-order conditions. For reactions with buffers (amine plus amine salt) the buffer components were in large excess of the ETP concentration, which was 2 × 10^{-5} mol dm^{-3}. For reactions with amines in the absence of added amine salts a sufficient excess of amine was used that >95% conversion into adduct was achieved at equilibrium. Under these conditions,[23] eqn. (1) applies.

$$\ln\left[\frac{A_\infty}{A_\infty - A}\right] = k_{obs} \cdot t \qquad (1)$$

It is assumed that the zwitterionic forms may be treated as steady-state intermediates, so that the general rate expression for reaction at the 3-position to produce adducts **4** is eqn. (2).



Scheme 2

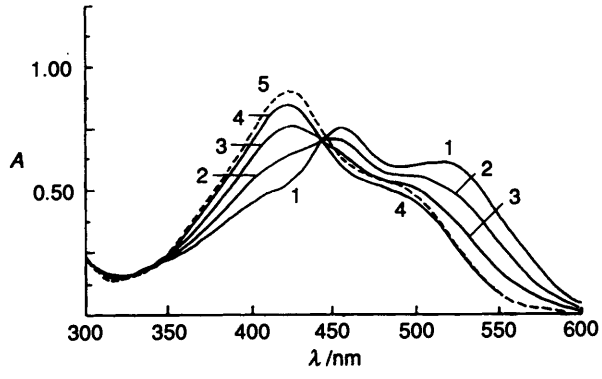


Fig. 1 Visible spectra of ETP (4×10^{-5} mol dm^{-3}) in DMSO containing pyrrolidine (0.05 mol dm^{-3}). The spectra change with time in the sequence 1 ⟶ 4. Spectrum 1 corresponds to the adduct **4**, NRR′ = NC_4H_8. Spectrum 5 is *N*-pyrrolidino-2,4,6-trinitrobenzene (4×10^{-5} mol dm^{-3}) with 0.05 mol dm^{-3} pyrrolidine.

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

The overall equilibrium constant, $K_{c,3}$, for conversion of ETP into adduct **4** is defined by eqn. (3), and is related to rate coefficients by eqn. (4).

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

$$K_{c,3} = \frac{k_3}{k_{-3}} \cdot \frac{k_{Am}}{k_{AmH^+}} \quad (4)$$

The formation of the substitution products **5** may involve (i) rate-determining production of **3** followed by rapid loss of the ethylthio group, or (ii) a rapid equilibrium to give **3** followed by rate-determining loss of the ethylthio group. Taking into account the rapid reversible reaction at the 3-position, the rate expressions for the two possibilities, (i) or (ii), are eqn. (5) and eqn. (6) respectively. In the latter equation $K_{c,1}$ is the equilibrium constant for formation of **3** from ETP.

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])} \cdot \frac{1}{\left(1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}\right)} \quad (5)$$

$$k_{slow} = \frac{k_4 \cdot K_{c,1}[Am]^2}{\left(1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}\right)} \quad (6)$$

It is convenient to define a modified rate coefficient, k^1_{slow}, by eqn. (7), so that eqns. (5) and (6) may be written as eqn. (8) and eqn. (9) respectively.

$$k^1_{slow} = k_{slow}\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right) \quad (7)$$

$$k^1_{slow} = \frac{k_1 \cdot k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \quad (8)$$

$$k^1_{slow} = k_4 K_{c,1}[Am]^2 \quad (9)$$

Reaction with Butylamine.—Data are in Table 2. In the absence of added butylammonium perchlorate values of k_{fast}, relating to formation of the 3-adduct, increase linearly with amine concentration indicating that $k_{Am}[Am] \gg k_{-3}$. We are able to set a limit of $k_{Am}/k_{-3} > 500$ dm^3 mol^{-1}. Eqn. (2) thus reduces to eqn. (10).

$$k_{fast} = k_3[Am] + \frac{k_{-3} \cdot k_{AmH^+}}{k_{Am}} \frac{[AmH^+]}{[Am]} \quad (10)$$

Table 2 Kinetic and equilibrium data for reaction of ETP with butylamine in DMSO at 25 °C

$[BuNH_2]$/mol dm^{-3}	$[BuNH_3ClO_4]$/mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[a]	A[b] (530 nm)	$K_{c,3}$[c]	k_{slow}/s^{-1}	k_{calc}[d]
0.01	—	7.8	8.0	–	—	—	—
0.02	—	15	16	–	—	—	—
0.04	—	31	32	–	—	—	—
0.07	—	60	56	–	—	—	—
0.10	—	80	80	0.025	—	—	—
0.005	0.01	—	—	—	—	0.037	0.039
0.01	0.01		—	0.0031	14	0.069	0.070
0.02	0.01	55	52	0.0068	9	0.112	0.116
0.03	0.01	45	48	0.0106	8	0.142	0.138
0.04	0.01	49	50	0.0138	8	0.150	0.143
0.05	0.01	56	54	0.0179	10	0.124	0.114

[a] Calculated from eqn. (10) with k_3 800 dm^3 mol^{-1} s^{-1} and $k_{-3} \cdot k_{AmH^+}/k_{Am}$ 71 s^{-1}. [b] Absorbance at completion of rapid colour-forming reaction, measured by stopped-flow with 2 mm pathlength cell. [c] Calculated using eqn. (3) in the form $\frac{A}{(0.025 - A)} \cdot \frac{[AmH^+]}{[Am]^2}$. [d] Calculated as $\frac{k_1[Am]}{\left(1 + \frac{A}{0.025 - A}\right)}$ with k_1 8 dm^3 mol^{-1} s^{-1}.

Table 3 Kinetic and equilibrium data for formation of **4**, NRR′ = NC_4H_8 from ETP and pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/mol dm^{-3}	[Pyrrolidinium perchlorate]/mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[a]	A(434 nm)[b]	$K^c_{c,3}$/dm^3 mol^{-1}
0.006	—	12	11	—	—
0.008	—	19	18	—	—
0.010	—	26	26	—	—
0.015	—	51	51	—	—
0.0175	—	61	65	—	—
0.025	—	109	112	—	—
0.030	—	148	147	0.051	—
0.035	—	190	184	0.051	—
0.005	0.01	56	53	0.006	53
0.010	0.01	63	65	0.0172	51
0.015	0.01	83	85	0.0269	50
0.020	0.01	107	110	0.0374	69

[a] Calculated from eqn. (2) with k_3 9000 dm^3 mol^{-1} s^{-1}, k_{Am}/k_{-3} 40 dm^3 mol^{-1} and k_{AmH^+} 5500 dm^3 mol^{-1} s^{-1}. [b] Measured by stopped-flow spectrophotometry with a 2 mm pathlength cell. [c] Calculated as $\frac{A}{(0.051 - A)} \cdot \frac{[AmH^+]}{[Am]^2}$.

The values in Table 2 accord with this equation with k_3 800 dm^3 mol^{-1} s^{-1}, and $k_{-3} \cdot k_{AmH^+}/k_{Am}$ 71 s^{-1}. Combination of these values leads, using eqn. (4), to a value for $K_{c,3}$ of 11 dm^3 mol^{-1} which is in acceptable agreement with that obtained from absorbance measurements at completion of the more rapid reaction.

Values for k_{slow}, the rate constant associated with attack at the 1-position, are also in Table 2. Values of k^1_{slow} (not shown) were calculated from eqn. (7) using the known value of $K_{c,3}$ and are linear in amine concentration. This indicates that the condition $k_{Am}[Am] \gg k_{-1}$ applies, leading to eqn. (11). Values of k_{slow} calculated with a value for k_1 of 8 dm^3 mol^{-1} s^{-1} are in excellent agreement with experimental values.

$$k^1_{slow} = k_1[Am] \quad (11)$$

The results show that in the formation of the 3-adduct **4** attack by amine is rate-determining, and that the proton transfer step is rapid. Also in the nucleophilic substitution the results accord with rate-limiting attack by amine at the 1-position followed by rapid proton transfer and rapid loss of the ethylthio group.

Reaction with Pyrrolidine.—Results for attack at the 3-position leading to **4**, NRR′ = NC_4H_8 are in Table 3. Data obtained in the absence of added pyrrolidinium perchlorate show that the dependence of k_{fast} on amine concentration is between one and two. This indicates that proton transfer is partially rate limiting. Values calculated from eqn. (2) with k_3 9000 dm^3 mol^{-1} s^{-1} and k_{Am}/k_{-3} 40 dm^3 mol^{-1} gave an excellent fit with experimental data. These values, together with a value for k_{AmH^+} of 5500 dm^3 mol^{-1} s^{-1}, also accommodated the data in the presence of 0.01 mol dm^{-3} pyrrolidinium perchlorate. Values of the rate coefficients lead, using eqn. (4), to a value for $K_{c,3}$ of 65 ± 10 dm^3 mol^{-1}. The value obtained from absorbance data is 55 ± 10 dm^3 mol^{-1}.

Rate data for the slower reaction leading to displacement of the ethylthio group are in Table 4. Values of k^1_{slow}, calculated from eqn. (7) with $K_{c,3}$ 60 dm^3 mol^{-1}, show an almost squared dependence on the amine concentration as seen from the final column of Table 4. In fact the values of k^1_{slow} depend strongly on the value of $K_{c,3}$, so that the slight decrease in values of $k^1_{slow}/[Am]^2$ with increasing amine concentration is not experimentally secure. The results show that proton transfer is completely or largely rate determining in the slower reaction.

Reaction with Piperidine.—Results for the rapid reaction producing the 3-adduct **4**, NRR′ = NC_5H_{10} are in Table 5. 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 determining in the formation of **4**. The results allow us to obtain a limit of $k_{Am}/k_{-3} < 3$. With this condition, eqn. (2) simplifies to give eqn. (12) and values calculated with $k_3 \cdot k_{Am}/k_{-3}$ 1.5 ×

Table 4 Kinetic data for reaction of pyrrolidine at the 1-position of ETP in DMSO at 25 °C

[Pyrrolidine]/mol dm^{-3}	[Pyrrolidinium perchlorate]/mol dm^{-3}	$k_{slow}/10^{-3}$ s^{-1}	k^1_{slow}[a]/10^{-3} s^{-1}	$\frac{k^1_{slow}}{[Am]^2}$
0.01	0.01	4.0	6.4	64
0.02	0.01	7.9	27	67
0.03	0.01	8.7	56	62
0.04	0.01	9.1	9.6	60
0.05	0.01	9.4	150	60
0.06	0.01	8.9	200	56

[a] Calculated from eqn. (7) with $K_{c,3}$ 60 dm^3 mol^{-1}

Table 5 Kinetic and equilibrium data for reaction of ETP with piperidine in DMSO at 25 °C

[Piperidine]/mol dm^{-3}	[Piperidinium chloride]/mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[a]	A(434 nm)[b]	$K^c_{c,3}$/dm^3 mol^{-1}
0.010	—	1.68	1.5	—	—
0.015	—	3.26	3.4	—	—
0.020	—	5.9	6.0	—	—
0.025	—	9.5	9.4	—	—
0.030	—	14	14	—	—
0.040	—	24	24	0.068	—
0.050	—	38	38	0.068	—
0.006	0.01	5.4	5.5	0.009	42
0.008	0.01	6.1	6.0	0.014	40
0.010	0.01	6.7	6.5	0.018	36
0.015	0.01	8.7	8.4	0.028	31
0.020	0.01	11.2	11.0	0.043	43
0.025	0.01	16.0	14.4	0.047	36
0.035	0.01	24	23	0.056	38
0.040	0.01	29	29	0.061	—
0.050	0.01	41	42	0.064	—

[a] Calculated from eqn. (12) with $k_3 \cdot k_{Am}/k_{-3}$ 1.5 × 10^4 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 500 dm^3 mol^{-1} s^{-1}. [b] Equilibrium absorbance. [c] Calculated as $\frac{A}{(0.068 - A)} \cdot \frac{[AmH^+]}{[Am]^2}$.

$$k_{fast} = \frac{k_3 \cdot k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad (12)$$

10^4 dm^6 mol^{-2} s^{-1} and with k_{AmH^+} 500 dm^3 mol^{-1} s^{-1} give excellent agreement with experimental results. Combination of these values gives a value for $K_{c,3}$ of 30 dm^3 mol^{-1} which is in acceptable agreement with that, 38 dm^3 mol^{-1}, obtained from absorbance data.

There is some evidence [14] that the nature of the counter-anion may affect values of rate and equilibrium constants in reactions of this type by association with the substituted ammonium ions. However using piperidinium perchlorate values for $K_{c,3}$ 37 dm^3 mol^{-1} and k_{AmH^+} 440 dm^3 mol^{-1} s^{-1} were obtained which were within experimental error of those found using the chloride salt.

Discussion

When amine is in large excess of ETP the results are in accord with Scheme 2, in which rapid reversible attack at the 3-position is followed by slower displacement of the ethylthio group.

Reaction at Unsubstituted Ring Positions.—The kinetic results show, interestingly, that the rate-determining step for formation of adducts **4** changes from attack by the amine in the case of butylamine, to proton transfer in the case of piperidine with pyrrolidine showing intermediate behaviour. Values of rate and equilibrium constants are summarised in Table 6, where they are compared with data for 2,4,6-trinitrophenetole (TNP) and for trinitrobenzene (TNB). For each amine, values of k_3, the rate constant for attack by amine, and $K_{c,3}$ the equilibrium constant for adduct formation, are nearly two orders of magnitude smaller for ETP (and for TNP) than for TNB. This may be attributed to the steric effect of the 1-substituent which results in twisting of the nitro groups at the 2- and 6-positions from the ring-plane, thus reducing their electron-withdrawing capability.[24] The effect is slightly larger for ETP than for TNP although the difference is not large. Nevertheless values of k_{AmH^+} are, for a given amine, independent of the nature of the nitro-compound. This reflects the fact that reaction is, in each case, occurring at an unsubstituted ring-position, so that steric effects *at the reaction centre* will be similar for the three substrates. It is also interesting that values of the ratio k_{Am}/k_{-3} do not vary much as the nature of the nitro-compound is changed. It has been argued previously [23,25] 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. This ratio is not expected [23,25] to vary greatly with the nature of the substrate or the amine. It follows that since, for a given amine, values of k_{AmH^+} and of k_{Am}/k_{-3} are invariant then values of k_{-3} must also be invariant. Hence the transition state for nucleophilic attack by amine at the 3-position is likely to be product-like.

When comparing data for the three amines it must be noted that attack is occurring at an unsubstituted ring position so there is little steric hindrance to nucleophilic attack. Thus values of k_3 which increase in the order butylamine < piperidine, pyrrolidine reflect the relative basicities of the amines. Values of $K_{c,3}$ the equilibrium constant for adduct formation are in the same order. The most important variation on changing the amine is in the rate constant for proton transfer. Thus the value of k_{AmH^+} decreases by an order of magnitude from butylamine to pyrrolidine and by another order of magnitude from pyrrolidine to piperidine. These changes probably indicate increasing steric hindrance to approach of the reagents for the proton

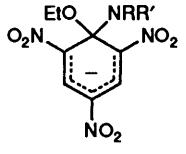
Table 6 Comparison of kinetic and equilibrium data for reaction at unsubstituted ring positions of ethyl thiopicrate (ETP), 2,4,6-trinitrophenetole (TNP) and 1,3,5-trinitrobenzene (TNB)[a]

	k_3/dm^3 mol^{-1} s^{-1}			$K_{c,3}$/dm^3 mol^{-1}			$\left(\frac{k_{-3}\cdot k_{AmH^+}}{k_{Am}}\right)$/s^{-1}		
Amine	ETP	TNP	TNB	ETP	TNP	TNB	ETP	TNP	TNB
Butylamine	800	3 200	45 000	11	15	1 000	71	210	45
Pyrrolidine	9 000	—	7.5 × 10^5	60	—	3 500	150	—	210
Piperidine	>5 000	>9 000	>2 × 10^5	35	27	2 140	>170	>320	>900
	k_{AmH^+}/dm^3 mol^{-1} s^{-1}			$\left(\frac{k_{Am}}{k_{-3}}\right)$/dm^3 mol^{-1}					
Amine	ETP	TNP	TNB	ETP	TNP	TNB			
Butylamine	>3.6 × 10^4	>4.2 × 10^4	6 × 10^4	>500	>200	1 200			
Pyrrolidine	5 500	—	3 000	40	—	14			
Piperidine	500	1 600	280	<3	<5	<10			

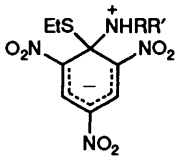
[a] Data have not been statistically corrected. Results for TNP are from ref. 14, and for TNB from refs. 18 and 23.

transfer step from substituted ammonium ion to **4**. This factor will similarly influence the values of k_{Am} for proton transfer from the zwitterionic intermediates to amine and will be the major effect in reducing the value of k_{Am}/k_{-3} in the series butylamine, pyrrolidine, piperidine. Hence the change in the nature of the rate-determining step from attack by amine with butylamine to proton transfer with piperidine is a consequence of the slower rate of proton transfer in the latter case.

Reaction at the 1-*Position.*—Whereas the rate and equilibrium constants for reaction at the 3-position of ETP have similar values to those for reaction with TNP there are major differences for reaction at the 1-position. In the reaction of TNP with amine intermediates of structure **6** are observable by UV–VIS and NMR spectroscopy[14] and the kinetics of their formation and decay may be determined. The corresponding intermediates **3** are not observed during reactions of ETP.



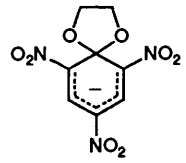
6



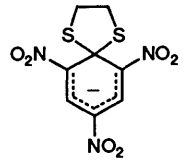
7

In the reaction of ETP with butylamine the substitution of the ethylthio group shows an accurately first-order dependence on the amine concentration indicating that nucleophilic attack at the 1-position is rate determining. The value for k_1 is 8 dm^3 mol^{-1} s^{-1} which is considerably less than the value for k_3 (800 dm^3 mol^{-1} s^{-1}) and is also much smaller than the corresponding value for k_1 (250 dm^3 mol^{-1} s^{-1}) for reaction of butylamine with TNP. This decrease may reflect the greater steric bulk of the ethylthio group compared to the ethoxy group which reduces the rate constant for nucleophilic attack at the 1-position. An additional factor may be the lower electronegativity of sulfur relative to oxygen which will decrease the positive charge at the 1-position of ETP relative to TNP. The fact that attack by butylamine at the 1-position is rate determining shows that, if substitution occurs by the mechanism of Scheme 2, then the proton transfer step and loss of the ethylthio group are rapid processes. The latter is in accord with the low intrinsic barrier expected for loss of the sulfur base.[8] A further possibility (the k_2 step in Scheme 1) is that the zwitterion **7** decomposes spontaneously to products without forming the anion **3**. We think this unlikely since this step would involve proton transfer to sulfur which is known to be a poor hydrogen-bond acceptor[26] and to have relatively low affinity for protons.[27]

The kinetic data for reaction of ETP with pyrrolidine show that in the substitution reaction proton transfer is rate limiting, or largely rate limiting. One possibility is that proton transfer from the zwitterionic intermediate **7**, RR′ = $(CH_2)_4$ to pyrrolidine is the slow step. Treatment of the data in Table 4 using eqn. (8) leads to values K_1k_{Am} 60 dm^6 mol^2 s^{-1} and k_{Am}/k_{-1} < 5 dm^3 mol^{-1}. This is smaller than the corresponding value of k_{Am}/k_{-3} (40 dm^3 mol^{-1}), but this is to be expected since there is likely to be greater steric hindrance to proton transfer in the zwitterion formed by attack at the 1-position so that k_{Am} will be reduced. The second possibility is that the rate-limiting step is k_4 involving proton transfer from pyrrolidinium ions to the anionic adduct **3**. In this case the data in Table 4 and use of eqn. (9) lead to a value for $k_4K_{c,1}$ of 60 dm^6 mol^2 s^{-1}. If k_4 were the rate-determining step then it might be expected that the intermediate **3** should be observed during the reaction, and the failure to observe this species would appear to rule out this possibility. However if the 1,1-adduct **3** were appreciably less thermodynamically stable than its 1,3-isomer **4**, $K_{c,3} \gg K_{c,1}$, then the failure to observe it would be explained. Usually 1,1-adducts have considerably higher thermodynamic stabilities than their 1,3-isomers, due in part to the relief in steric strain as the 1-substituent is rotated from the ring plane on adduct formation.[22] However it might be argued that adducts **3** containing two bulky groups at the 1-position are sterically disfavoured. Nevertheless related adducts **1** and **2**, albeit with spiro-structures, have been observed spectroscopically. Further if k_4 were rate limiting then the slow step would involve proton transfer from a pyrrolidinium cation to the sulfur of **3**. This seems unlikely in view of the low proton basicity of sulfur. For example, although ring-opening of the spiro-adduct **8** is acid catalysed, no catalysis is observed in the opening of the dithiolane complex **9**.

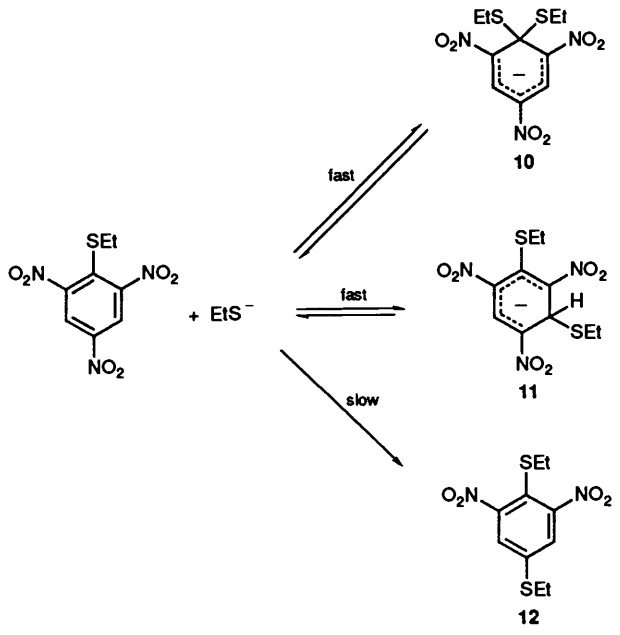


8

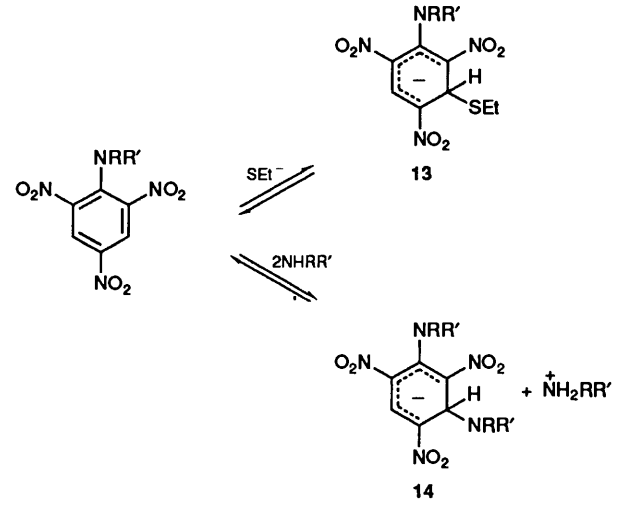


9

We think it more likely that the rate-determining step is proton transfer from the zwitterion **7** to amine, followed by rapid expulsion of ethanethiolate ion from **3**. This would accord with the low energy barrier expected for loss of the sulfur base.[8]



Scheme 3



Scheme 4

Replacement of the ethylthio group by piperidine was considerably slower than by pyrrolidine and kinetic measurements were not made. NMR measurements show that substitution by piperidine does occur although there is no build up in concentration of the intermediate **3**, NRR′ = NC_5H_{10}. We will briefly comment on why this reaction is so slow. Again there are two possibilities. The first is that proton transfer from zwitterion to amine, the k_{Am} step, is rate limiting. The value of k_{Am} is expected to be considerably slower for the reaction of piperidine owing to its increased steric requirements compared to pyrrolidine. For example the data for reaction at the 3-position indicate that proton transfer is an order of magnitude slower for the reaction involving piperdine than for that with pyrrolidine. Hence this provides a reasonable explanation for the slowness of the piperidine substitution. The second possibility is rate-limiting loss of the ethylthio group catalysed by piperidinium ions, the k_4 step. There is evidence[15,16] that piperidine has greater steric requirements than pyrrolidine for processes involving motion of the amino group into the ring-plane. Hence a lower value of k_4 would be expected for the piperidine reaction. However the non-observation of the intermediate **3** means that this latter explanation will only hold if the adduct **3** has considerably lower thermodynamic stability than its isomer **4**. On balance we favour the former explanation.

^{1}H *NMR Measurements.*—Spectra were recorded with ETP (0.1 mol dm^{-3}) and with amines in the concentration range (0.05–0.6 mol dm^{-3}). Displacement of the ethylthio group resulted, eqn. (13), in the formation of a sulfur nucleophile which

$$EtSH + Am \rightleftharpoons EtS^- + AmH^+ \qquad (13)$$

could effectively compete with the amine. Products were observed of attack of ethanethiolate ions on both the unreacted substrate, ETP, and on the substitution products, the *N*-substituted-2,4,6-trinitroanilines. Data are in Table 1.

The reaction of ETP with excess piperidine resulted in the rapid formation of the 3-adduct **4**, NRR′ = NC_5H_{10} with ring-proton bands at δ 8.45 and 5.68. At no stage in the reaction were bands observed attributable to the 1-adduct **3**, NRR′ = NC_5H_{10}. With time the bands due to the 3-adduct decreased in intensity and new bands were observed attributable to attack of ethanethiolate ions on ETP, Scheme 3, and also to attack of both ethanethiolate and piperidine on the reaction product, *N*-piperidino-2,4,6-trinitrobenzene, Scheme 4.

The system ETP plus ethanethiolate ions has been examined previously[20] and comparison of the NMR bands observed in the present system with those reported shows the transient formation of **10**, δ 8.36 and **11**, δ 5.99 and 8.31 and the irreversible formation of **12**, δ 8.13. The displacement of the 4-nitro-group in ETP by ethanethiolate ions is an interesting reaction which has been reported by Pietra and co-workers.[28] Bands due to the ring hydrogens of **13** at δ 6.09 and 8.31 and **14** at δ 5.55 and 8.45 increased in intensity during the reaction and eventually the spectrum consisted of these together with bands due to **12**. In agreement with these results the NMR spectrum of the solid formed on acidification of a preparative-scale experiment consisted of bands due to **12** and to *N*-piperidino-2,4,6-trinitrobenzene, **5**.

NMR spectra of ETP and pyrrolidine or butylamine indicated the rapid displacement of the ethylthio group, although species of structure **3** were not observed. At completion the major species were **12** with **13**, NRR′ = NC_4H_{10} from pyrrolidine or **13**, NRR′ = NHBu from butylamine.

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