Kinetics and Mechanism of the Aminolysis of 2,4-Dinitrophenyl and 2,4,6-Trinitrophenyl Thiolacetates

Enrique A. Castro * and Carmen Ureta
Facultad de Quimica, Pontificia Universidad Católica de Chile, Casilla 6177, Santiago, Chile

The reactions of the title substrates with alicyclic secondary amines and pyridines are subject to a kinetic study in water [25 °C, ionic strength 0.2 mol dm^{-3} (KCl)]. The Brønsted-type plots obtained for all reaction series are non-linear, indicating the existence of a tetrahedral intermediate ($T^{\pm}$) in the reaction pathway and a change in the rate-limiting step involving formation and breakdown of $T^{\pm}$. Calculated curves based on the above hypothesis fit the experimental data well. From estimations of both the pK_a of the $T^{\pm}$ formed in the reactions with secondary amines and the rate of arylthiolate ion expulsion from $T^{\pm}$ (k_2) it is deduced that the rate coefficient for proton transfer from $T^{\pm}$ to a base is lower than k_2. The centre of the Brønsted-type curvature for the reactions of the dinitro derivative lies at $pK_a = pK_a^{\circ} = 8.9$ (alicyclic amines) and 6.6 (pyridines). For 2,4,6-trinitrophenyl thiolacetate, $pK_a^{\circ} = 7.8$ (alicyclic amines) and 4.9 (pyridines). These figures show that pyridines leave $T^{\pm}$ at a rate (k_{-1}) slower than isobasic secondary amines (the k_2 value is independent of the amine nature). From estimations of k_{-1} and k_2 based on the aminolysis of other aryl thiolacetates the pK_a° values of both reaction series are predicted. These show reasonable agreement with the experimental values. Comparison of these reactions with the aminolyses of aryl acetates indicates that the 'push' provided by ArO (to expel a given amine) from an analogous oxy-$T^{\pm}$ is slightly stronger than that exerted by an isobasic ArS group in $T^{\pm}$.

Although the mechanism of the aminolysis of oxyesters has been extensively studied,[1,2] little is known on that for the aminolysis of thiol esters in water. Most of the latter reactions have been investigated in aprotic solvents,[3] and only a few of them in aqueous solution.[4,5]

Following our kinetic studies on the aminolysis (alicyclic amines) of phenyl and *p*-nitrophenyl thiolacetates in water,[6] we now report a kinetic investigation on the reactions of the title substrates with secondary alicyclic amines and pyridines in aqueous solution. The aim is to complete the previous study and shed more light on the mechanism of the aminolysis of thiolesters. We have included pyridines in this work in order to compare leaving abilities between these amines and secondary amines from a putative tetrahedral intermediate in the reaction.

Experimental

Materials.—The alicyclic amines[6] and pyridines[7] were purified prior to use as previously reported.

S-2,4-Dinitrophenyl thioacetate (DNPTA) was prepared from acetyl chloride and 2,4-dinitrobenzenethiol (DNBSH) in pyridine, according to literature.[8] Previously, DNBSH was obtained by modification of a reported procedure,[9] whereby the solid residue was dissolved in cold aqueous 2 mol dm^{-3} NaOH, instead of refluxing in 4 mol dm^{-3} aqueous NaOH. DNPTA was identified by ^1H NMR analysis; m.p. 80 °C.

S-2,4,6-Trinitrophenyl thioacetate (TNPTA) was synthesized by a modification of the reported procedure.[10] An ammonium salt of 2,4,6-trinitrobenzenethiolate ion was added to cold acetyl chloride, the mixture stirred for 15 min, and then poured on ice–water. A yellow compound precipitated with m.p. 102–103 °C (from chloroform–60–80 °C light petroleum). Identification was confirmed by IR and NMR analysis.

Determination of pK_a.—Those of the conjugate acids of the alicyclic amines under the kinetic conditions: *T* 25.0 ± 0.1 °C, aqueous solution, *I* 0.2 mol dm^{-3} (maintained with KCl), have been previously reported.[6] The pK_a of the pyridinium ions were measured under the above conditions, either spectrophotometrically at λ 260–277 nm with a Perkin-Elmer Lambda 3 instrument, or potentiometrically with a Radiometer titration apparatus previously described.[7c] The first method was employed for the four less basic pyridines (with citrate buffers) and the two more basic one (borate buffers), whereas the potentiometric method was used for the rest of the pyridines.

The pK_a of DNBSH was measured spectrophotometrically at λ 400 nm under the conditions above in 0.02 mol dm^{-3} citrate buffers, $[DNBSH]_{tot} = 4 \times 10^{-5}$ mol dm^{-3}. The pK_a value obtained was 3.4 ± 0.1.

Kinetic Measurements.—2,4-Dinitrophenyl and 2,4,6-trinitrobenzenethiolate ion release was followed spectrophotometrically at λ 400 and 390 nm, respectively, in all the reactions studied, under the above experimental conditions using a Perkin-Elmer Lambda 3 spectrophotometer. In all cases the reactions were started by the addition (6–15 mm^3) of a substrate stock solution in acetonitrile into the kinetic solutions (3 cm^3) in 1 cm cells placed in the thermostatted (*T* 25.0 ± 0.1 °C) compartment of the instrument. The initial substrate concentration was 3–5 × 10^{-5} mol dm^{-3} and acetonitrile never exceeded 0.4% in the kinetic solutions.

External buffers, such as citrate, acetate, phosphate and borate, were employed in most of the kinetic runs. These were not used in the reactions of DNPTA with piperazinium and 1-(β-hydroxyethyl)piperazinium cations and pyridine, nor in the reactions of TNPTA with 1-(β-hydroxyethyl)piperazinium cation and 4-cyanopyridine, where the pH values were within the buffering capacity of the amines. At least three pH values were used for the reactions of each amine. The pH measurements were carried out as above.[7c]

In all cases, under amine excess, pseudo-first-order rate coefficients (k_{obs}) were found. The experimental conditions of the kinetics and the values of k_{obs} are shown in Table 1.

Product Studies.—Appearance followed by disappearance of a species was detected spectrophotometrically at λ 310 nm, during the reaction of DNPTA with 4-(dimethylamino)pyridine under the conditions described in Table 1. This intermediate is

Table 1 Experimental conditions and k_{obs} for the aminolysis of DNPTA and TNPTA[a]

Amine	$[N]_{tot}/10^{-2}$ mol dm^{-3}[b]	pH	$k_{obs}/10^{-3}$ s^{-1}	Number of runs
S-2,4-Dinitrophenyl thioacetate (DNPTA)				
Piperidine[c]	0.03–1.21	8.7–9.3	4.1–39.6	24
Piperazine[d]	0.08–3.00	6.7–7.3	3.4–80.4	31
1-(β-Hydroxyethyl)-piperazine[b]	0.10–2.04	6.7–7.5	2.0–47.6	31
Morpholine[d]	0.07–1.38	6.8–7.5	3.5–78.6	24
1-Formylpiperazine[d]	0.05–1.20	6.6–7.3	2.8–42.2	24
Piperazinium ion	0.24–6.00	5.2–5.8	2.6–37.0	23
(1-β-Hydroxyethyl)-piperazinium ion	0.85–8.46	4.2–4.6	0.6–4.1	23
4-(Dimethylamino)-pyridine[d]	0.09–5.40	6.7–7.3	0.4–42.5	25
4-Aminopyridine[d]	0.15–3.00	6.7–7.3	2.2–44.1	24
3,4-Dimethylpyridine[e]	0.07–1.40	4.7–5.3	1.0–19.5	24
4-Methylpyridine[e]	0.07–1.48	4.8–5.4	1.6–29.8	24
3-Methylpyridine[e]	0.05–0.75	5.2–6.0	2.4–55.0	32
Pyridine	0.04–1.60	5.1–5.7	1.9–31.6	23
Nicotinamide[a]	0.50–10.00	4.8–5.4	1.7–27.6	24
3-Chloropyridine[e]	1.60–16.00	4.8–5.4	2.1–17.9	24
4-Cyanopyridine[e]	2.00–20.00	4.7–5.4	0.3–3.4	23
3-Cyanopyridine[e]	3.20–32.00	4.8–5.4	0.2–1.9	24
S-2,4,6-Trinitrophenyl thioacetate (TNPTA)				
Piperidine[f]	0.06–0.60	8.0–8.6	3.3–62.3	15
Piperazine[g]	0.03–0.30	6.6–7.5	13.2–201.3	16
1-(β-Hydroxyethyl)-piperazine[g]	0.03–0.30	6.7–7.5	2.4–86.1	23
Morpholine[g]	0.04–1.00	6.3–6.9	5.8–88.2	15
1-Formylpiperazine[h]	0.04–0.95	5.7–6.3	4.6–48.1	15
1-(β-Hydroxyethyl)-piperazinium ion	0.70–7.00	4.2–4.6	5.3–66.0	15
Piperazinium ion[i]	0.04–1.00	4.9–5.5	6.2–71.3	14
4-(Dimethylamino)-pyridine[d]	0.13–2.50	6.7–7.3	5.2–85.0	15
4-Aminopyridine[d]	0.08–1.50	6.7–7.3	3.7–70.7	23
3,4-Dimethylpyridine[j]	0.07–2.80	4.3–4.9	6.3–76.5	24
4-Methylpyridine[j]	0.14–2.80	4.3–4.9	10.0–143.6	15
3-Methylpyridine[j]	0.06–1.10	4.3–4.9	8.6–139.8	15
Pyridine[j]	0.06–0.74	4.3–4.9	7.7–109.4	15
Nicotamide[j]	0.13–5.00	2.7–3.3	6.3–71.3	15
3-Chloropyridine[e]	0.10–4.00	2.7–3.3	3.8–67.0	16
4-Cyanopyridine	0.75–12.50	1.9–2.5	8.0–69.8	15
3-Cyanopyridine[e]	1.60–16.00	2.7–3.3	7.1–82.9	15

[a] In aqueous solution, at 25 °C, ionic strength 0.2 mol dm^{-3} (KCl). [b] Total amine concentration (protonated plus free-amine forms). [c] In the presence of 0.005 mol dm^{-3} borate buffer. [d] In the presence of 0.005 mol dm^{-3} phosphate buffer. [e] In the presence of 0.005 mol dm^{-3} citrate buffer. [f] In the presence of 0.02 mol dm^{-3} borate buffer. [g] In the presence of 0.02 mol dm^{-3} phosphate buffer. [h] In the presence of 0.02 mol dm^{-3} citrate buffer. [i] In the presence of 0.01 mol dm^{-3} citrate buffer. [j] In the presence of 0.005 mol dm^{-3} acetate buffer.

presumably 1-acetyl-(4-dimethylamino)pyridinium ion, which has also been observed spectrophotometrically at similar wavelengths in other reactions.[11]

The 2,4-dinitrobenzenethiolate ion was identified as one of the final products in the above reaction by comparison of the UV–VIS spectrum (λ 320–500 nm) after completion of the reaction with that of an authentic sample of the product, under the same conditions.

Results

The kinetic law found for all the reactions studied in this work, except those of the two substrates with piperazine and 1-(β-hydroxyethyl)piperazine, is shown in eqns. (1) and (2) where

Table 2 Values of pK_a of the conjugate acids of the amines and rate coefficients obtained in the aminolysis of DNPTA and TNPTA[a]

Amine	pK_a	k_N/dm^3 mol^{-1} s^{-1} DNPTA	k_N/dm^3 mol^{-1} s^{-1} TNPTA
Piperidine	11.24 ± 0.04	1080 ± 80	6720 ± 450
Piperazine	9.94 ± 0.04	1060 ± 200	5680 ± 1 400
1-(β-Hydroxyethyl)-piperazine[b]	9.38 ± 0.03	364 ± 27	2000 ± 100
Morpholine	8.78 ± 0.03	230 ± 20	1650 ± 180
1-Formylpiperazine	7.98 ± 0.03	50 ± 3	610 ± 50
Piperazinium ion	5.81 ± 0.03	2.4 ± 0.1	44 ± 3
1-(β-Hydroxylethyl)-piperazinium ion[c]	5.9 ± 0.2[d]	2.3 ± 0.2	43 ± 4
4-(Dimethylamino)-pyridine	9.87 ± 0.03	576 ± 26	2460 ± 220
4-Aminopyridine	9.37 ± 0.03	333 ± 25	1180 ± 230
3,4-Dimethyl pyridine	6.77 ± 0.03	85 ± 5	660 ± 50
4-Methylpyridine	6.25 ± 0.03	29 ± 1	310 ± 30
3-Methylpyridine	5.86 ± 0.03	17 ± 1	250 ± 20
Pyridine	5.37 ± 0.03	6.0 ± 0.4	100 ± 10
Nicotinamide	3.43 ± 0.06	0.26 ± 0.03	10 ± 1
3-Chloropyridine	2.97 ± 0.06	0.11 ± 0.01	4.8 ± 0.4
4-Cyanopyridine	2.2 ± 0.1	(1.5 ± 0.2) × 10^{-2}	1.4 ± 0.1
3-Cyanopyridine	1.6 ± 0.2	(5.7 ± 0.7) × 10^{-3}	0.43 ± 0.03

[a] Both pK_a and k_N were obtained in aqueous solution at 25.0 ± 0.1 °C, *I* 0.2 mol dm^{-3} (KCl). The errors shown are standard deviations. [b] This is compound **1** of Scheme 1. [c] This is compound **2** of Scheme 1. [d] This is pK_{42} of Scheme 1.

$$\frac{d[ArS^-]}{dt} = k_{obs}[substrate] \quad (1)$$

$$k_{obs} = k_0 + k_N F_N [N]_{tot} \quad (2)$$

ArS^- is 2,4-dinitrophenyl or 2,4,6-trinitrobenzenethiolate, k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrate, respectively, F_N is the free-amine fraction and $[N]_{tot}$ is the concentration of total amine (free-amine plus its conjugate acid).

Plots of k_{obs} *vs.* $[N]_{tot}$ at constant F_N (pH) values were linear for the above reactions. The k_N values were obtained from the slopes of these plots, and found to be pH-independent. The k_N values for these reactions are shown in Table 2. The value of k_0 (intercept of the above plot) was either negligible or small compared to the second term of eqn. (2), and the most reliable value for k_0 was obtained in the reaction of DNPTA with 3-cyanopyridine, in the presence of citrate buffer (5 × 10^{-3} mol dm^{-3}), at the conditions shown in Table 1 Under these conditions, $k_0 = (1.2 \pm 0.2) \times 10^{-4}$ s^{-1}.

The rate law exhibited by the reactions of the substrates with piperazine can be described by eqns. (1) and (3), where NH and N represent piperazinium monocation and piperazine, respectively. Eqn. (3) depicts the simultaneous attack on the

$$k_{obs} = k_0 + k_{NH}[NH] + k_N[N] \quad (3)$$

substrate by the above two species. This took place due to the low pH values used (Table 1) relative to the pK_a of piperazinium ion. It was not possible to measure the kinetics of these reactions at higher pH values as these were too fast. Replacing $[NH] = F_{NH}[NH]_{tot}$ and $[N] = F_N[N]_{tot}$ (where F_{NH} is the monocation fraction) in eqn. (3), gives eqn. (4), where N_{tot} also includes the

$$k_{obs} = k_0 + (k_{NH}F_{NH} + k_N F_N)[N]_{tot} \quad (4)$$

dication species. The values of F_{NH} and F_N can be calculated from $F_{NH} = F_N[H^+]/K_{NH}$ and eqn. (5), where K_{NH2} and K_{NH} are

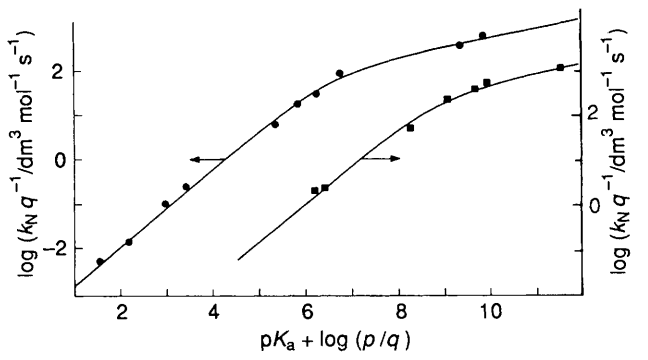


Fig. 1 Brønsted-type plots (statistically corrected) obtained in the reactions of DNPTA with pyridines (●) and alicyclic amines (■) in water at 25 °C, *I* 0.2 mol dm^{-3} (KCl). The points are experimental and the curves calculated (see text).

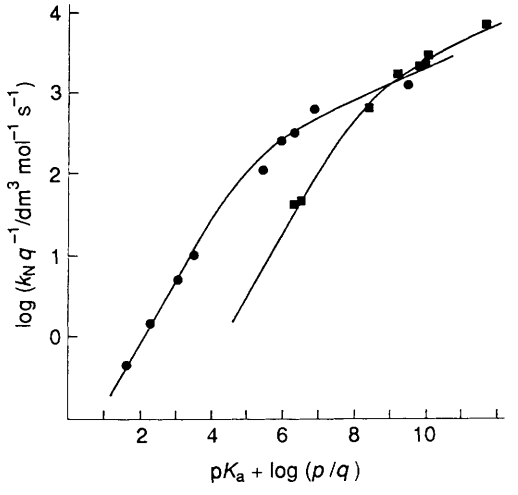


Fig. 2 Brønsted-type plots obtained in the reactions of TNPTA with secondary alicyclic amines (■), and pyridines (●). The data for the alicyclic amines are statistically corrected. The points are experimental and the lines calculated (see text).

$$F_N = (1 + [H^+]/K_{NH} + [H^+]^2/K_{NH}K_{NH2})^{-1} \quad (5)$$

the ionization constants of the dication and monocation species, respectively.

Plots of eqn. (4) at constant pH were linear. Dividing the slopes (k_{Nobs}) by F_{NH}, gives eqn. (6). For the reactions of each

$$\frac{k_{Nobs}}{F_{NH}} = k_{NH} + k_N \frac{F_N}{F_{NH}} \quad (6)$$

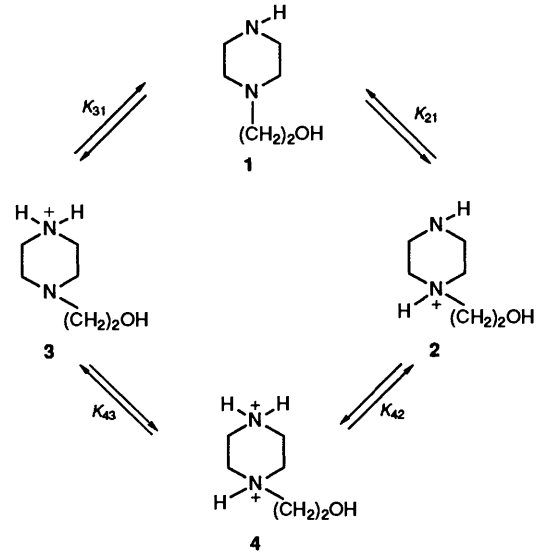
substrate a plot of the left-hand side of this equation against F_N/F_{NH} was linear, with the intercept k_{NH} = 2.3 ± 0.4 dm^3 mol^{-1} s^{-1} (DNPTA) and 48 ± 5 dm^3 mol^{-1} s^{-1} (TNPTA), and the slope k_N = 1 060 ± 200 dm^3 mol^{-1} s^{-1} (DNPTA) and 5 680 ± 1 400 dm^3 mol^{-1} s^{-1} (TNPTA).

In order to get a more reliable value of k_{NH}, the above reactions were also studied at pH values similar to the pK_a of piperazinium dication (see Table 1). Under these conditions $k_N F_N \ll k_{NH}F_{NH}$, and k_{NH} was easily obtained from plots of eqn. (4) at constant F_{NH}, giving values of 2.4 ± 0.1 dm^3 mol^{-1} s^{-1} (DNPTA) and 44 ± 3 dm^3 mol^{-1} s^{-1} (TNPTA), which satisfactorily agree with ones found at higher pH values.

The reactions of DNPTA and TNPTA with 1-(β-hydroxyethyl)piperazine obeys the kinetic law given by eqns. (1) and (7),

$$k_{obs} = k_0 + (k_{N1}F_1 + k_{N2}F_2)[N]_{tot} \quad (7)$$

where the subindices 1 and 2 refer to the species shown in Scheme 1, and k_N and F are the rate coefficient for aminolysis and the amine fraction, respectively.



Scheme 1

The values of the ionization constants K_{31} and K_{43} of Scheme 1 were determined potentiometrically at the kinetic conditions, giving pK_{31} = 9.38 ± 0.03 and pK_{43} = 4.56 ± 0.03. A value of 8.04 for pK_{21} was calculated as stated in the Appendix. The pK_{42} value of Scheme 1 can be deduced from the other pK_a of the scheme: pK_{42} = pK_{31} + pK_{43} − pK_{21} = 5.90.*

The molar fractions (*F*) of the species shown in Scheme 1 are given by eqns. (8)–(11), where the subindices refer to those species.

$$F_1 = (1 + [H^+]/K_{31} + [H^+]/K_{21} + [H^+]^2/K_{31}K_{43})^{-1} \quad (8)$$

$$F_2 = F_1[H^+]/K_{21} \quad (9)$$

$$F_3 = (1 + [H^+]/K_{43} + K_{31}/[H^+] + K_{31}/K_{21})^{-1} \quad (10)$$

$$F_4 = F_3[H^+]/K_{43} \quad (11)$$

Plots of eqn. (7) at constant pH were linear. Dividing the slope ($k_{N\,obs}$) by F_2, gives: $k_{N\,obs}/F_2 = k_{N2} + k_{N1}F_1/F_2$. A plot of $k_{N\,obs}/F_2$ *vs.* F_1/F_2 gave a straight line, with k_{N2} and k_{N1} as intercept and slope, respectively. A more reliable value of k_{N2} was obtained at lower pH (4.2–4.6) whereby the reaction of **1** was negligible compared with that of **2**. The k_N values for the reactions of the two substrates with **1** and **2** are shown in Table 2.

We believe that eqn. (7) describes the simultaneous aminolysis of the substrates by **1** and **2** of Scheme 1, since (*i*) both points fit satisfactorily on the Brønsted-type curves (Figs. 1 and 2), and (*ii*) the attack of **3** on the substrate (instead of **2**) can be excluded for steric reasons. Nevertheless, in order to test the latter hypothesis we studied the reaction of DNPTA with *N*-(β-hydroxyethyl)morpholine. The k_N value obtained was *ca.* 0.01 dm^3 mol^{-1} s^{-1}, which is extremely low for an amine of pK_a 7.18. This strongly suggests that **3** is not participating in the aminolysis above.

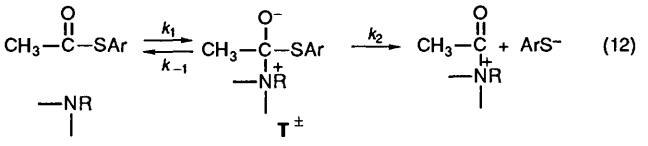
The pK_a and k_N values obtained in this work are shown in Table 2. Some of these values for the reactions of alicyclic amines were statistically corrected,[12] with p = 2 (except piperazinium dication with p = 4) and q = 2 (piperazine only), before plotting the Brønsted-type equation. There was no

* Strictly, $10^{-4.56} = K_{42} + K_{43}$ and $10^{9.38} = K_{21}^{-1} + K_{31}^{-1}$.[13] Since $K_{21} = 10^{-8.04}$ and $K_{42} = K_{31}K_{43}/K_{21}$, it follows that p$K_{42}$ remains the same (5.90), and pK_{31} and pK_{43} have a negligible variation.

correction for the reactions with pyridines ($p = q = 1$). The Brønsted-type plots for the reactions of DNPTA and TNPTA with these two types of amines are shown in Figs. 1 and 2, respectively.

Discussion

The curves in Figs. 1 and 2 were calculated by means of a semiempirical equation[6,7,14,15] based on the presence of a tetrahedral intermediate ($T^{\pm}$) and a change in the rate-determining step from k_1 to k_2 [eqn. (12)] as the basicity of the amine increases. In eqn. (12), –NR represents either a pyridine

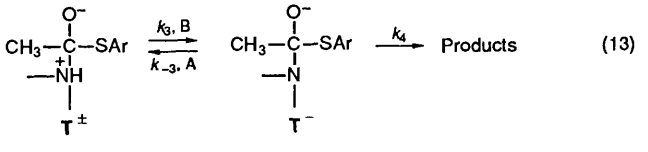


(12)

or a secondary alicyclic amine (R = H). The curves were fitted with the following semiempirical parameters: (*i*) Reactions of DNPTA: $\beta_1 = 0.2$ and $\beta_2 = 0.85$ for both series of amines, log $k_N^\circ = 2.2$ and $pK_a^\circ = 8.9$ for the alicyclic amines, and log $k_N^\circ = 1.7$ and $pK_a^\circ = 6.6$ for the pyridines. (*ii*) Reactions of TNPTA: $\beta_1 = 0.20$ and $\beta_2 = 0.80$ for both series, log $k_N^\circ = 2.7$ and $pK_a^\circ = 7.8$ for the alicyclic amines, and log $k_N^\circ = 2.0$ and $pK_a^\circ = 4.9$ for the pyridines. β_1 and β_2 are the slopes at high and low amine basicity, respectively, pK_a° is the pK_a value at the curvature centre [where $k_{-1} = k_2$ in eqn. (12)] and k_N° is the value of k_N corresponding to pK_a°. The errors involved in the above parameters are 0.05 in the β values, and 0.2 in the values of log k_N° and pK_a°.

The magnitudes of β_1 and β_2 are in accord (within experimental error) with those obtained in the aminolysis of *S*-*p*-nitrophenyl thioacetate[6] and other reactive aryl acetates and carbonates,[1,2,7,14,15] confirming that they should not change significantly with reactivity.[14–16]

In this paper we claim that the mechanism of the reactions of the substrates with both series of amines can be described completely by eqn. (12), *i.e.*, there are no complications such as acid–base catalysis for the reactions of the secondary amines. If a reaction pathway of that kind competing with k_2 were present [eqn. (13), where A and B are any acid and base, respectively]



(13)

either a pH-dependence on k_N or a kinetics second-order in amine would be observed. Since neither occurred, paths such as eqn. (13) can be ruled out for the reactions of the secondary amines with DNPTA and TNPTA.

The above conclusion can be confirmed by estimation of the values of the pK_a of $T^{\pm}$ and k_3, k_{-3}, k_4 and k_2. These estimations (see Appendix) yield $k_4 \gg k_{-3}$ [A], *i.e.*, the k_3 step is rate determining in eqn. (13), and $k_2 \gg k_3$ [B].

Therefore, it is clear that for all the reactions under the present study the pathway described by eqn. (13) is kinetically unimportant compared to the k_2 step of eqn. (12), and therefore the breaks exhibited by the Brønsted-type plots obtained in the present work (Figs. 1 and 2) should be due to the change in the rate-limiting steps discussed above in relation to the mechanism of eqn. (12).

Internal proton transfer within the intermediates $T^{\pm}$ to form a neutral tetrahedral intermediate and protonation of the former to yield a cationic intermediate have rates slower than expulsion of $DNPS^-$ or $TNPS^-$ from $T^{\pm}$ under the experimental conditions of the reactions, as shown by calculations similar to those carried out in the reactions of secondary alicyclic amines with 2,4-dinitrophenyl acetate.[17]

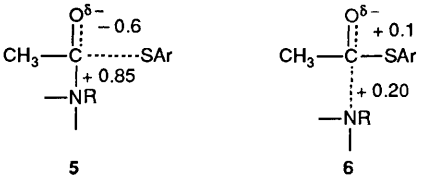
The fact that neither kinetics second-order in amine nor pH-dependence on the true k_N (not $k_{N\,obs}$) were found confirms that proton transfers concerning the zwitterionic tetrahedral intermediate $T^{\pm}$ are not kinetically significant and the mechanism of the reactions studied in this work is that described in eqn. (12).

The values of k_2 for $TNPS^-$ and $DNPS^-$ expulsion can be assessed from the estimated value of *p*-nitrobenzenethiolate ion expulsion from the zwitterionic tetrahedral intermediate formed in the aminolysis (secondary alicyclic amines) of *S*-*p*-nitrophenyl thioacetate (*ca.* 1×10^9 s^{-1}),[6] and assuming a sensitivity of log k_2 to the leaving ArS^- basicity of $\beta_{1g} = -0.3$.*[18] From these data, eqn. (14) can be deduced for ArS^- expulsion from $T^{\pm}$ of

$$\log k_2 = 10.4 - 0.3\, pK_a\,(1g) \qquad (14)$$

eqn. (12) (–NR is any amine), where pK_a (1g) is the pK_a of ArSH. It is noteworthy that k_2 is independent of the amine nature and basicity since the amine moiety of $T^{\pm}$ cannot exert a 'push' to expel ArS^-.[14] From eqn. (14) it follows that the rate of expulsion of $DNPS^-$ and $TNPS^-$ from $T^{\pm}$ are $k_2 = 2.4 \times 10^9$ s^{-1} and 1.0×10^{10} s^{-1}, respectively [pK_a (1g) = 3.4 and 1.4, respectively]. The rate of expulsion of a secondary alicyclic amine from $T^{\pm}$ (k_{-1}) can be determined if the sensitivities of log k_{-1} to the amine (β_N) and arylthiolate ion (β_{1g}) basicities are known.

The slope of the Brønsted-type plots shown in Fig. 1 (DNPTA reactions) at low and high amine basicities are $\beta_2 = 0.85$ and $\beta_1 = 0.20$, respectively, which means that there is a charge development on the nitrogen atom (relative to that of the equilibrium protonation) of +0.85 in the transition state for the second step **5** and +0.20 in that for the first step **6**, for both reaction series. Assuming that k_2 is amine-independent an effictive charge of +0.85 can be assigned to the amine nitrogen



atom of $T^{\pm}$.[14] The value of β_N for k_{-1} is therefore 0.20–0.85 = −0.65. This β_N value is constant in going from Ar = phenyl to 2,4-dinitrophenyl but for 2,4,6-trinitrophenyl $\beta_N = -0.60$, since $\beta_2 = 0.80$ (Fig. 2).

The Brønsted-type plots (not shown) of log k_N against the basicity of ArS^- for piperazinium ion and 1-formylpiperazine (this work and ref. 6) are linear with slopes $\beta_{1g} = -1.0$. For these reactions expulsion of ArS^- from $T^{\pm}$ is rate determining.[6] The corresponding plot for the reactions of piperidine with TNPTA, DNPTA and *p*-nitrophenyl thiolacetate, where the rate-determining step is formation of $T^{\pm}$ from reactants,[6] shows β_{1g} *ca.* −0.3.† Since an effective charge of +0.4 on the sulphur

* Based on the rates of expulsion of ArS^- from $MeCH(O^-)SAr$,[18] and assuming that this value of β_{1g} does not change on substitution of an amine for H.

† In fact, for these reactions the plot log k_N *vs.* pK_a (1g) exhibits a slope $\beta_{1g} = -0.5$ (only 3 points); nevertheless, the point for phenylthiolacetate also falls on the same straight line. Since for the latter reaction expulsion of phenylthiolate ion from $T^{\pm}$ is rate determining,[6] we believe that the correlation of the latter reaction is fortuitous, due to experimental error. Therefore, β_{1g} for the reactions of piperidine with the three most reactive esters should be lower than −0.5, and we tentatively assume $\beta_{1g} = -0.3$.

atom of MeCOSAr has been determined,[19] the corresponding charge on **5** should be 0.4–1.0 = −0.6 and on **6**, 0.4–0.3 = +0.1,[14,19] as indicated in these structures. Since $\beta_{1g} = -0.3$ for k_2 (see above) the effective charge on the sulfur atom of $T^{\pm}$ is −0.6 − (−0.3) = −0.3. Therefore, β_{1g} for k_{-1} should be + 0.1 −(−0.3) = +0.4.

The effective charges determined for $T^{\pm}$, **5** and **6** are rough estimates [except perhaps those of +0.85 on the N atoms of $T^{\pm}$ and **5**, and −0.6 on the S atom of **5**] and more data is needed either to confirm or correct these charges. With the values of β_N and β_{1g} for k_{-1}, and the $pK_a°$ and k_2 values found in this work for the reactions of DNPTA with alicyclic amines, eqn. (15) can be

$$\log k_{-1} = 13.8 - 0.65\ pK_a\ (N) + 0.4\ pK_a\ (1g) \quad (15)$$

deduced for expulsion of a secondary alicyclic amine from $T^{\pm}$.[17] This equation should apply from Ar = phenyl to 2,4-dinitrophenyl, but extension of its validity to the trinitro derivative requires $\beta_N = -0.60$ instead of −0.65 (see above).

For the reactions of *S*-phenyl and *S*-*p*-nitrophenyl thioacetates[6] and DNPTA with pyridines β_N for k_{-1} is −0.65, the same value as that for secondary alicyclic amines (for TNPTA $\beta_N = -0.60$ for both amine series). The β_{1g} value for k_{-1} is not known for the reactions of pyridines, nevertheless it is reasonable to assume the same value as for secondary amines since β_{1g} for k_{-1} is independent of the amine nature in the aminolysis of aryl acetates.[1,14,17] With the β_N and β_{1g} values for k_{-1}, the $pK_a°$ value obtained in the pyridinolysis of DNPTA and

$$\log k_{-1} = 12.3 - 0.65\ pK_a\ (N) + 0.4\ pK_a\ (1g) \quad (16)$$

k_2, one gets eqn. (16) for the rate of expulsion of pyridines from $T^{\pm}$. Again, this equation should be corrected with $\beta_N = -0.60$ when extended to TNPTA reactions. It is noteworthy that β_N and β_{1g} for k_{-1} in the present reactions, are the same as those found in the aminolysis of aryl acetates,[14] whereas β_{1g} for k_2 is different from that ($\beta = -0.5$) for the oxyesters.[14,17]

The reactions of *S*-*p*-nitrophenyl thioacetate with secondary alicyclic amines can be helpful to test the validity of eqns. (14) and (15). For pK_a (1g) = 4.6 (pK_a of *p*-nitrophenylthiol) these equations give $pK_a°$ (N) = 10.2*, which satisfactorily agrees with the experimental $pK_a° = 10.5$.[6] For the reactions of TNPTA with the above amines the equations predict $pK_a° = 7.3$ [pK_a (1g) = 1.4]; the experimental value is $pK_a° = 7.8$ (this work), in fair agreement with the predicted value considering the errors involved in the experimental $pK_a°$ and in the coefficients of the equations. For the reactions of the same amines with phenyl thiolacetate [pK_a (1g) = 6.5] eqn. (14) and (15) predict a $pK_a° = 12.2$, which is consistent with the fact that a linear Brønsted-type plot, up to pK_a (N) = 11.5, was obtained for these reactions.[6]

Eqn. (16) can only be tested for the pyridinolysis of TNPTA (with $\beta_N = -0.6$) since there is no data on the pyridinolysis of *S*-phenyl and *S*-*p*-nitrophenyl thioacetates. From eqns. (14) and (16) a $pK_a°$ value of 4.8 is deduced; the experimental value is $pK_a° = 4.9$ (this work). Comparison of eqns. (15) and (16) shows that pyridines are worse leaving groups from $T^{\pm}$ than alicyclic amines of the same basicity, k_{-1} being *ca.* 30 times larger for the latter amines. This result is similar to that found in the aminolysis of 2,4-dinitrophenyl acetate (pyridines and secondary alicyclic amines)[17] and *p*-nitrophenyl phenyl carbonate.[14] The order of leaving abilities of isobasic amines from the tetrahedral intermediate formed in the latter reactions was found to be quinuclidines > pyridines > imidazoles.[14] Also aliphatic amines are expelled much faster than isobasic imidazoles from phthalimidium addition compounds.[20]

The fact that (hypothetical) pyridines of basicities 6.6 and 4.9 and secondary amines of basicities 8.9 and 7.8 leave the corresponding tetrahedral intermediates $T^{\pm}$ as fast as 2,4-dinitro and 2,4,6-trinitrophenylthiolate ions (of basicities 3.4 and 1.4, respectively) shows that amines are much better leaving groups from $T^{\pm}$ than arylthiolate ions of equal basicity. The same conclusion was reached in the aminolysis of *S*-*p*-nitrophenyl and *S*-phenyl thioacetates.[6] Quantification of the k_{-1}/k_2 ratio [eqn. (12)] for isobasic species can be achieved through eqns. (14)–16). For the reactions of DNPTA, pK_a (N) = pK_a (1g) = 3.4, the results are $k_{-1}/k_2 = 3.7 \times 10^3$ for the secondary alicyclic amine and 120 for the pyridine. Similar ratio values are obtained for the TNPTA reactions. In the aminolysis of aryl acetates and carbonates it has been found that amines are also expelled much faster than isobasic aryloxide ions from a tetrahedral intermediate.[2,7d,14,17,20] It is not clear that the leaving abilities of amines are greater than those of isobasic arenethiolate ions regardless of the species from which they depart. Pyridine was found to leave from $X–CH_2CHSO_2OR$ (X is the leaving group) 10 times faster than benzenethiolate ion,[21] but the former is 1 pK_a unit less basic than the latter.

Comparison of eqns. (15) and (16) with the corresponding eqns. for amine expulsion from the oxyanalogue of $T^{\pm}$,[17] show that a given amine is expelled slightly faster (*ca.* 4 times) from the oxy compound than from a thioanalogue tetrahedral intermediate $T^{\pm}$ possessing an isobasic ArS group. This is consistent with the findings of Hupe and Jencks in that the 'push' provided by RS in the anionic tetrahedral intermediate formed in the reactions of thiolanions with aryl acetates is less than by an isobasic R′O group in the same intermediate.[19]

Appendix

The value of pK_{21} was calculated in the following way: the pK_a of morpholinium and *N*-(β-hydroxyethyl)morpholinium ions were measured potentiometrically under the reaction conditions, and showed the values 8.78 ± 0.03 and 7.18 ± 0.03, respectively. There is, therefore, a pK_a decrease of 1.6 units when replacing H by $(CH_2)_2OH$ at the N atom of morpholinium ion. Applying the same difference to piperazinium ion (pK_a 9.94 ± 0.04, determined experimentally) and taking into account a statistical correction (morpholine has only one basic site whereas piperazine has two),[12] one finds $pK_{21} = 9.94 - 0.3 - 1.6 = 8.04$.

The pK_a of $T^{\pm}$ in eqn. (13) can be estimated as follows: the pK_a of the zwitterionic tetrahedral intermediate formed in the reactions of *p*-nitrophenyl thioacetate with a secondary alicyclic amine has been estimated, by following Jenck's procedure,[22] as 0.5 pK_a unit less than that of the parent aminium ion.[6] The σ_I value for the 2,4-dinitrophenylthio group (DNPS) is not known but it can be determined by extrapolation of a plot of σ_I (ArO) *vs.* σ_I (ArS), following Guthrie's method,[23] and using the σ_I values: 0.53,[23] 0.47[23] and 0.39[24] for 2,4-dinitro, *p*-nitro and unsubstituted phenoxy groups, respectively, and 0.35[25,26] and 0.30[24] for *p*-nitro and unsubstituted phenylthio groups, respectively. The mentioned extrapolation gives σ_I(DNPS) = 0.39. Substitution of *p*-nitrophenylthio by DNPS in the intermediate above, further lowers its pK_a by $\Delta pK_a = 7.3$ (0.39–0.35) = 0.3 unit;[6] therefore the pK_a of $T^{\pm}$ in eqn. (13) with ArS = DNPS can be estimated as 0.8 unit below that of the parent aminium ion.

It is not possible to obtain σ_I for the 2,4,6-trinitrophenylthio group (TNPS) in the same way as σ_I (DNPS) was obtained, since σ_I (TNPO) is not known. Nevertheless, the former value could in principle be found by extrapolation of the linear pK_a (ArSH) *vs.* σ_I (ArS) plot for the three substituents mentioned

* This is the pK_a (N) value at which $k_{-1} = k_2$, *i.e.*, at which eqns. (14) and (15) are equal.

above. Unfortunately, the pK_a of TNBSH is not known and could not be obtained experimentally due to decomposition problems. Nevertheless it can be estimated from extrapolation of a pK_a (ArSH) *vs.* pK_a (ArOH) plot, using the experimental values at 25 °C for Ar = phenyl, *p*-nitrophenyl and 2,4-dinitrophenyl,[6,13] and the pK_a of 2,4,6-trinitrophenol.[26] This procedure gives pK_a (TNBSH) = 1.4. With this value, the extrapolation of the pK_a (ArS) *vs.* σ_I(ArS) plot yields σ_I (TNPS) = 0.44.

The pK_a of $T^{\pm}$ in eqn. (13) for ArS = TNPS can be deduced from that for ArS = DNPS. The pK_a lowering is in this case: $\Delta pK_a = 7.3\,(0.44 - 0.39) = 0.4$, and therefore the pK_a of $T^{\pm}$ for the trinitro derivative is 1.2 pK_a units smaller than that of the parent aminium ion. A similar calculation based on the pK_a of $T^{\pm}$ and σ_I for the *p*-nitro derivative gives the same pK_a of $T^{\pm}$ for the trinitro species.

With the pK_a values of the addition intermediates $T^{\pm}$, the values of k_3 and k_{-3} of eqn. (13) can be assessed. The most favourable proton transfer from $T^{\pm}$ to a base B, under the reactions conditions, is that taking place in the reactions of TNPTA with piperazinium ion, where citrate buffer was used to maintain the pH. In this case, the pK_a of $T^{\pm}$ is 5.81 − 1.2 = 4.6, and since piperazinium ion and the two main forms of the citrate bases (the pK_a values concerned are 4.8 and 6.4),[13] are more basic than the intermediate T^- of eqn. (13), it follows that the proton transfers to these bases are all thermodynamically favourable, and we can assume $k_3 = 10^{10}$ $dm^3\ mol^{-1}\ s^{-1}$.[27] Considering the concentrations of the bases involved (Table 1) it follows that $k_3[B]$ is *ca.* $10^8\ s^{-1}$ (this includes the sum of all the rates of proton transfer). Likewise, it can be shown[27] that the rate of protonation of T^- by A (thermodynamically unfavourable) is much smaller than the rate of $TNPS^-$ expulsion from T^-, *i.e.*, $k_{-3}[A] \ll k_4$. The value of k_4 should be larger than that of k_2 of eqn. (12) (k_2 is *ca.* 10^{10} s^{-1} for $TNPS^-$ expulsion, see text) in view of the 'push' provided by the amino moiety in T^- to expel $TNPS^-$ which is not possible in $T^{\pm}$.

Similar calculations concerning the rate coefficients involved in eqn. (13) for different A, B, $T^{\pm}$ and T^- show that $k_{-3}[A] \ll k_4$; therefore in the above eqn. $k_3[B]$ is rate determining. On the other hand estimation of k_2 for $DNBS^-$ expulsion (see text) yields $k_2 \gg k_3[B]$.

Acknowledgements

We thank FONDECYT (Project No. 443/89) for financial assistance to this work.

References

1 S. J. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.
2 A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7018.
3 N. M. Oleinik, L. M. Litvinenko, L. P. Kurchenko, S. E. Terekhova and Z. P. Gelbina, *Zh. Org. Khim.*, 1976, **12**, 2374; F. Dutka, T. Komives and A. F. Marton, *Magy. Kem. Foly*, 1976, **82**, 465; T. Komives, A. F. Marton and F. Dutka, *Z. Naturforsch. B*, 1975, **30**, 138.
4 R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, 1969, **91**, 737; R. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, 1969, **91**, 2358.
5 P. Campbell and B. A. Lapinskas, *J. Am. Chem. Soc.*, 1977, **99**, 5378.
6 E. A. Castro and C. Ureta, *J. Org. Chem.*, 1989, **54**, 2153.
7 (*a*) P. M. Bond, E. A. Castro and R. B. Moodie, *J. Chem. Soc., Perkin Trans. 2*, 1976, 68; (*b*) E. A. Castro and C. L. Santander, *J. Org. Chem.*, 1985, **50**, 3595; (*c*) E. A. Castro and G. B. Steinfort, *J. Chem. Soc., Perkin Trans. 2*, 1983, 453; (*d*) E. A. Castro and F. J. Gil, *J. Am. Chem. Soc.*, 1977, **99**, 7611.
8 A. Frankfater and F. J. Kazdy, *J. Am. Chem. Soc.*, 1971, **93**, 4039.
9 N. Kharasch and A. J. Parker, *J. Org. Chem.*, 1959, **24**, 1029.
10 G. P. Sharmin, V. V. Nurgatin and L. A. Trutneva, *Zh. Org. Khim.*, 1972, **8**, 1490.
11 E. Guibé-Jampel, G. Le Corre and M. Wakselman, *Tetrahedron Lett.*, 1979, 1157; C. Castro and E. A. Castro, *J. Org. Chem.*, 1981, **46**, 2939.
12 R. P. Bell, *The Proton in Chemistry*, Methuen, London, 1959, p. 159.
13 A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, 2nd edn, Chapman and Hall, London, 1971, p. 79.
14 M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963, 6970.
15 D. J. Palling and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 4869.
16 C. D. Johnson and K. Schofield, *J. Am. Chem. Soc.*, 1973, **95**, 270.
17 E. A. Castro and C. Ureta, *J. Org. Chem.*, 1990, **55**, 1676.
18 H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 7931.
19 D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 451.
20 N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 499.
21 J. F. King, J. H. Hillhouse, T. M. Lauriston and K. C. Khemani, *Can. J. Chem.*, 1988, **66**, 1109.
22 J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, 1973, **95**, 5637; J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 1436.
23 J. P. Guthrie and D. C. Pike, *Can. J. Chem.*, 1987, **65**, 1951.
24 M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.
25 M. Charton, *Prog. Phys. Org. Chem.*, 1987, **16**, 287.
26 D. D. Perrin, B. Dempsey and E. P. Serjeant, pK_a *Prediction for Organic Acids and Bases*, Chapman and Hall, London, 1981.
27 M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 1.

Paper 0/03361H
Received 24*th July* 1990
Accepted 31*st August* 1990