Structure–Reactivity Correlations in the Aminolysis of Phenyl and *p*-Nitrophenyl Thiolacetates

Enrique A. Castro* and Carmen Ureta

Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 6177, Santiago, Chile

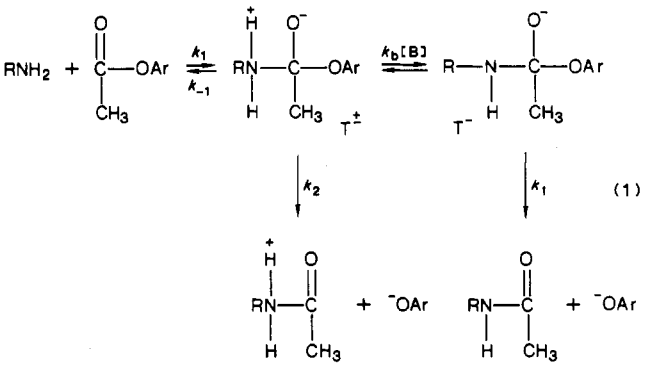
Received August 23, 1988

Second-order rate constants (k_N) for the nucleophilic reactions of piperidine, morpholine, piperazine, and N-substituted piperazines with the title substrates are reported in water, at 25 °C, ionic strength 0.2 M (maintained with KCl). The Brønsted-type plot obtained for the aminolysis of phenyl thiolacetate is linear while that for the *p*-nitrophenyl derivative (NPTA) is curved, with the center of curvature at $pK_a = 10.5$ (pK_a^0). According to these results the most likely mechanism involves a zwitterionic tetrahedral intermediate ($T^{\pm}$), for which decomposition to products is the rate-limiting step for all the reactions, except that of NPTA with piperidine. For this reaction the formation of $T^{\pm}$ is rate determining. A semiempirical equation based on the above hypothesis accounts for the Brønsted-type curve obtained in the aminolysis of NPTA. Estimation of the microscopic rate constants involved, in a possible more general reaction scheme and evaluation of the pK_a's of $T^{\pm}$ indicate that expulsion of the leaving group of the substrate from $T^{\pm}$ is faster than deprotonation of $T^{\pm}$ by a base, precluding therefore the formation of an anionic tetrahedral intermediate. The fact that $pK_a^0 = 10.5$ for the NPTA reactions means that an (hypothetical) amine of $pK_a = 10.5$ leaves $T^{\pm}$ as readily as *p*-nitrothiophenoxide ion ($pK_a = 4.6$). From these and other data it is calculated that the nucleofugality from $T^{\pm}$ of an amine of $pK_a = 4.6$ is ca. 3×10^4 times larger than that of *p*-nitrothiophenoxide ion. The estimated pK_a^0 values for the aminolysis of (hypothetical) aryl acetates with leaving groups of $pK_a = 4.6$ and 6.5 (the same pK_a as thiophenol) are $pK_a^0 = 8.0$ and 9.0, respectively, which gives nucleofugality ratios (a given amine/aryl oxide ion) from the oxy $T^{\pm}$ smaller than those from the corresponding sulfur $T^{\pm}$. It is claimed that expulsion of ArS^- from $T^{\pm}$ is only slightly slower than that of an isobasic ArO^- from the oxy $T^{\pm}$. Therefore, the above results indicate that the "push" provided by ArS in $T^{\pm}$ to expel a given amine is much stronger than that exerted by an isobasic ArO in the oxy $T^{\pm}$. Activation parameters are reported for the reactions of the title substrates with piperidine, piperazine, and *N*-formylpiperazine.

Introduction

The aminolysis of aryl acetates has been the subject of numerous kinetic studies. Structure–reactivity correlations, specially Brønsted plots have been used in these reactions as mechanistic criteria.[1-4] Most of these reactions are nucleophilic and in some of them curved Brønsted-type plots have been found, which have been explained by the existence of at least one tetrahedral intermediate in the reaction path and a change in the rate-determining step. For instance, with substrates possessing good nucleofuges the change mentioned is from the k_2 to the k_1 step as the amine becomes more basic (eq 1).[3,4] For less reactive substrates $T^{\pm}$ is less unstable and $k_b[B] \gg k_2$ (B is any base). Therefore, if B is RNH_2, second-order rate constants in amine are found when the k_b step is rate determining.[3]

Obviously, the reaction scheme is much simpler than that depicted by eq 1 when the nucleophile is a tertiary amine. The interpretation of the curved Brønsted-type plots is in this case straightfoward since only $T^{\pm}$ is involved as intermediate. In these reactions the influence of the nature of the substrate's nucleofuge and nonleaving group on the nucleofugalities of amines and aryl oxides from $T^{\pm}$



has been extensively studied.[4-6]

In spite of the great deal of information available on the aminolysis of oxyesters, little is known on the aminolysis of thiolesters. Some reports on the latter reactions include intramolecular as well as intermolecular aminolysis of alkyl thiolacetates and thiolformates,[7] and aminolysis of aryl thiolacetates in aprotic solvents.[8] Also, the aminolysis of *p*-nitrophenyl thionbenzoate has been kinetically studied.[9]

(1) (a) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622. (b) Bruice, T. C.; Hegarty, A. F.; Felton, S. M.; Donzel, A.; Kundu, N. G. *J. Am. Chem. Soc.* **1970**, *92*, 1370. (c) Butler, A. R.; Robertson, I. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 660. (d) Singh, T. D.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 3867. (e) Marton, A. F.; Komives, T.; Dutka, F. *Radiochem. Radioanal. Lett.* **1978**, *32*, 1. (f) Deady, L. W.; Finlayson, W. L. *Aust. J. Chem.* **1980**, *33*, 2441. (g) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580. (h) Deady, L. W.; Finlayson, W. L. *Aust. J. Chem.* **1983**, *36*, 1951. (i) Kovach, I. M.; Belz, M.; Larson, M.; Rousy, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7360.

(2) (a) Fishbein, J. C.; Baum, H.; Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 5790. (b) Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 159. (c) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans 2* **1976**, 68.

(3) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.

(4) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.

(5) (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (b) Gresser, M. J.; Jencks, W. P. *Ibid.* **1977**, *99*, 6970.

(6) (a) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611. (b) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453. (c) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595.

(7) Barnett, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 4199. Blackburn, G. M. *J. Chem. Soc., Chem. Commun.* **1970**, 249. Tao, N. S.; Scheithauer, S.; Mayer, P. *Z. Chem.* **1972**, *12*, 133.

(8) Oleinik, N. M.; Litvinenko, L. M.; Kurchenko, L. P.; Terekhova, S. E.; Gelbina, Z. P. *Zh. Org. Khim.* **1976**, *12*, 2374; *Chem. Abstr.* **1977**, *86*, 88982*f*. Dadali, V. A.; Pachenko, B. V.; Litvinenko, L. M. *Zh. Org. Khim.* **1980**, *16*, 1725; *Chem. Abstr.* **1981**, *94*, 3402*j*. Oleinik, N. M.; Kurchenko, L. P.; Sadovskii, Y. S.; Litvinenko, L. M. *Zh. Org. Khim.* **1977**, *13*, 2118; *Chem. Abstr.* **1978**, *88*, 50090*s*. Dutka, F.; Komives, T.; Marton, A. F. *Magyar Kem. Foly.* **1976**, *82*, 465. Komives, T.; Marton, A. F.; Dutka, F. *Z. Naturforsh* **1975**, *30B*, 138. Oleinik, N. M.; Litvinenko, L. M.; Kurchenko, L. P.; Padchenko, N. D.; Geller, G. K. *Ukr. Khim. Zh.* **1975**, *41*, 918; *Chem. Abstr.* **1976**, *84*, 4050*y*.

(9) Campbell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378.

0022-3263/89/1954-2153$01.50/0

In order to shed some light to the mechanism of the aminolysis of thiolesters we have chosen to start our investigations with the reactions of secondary amines with phenyl and *p*-nitrophenyl thiolacetates in aqueous solution. The aim is to compare this mechanism with the one described for aryl acetates (eq 1).[3]

Experimental Section

Materials. 1-Formyl- and 1-(β-hydroxyethyl)piperazines, from Sigma, were purified by distillation at reduced pressure. Morpholine, from Merck, and piperidine, from Fluka, were distilled. Piperazine, from Sigma, was purified by sublimation.

Phenyl and *p*-nitrophenyl thiolacetates (PTA and NPTA) were prepared from acetyl chloride and the corresponding thiophenol in pyridine, according to a reported procedure.[10] Identification was achieved by NMR analysis. NPTA melted at 82–83 °C (lit.[10] mp 82.3–82.6 °C).

Kinetic Methods. The reactions of piperidine with PTA were followed either potentiometrically (Radiometer pH-stat) or spectrophotometrically (Pye Unicam SP 1800). All the other reactions were studied by means of a Perkin-Elmer Lambda 3 or a Pye-Unicam SP-1800 spectrophotometers, following the release of the corresponding thiophenol and/or its conjugate base at 260–270 nm (thiophenol) and 412 nm (*p*-nitrothiophenol). The reactions were started by addition of a solution (7–10 μL) of the substrate in acetonitrile into the kinetic solutions (3 mL) contained in 1-cm cells placed in the thermostated compartment (±0.1 °C) of the spectrophotometer. The acetonitrile content of the kinetic solutions never exceeded 0.3%. The initial concentration of the substrate was (2–7) × 10^{-5} M, and the amine was at least in 10-fold excess over the substrate. The experimental conditions of the reactions are described in Table I.

Pseudo-first-order rate constants (k_{obsd}) were found throughout by means of the "infinity" method. The runs showing correlation coefficients worse than 0.999 were discarded. The values of k_{obsd} obtained in all the reactions are shown in Table I.

Determination of pK_a. These were carried out for thiophenol, *p*-nitrothiophenol, and the conjugate acids of the amines in the same experimental conditions of the kinetic measurements. Potentiometric as well as spectrophotometric methods were employed. Details of determinations of pK_a have been previously reported.[6b,11] Wavelengths used in the spectrophotometric methods were 218 (piperidinium ion), 220 (piperazinium ion), 260 (thiophenol), and 412 nm (*p*-nitrothiophenol). Borate, acetate, and phosphate were used as buffers. The pK_a values obtained are shown in Table II.

Product Studies. The reactions of phenyl thiolacetate with 1-formylpiperazine and piperidine gave 1-formyl-4-acetylpiperazine and 1-acetylpiperidine, respectively, and also thiophenoxide ion as final products. The analysis was carried out by UV–vis scanning of the kinetic samples after completion of the reactions followed by comparison of these spectra with those of authentic samples of the products under identical experimental conditions. For the reaction with piperidine (pH 9) λ_{max} was 206 nm for the amide and 260 nm for thiophenoxide ion; for that with 1-formylpiperazine (pH 8) λ_{max} of the corresponding amide was 218 nm. The latter reaction was carried out at a much lower amine concentration than those used in the kinetic runs in order to blank out the amine satisfactorily. Under this condition the reaction is very slow, and it was found that thiophenoxide ion slowly decomposes to diphenyl disulfide,[12,13] as indicated by a slow absorbance decrease at 260 nm. This slow oxidation of thiophenoxide ion was not a problem in the kinetic runs since these were much faster (amine concentration was much larger) and no decrease of absorbance at 260 nm was observed within the reaction time (good pseudo-first-order kinetics were found by following thiophenoxide ion formation).

(10) Frankfater, A.; Kazdy, F. J. *J. Am. Chem. Soc.* **1971**, *93*, 4039.
(11) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971.
(12) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(13) Oswald, A. A.; Wallace, T. J. In *The Chemistry of Organic Sulfur Compounds*, 1st ed.; Kharasch, N., Meyers, C. Y., Eds.; Pergamon: New York, 1966; Vol. 2, p 205. Ohno, A.; Oae, S. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; p 156.

Table I. Experimental Conditions and k_{obsd} for the Aminolysis of Phenyl and *p*-Nitrophenyl Thiolacetates in Water[a]

amine	10^2[N]$_{tot}$,[b] M	F_N[c]	10^3k_{obsd}, s^{-1}	no. of runs
	Phenyl Thiolacetate (PTA)			
piperidine[d]	1.5–15.0	0.004	3.0–22.3	10
	0.8–7.5	0.008	2.3–17.7	7
	0.4–3.8	0.016	2.3–18.8	7
at 15.0 °C	1.0–10.0	0.016	2.7–25.6	7
at 35.0 °C	0.7–6.8	0.016	5.6–49.0	8
at 45.0 °C	0.7–6.1	0.015	5.7–51.4	7
piperazine	0.4–3.8	0.334	4.2–48.9	9
	0.4–3.8	0.500	6.4–64.3	8
	0.2–1.9	0.671	4.8–49.1	9
at 15.0 °C	0.4–3.6	0.500	2.8–33.4	8
at 35.0 °C	0.1–0.9	0.500	1.9–25.2	8
at 45.0 °C	0.1–0.9	0.500	3.3–40.0	8
1-(β-hydroxyethyl)-piperazine	0.5–5.1	0.334	1.4–15.1	16
	0.3–2.5	0.500	1.1–9.1	8
	0.3–2.8	0.676	1.6–13.8	8
morpholine	2.0–20.0	0.350	2.3–23.2	10
	2.0–20.0	0.500	3.1–33.7	10
	1.0–10.0	0.676	2.0–21.1	8
1-formylpiperazine	3.0–30.2	0.355	0.5–4.4	8
	3.1–31.1	0.500	0.6–6.1	8
	3.6–35.8	0.676	1.1–9.7	8
at 15.0 °C	3.6–35.7	0.645	0.5–5.6	7
at 35.0 °C	3.1–30.8	0.477	1.2–10.8	7
at 45.0 °C	3.1–30.8	0.483	2.1–18.2	7
piperazinium ion[e]	10.1–35.3	(pH 6.0)	0.08–0.3	6
	15.0–55.0	(pH 7.0)	0.6–2.1	8
	15.0–55.0	(pH 7.2)	0.8–3.2)	8
	15.0–55.0	(pH 7.4)	1.4–6.0	8
	15.0–50.0	(pH 7.62)	2.2–8.6	8
	15.0–55.0	(pH 7.8)	3.1–14.3	9
	15.0–55.0	(pH 8.0)	5.1–20.7	8
	p-Nitrophenyl Thiolacetate (NPTA)			
piperidine[d]	0.25–2.5	0.006	3.0–33.0	8
	0.25–2.5	0.011	5.5–56.1	8
	0.13–1.3	0.022	4.9–60.7	8
at 15.0 °C	0.50–4.5	0.010	5.2–50.4	7
at 35.0 °C	0.13–1.3	0.011	5.9–57.3	8
at 45.0 °C	0.08–0.8	0.012	6.4–53.2	9
piperazine	0.02–0.20	0.334	5.1–57.3	8
	0.02–0.10	0.500	9.2–52.6	8
	0.02–0.16	0.630	10.8–81.9	10
1-(β-hydroxyethyl)-piperazine	0.04–0.4	0.334	3.6–41.8	8
	0.04–0.4	0.500	5.2–55.9	7
	0.02–0.2	0.676	3.8–39.8	8
morpholine	0.10–1.0	0.349	4.7–52.3	8
	0.05–0.5	0.500	3.5–39.5	8
	0.04–0.4	0.624	3.5–36.2	8
1-formylpiperazine	0.63–6.3	0.355	4.7–49.2	8
	0.32–3.1	0.500	3.1–35.8	7
	0.32–3.1	0.676	4.8–46.7	8
at 15.0 °C	0.97–9.7	0.500	4.9–51.1	7
at 35.0 °C	0.31–3.3	0.500	4.9–54.1	8
at 45.0 °C	0.15–1.5	0.500	4.4–43.0	8
piperazinium ion	0.8–7.2	0.382	0.2–1.9	7
	1.0–10.0	0.500	0.4–3.4	9
	1.0–10.0	0.660	0.5–5.0	9

[a] At 25.0 °C and ionic strength 0.2 M (maintained with KCl), unless otherwise noted. [b] Total concentration of amine (free base plus protonated forms). [c] Fraction of free-base amine, except for the reactions of piperazinium ion with PTA. [d] Borate (H_3BO_3 + $H_2BO_3^-$) was used as buffer (total concentration 0.02 M), except in the reaction with PTA at 25.0 °C, which was followed by pH-stat without buffer. [e] Ionic strength was 0.6 M (KCl), except for the runs at pH 6.0, where 0.8 M (KCl) was used. The free-amine fractions of piperazinium ion and piperazine at μ 0.6 M were calculated through eq 4 and 5, respectively (see Results).

Results

The rate law found for the reactions under study is given by eq 2, where S is the substrate, k_N is the rate constant for aminolysis, F_N is the free-amine fraction, and [N]$_{tot}$ is

Table II. pK_a Values of Acids and Second-Order Rate Constants (k_N) for the Aminolysis of Phenyl Thiolacetate (PTA) and *p*-Nitrophenyl Thiolacetate (NPTA) in Water[a]

amine	pK_a[b]	k_N, s^{-1} M^{-1} PTA	k_N, s^{-1} M^{-1} NPTA
piperidine	11.21 ± 0.04	22.3 ± 1.5	213 ± 13
at 15.0 °C	11.39 ± 0.05	16.0 ± 1.6	108 ± 8
at 35.0 °C	11.09 ± 0.04	45.6 ± 2.5	400 ± 20
at 45.0 °C	10.73 ± 0.03	56.9 ± 4.4	589 ± 60
piperazine	9.94 ± 0.04	3.9 ± 0.3	97 ± 7
at μ = 0.6 M	10.03 ± 0.07	4.3 ± 0.2[c]	
at 15.0 °C		1.9 ± 0.1	
at 35.0 °C		5.8 ± 0.3	
at 45.0 °C		9.2 ± 0.6	
1-(β-hydroxyethyl)piperazine	9.38 ± 0.03	0.77 ± 0.05	29 ± 2
morpholine	8.78 ± 0.03	0.32 ± 0.03	15 ± 1
1-formylpiperazine	7.98 ± 0.03	$(3.9 \pm 0.3) \times 10^{-2}$	2.2 ± 0.1
at 15.0 °C	8.20 ± 0.03	$(2.4 \pm 0.2) \times 10^{-2}$	1.1 ± 0.1
at 35.0 °C	7.77 ± 0.03	$(7.3 \pm 0.4) \times 10^{-2}$	3.4 ± 0.2
at 45.0 °C	7.58 ± 0.03	$(11.7 \pm 1) \times 10^{-2}$	5.6 ± 0.4
piperazinium ion	5.81 ± 0.03	$(1.6 \pm 0.3) \times 10^{-3}$[d]	0.07 ± 0.01
at μ = 0.6 M	5.99 ± 0.03		
at μ = 0.8 M	6.05 ± 0.03	$(1.6 \pm 0.2) \times 10^{-3}$	
acid			
thiophenol	6.51 ± 0.05		
p-nitrothiophenol	4.61 ± 0.03		

[a] At 25.0 °C and ionic strength 0.2 M (KCl), unless otherwise stated. The errors shown in this table are standard deviations. [b] Of the conjugate acid of the amine, unless otherwise noted, obtained in the same experimental conditions of the kinetics. [c] Obtained from plots of k_{obsd} vs. $[N]_{tot}$ at pH 7.0–8.0, as described in Results. [d] Values obtained at μ 0.8 M and assumed to be the same at μ 0.2 M (see Results).

the concentration of total amine (free base plus its conjugate acid). The rate constant for hydrolysis of the

$$-\frac{d[S]}{dt} = k_{obsd}[S]; \; k_{obsd} = k_N F_N [N]_{tot} \qquad (2)$$

substrate was negligible compared to that for its aminolysis in all the kinetic runs. The k_N values were obtained by dividing by F_N the slopes of linear k_{obsd} vs $[N]_{tot}$ plots at constant F_N (i.e. constant pH). No dependence of k_N on F_N was found, except for the reaction of PTA with piperazinium ion (see below). The values of k_N for all the reactions studied are gathered in Table II.

In order to study the slow reaction of PTA with piperazinium ion it was necessary to use large concentrations of amine and high F_N values in order to increase the reaction rate and hence to avoid the problem due to the slow oxidation of thiophenoxide ion (see Experimental Section). Therefore, this reaction had to be studied at higher ionic strength (μ) than 0.2 M. At μ 0.6 M, pH range 7–8, the k_N values obtained from the slopes of k_{obsd} vs $[N]_{tot}$ plots at constant pH ($k_{N,obsd}$) showed a dependence on pH given by eq 3, where k_{PAH} and k_{PA} are the second-order rate

$$k_{N,obsd} = k_{PAH} + k_{PA}\frac{F_{PA}}{F_{PAH}} \qquad (3)$$

constant (k_N) for piperazinium ion and piperazine attack to PTA, respectively, and F_{PAH} and F_{PA} are the corresponding amine fractions (F_N), given by eq 4 and 5, respectively. In these equations pK_{PAH} and pK_{PA} are the

$$F_{PAH} = [1 + 10^{(pK_{PAH}-pH)} + 10^{(pH-pK_{PA})}]^{-1} \qquad (4)$$

$$F_{PA} = [1 + 10^{(pK_{PA}-pH)} + 10^{(pK_{PAH}+pK_{PA}-2pH)}]^{-1} \qquad (5)$$

pK_a of the conjugate acids of piperazinium ion and piperazine at μ 0.6 M, respectively. These pK_a values were determined experimentally and are shown in Table II.

The rate law given by eq 3 accounts for the simultaneous attack on PTA by piperazinium ion and piperazine, since in this case k_{obsd} is given by eq 6 and dividing by F_{PAH} the slope of a given k_{obsd} vs $[N]_{tot}$ plot, which is $k_{N,obsd}$, one obtains eq 3.

$$k_{obsd} = (k_{PAH}F_{PAH} + k_{PA}F_{PA})[N]_{tot} \qquad (6)$$

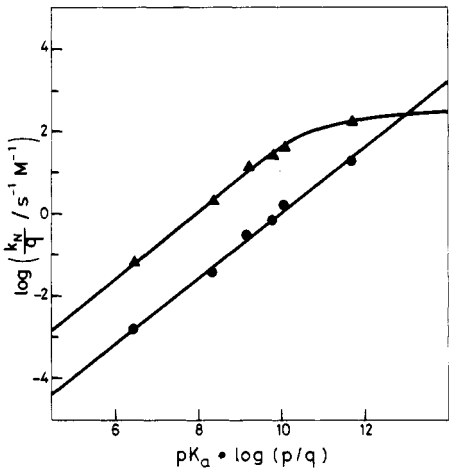


Figure 1. Brønsted-type plots (statistically corrected) obtained in the aminolysis of phenyl thiolacetate (PTA, ●) and *p*-nitrophenyl thiolacetate (NPTA, ▲) in water at 25 °C, μ 0.2 M (KCl). The points are experimental, and the line for NPTA was calculated by means of eq 8, with log k_N^0 = 1.98, pK_a^0 = 10.47, β_2 = 0.86, and β_1 = 0.10.

By plotting $k_{N,obsd}$ against F_{PA}/F_{PAH} for the above reaction a value of 4.3 ± 0.2 s^{-1} M^{-1} for the slope (k_{PA}) is found. This is similar to the k_N value obtained for the reaction of piperazine with PTA at μ 0.2 M (Table II). Unfortunately a value of k_N for piperazinium ion (k_{PAH}) could not be determined as intercept of the above plot since the error involved was too large. In order to obtain this value it was necessary to work at pH 6.0 and μ 0.8 M. At this pH, F_{PA} is very small and the contribution of the free-base piperazine reaction is negligible compared to that of piperazinium ion. In this case, k_{PAH} was determined as the slope of a k_{obsd} vs $[N]_{tot}$ plot, divided by the value of F_{PAH} at μ 0.8 M. The fact that the k_N value for piperazinium ion at μ 0.8 M correlates well with those at μ 0.2 M for the other amines on the Brønsted-type plot obtained in the aminolysis of PTA (see Figure 1) indicates that there is little influence of μ on the k_N value of piperazinium ion. This is understandable in view of the fact that the k_2 step of eq 1 is rate determining for the reaction of this ion (see

Table III. Activation Parameters Found in the Aminolysis of Phenyl Thiolacetate (PTA) and *p*-Nitrophenyl Thiolacetate (NPTA) in Water[a]

	PTA		NPTA	
amine	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
piperidine	7.6 ± 2.2	−26.7 ± 7.3	9.8 ± 1.2	−15.2 ± 3.9
piperazine	8.7 ± 1.2	−27.0 ± 3.9[b]		
1-formyl-piperazine	9.2 ± 0.8	−34.1 ± 2.6	9.1 ± 1.3	−26.6 ± 4.2

[a] Ionic strength 0.2 M (KCl). The errors shown are standard deviations. [b] This value is −27.7 ± 3.9 if statistically corrected with $q = 2$.

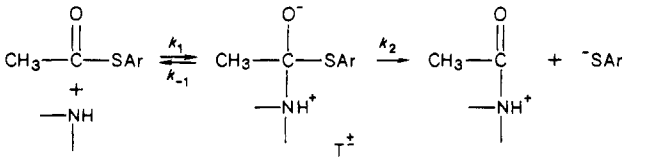
Discussion) and both the transition state involved and piperazinium ion are ionic. There are some reactions between neutral polar molecules and ions that show small primary salt effects.[14]

With the k_N and pK_a data at 25 °C, μ 0.2 M, shown in Table II, the Brønsted-type plots for the aminolysis of PTA and NPTA were drawn. Both the k_N and pK_a values were statistically corrected with $q = 1$ (except piperazine with $q = 2$) and $p = 2$ (except piperazinium ion with $p = 4$).[15] The plots are shown in Figure 1. The statistical corrections suggested by Wells[16] do not alter the shapes of the Brønsted-type plots in Figure 1; these corrections merely displace the plots by 0.3 pK_a unit.

Activation parameters were obtained for the reactions of various amines with PTA and NPTA. The experimental conditions for these reactions are shown in Table I, and the k_N values obtained at several temperatures are gathered in Table II. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined from the slope and intercept, respectively, of Eyring plots ($\ln k_N/T$ against $1/T$). The values of the activation parameters obtained are shown in Table III.

Discussion

As seen in Figure 1, the Brønsted-type plot obtained in the aminolysis of PTA is linear while that for NPTA is nonlinear. The latter curve can be explained by a change in the rate-determining step from k_2 to k_1 (eq 7, SAr =



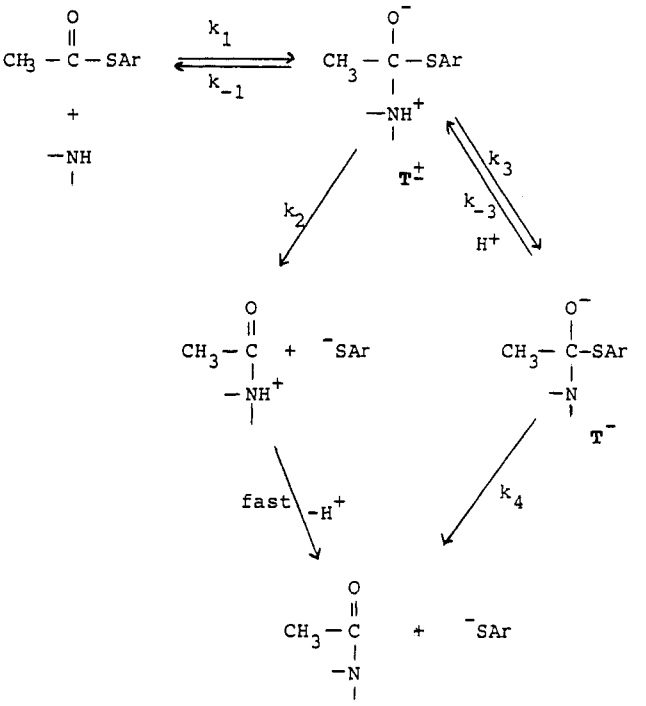
(7)

p-nitrothiophenoxy and >NH represents a seconary amine) as the nucleophile becomes more basic.[4-6,12] On the basis of the above scheme and by applying the steady state approximation to $T^{\pm}$, one gets $k_N = k_1k_2/(k_{-1} + k_2)$, where k_N is the macroscopic nucleophilic rate constant. From this relation and by applying the Brønsted-type equation to the microscopic rate constants, one obtains eq 8,[4-6,12] where pK_a^0 is the pK_a value at the center of the

$$\log \frac{k_N}{k_N^0} = \beta_2(pK_a - pK_a^0) - \log \frac{1+a}{2} \qquad (8)$$

$$\log a = (\beta_2 - \beta_1)(pK_a - pK_a^0)$$

Scheme I



Brønsted-type curvature, k_N^0 is its corresponding k_N value, and β_2 and β_1 are the slopes of the linear portions of the Brønsted-type plot at low and high pK_a values, respectively. The best values found for these four parameters by least-squares fitting of eq 8 to the experimental data are $\log k_N^0 = 1.98 \pm 0.05$, $pK_a^0 = 10.47 \pm 0.1$, $\beta_1 = 0.10 \pm 0.05$, and $\beta_2 = 0.86 \pm 0.05$.

The value of $\beta_1 = 0.1$ obtained for the NPTA reactions is similar to the Brønsted-type slope found in the aminolysis of *O*-esters and related substrates when the formation of $T^{\pm}$ is rate determining.[4-6,17]

The Brønsted-type slope for the aminolysis of PTA is 0.83 ± 0.09, very similar to β_2 for the NPTA reactions, which means that for the former reactions the k_2 step of eq 7 is rate determining. Similar slopes have been found in the aminolysis of *O*-esters and other acyl compounds when the decomposition to products of $T^{\pm}$ is the rate-limiting step.[4-6,17]

At the center of the Brønsted-type curvature $k_{-1} = k_2$ (eq 7). The fact that $pK_a^0 \approx 10.5$ for the reactions of NPTA means that an (hypothetical) amine of $pK_a = 10.5$ leaves the zwitterionic tetrahedral intermediate ($T^{\pm}$ of eq 7) as fast as *p*-nitrothiophenoxide ion ($pK_a = 4.6$, Table II). This means that secondary amines are much better nucleofuges from $T^{\pm}$ than aryl sulfide ions of the same basicity. In fact, an amine of $pK_a = 4.6$ will leave $T^{\pm}$ ca. (3×10^4)-fold faster than *p*-nitrothiophenoxide ion.[18]

(14) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: London, 1961; p 150.
(15) Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1959; p 159.
(16) Wells, P. R. *Linear Free Energy Relationships*; Academic: London, 1968; p 89.
(17) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869. Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442. Hall, W. E.; Higuchi, T.; Pitman, I. H.; Uekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153.
(18) This result was obtained as follows:

$$\beta_2 = \frac{d(\log K_1k_2)}{dpK_a} = \frac{d(\log k_1)}{dpK_a} + \frac{d[\log (k_2/k_{-1})]}{dpK_a} = 0.86$$

Since $\beta_1 = \dfrac{d(\log k_1)}{dpK_a} = 0.10$, it follows that

$$\frac{d[\log (k_2/k_{-1})]}{dpK_a} = 0.86 - 0.10 = 0.76$$

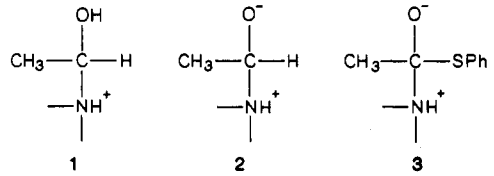
Integrating this expression between (k_2/k_{-1}) at $pK_a = 4.6$ and $(k_2/k_{-1}) = 1$ at $pK_a = pK_a^0 = 10.5$, one gets $(k_{-1}/k_2) = 3 \times 10^4$ at $pK_a = 4.6$.

A more general mechanism (than that depicted in eq 7) for the reactions presented in this paper is outlined in Scheme I.[19] In this mechanism the deprotonation of $T^{\pm}$ to give T^- can in principle be carried out by the solvent, hydroxide ion, or another amine molecule, under the experimental conditions employed. If this step were rate determining, only deprotonation of $T^{\pm}$ by the solvent would be compatible with the facts that the kinetics are first-order in amine and k_N is pH independent.

If $T^{\pm}$ of Scheme I were at equilibrium with T^- and the k_4 step were rate limiting, k_N would be pH dependent, which was not observed. Therefore, the only way the k_3 and k_4 paths of Scheme I can be significant under the experimental conditions of the reactions is that $k_3[H_2O] > k_2$ and $k_4 \gg k_{-3}[H^+]$, the latter condition being essential for k_3 to be totally or partially (together with k_2) rate determining.

In order to check whether deprotonation of $T^{\pm}$ by water is significant we will estimate the values of k_3 and k_2 of Scheme I. The former value can only be assessed with the knowledge of the pK_a of $T^{\pm}$, which will be considered first.

The pK_a of the conjugate acid of alicyclic secondary amines such as piperidine and morpholine is *lowered* 1 unit by addition of a methyl group to the N atom.[20] Addition of OH to the methyl group further lowers the above pK_a by 1.88 units,[21,22] and substitution of CH_3 for H in the α-position increases the pK_a by 0.3 unit.[22] Therefore, the pK_a (NH^+) of 1 should be 2.6 units below that of the parent aminium ion.



1 2 3

Substitution of O^- for OH in 1 increases the pK_a by 4.8 units;[22-24] as a result the pK_a of **2** should be 2.2 units higher than that of the parent aminium ion.

In order to obtain the pK_a of **3**, which is one of the forms of $T^{\pm}$ in Scheme I, we will use linear free-energy correlations following Jencks's procedure.[22] The pK_a's of some aliphatic ammonium ion, $XCH_2NR_1R_2H^+$, have been satisfactorily correlated with a value of $\rho_I = -8.0$.[22,25] Inclusion of a series N-substituted morpholinium ions gives $\rho_I = -7.3$.[22,25] Since $\sigma_I = 0.30$ for the thiophenyl group,[26] it follows that addition of SPh to **2** should change its pK_a by $(-7.3) \times 0.30 = -2.2$ units. Therefore, the pK_a of **3** should be about the same as that of the parent alicyclic ammonium ion.

Let us now estimate the pK_a value of the other form of $T^{\pm}$ (4:Ar = 4-nitrophenyl). The acid dissociation of $ArCH_2NH_3^+$ in water, at 25 °C has been satisfactorily correlated with $\rho = 1.05$ and σ^0 values,[27] and also by dual substituent parameter treatment with $\rho_I = 1.082$, $\rho_R = 1.057$, and σ_I and σ_R^0 values.[28] Using for the *p*-nitro substituent the corresponding σ values,[27,28] one gets by the two treatments: $\Delta pK_a = -0.86$. For transmission of substituent effects through a sulfur atom a fall-off factor of 1.63 can be assumed by comparison of $\rho = 0.49$ for acid dissociation of $ArCH_2COOH$ with $\rho = 0.30$ for ionization of $ArSCH_2COOH$ in water at 25 °C.[29] Therefore $\Delta pK_a = -0.86/1.63 = -0.5$ for $p\text{-}NO_2PhSCH_2NH_3^+$ compared to the unsubstituted acid. Assuming the same ΔpK_a for the acid dissociation of **4** relative to **3**, one concludes that the pK_a of **4** should be 0.5 pK_a unit lower than that of the parent aminium ion.

Another estimate of the above ΔpK_a can be made by using $\sigma_1 = 0.35$ for the (4-nitrophenyl)thio group.[30] Substitution of PhS by the former group gives $\Delta pK_a = (-7.3) \times (0.35 - 0.30) = -0.4$ for **4** compared to **3**, i.e. the pK_a of **4** is 0.4 pK_a unit lower than that of the parent aminium ion.

An independent evaluation of the pK_a of **3** can be carried out by starting with the $pK_a = 7.27$ (water, 25 °C) of $CH_3C(OH)(O^-)ImH^+$, where Im = 1-imidazolyl.[31] Using $\rho^* = -0.30$ for the pK_a correlation of XCH_2ImH^+ and $\sigma^* = 1.87$[32] and $\sigma^* = 1.34$[31] for SPh and OH substituents, respectively, one gets a $pK_a = 7.27 - 0.30(1.87 - 1.34) = 7.11$ for $CH_3C(SPh)(O^-)ImH^+$. Since the pK_a of imidazolium ion in water at 25 °C is 7.0,[20,31] we conclude that ΔpK_a between the former and the latter compound is 0.1, which satisfactorily compares with $\Delta pK_a = 0$ for **3** relative to the parent aminium ion.

The pK_a estimates of the two forms of $T^{\pm}$ of Scheme I are obviously not precise, and we can assume an error of ± 0.5 pK_a unit for each one.

With the pK_a values of $T^{\pm}$ we can now evaluate k_3 of Scheme I. The proton transfer involved (from $T^{\pm}$ to water) is thermodynamically unfavorable since the pK_a of the most acidic form of $T^{\pm}$ (i.e. **4** with the piperazinium dication moiety) is 5.8 − 0.5 = 5.3, whereas the pK_a of the hydronium ion is −1.75. Since the k_{-3} step is thermodynamically favorable we can assume $\log k_{-3} = 9.3$,[23,33] and k_3 will be given by: $\log k_3 = 9.3 + (-1.75 - 5.3) = 2.2$,[33] hence $k_3 = 158\ s^{-1}\ M^{-1}$ for the most acidic $T^{\pm}$. Multiplying this value by 55.5 M (the water "concentration" in the solutions) gives $k'_3 = 8.8 \times 10^3\ s^{-1}$ as an upper limit for the proton transfer to water from any $T^{\pm}$.

We will determine now the value of k_2 is Scheme I. In order to do this let us first estimate the corresponding rate constant for the oxy analogue of $T^{\pm}$ (since there are much more kinetic data on *O*-esters than on *S*-esters).

The rate of expulsion of 4-methoxypyridine *N*-oxide ($pK_a = 2.1$) from the zwitterionic tetrahedral intermediate formed in the reaction of 1-acetoxy-4-methoxypyridinium ion with methylamine has been calculated as $3 \times 10^{10}\ s^{-1}$ (water, 25 °C).[3] From the effective charge density map for the aminolysis of *O*-aryl acetates, it can be deduced that the acidity of the ammonium moiety of the $T^{\pm}$ formed in these reactions does not affect the rate of expulsion from $T^{\pm}$ of the leaving group of the substrate.[5a] The same map also shows that the above expulsion rate is affected by the basicity of the leaving group of the substrate through a β_{lg}

(19) Scheme I describes part of an even more general mechanism for ester aminolysis by primary and secondary amines, which include acid catalysis.[3] Since the reactions studied in this paper did not exhibit the above catalysis, the corresponding pathways were not included in Scheme I.

(20) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965.

(21) Kallen, R. G.; Jencks, W. P. *J. Biol. Chem.* **1966**, *241*, 5864. Hine, J.; Via, F. A.; Gotkis, J. K.; Craig, J. C., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 5186.

(22) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

(23) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637.

(24) Obtained by comparison of pK_4 and pK_1 of eq 23 in ref 22 and the corresponding pK_a's of eq 13 in ref 23.

(25) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441.

(26) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222.

(27) Reference 16, p 12.

(28) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1.

(29) Shorter, J. *Correlation Analysis in Organic Chemistry: An Introduction to Linear Free-Energy Relationships*; Oxford: Oxford, 1973.

(30) Charton, M. *Prog. Phys. Org. Chem.* **1987**, *16*, 287. We thank a referee for communicating this to us.

(31) Guthrie, J. P.; Pike, D. C. *Can. J. Chem.* **1987**, *65*, 1951.

(32) $\sigma^* = 0.30 \times 6.23$, where 0.30 is the σ_I value of SPh.[26]

(33) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

= −0.5.[5a] With these data it follows that the rate of expulsion of ArO^- from $T^\pm$ is given by eq 9 (water, 25 °C),

$$\log k_2 = 11.53 - 0.5pK_a(lg) \quad (9)$$

independent of the amine moiety in $T^\pm$. For expulsion of ArO^- of pK_a = 6.5 and 4.6 (which have the same basicities as PhS^- and $p\text{-}NO_2PhS^-$, respectively), eq 9 gives ca. 2×10^8 s^{-1} and 2×10^9 s^{-1}, respectively. Since it is known that ArS^- is a poorer nucleofuge from a tetrahedral intermediate than ArO^- of the same basicity,[12,34] it follows that the values of k_2 from **3** and **4** should be $<2 \times 10^8$ and $<2 \times 10^9$ s^{-1}, respectively.

It is difficult to find in the literature rate constants for expulsion of ArS^- from tetrahedral intermediates, which could be compared to the above values of k_2 from $T^\pm$ of Scheme I. The rates of expulsion of $p\text{-}MeOPhS^-$ (pK_a very similar to PhS^-) and $p\text{-}NO_2PhS^-$ from the intermediate $MeC(O^-)(H)SAr$ formed in the reactions of thiolate ions with acetaldehyde have been estimated as 1×10^9 and 6×10^9 s^{-1}, respectively (water, 25 °C),[35] although the authors point out that these rates could be overestimated.[35] Substitution of $-NH^+$ for H should increase these figures but not very much in view that ArS^- is a good leaving group and the above rates are already very large. Since the estimations of nucleofugalities from tetrahedral intermediates are subject to errors of ca. 1 order of magnitude, it is reasonable to assume that the k_2 values predicted by eq 9 are correct and that the values of k_2 from **3** and **4** could be ca. 1×10^8 and 1×10^9 s^{-1}, respectively.[36]

Comparison of the estimated k_2 and k_3 values in Scheme I shows that the path through k_3 and k_4 steps are not important for the reactions presented in this work. Even if deprotonation of $T^\pm$ were performed by another amine molecule, its rate constant would be ca. 10^9 s^{-1} M^{-1} (thermodynamically favorable for deprotonation of **4** and neither favorable nor unfavorable for **3**),[23,33] which multiplied by the free-amine concentrations employed in the kinetic solutions ($[N]_{tot} \times F_N$ in Table I) gives rates of 10^5–10^8 s^{-1} (only in a few cases 10^8 s^{-1}). The rates are smaller than the estimated k_2 values and explains why kinetics second order in amine were not found.

We conclude, therefore, that the mechanism described by eq 7 is sufficient to account for the results obtained in the title reactions, under the experimental conditions shown in Table I.

Let us now estimate the k_{-1} values of eq 7. In order to do this, we will evaluate first the corresponding k_{-1} from the *O*-aryl derivatives of $T^\pm$, with the same ArO^- basicity as PhS^- and $p\text{-}NO_2PhS^-$ (pK_a = 6.5 and 4.6, respectively).

The effective charge density map for the aminolysis of *O*-aryl acetates shows that the sensitivity of the rate of amine expulsion from $T^\pm$ to the basicity of ArO^- is β_{lg} = +0.4 and the above sensitivity to the basicity of the amine is β_N = −0.7.[5a] The rate of methylamine expulsion from the $T^\pm$ formed in the hydrolysis of *p*-tolyl *N*-methylacetimidate $(MeNH_2C(O^-)(Me)OPh\text{-}p\text{-}Me)^+$ in water at 25 °C has been estimated to be 3×10^9 s^{-1}.[37] With the above data and the pK_a's of $MeNH_3^+$ and *p*-cresol (10.8 and 10.2, respectively), one obtains eq 10 for the rate of amine expulsion (water, 25 °C) from the O-analogues of $T^\pm$ of eq 7. In eq 10, $pK_a(lg)$ and $pK_a(N)$ are the pK_a of the conjugate acids of ArO^- and the amine, respectively.

$$\log k_{-1} = 12.96 + 0.4pK_a(lg) - 0.7pK_a(N) \quad (10)$$

In order to test whether the estimations of k_2 and k_{-1} from the O-analogues of $T^\pm$ in eq 7 are correct, we will apply eq 9 and 10 to the aminolysis of 2,4-dinitrophenyl acetate ($pK_a(lg)$ = 4.0 in water, 25 °C). Equations 9 and 10 predict that for this reaction series pK_a^0 = 7.2.[38] The experimental value found in the pyridinolysis of the above substrate in water at 25 °C was pK_a^0 = 7.3.[4]

For the aminolysis of *p*-nitrophenyl acetate ($pK_a(lg)$ = 7.2 in water at 25 °C), eq 9 and 10 predict pK_a^0 = 11.3, which is reasonable in view that linear Brønsted-type plots up to pK_a = 10 and 11 were found in the pyridinolysis[2c] and aminolysis[1a] (primary and secondary amines mainly) of the above ester.

Equations 9 and 10 cannot predict pK_a^0 values for the aminolysis of phenyl aryl carbonates since (i) the effective charge density map obtained for these reactions[5a] is different from the one found in the aminolysis of aryl acetates[5a] and (ii) the original estimations of k_2 and k_{-1},[3,37] from which eq 9 and 10 were derived, refer only to the aryl acetate series.

From eq 9 and 10 it follows that pK_a^0 should be 9.0 and 8.0 for the aminolysis of aryl acetates with $pK_a(lg)$ = 6.5 and 4.6, respectively. The fact that the experimental pK_a^0 in the aminolysis of PTA and NPTA are >11.5 and 10.5, respectively (see Figure 1) means that k_{-1}/k_2 for a given amine is much larger for the *S*-aryl derivatives compared to the isobasic O-analogues. Considering that the estimated k_2 values of **3** and **4** are ca. 1×10^8 and 1×10^9 s^{-1}, respectively (only a little smaller than those of the corresponding isobasic O-derivatives), it follows that k_{-1} for **3** and **4** must be much larger than k_{-1} for the isobasic O-analogues. In other words, the "push" provided by the ArS group in $T^\pm$ to expel a given amine is larger than that exerted by an isobasic ArO group in a similar intermediate.

It is known that the "push" provided by RO in the tetrahedral intermediate ArCH(OR)(SR) to expel RS^- (the same R) is stronger than that provided by RS to expel RO^-.[34a] The same conclusion has been reached in similar works,[12,39] but it must be realized that RO^- is much more basic than RS^-. It is therefore conceivable that the "push" provided by the ArS group in $T^\pm$ of eq 7 to expel the amine be stronger than that exerted by an *isobasic* ArO group in an analogue $T^\pm$.

Preliminary results on the aminolysis (alicyclic amines) of 2,4-dinitrophenyl thiolacetate show a nonlinear Brønsted-type plot with pK_a^0 ca. 9.8.[40] In this case $pK_a(lg)$ = 3.4,[40] and eq 9 and 10 predict a pK_a^0 = 6.4 for the aminolysis of an aryl acetate with $pK_a(lg)$ = 3.4. This means that k_{-1}/k_2 for a given amine is much larger for the sulfur zwitterionic intermediate compared to the isobasic oxy analogue. Moreover, for the aminolysis of 2,4-dinitrophenyl acetate, both the predictions of eq 9 and 10 and the experimental results give pK_a^0 ca. 7.3,[4] which means that k_{-1}/k_2 (constant amine) for the above sulfur species is even larger than for the oxy analogue *with the same Ar group*. If k_2 for the sulfur intermediate is slightly smaller than for the isobasic oxy analogue (see above) and similar to k_2 for the oxy analogue with the same aryl group (since 2,4-dinitrophenoxide ion is more basic than its S-analogue),

(34) (a) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476. (b) Douglas, K. T.; Alborz, M. *J. Chem. Soc., Chem. Commun.* **1981**, 551. (c) Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186.

(35) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931.

(36) These values cannot be lower than stated in order to be compatible with those estimated in ref 35. On the other hand, they cannot be larger than those estimated for the isobasic O-analogues (see above), hence k_2 for **3** and **4** should be in the range (1–2) $\times 10^8$ s^{-1} and (1–2) $\times 10^9$ s^{-1}, respectively.

(37) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7031.

(38) This is the $pK_a(N)$ value for which $k_2 = k_{-1}$, i.e. eq 9 = eq 10.

(39) Santry, L. J.; McClelland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167.

(40) Castro, E. A.; Ureta, C., preliminary results in water, 25 °C, μ = 0.2 M (KCl).

it follows that the "push" provided by 2,4-$(NO_2)_2C_6H_3S$ to expel a given amine from $T^{\pm}$ is not only greater than that exerted by an isobasic ArO in an analogue intermediate, but also greater than the "push" provided by 2,4-$(NO_2)_2C_6H_3O$ in a similar species. The latter conclusion can be explained by the small ΔpK_a (=0.6) between 2,4-dinitrophenol and its sulfur analogue.

Acknowledgment. This research was financially supported by "Dirección de Investigación de Universidad Católica de Chile" (DIUC), to which we are indebted.

Registry No. PTA, 934-87-2; NPTA, 15119-62-7; 1-formylpiperazine, 7755-92-2; piperidine, 110-89-4; piperazine, 110-85-0; 1-(β-hydroxyethyl)piperazine, 103-76-4; morpholine, 110-91-8; piperazinium ion, 22044-09-3.

Regiospecific Lithiation of Phenoxazine Ortho to the Oxygen Atom. Synthesis of 4-Mono- and 4,6-Disubstituted Phenoxazine Derivatives[1,2]

Yulia Antonio, Patricia Barrera, Olga Contreras, Fidencio Franco, Edvige Galeazzi, Josefina Garcia, Robert Greenhouse, Angel Guzmán, and Esperanza Velarde

Syntex, S.A., División de Investigación Apartado Postal 10-820, 11000 México, D.F., México

Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304

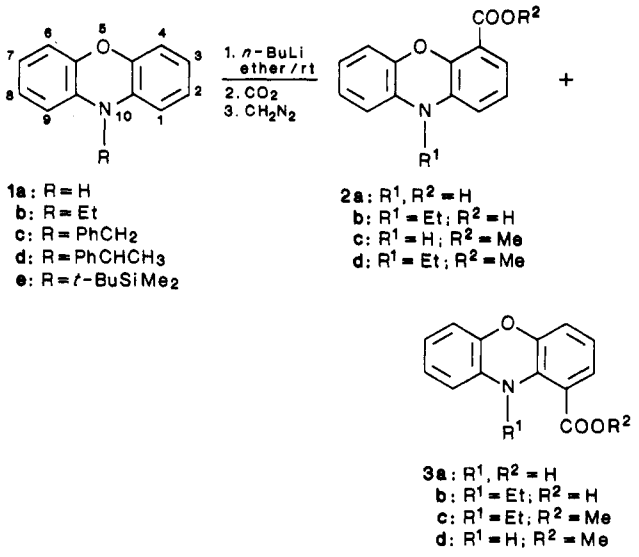
Received January 13, 1988

Under appropriate conditions, phenoxazine bearing a sterically demanding, bulky N-substituent (e.g., α-methylbenzyl or *tert*-butyldimethylsilyl) undergoes lithiation at C-4 or at C-4 and C-6 with *n*-butyllithium in THF solution. The lithiated species react with a variety of electrophilic reagents and upon subsequent N-deprotection provide access to 4-mono- or 4,6-disubstituted phenoxazines. This process is of particular synthetic utility (36–54% yields) when the N-substituent is *tert*-butyldimethylsilyl.

Nearly three decades ago, Gilman and Moore[3] reported that lithiation of phenoxazine (**1a**) and 10-ethylphenoxazine (**1b**) with *n*-butyllithium in ether followed by carbonation gave phenoxazine-4-carboxylic acid (**2a**) and the corresponding 10-ethyl derivative **2b** (Scheme I). Ten years later, Blank and Baxter[4] proved, by an unequivocal synthesis, that the carboxylic acid obtained by Gilman and Moore actually was phenoxazine-1-carboxylic acid (**3a**). The structure of the supposed 10-ethylphenoxazine-4-carboxylic acid was, however, apparently never questioned (see below).

In connection with one of our medicinal chemical programs, various 4-mono- and 4,6-disubstituted phenoxazine derivatives were required as synthetic intermediates. It was reasoned that lithiation of phenoxazine bearing a sterically demanding (and removable) nitrogen substituent should occur preferentially ortho to the oxygen atom and thus provide access to the required monosubstituted and/or disubstituted compounds. Support for this supposition was derived from a repetition of the Gilman and Moore lithiation–carbonation experiment on 10-ethylphenoxazine. Esterification of the crude product with diazomethane and preparative thin-layer chromatographic separation of the mixture, followed by saponification of the individual esters, provided two carboxylic acids in 13% and 22% yields. The more abundant product had a melting point (163–164 °C) that closely matched (mp 163.5–165 °C) that reported[3] for **2b**, while the less abundant acid (mp 149 °C), presumed to be **3b**, had previously not been reported. The structures of both carboxylic acids

Scheme I



were confirmed in the manner described in the latter part of this paper (see below).

The benzyl and trialkylsilyl moieties were selected for examination as substituents that might direct lithiation to C-4 (and C-6) of the phenoxazine nucleus. Lithiation of 10-benzylphenoxazine (**1c**) with 1 equiv of *n*-butyllithium in THF–hexane (0 °C, 15 min) followed by quenching with deuterium oxide, gave monodeuterated **1c** (52% d_1) with >99% of the label in the methylene carbon atom of the benzyl group.[6] The lithiation of 10-(α-methylbenzyl)phenoxazine (**1d**) and 10-(*tert*-butyldimethylsilyl)phenoxazine (**1e**)[7] was then examined since

(1) Contribution No. 753 from the Syntex Institute of Organic Chemistry.
(2) Presented in part at the 69th Canadian Chemical Conference, Saskatoon, Sask., Canada, June 1–4, 1986.
(3) Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1958**, *80*, 2195. A very similar ratio of the 1- and 4-carboxylic acids has been observed in the lithiation–carboxylation of 10-methylphenothiazine: Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1979**, *26*, 1; see especially p 47.
(4) Blank, B.; Baxter, L. L. *J. Med. Chem.* **1968**, *11*, 807.
(5) Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1957**, *79*, 3485.
(6) This experiment was performed in duplicate, and the deuterium incorporations reported are the arithmetic means.
(7) The trimethylsilyl analogue of **1e** was prepared in the same manner but it was too hydrolytically sensitive to be of use in the lithiation reactions.

0022-3263/89/1954-2159$01.50/0