Kinetics and Mechanism of the Aminolysis of 4-Nitrophenyl and 2,4-Dinitrophenyl 4-Methylphenyl Carbonates in Aqueous Ethanol

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ABSTRACT: The reactions of 4-methylphenyl 4-nitrophenyl carbonate (MPNPC) and 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC) with a series of secondary alicyclic amines are subjected to a kinetic investigation in 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl). Under amine excess over the substrate, pseudo-first-order rate coefficients (k_{obs}) are obtained. Plots of k_{obs} against [amine] are linear, with k_N as slopes. A biphasic Brönsted-type plot for k_N is obtained for the aminolysis of MPNPC, with slopes $\beta_1 = 0.2$ (high pK_a) and $\beta_2 = 0.9$ (low pK_a). This is in accordance with a stepwise mechanism, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), and a change in the rate-determining step, from formation to breakdown of $T^{\pm}$ as the amine pK_a decreases. For the aminolysis of MPDNPC, a slightly curved Brönsted-type plot for k_N is obtained, with $\beta_1 = 0.1$ (low pK_a) and $\beta_2 = 0.55$ (high pK_a). This is consistent with a concerted mechanism. © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 309–315, 2002

INTRODUCTION

Much attention has been drawn to the kinetics and mechanism of the aminolysis of carboxylic acid derivatives such as esters [1] and alkyl aryl carbonates [2,3]. Nonetheless, little is known on the kinetics of the aminolysis of diaryl carbonates [4]. Some of the above reactions have been found to proceed through a zwitterionic tetrahedral addition intermediate ($T^{\pm}$, stepwise mechanism) [1,2,4] and other reactions take place with no intermediate (concerted mechanism) [3].

Gresser and Jencks [4] found a linear Brönsted-type plot with slope 1.0 for the reactions of quinuclidines with phenyl 4-nitrophenyl carbonate (PNPC) in water. This was attributed to a stepwise mechanism, with rate-determining decomposition of $T^{\pm}$ to products [4]. It was also found in this work that the same aminolysis of phenyl 2,4-dinitrophenyl carbonate (PDNPC) in the same solvent exhibits a curved Brönsted plot, which

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was explained by a stepwise mechanism with a change in the rate-limiting step as the amine basicity varies [4].

Recently, we have studied kinetically the reactions of secondary alicyclic amines with 4-methylphenyl 4-nitrophenyl thionocarbonate (MPNPTOC) in aqueous ethanol, where a linear Brönsted plot of slope $\beta = 0.25$ was found, consistent with a stepwise mechanism where the formation of $T^{\pm}$ is rate-limiting [5].

In order to shed more light on the mechanism of the aminolysis of diaryl carbonates and with the aim to assess the effects of different groups on the kinetics and mechanism, we investigate in this work the reactions of 4-methylphenyl 4-nitrophenyl carbonate (MPNPC) and 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC) with secondary alicyclic amines in aqueous ethanol. We compare the kinetic results between the aminolyses of MPNPC and MPDNPC to evaluate the effect of the leaving group. We also compare the title reactions with the quinuclidinolysis of PNPC and PDNPC in water to study the effects of the amine nature and solvent. Lastly, we compare the aminolysis of MPNPC with the same aminolysis of MPNPTOC in the same solvent [5] to assess the effect of the electrophilic group (CO vs. CS).

EXPERIMENTAL

Materials

The secondary alicyclic amines were purified as described [6]. The products of the reactions, the 4-methylphenyl carbamates of piperidine and morpholine, were synthesized as reported [7].

The substrates, MPNPC and MPDNPC, have not been synthesized previously, according to our knowledge. They were prepared as follows: To a solution of 4-nitrophenol (2.01 g, 14.5 mmol) or 2,4-dinitrophenol (2.67 g, 14.5 mmol) in THF (10 ml) in a Schlenk round-bottomed flask, a solution (9.1 ml, 14.5 mmol) of 1.6 M butyllithium (Aldrich) was added slowly under nitrogen atmosphere. The product, lithium 4-nitrophenoxide or lithium 2,4-dinitrophenoxide, was rapidly transferred to a compensation funnel, under nitrogen. In another Schlenk round-bottomed flask, tolyl chloroformate (Aldrich, 2.47 g, 14.5 mmol) was dissolved in anhydrous THF (10 ml) under nitrogen and the flask placed in an ethanol–liquid nitrogen bath (ca. -40°C). The compensation funnel was attached to the flask and lithium 4-nitrophenoxide or lithium 2,4-dinitrophenoxide solution added dropwise with stirring for 2 h. The mixture was left overnight with stirring under nitrogen at ambient temperature. Chloroform (50 ml) was added to this mixture and the solution washed with water. The organic layer was dried with $MgSO_4$, filtered under vacuum, and the solvent evaporated off.

The crystallized (diethyl ether) MPNPC melted at 136.2–137.1°C, and was identified as follows: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 2.38 (s, 3H), 7.19 (m, 4H), 7.48 (d, 2H, $J = 9.1$ Hz), 8.30 (d, 2H, $J = 9.1$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) ∂ 20.67 (CH_3), 120.41 (C-2′/6′), 121.76 (C-2/6), 125.37 (C-3/5), 130.22 (C-3′/5′), 136.53 (C-4′), 145.58 (C-4), 148.60 (C-1′), 151.23 (C-1), 155.36 (C═O). Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.72; H, 3.88; N, 5.11.

The crystallized (diethyl ether) MPDNPC melted at 136.7–137.4°C, and was identified as follows: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 2.38 (s, 3H), 7.19 (m, 4H), 7.66 (d, 1H, $J = 8.9$ Hz), 8.58 (dd, 1H, $J_1 = 8.9$ Hz, $J_2 = 2.7$ Hz), 9.04 (1H, $J = 2.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) ∂ 20.91 (CH_3), 120.36 (C-2′/6′), 122.13 (C-6), 126.28 (C-3), 129.52 (C-5), 130.31 (C-3′/5′), 136.92 (C-4′), 141.20 (C-2), 145.47 (C-4), 148.36 (C-1), 148.63 (C-1′), 150.33 (C═O). Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.83; H, 3.17; N, 8.80. Found: C, 52.74; H, 2.93; N, 8.68.

Kinetic Measurements

These were carried out by means of a Hewlett Packard 8453 diode array spectrophotometer in 44 wt% ethanol–water, at 25.0 ± 0.1°C, ionic strength 0.2 M (maintained with KCl). The reactions of MPNPC were followed at 400 nm (appearance of 4-nitrophenoxide anion) except that with piperazinium ion, which was followed at 330 nm (appearance of 4-nitrophenol). On the other hand, the aminolysis of MPDNPC was studied at 360 nm (following the appearance of 2,4-dinitrophenoxide anion). All reactions were investigated under excess of the amine over the substrate (20-fold at least). The initial substrate concentration was 2.5×10^{-5} M. Pseudo-first-order rate coefficients (k_{obs}) were found for all reactions; these were determined by means of the infinity method [plots of $\ln(A_\infty - A)$ vs. time, where A_∞ and A are the absorbances at infinity and t times].

Three pH values were employed in the reactions with each amine. These pH values were maintained by the amine as its own buffer (pH near the pK_a of its conjugate acid), except in the reaction of MPNPC with 1-(2-hydroxyethyl)piperazinium cation (HPA), where the pH was maintained by partial ionization of 1-(2-hydroxyethyl)piperazinium dication (HPAH). The pK_a value of the conjugate acid of HPA is 5.6 under the experimental conditions of the reactions [8].

The experimental conditions of the reactions and the k_{obs} values are shown in Tables I and II.

Table I Experimental Conditions and k_{obs} Values for the Aminolysis of MPNPC[a]

Amine	pH	F_N[b]	10^3 [N]$_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of Runs
Piperidine	10.52	0.333	0.3–2.7	3.7–44.0	9
	10.82	0.50	0.3–3.0	7.1–71.0	9
	11.12	0.667	0.3–3.0	15.0–100	9
Piperazine	9.41	0.333	1–10	9.9–56.0	10
	9.71	0.50	1–10	8.1–84.0	10
	10.01	0.667	1–10	11.0–120	10
1-(2-Hydroxyethyl)piperazine	8.79	0.333	0.6–6.0	5.2–54.0	10
	9.09	0.50	0.6–6.0	10.0–80.0	10
	9.39	0.667	0.6–6.0	11.0–110	10
Morpholine	8.18	0.333	10–100	8.5–65.0	9
	8.48	0.50	10–100	10.0–95.0	10
	8.78	0.667	10–100	13.0–120	10
1-Formilpiperazine	7.33	0.333	10–100	0.74–6.8	10
	7.63	0.50	10–100	0.97–9.1	10
	7.93	0.667	10–100	1.40–13.0	10
Piperazinium ion	5.07	0.333	10–90	0.022–0.13	9
	5.37	0.50	10–100	0.023–0.25	10
	5.67	0.667	10–100	0.033–0.37	10

[a]In 44 wt% ethanol–water, at 25°C, ionic strength 0.2 M (KCl).
[b]Free amine fraction.
[c]Concentration of total amine (free base plus protonated forms).

Table II Experimental Conditions and k_{obs} Values for the Aminolysis of MPDNPC[a]

Amine	pH	F_N[b]	10^3 [N]$_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of Runs
Piperidine	10.32	0.24	0.85–3.41	14.3–67.0	7
	10.82	0.50	0.85–3.41	42.3–149	7
	11.12	0.667	0.427–2.99	31.4–152	7
Piperazine	9.41	0.33	0.824–2.88	25.0–96.6	6
	9.71	0.50	0.843–2.95	32.6–131	6
	10.01	0.667	0.411–2.47	21.5–169	7
1-(2-Hydroxyethyl)piperazine	8.79	0.333	0.416–2.91	4.59–35.1	7
	9.09	0.50	0.416–2.91	9.69–54.7	7
	9.39	0.667	0.416–2.50	13.0–59.8	6
Morpholine	8.18	0.333	0.20–2.40	3.49–33.4	7
	8.48	0.50	0.20–2.40	3.21–44.8	5
	8.78	0.667	0.20–2.00	6.26–46.0	6
1-Formilpiperazine	7.33	0.333	0.20–2.40	1.48–8.99	7
	7.63	0.50	0.80–2.40	5.95–12.7	5
	7.93	0.667	0.40–2.40	3.65–16.2	6
Piperazinium ion	5.07	0.333	0.428–3.0	0.272–1.65	7
	5.37	0.50	0.402–2.81	0.417–2.25	6
	5.67	0.667	0.429–3.16	0.304–2.58	7
1-(2-Hydroxyethyl)piperazinium ion	4.3[d]	0.022	8.76–30.7	0.390–1.19	6
	4.6[d]	0.029	8.92–31.2	0.462–1.41	6
	4.9[d]	0.034	9.01–31.5	0.575–1.62	6

[a]In 44 wt% ethanol–water, at 25°C, ionic strength 0.2 M (KCl).
[b]Free amine fraction.
[c]Concentration of total amine (free base plus protonated forms).
[d]Reactive species is HPA (see text, pK_a of conjugate acid 5.6 [8]). Buffer is due to partial ionization of the dication HPAH (see text).

Product Studies

The 4-methylphenyl carbamates of piperidine and morpholine were identified as one of the final products of the reactions of both substrates with these two amines. This was carried out by comparison of the UV–vis spectra after completion of these reactions with those of authentic samples of the above carbamates, under the same experimental conditions. 4-Nitrophenoxide anion or 2,4-dinitrophenoxide anion were identified as the other product of the aminolysis of MPNPC or MPDNPC, respectively. This was achieved by comparison of the UV–vis spectra after completion of these reactions with those of authentic samples of sodium 4-nitrophenoxide or sodium 2,4-dinitrophenoxide under the kinetic conditions.

RESULTS AND DISCUSSION

The kinetic law obtained under the reaction conditions is that described in Eq. (1), where P is 4-nitrophenoxide anion (4-nitrophenol in the reaction of MPNPC with piperazinium ion) or 2,4-dinitrophenoxide anion, S is the substrate (MPNPC or MPDNPC), and k_{obs} is the pseudo-first-order rate coefficient (excess of amine was used throughout).

$$\frac{d[P]}{dt} = k_{obs}[S] \quad (1)$$

Plots of k_{obs} against [NH] at constant pH are linear in accordance with Eq. (2), where NH represents a secondary alicyclic amine free base, and k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrates, respectively.

$$k_{obs} = k_0 + k_N[NH] \quad (2)$$

For the reactions of MPDNPC with PI and PA, the k_0 values were negligible compared to the aminolysis term in Eq. (2).

The second-order rate coefficients for aminolysis (k_N) were obtained as the slopes of plots of Eq. (2) and were pH-independent. These values, together with those of the pK_a of the conjugate acids of the amines, are shown in Table III. Figure 1 shows the Brönsted-type plots obtained for k_N. The plots are statistically corrected with $p = 2$ for the aminium ions, except $p = 4$ for piperazinium dication, and $q = 1$ for the amines, except piperazine with $q = 2$ [5–10]. As seen in Fig. 1, the Brönsted plots for the aminolysis of both substrates are nonlinear.

The nonlinear Brönsted plot for MPNPC can be explained by the mechanism described in Scheme 1, where NH represents a secondary alicyclic amine. The

Table III Values of pK_a for the Conjugate Acids of Secondary Alicyclic Amines and k_N Values for the Reactions of These Amines with MPNPC and MPDNPC[a]

		k_N (s^{-1} M^{-1})	
Amine	pK_a	MPNPC	MPDNPC
Piperidine	10.82	50 ± 1	84 ± 3
Piperazine	9.71	17 ± 0.3	103 ± 4
1-(2-Hydroxyethyl)-piperazine	9.09	2.7 ± 0.1	36 ± 1
Morpholine	8.48	1.8 ± 0.1	34 ± 1
1-Formylpiperazine	7.63	0.19 ± 0.01	9.8 ± 0.4
1-(2-Hydroxyethyl)-piperazinium ion	5.60		1.41 ± 0.04
Piperazinium ion	5.37	0.0057 ± 0.0002	1.26 ± 0.07

[a] Both the pK_a and k_N values were determined in 44 wt% aqueous ethanol, at 25.0°C, ionic strength 0.2 (KCl).

Brönsted break results from a change in the rate-determining step, from breakdown of the zwitterionic tetrahedral intermediate ($T^{\pm}$) to products (k_2 step), to $T^{\pm}$ formation (k_1 step) as the amine basicity increases [1b,2,4]. Also, a linear Brönsted-type plot for the aminolysis of MPNPC could be drawn, and this would be also consistent with the mechanism depicted by Scheme 1, where the k_2 step would be rate-limiting.

The curved lines of the Brönsted plots in Fig. 1 were calculated by means of a semiempirical equation [Eq. (3)] based on the existence of the intermediate $T^{\pm}$ in Scheme 1 [1b,2b,2c,6,9,11]. Similar equations have been reported, which satisfactorily account for stepwise mechanisms [4,12].

In Eq. (3), β_1 and β_2 are the Brönsted slopes at high and low pK_a, respectively, and k_N^{o} and pK_a^{o} are the corresponding values at the center of the curvature.

$$\log\left(k_N/k_N^{o}\right) = \beta_2\left(pK_a - pK_a^{o}\right) - \log[(1+a)/2] \quad (3)$$

$$\log a = (\beta_2 - \beta_1)\left(pK_a - pK_a^{o}\right)$$

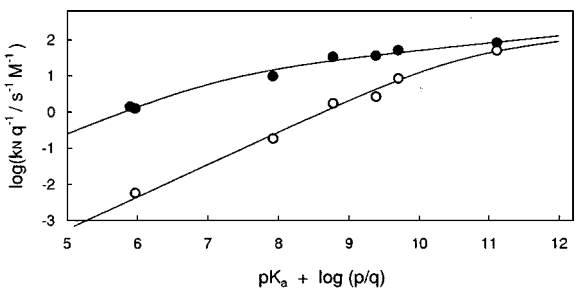
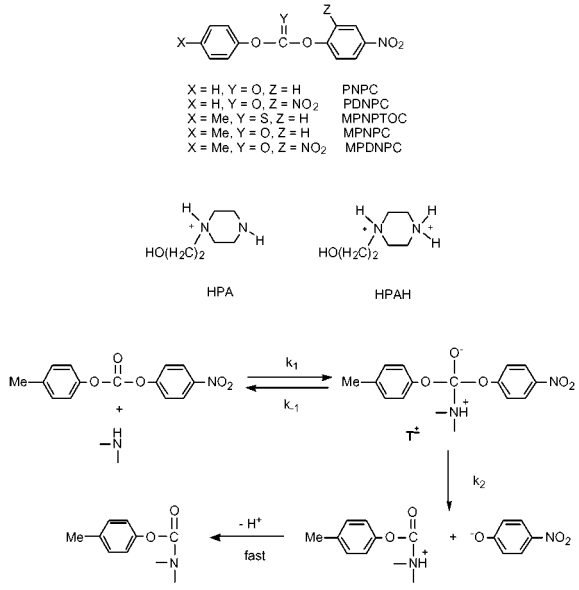


Figure 1 Brönsted-type plots (statistically corrected) for k_N obtained in the reactions of MPNPC (○) and MPDNPC (●) with secondary alicyclic amines in 44 wt% ethanol–water, 25.0°C, ionic strength 0.2 (KCl).



Scheme 1

The Brönsted curves in Fig. 1 were calculated with the following parameters: $\log k_N^o = 1.38$, $pK_a^o = 10.5$, $\beta_1 = 0.2$, and $\beta_2 = 0.9$ ($n = 7$, $R^2 = 0.991$) for MPNPC and $\log k_N^o = 1.46$, $pK_a^o = 8.9$, $\beta_1 = 0.1$, and $\beta_2 = 0.55$ ($n = 8$, $R^2 = 0.991$) for MPDNPC. The errors of the slopes are ± 0.1, and those of pK_a^o and $\log k_N^o$ are ± 0.2 and ± 0.1, respectively.

The values $\beta_1 = 0.2$ and $\beta_2 = 0.9$ found for the aminolysis of MPNPC are in accord with the values reported for other reactions governed by stepwise mechanisms: $\beta_1 = 0.1$–0.3 and $\beta_2 = 0.8$–1.1 [1b,2,4–9,11,12].

Nevertheless, the value $\beta_2 = 0.55$ obtained for the aminolysis of MPDNPC is not in agreement with the value of the Brönsted slope when breakdown of the tetrahedral intermediate to products is the rate-determining step. The slight curvature of the Brönsted plot for the reactions of MPDNPC is consistent with a concerted mechanism [13], although a stepwise process cannot rigorously be excluded.

A linear Brönsted-type plot of slope $\beta = 1.0$ was found by Gresser and Jencks in the reactions of PNPC with quinuclidines in water [4]. These tertiary alicyclic amines cover a pK_a range very similar to that of the secondary alicyclic amines used in this work. The reason why the pK_a value at the center of the Brönsted curvature (pK_a^o) is lower for the reactions of MPNPC ($pK_a^o = 10.5$, this work) than that for the reactions of PNPC ($pK_a^o > 11.5$ [4]) is the following.

It was found that quinuclidines are better leaving groups from a zwitterionic tetrahedral intermediate ($T^{\pm}$) than isobasic secondary alicyclic amines [14]. This means a larger k_{-1} (see Scheme 1) value for a quinuclidine compared to an isobasic secondary amine. This fact shifts the pK_a position of the Brönsted break toward the right, i.e., toward larger pK_a^o values [15]. The rate constant for nucleofuge expulsion from $T^{\pm}$ (k_2 in Scheme 1) also influences the pK_a^o value [15]. The magnitude of k_2 does not change significantly with the amine nature since the amino moiety in $T^{\pm}$ cannot exert its push to expel the nucleofuge because it lacks an electron pair [4].

On the other hand, the change of solvent from water to ethanol–water should also mean a larger k_{-1} value, in view that the transition state for amine expulsion is less polar than the intermediate $T^{\pm}$ [4]. The value of k_2 should be little affected by the solvent nature because of the fact that both the transition state for leaving group expulsion and the intermediate $T^{\pm}$ are highly polar [4]. Therefore, the effect of the larger nucleofugalities of quinuclidines than isobasic secondary amines and the effect of the change of solvent from water to ethanol–water should point in opposite directions.

Addition of a methyl group to the "nonleaving" moiety of the substrate should not change the k_{-1} nor the k_2 value significantly since the inductive effects of phenoxy and 4-methylphenoxy are similar. It is known that the inductive effects from groups attached to the central carbon of a $T^{\pm}$ intermediate are more important than the resonance effects [16]. The Hammett inductive substituent constant for 4-methylphenoxy is unknown to us, but those for 4-methylphenyl and phenyl are $\sigma_I = 0.12$ for both [17]. Consequently, it is reasonable to assume that the σ_I values for 4-methylphenoxy and phenoxy are also similar. Therefore, the push exerted by these two groups in a tetrahedral intermediate $T^{\pm}$ to expel either the amine or the nucleofuge should be similar [4].

In conclusion, the larger pK_a^o value found for the reactions of quinuclidines with PNPC in water [4] compared to that for the reactions of secondary alicyclic amines with MPNPC in ethanol–water (this work) should be due to the greater nucleofugality of quinuclidines than isobasic secondary amines from $T^{\pm}$, which is only partially compensated by the change of solvent.

If the mechanism for the reactions of MPDNPC with secondary alicyclic amines were stepwise, a comparison of the k_N values for these reactions with those of MPNPC would show that the former is much more reactive than the latter toward secondary amines when breakdown of $T^{\pm}$ to products is rate-determining (e.g., k_N for MPDNPC is ca. 300-fold greater than MPNPC in the low pK_a region). This is reasonable in terms of the stronger electron withdrawal of 2,4-dinitrophenoxy, relative to 4-nitrophenoxy, from both the substrate and $T^{\pm}$, resulting in greater values of both K_1 ($=k_1/k_{-1}$) and

k_2, respectively. Nevertheless, if formation of $T^{\pm}$ were rate limiting for the aminolysis of MPDNPC at the high pK_a region of the Brönsted plot, their k_1 values would be much larger than those for the aminolysis of MPNPC. As seen in Fig. 1, the k_1 values are only slightly larger for MPDNPC, despite the different electrophilic ability of the carbonyl groups of the two compounds. This analysis suggests that the aminolysis of these two substrates occur by different mechanisms, and gives support to a concerted mechanism for the aminolysis of the dinitro derivative.

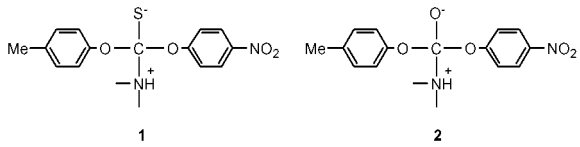
The concerted aminolysis of MPDNPC in aqueous ethanol (this work) seems to be in contrast to the stepwise mechanism found for the reactions of PDNPC with quinuclidines in water [4]. Assuming the effect of Me addition to the nonleaving group on the stability of the intermediate $T^{\pm}$ is negligible, the above change in mechanism should be due to the solvent change. In fact, secondary alicyclic amines should stabilize $T^{\pm}$ in view of their lower nucleofugalities compared to isobasic quinuclidines (see above). On the other hand, the less polar solvent, aqueous ethanol, should destabilize $T^{\pm}$ in comparison to water, because of the ionic nature of this intermediate [4,18,19]. Therefore, the above change in mechanism could be due to a great destabilization of $T^{\pm}$ in aqueous ethanol, despite its stabilization by secondary alicyclic amines.

It has been reported that the reactions of secondary alicyclic amines with methyl 2,4-dinitrophenyl carbonate in water are driven by a stepwise mechanism [20]. Substitution of methoxy by 4-methylphenoxy as the nonleaving group and the change of solvent, from water to aqueous ethanol, should both destabilize the intermediate $T^{\pm}$ and therefore, it is reasonable a change to a concerted mechanism for the reactions of MPDNPC in aqueous ethanol.

In the reactions of secondary alicyclic amines with 4-methylphenyl 4-nitrophenyl thionocarbonate (MPNPTOC) in 44 wt% ethanol–water, the plots k_{obs} vs [NH] are nonlinear upwards, indicating a variable order in amine (between 1 and 2) [5]. These plots were explained through a reaction mechanism similar to that described in Scheme 1, but with an additional path: a proton transfer (k_3 step, partially rate-determining) from $T^{\pm}$ to an amine (NH) to yield and an anionic intermediate (T^-), which decomposes rapidly to products [5].

For these reactions it was estimated that $k_3[NH] \geq k_2$ [5]. The reason why the order in amine is unity for the same aminolysis of MPNPC seems to be that (1) the value of k_2 is greater for the aminolysis of MPNPC compared to the corresponding thionocarbonate, and (2) the value of k_3 is similar for the reactions of both substrates, as explained below.

The value of k_2 for the intermediate **1** has been estimated as $(0.9–1.5) \times 10^7$ s^{-1} [5]. Substitution of S^- by O^- in **1** (to yield **2**) should result in a larger k_2 value, in view of the stronger driving force of O^-, compared to that of S^-, in a tetrahedral intermediate to form a double bond and expel a nucleofuge [21].



In order to compare the k_3 values for the aminolysis of MPNPTOC and MPNPC, those for the pK_a of the tetrahedral intermediates **1** and **2** should be previously known. The pK_a value of **1** has been estimated as 5.4 pK_a units lower than that of the corresponding protonated amine [5]. This was achieved by employing Hammett inductive σ_I values for the substituents attached to the central carbon of **1**, using Jencks' procedure [16]. Employing $\sigma_I = 0.03$ and –0.26 for S^- and O^-, respectively [17], and $\rho_I = –9.2$ [22], the pK_a difference between **1** and **2** can be determined. This gives $pK_a = –9.2\ (0.03 + 0.26) = –2.67$. Therefore, the pK_a of **2** should be $5.4 - 2.7 = 2.7$ pK_a units less than that of the corresponding aminium ion. This means that the proton transfer from any of these zwitterionic intermediates (**1** or **2**) to the free amine to yield the corresponding anionic intermediate is thermodynamically favorable and diffusion controlled [16,23]. Therefore, the k_3 value for **1** and **2** should be ca. 10^{10} $s^{-1}\,M^{-1}$ in water [13a,23,24] and 2×10^9 s^{-1} $M^{-1}$for piperazinium ion and 4×10^9 s^{-1} M^{-1} for the other secondary alicyclic amines in 44 wt% ethanol–water [5,25].

Therefore, the simple reaction mechanism found in the aminolysis of MPNPC [Eq. (2) and Scheme 1], relative to the less simple one for the corresponding thionocarbonate, should be due to the fact that for the latter reactions $k_2 \leq k_3$[amine], whereas $k_2 > k_3$[amine] for the reactions of the carbonate (being the range of amine concentration about the same in the reactions of a given amine with both substrates).

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