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Stepwise Mechanism of the Aminolysis of *O*-Ethyl *S*-(4-Nitrophenyl) Thiocarbonate

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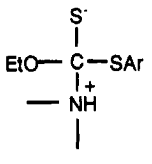
The reactions of secondary alicyclic amines with the title substrate (NPTC) are subjected to a kinetic study in water, 25.0 °C, ionic strength 0.2 M (KCl). The reactions are first order in both the amine and NPTC. The Brönsted-type plot for the second-order rate coefficient is biphasic, with slopes $\beta_1 = 0.2$ and $\beta_2 = 0.8$ at high and low pK_a values, respectively. The Brönsted plot is explained by the presence of a zwitterionic tetrahedral intermediate and a change in the rate-determining step. The center of the Brönsted curvature is p$K_a{}^\circ = 10.7$. A semiempirical equation based on the above hypothesis accounts for the experimental results. The value of p$K_a{}^\circ = 10.7$ is larger than those found in the same aminolyses of *O*-ethyl 4-nitrophenyl dithiocarbonate and *S*-(4-nitrophenyl) thioacetate, favoring amine expulsion from the tetrahedral intermediate (relative to 4-nitrobenzenethiolate ion expulsion) in the NPTC reaction. By comparison of the stepwise reaction under study with the concerted aminolysis of *O*-ethyl *S*-(2,4-dinitrophenyl) thiocarbonate it is concluded that the introduction of a second nitro group to the tetrahedral intermediate formed in the present reactions destabilizes the intermediate to such an extent that it becomes a transition state and a concerted mechanism is enforced.

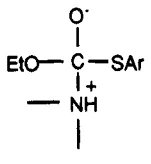
Introduction

We are interested in the mechanistic study of the aminolysis of reactive thiocarboxylic derivatives and the question of the stability of the putative tetrahedral intermediate occurring in some of these reactions. We have found that the reactions of secondary alicyclic amines with 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates in water are stepwise, proceeding through the zwitterionic tetrahedral intermediates **1** (Ar = 2,4-dinitrophenyl (DNP) or 2,4,6-trinitrophenyl (TNP)).[1] On the other hand, the reactions of the the same amine series with *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiocarbonates in water are concerted, indicating that the intermediates **2** (Ar = DNP or TNP) are not formed due to their high instability.[2,3] In other words, the change of S^- to O^- in **1** (Ar = DNP or TNP) destabilizes the intermediate to the point that it becomes a transition state and an enforced concerted mechanism takes place.[2,3]



$$\mathrm{EtO{-}\underset{\overset{+}{N}H}{\overset{S^-}{C}}{-}SAr}$$

1



$$\mathrm{EtO{-}\underset{\overset{+}{N}H}{\overset{O^-}{C}}{-}SAr}$$

2

The instability of the zwitterionic tetrahedral intermediate depends also on the other groups bound to it. For instance, it has been found that in the aminolyses of aryl acetates[4] and diaryl carbonates[5] the lower the basicity of ArO in the intermediate the faster the rate of expulsion of ArO^- from it and the greater the destabilization of the intermediate.[4,5] It is reasonable, therefore, to expect a stabilization of **2** by increasing the basicity of ArS. We report in the present work that the reactions of secondary alicyclic amines with *O*-ethyl *S*-(4-nitrophenyl) thiocarbonate in water are stepwise, indicating therefore that the substitution of Ar = DNP or TNP in **2** by 4-nitrophenyl makes possible the existence of the intermediate.

Experimental Section

Materials. The secondary alicyclic amines were purified as described.[6] *O*-Ethyl *S*-(4-nitrophenyl) thiocarbonate (NPTC) was prepared as reported and identified by NMR and IR analyses.[7]

Kinetic Measurements. These were performed spectrophotometrically, following the 4-nitrobenzenethiolate anion release at 412 nm, by the instrument and method previously described.[6] The initial NPTC concentration was 5×10^{-4} M. The reactions were followed for at least 4 half-lives, except those of piperazinium ion where the initial rate method was employed. Under excess amine pseudo-first-order rate coefficients (k_{obsd}) were found in all cases. The experimental conditions of the reactions and the k_{obsd} values are shown in Table 1.

Product Studies. 4-Nitrobenzenethiolate anion was identified as one of the final products of the aminolysis of NPTC. This was achieved by comparison of the UV–vis spectrum at the end of some reactions with that of an authentic sample of 4-nitrobenzenethiol under the same experimental conditions.

Results and Discussion

The reactions under study are described by the rate laws of eqs 1 and 2, where NPS^- and N represent 4-nitrobenzenethiolate anion and the free amine, respectively; k_o and k_N are the rate coefficients for hydrolysis

$$\frac{d[NPS^-]}{dt} = k_{obsd}[NPTC] \tag{1}$$

$$k_{obsd} = k_o + k_N[N] \tag{2}$$

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Table 1. Experimental Conditions and k_{obsd} Values for the Reactions of Secondary Alicyclic Amines with NPTC[a]

amine (pK_a)[b]	pH	10^3 $[N]_{tot}$,[c] M	$10^3 k_{obsd}$, s^{-1}	no. of runs
piperidine (11.24)	10.94	4−100	6.6−72	7
	11.24	4−80	8.1−85	6
	11.54	4−80	11−124	7
piperazine (9.94)	9.64	20−100	4.1−20	6
	9.94	10−100	2.9−34	7
	10.24	10−100	4.2−43	7
1-(2-hydroxyethyl)-piperazine (9.38)	9.38	10−120	0.91−12	7
	9.68	10−110	1.4−14	7
	9.98	10−100	1.7−14	7
morpholine (8.78)	8.48	10−140	0.41−5.8	7
	8.78	40−140	2.5−8.4	6
	9.08	10−140	0.72−11	8
1-formylpiperazine (7.98)	7.98	30−300	0.37−4.0	7
	8.28	30−300	0.44−5.1	7
	8.58	30−300	0.62−5.9	6
piperazinium ion (5.81)	5.50	40−80	0.0035−0.011	5
	5.80	30−80	0.0091−0.018	6
	6.20	20−120	0.0066−0.050	7

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). $[NPTC]_0 = 5 \times 10^{-5}$ M. [b] pK_a values under the reaction conditions. [c] Total amine concentration (free amine plus protonated forms).

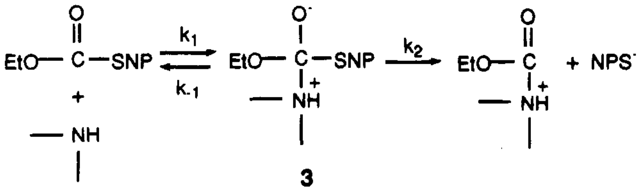
Table 2. Statistically Corrected Values of the pK_a of the Protonated Amines and of k_N for the Aminolysis of NPTC[a]

amine	$pK_a + \log (p/q)$[b]	k_N/q,[b] s^{-1} M^{-1}
piperidine	11.54	2.1
piperazine	9.94	0.33
1-(2-hydroxyethyl)piperazine	9.68	0.19
morpholine	9.08	0.12
1-formylpiperazine	8.28	0.025
piperazinium ion	6.41	0.0005

[a] Both pK_a and k_N values under the conditions shown in Table 1. [b] Statistical corrections:[8] $p = 2$ for all amines, except piperazinium ion, for which $p = 4$; $q = 1$ for all amines, except piperazine, for which $q = 2$.

and aminolysis of the substrate (NPTC), respectively. The hydrolysis reaction was generally negligible compared to the aminolysis, except in the reaction with piperazinium cation, where a significant intercept was exhibited in the plots of k_{obsd} vs [N]. The value of k_N for the reaction of each amine was obtained as the slope of a linear k_{obsd} vs [N] plot, k_N being independent of pH. The values of k_N, statistically corrected,[8] are shown in Table 2.

With the data of Table 2 the Brönsted-type plot of Figure 1 was obtained. The plot can be explained through the existence of a zwitterionic tetrahedral intermediate (**3**) in the reaction path and a change in the rate-determining step from that for k_2 to that for k_1 (eq 3) as the basicity of the amine increases.[1,4-6] The solid line in Figure 1 was calculated by means of a semiempirical equation based on the above hypothesis (eq 4)[5,9] with the following parameters: $\log k_N^\circ = -0.04$, $pK_a^\circ = 10.7$, $\beta_1 = 0.2$, $\beta_2 = 0.8$; ($R^2 = 0.9927$). β_1 and β_2 are the slopes of the lines at high and low basicity of the amines, respectively, pK_a° is the pK_a value at the center of curvature, and k_N° is the k_N value corresponding to pK_a°.



$$\mathrm{EtO{-}C({=}O){-}SNP} + \mathrm{{-}NH{-}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{EtO{-}C(O^-)(SNP){-}\overset{+}{N}H{-}}\ (\mathbf{3}) \xrightarrow{k_2} \mathrm{EtO{-}C({=}O){-}\overset{+}{N}H{-}} + \mathrm{NPS^-} \qquad (3)$$

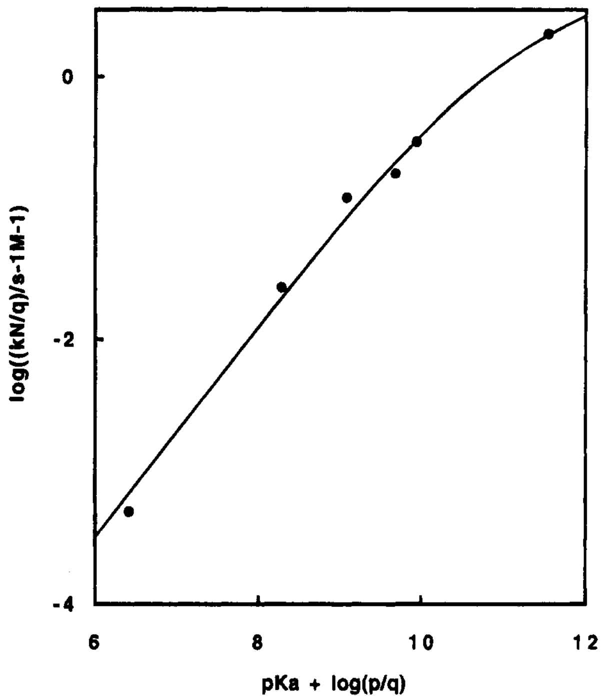


Figure 1. Brönsted-type plot (statistically corrected) obtained in the reactions of secondary alicyclic amines with NPTC. The solid line was calculated through eq 4, and the points are experimental.

$$\log(k_N/k_N^\circ) = \beta_2(pK_a - pK_a^\circ) - \log[(1 + a)/2]$$

$$\log a = (\beta_2 - \beta_1)(pK_a - pK_a^\circ) \qquad (4)$$

The magnitudes of β_1 and β_2 are in agreement with the corresponding Brönsted slopes found in the aminolyses of aryl acetates and thioacetates,[4-6] diaryl carbonates,[5] *O*-alkyl aryl dithiocarbonates,[1] acetyl chloride, and methyl chloroformate.[9] All these reactions have been demonstrated to be stepwise through curved Brönsted-type plots similar to that shown in Figure 1.[1,4-6,9] A concerted process usually exhibits a linear Brönsted relationship with $\beta = 0.5-0.6$.[2,3]

The value of $pK_a^\circ = 10.7$ indicates that for an amine of $pK_a = 10.7$, $k_{-1} = k_2$ in eq 3. Since the pK_a of NPSH is 4.6,[6] it means that an amine isobasic to NPS^- leaves **3** much faster than the anion. This is in line with the findings in other similar aminolyses.[4-6]

The value of $pK_a^\circ = 10.7$ found in the reactions under study is 1.1 pK_a units larger than that obtained in the same aminolysis of 4-nitrophenyl *O*-ethyl dithiocarbonate.[10] This means an increase in the k_{-1}/k_2 ratio in the former reactions, i.e., expulsion of the amine from **3** (relative to NPS^- expulsion), is favored over expulsion from **4**.[5,6] By comparison of the k_{-1} and k_2 values found in the aminolysis of phenyl acetate and phenyl thionoacetate, it was concluded that the change of S^- to O^- in the zwitterionic tetrahedral intermediate increases both

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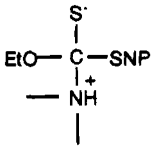

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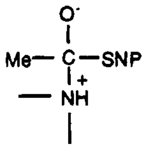

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values.[11] This was attributed to the superior ability of O^- to form a double bond and expel a nucleofuge, compared to S^-.[11,12] If the same effect can be extended to thiocarbonates and dithiocarbonates, the larger k_{-1}/k_2 ratio found for **3** than for **4** means that the rate of expulsion of a given amine from **3** (k_{-1}) increases more than that of NPS^- (k_2) by the change of S^- in **4** to O^- (to give **3**).

The $pK_a°$ value found in the present reactions is slightly larger than that reported in the same aminolysis of *S*-(4-nitrophenyl) thioacetate.[6] Since it has been found that the change of methyl to ethoxy in the zwitterionic tetrahedral intermediate increases both k_{-1} and k_2,[13] it means that this change in **5** (to yield **3**) enlarges both rate coeficients but k_{-1} more than k_2. Similar $pK_a°$ increases have been found in the aminolysis and pyridinolysis of 2,4-dinitrophenyl methyl carbonate, compared to the corresponding reactions of 2,4-dinitrophenyl acetate.[14,15] The higher instability of the tetrahedral intermediate due to the change of Me to MeO (or EtO) has been pointed out as responsible for the facts that a stepwise mechanism occurs in the aminolysis of *S*-(2,4-dinitrophenyl) thioacetate[16] and a concerted process is involved in the same aminolysis of *O*-ethyl *S*-(2,4-dinitrophenyl) thiocarbonate (DNPTC).[2] Likewise, the aminolysis of acetylpyridinium[17] and 1-(methoxycarbonyl)isoquinolinium[18] ions have been reported as stepwise and concerted, respectively.

By comparison of the concerted aminolysis of DNPTC[2] with the stepwise aminolysis of NPTC (this work) it can be concluded that there is a remarkable destabilization of the intermediate **3** by introducing a second nitro group to the nucleofuge. It is known that for a structurally homogeneous series of aryl acetates and carbonates the nucleofugality of ArO^- from the zwitterionic tetrahedral intermediate increases as the basicity of ArO^- decreases.[4,5,14a] The same is true for the leaving of ArS^- from the corresponding intermediate in the aminolysis of *S*-aryl thioacetates.[16] Therefore, the destabilization of **3** by introducing a second nitro group to NPS must arise from the lower basicity of DNPS, relative to NPS, which increases its nucleofugality from the intermediate and renders the latter highly unstable kinetically. The "intermediate" becomes then a transition state and the concerted mechanism is enforced.[19]

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