Concerted Mechanism of the Reactions of Secondary Alicyclic Amines with *O*-Ethyl *S*-(2,4,6-Trinitrophenyl) Thiocarbonate

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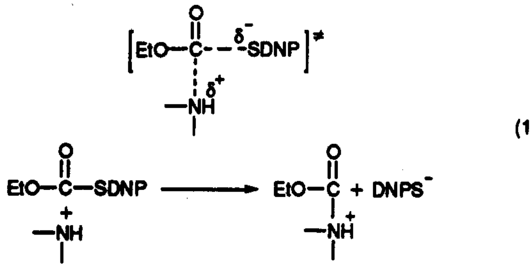
The title reactions are subjected to a kinetic study in water, 25.0 °C, ionic strength 0.2 M (KCl). Under amine excess, pseudo-first-order coefficients (k_{obsd}) are obtained. Plots of k_{obsd} vs free amine concentration at constant pH are linear, with the slope (k_N) independent of pH. The Brönsted-type plot (log k_N vs pK_a of the amine) found is linear, with slope $\beta = 0.48$, indicating a concerted mechanism. If the present reactions were stepwise, the hypothetical pK_a value at the Brönsted break (pK_a^0) would be 7.9, which is within the pK_a range of the amines (6.4–11.5). The fact that the Brönsted break is not observed confirms that the present reactions are concerted. With the data for the present reactions together with those for the same aminolysis of *O*-ethyl *S*-(2,4-dinitrophenyl) thiocarbonate, an equation relating log k_N with the pK_a of both the amine and the leaving group of the substrate is deduced. Comparison of the present reactions with similar aminolyses show that a tetrahedral addition intermediate is kinetically destabilized by the changes of the following groups attached to its central carbon: (i) methyl by ethoxy, (ii) S^- by O^-, and (iii) pyridino by an isobasic secondary alicyclic amino group.

Introduction

In a previous communication we proposed that the reactions of the title amines with *O*-ethyl *S*-(2,4-dinitrophenyl) thiocarbonate (DNPTC) proceed by a concerted mechanism (eq 1, DNP = 2,4-dinitrophenyl).[1] This was



(1)

based on the fact that a linear Brönsted-type plot of slope $\beta = 0.56$ was found. The stepwise mechanism was discarded in view that the predicted pK_a value of the center of the Brönsted curvature for this mechanism ($pK_a^0 = 9.3$) was within the pK_a range 6.4–11.5 for the amine series.[1]

We examine in this work the mechanism of the aminolysis (secondary alicyclic amines) of *O*-ethyl *S*-(2,4,6-trinitrophenyl) thiocarbonate (TNPTC), in order to confirm (or reject) the mechanism proposed above for the dinitro derivative. We find that the aminolysis of TNPTC also exhibits a linear Brönsted-type plot, with slope β ca. 0.5, indicating a concerted process and confirming, therefore, the concerted mechanism for the aminolysis of DNPTC.

Experimental Section

Materials. The secondary alicyclic amines were purified as described.[2] TNPTC was prepared as follows: To a solution of 1-chloro-2,4,6-trinitrobenzene (1.0 g, 4.0 mmol) in dimethylformamide (DMF, 10 mL) was added a solution of potassium *O*-ethyl thiocarbonate (0.58 g, 4.0 mmol) in DMF (30 mL) dropwise at room temperature. After 2 h water was added and the resulting solution extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with water to remove DMF. After drying, dichloromethane was removed by evaporation, yielding TNPTC (0.76 g, 2.4 mmol, 60% yield). TNPTC had mp 74–75 °C and was identified by the following analyses: IR (KBr) 1730 (C=O), 1545 and 1347 ($C–NO_2$), 1188 (C–O), 1063 (C–S), 852 (C–H, arom) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, 3H, $J = 7.1$ Hz), 4.37 (q, 2H, $J = 7.1$ Hz), 8.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.16 (CH_3), 66.98 (CH_2), 122.71 (C-3/5), 127.50 (C-1), 147.40 (C-4), 153.16 (C-2/6), 163.71 (C=O).

Kinetic Measurements. These were carried out by following the release of 2,4,6-trinitrobenzenethiolate ion at 400 nm by means of a Perkin-Elmer Lambda 3 spectrophotometer. The reactions were started by addition of a solution (ca. 15 μL) of the substrate (TNPTC) in ethanol into the kinetic solutions (2.5 mL) contained in 1-cm cells placed in the thermostated compartment (25.0 ± 0.1 °C) of the instrument. The initial concentration of TNPTC was ca. 6×10^{-5} M, and the amine was at least in 10-fold excess over the substrate.

Pseudo-first-order rate coefficients (k_{obsd}) were found in all cases from $\log(A_\infty - A)$ vs time plots, where A_∞ and A are the absorbances at the end of the reaction and at any time, respectively. The runs showing correlation coefficients worse than 0.999 were discarded. The experimental conditions of the reactions and the values of k_{obsd} are shown in Table I.

Product Studies. 2,4,6-Trinitrobenzenethiolate ion was identified as one of the final products of the reactions of TNPTC. This was achieved by comparison of the UV-vis spectra at the end of some reactions with that of an authentic sample of 2,4,6-trinitrobenzenethiol under the same experimental conditions.

Results and Discussion

Plots of k_{obsd} against [N], where N represents the free amine, at constant pH were linear, with the slope independent of pH. The rate law, therefore, is that shown in eqs 2 and 3, where TNP is 2,4,6-trinitrophenyl. The values

$$\frac{d[TNPS^-]}{dt} = k_{obsd}[TNPTC] \qquad (2)$$

$$k_{obsd} = k_N[N] \qquad (3)$$

of k_N for the reactions of each amine with TNPTC were obtained as the slopes of the above plots, and are shown

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

amine	pH	$10^3[N]_{tot}$[b] M	$10^2 k_{obsd}$, s^{-1}	no. of runs
piperidine	10.94	0.1–9	0.61–8.61	5
	11.24	0.1–6	1.02–8.83	5
	11.54	0.1–7	2.06–13.7	5
piperazine	9.64	0.3–35	0.205–13.3	7
	9.94	0.3–20	0.336–12.4	6
	10.24	0.3–16	0.420–12.0	6
1-(2-hydroxyethyl)piperazine	9.08	1–37	0.188–5.08	6
	9.38	1–30	0.26–6.58	6
	9.68	1–30	0.287–8.37	6
morpholine	8.48	3–55	0.502–6.73	6
	8.78	1–57	0.261–10.9	6
	9.08	5–50	1.31–11.9	6
1-formylpiperazine	7.68	6–145	0.302–5.31	7
	7.98	4–100	0.293–5.29	7
	8.28	2–70	0.159–5.05	7
piperazinium ion	5.50	20–80	0.140–0.320	5
	5.80	10–80	0.130–0.450	5
	6.20	40–120	0.358–0.862	5
	6.50	10–140	0.144–1.17	5

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Total amine concentration (free amine plus protonated forms).

Table II. Values of the pK_a of the Conjugate Acids of the Secondary Alicyclic Amines and k_N Values for the Aminolysis of TNPTC[a]

amine	pK_a + log(p/q)[b]	k_N/q, s^{-1} M^{-1} [c]
piperidine	11.54	27
piperazine	9.94	5.6
1-(2-hydroxyethyl)piperazine	9.68	4.2
morpholine	9.08	3.7
1-formylpiperazine	8.28	1.1
piperazinium ion	6.41	0.094

[a] In aqueous solution, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Statistically corrected[3] pK_a values: p = 2 for all amines, except piperazinium ion, for which p = 4; q = 1 for all amines, except piperazine for which q = 2. [c] The values of q is 2 for piperazine and 1 for the other amines.[3]

in Table II. A similar rate law was found previously for the aminolysis of DNPTC.[1]

Figure 1 shows the Brönsted-type plot (statistically corrected)[3] obtained in the present reactions (k_N and pK_a data of Table II), whose slope is $\beta = 0.48 \pm 0.09$, correlation coefficient 0.990. Also included is the linear Brönsted-type plot found in the aminolysis (secondary alicyclic amines) of DNPTC,[1] where a concerted mechanism was invoked.[1] The linearity and the values of the slopes ($\beta \approx$ 0.5–0.6) of both plots strongly suggests that both mechanisms are concerted. Furthermore, had the aminolysis of TNPTC been stepwise the predicted pK_a^0 value (= 7.9, see below) would be within the pK_a range of the amines employed. The fact that the Brönsted break is not observed in these reactions (Figure 1, pK_a range 6.4–11.5) confirms that the mechanism is most likely concerted.

In the stepwise aminolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates (DNPDTC and TNPDTC, respectively) a slower rate of amine attack (to form a tetrahedral intermediate) was found for TNPDTC relative to DNPDTC.[4] This was attributed to steric hindrance caused by the second *o*-nitro group of TNPDTC.[4] It is expected that a concerted process should proceed with less steric hindrance since the C–SAr bond is partially broken in the transition state (see eq 1). The fact that no steric hindrance is observed in Figure 1 gives further support to the claim that the aminolysis of both DNPTC and TNPTC are concerted.

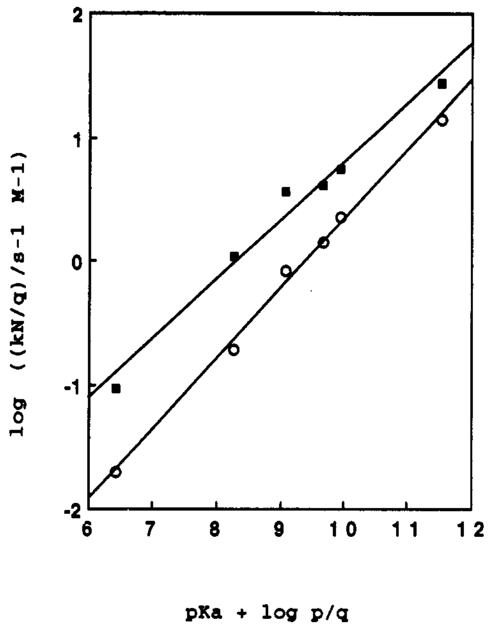

Figure 1. Brönsted-type plots (statistically corrected) obtained in the reactions of DNPTC (○, ref 1) and TNPTC (■, this work) with a series of secondary alicyclic amines. The value of the slope is β = 0.56 for DNPTC and β = 0.48 for TNPTC.

Since it is important that the hypothetical Brönsted break for a stepwise reaction (pK_a^0) be within the pK_a range of the amines employed in order to claim a concerted mechanism,[5] we will now estimate the hypothetical pK_a^0 value for the reactions of secondary alicyclic amines with TNPTC.

The stepwise pyridinolysis of methyl 2,4-dinitrophenyl carbonate (DNPC) exhibits a pK_a^0 value of 7.8,[6] whereas the same reaction of methyl 2,4,6-trinitrophenyl carbonate (TNPC) shows pK_a^0 = 6.5.[7] Hence, there is a pK_a^0 lowering of 1.3 units by introducing a third nitro group to DNPC.

On the other hand, there is a decrease of the pK_a^0 value of 1.7 units when comparing the stepwise pyridinolyses of *S*-(2,4-dinitrophenyl) thioacetate (DNPTA) and *S*-(2,4,6-trinitrophenyl) thioacetate (TNPTA), where the pK_a^0 values found are 6.6 and 4.9, respectively.[8] The reactions of the same substrates with secondary alicyclic amines show pK_a^0 values of 8.9 and 7.8 for DNPTA and TNPTA, respectively;[8] i.e., a pK_a^0 decrease of 1.1 units.

Taking into account the above results, we will assume a pK_a^0 lowering of 1.4 ± 0.3 units in going from the aminolysis (secondary alicyclic amines) of DNPTC to that of TNPTC. In view that for the former reactions a pK_a^0 = 9.3 was predicted[1] (had the reactions been stepwise), the latter reactions should exhibit a pK_a^0 = 7.9 ± 0.3 if they were stepwise.

Since the break is not observed in the Brönsted-type plot for the TNPTC reactions (Figure 1), where the pK_a range is 6.4–11.5, one can conclude that the reactions of

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secondary alicyclic amines with TNPTC are concerted, as well as those of DNPTC.[1]

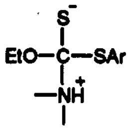
With the k_N and pK_a data of Table II and the corresponding data obtained in the aminolysis of DNPTC,[1] eq 4 can be derived by dual regression analysis (12 points,

$$\log k_N = (-4.3 \pm 0.2) - (0.19 \pm 0.03)pK_a(\mathrm{lg}) + (0.53 \pm 0.02)pK_a(\mathrm{N}) \quad (4)$$

correlation coefficient 0.992, standard error 0.120). In this equation (statistically corrected for k_N and pK_a) lg and N refer to the leaving group of the substrate and the nucleophile, respectively.

The value of the coefficient of pK_a(lg) in eq 4 ($\beta_{lg} = -0.19$) is subject to a rather large uncertainty in view that only two substrates are involved in the correlation. The absolute value of β_{lg} is low compared to the corresponding values found in similar concerted reactions.[9,10] This may indicate that breakage of the carbonyl carbon–sulfur bond is little advanced in the transition state of the present reactions (eq 1) compared to the other concerted reactions.[9,10] Nevertheless, the uncertainty involved in the β_{lg} value precludes a firm conclusion regarding this matter.

The reactions of secondary alicyclic amines with 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates are most probably stepwise as evidenced by the curved Brönsted-type plots obtained for these reactions.[4] These are likely to proceed through the zwitterionic tetrahedral intermediate 1. The difficulty of formation of the double C═S bond in 1 to yield either the reactants or the products has been mentioned as responsible for the relative kinetic stability of 1 compared to the hypothetical intermediate 2.[4] This difficulty in forming the C═S bond in 1 seems due to a weaker π-bonding energy of the thiocarbonyl group compared to carbonyl.[11] The change of S^- by O^- in 1 (with Ar = DNP or TNP) should therefore increase the rate of expulsion of both the amine and ArS^- from the "intermediate" 2 (Ar = DNP or TNP) in such a way that the latter becomes so unstable that it no longer exists.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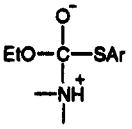
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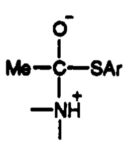
The aminolyses (secondary alicyclic amines) of DNPTA and TNPTA have been claimed stepwise, through intermediate 3.[8] This means that substitution of Me in 3 (Ar = DNP or TNP) by EtO destabilizes the resulting "intermediate" in such manner that it no longer exists and becomes a transition state. The higher instability of 2 compared to 3 has been ascribed to the additional push exerted by EtO in 2 to expel both the amine and ArS^- from the "intermediate".[1] This is in line with the finding that the methoxycarbonyl transfer from isoquinoline to pyridines is concerted,[9] whereas the acetyl transfer between pyridines is stepwise.[12]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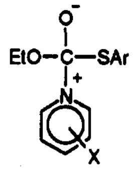
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On the other hand it seems that the pyridinolysis of DNPTC and TNPTC are stepwise, on the basis of nonlinear Brönsted-type plots.[13] Namely, these reactions occur through the zwitterionic tetrahedral intermediate 4.

The higher instability of 2 compared to 4 should arise from the fact that secondary alicyclic amines are much better nucleofuges from a tetrahedral intermediate than isobasic pyridines.[8,14] This has been found by comparison of the aminolysis and pyridinolysis of DNPTA and TNPTA,[8] and those of 2,4-dinitrophenyl acetate and 2,4-dinitrophenyl methyl carbonate.[14] Gresser and Jencks have found that in the aminolysis of *p*-nitrophenyl phenyl carbonate the sequence of nucleofugalities of isobasic amines from the tetrahedral intermediate formed in these reactions is quinuclidines > pyridines > imidazoles.[15] All these results indicate that substitution of the pyridino moiety of 4 (Ar = DNP or TNP) by an isobasic alicyclic amine destabilizes the intermediate to the point that it becomes nonexistent; i.e. it is transformed in a transition state, and the reaction is enforced to a concerted mechanism.

It is known that the less basic the leaving group of the substrate (within a homogeneous series of substrates) the larger is its rate of expulsion from the intermediate.[16] Since the "intermediates" 2 with Ar = DNP and TNP do not exist, it is possible that if Ar is changed to a more basic group such as *p*-nitrophenyl or phenyl the intermediate 2 could be less unstable and a stepwise mechanism could occur. We are at present studying the reactions of secondary alicyclic amines with *S*-(*p*-nitrophenyl) and *S*-phenyl *O*-ethyl thiocarbonates in order to find out if there is a change in mechanism by introducing these more basic groups.

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