Kinetics and Mechanism of the Reactions of Quinuclidines with Ethyl *S*-Aryl Thiolcarbonates

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Received June 28, 1999

The reactions of quinuclidines with ethyl *S*-(4-nitrophenyl) thiolcarbonate (NPTC), ethyl *S*-(2,4-dinitrophenyl) thiolcarbonate (DNPTC), and ethyl *S*-(2,4,6-trinitrophenyl) thiolcarbonate (TNPTC) are subjected to a kinetic study in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl). The reactions are studied by following spectrophotometrically (400 nm) the release of the corresponding substituted benzenethiolate anion. Under quinuclidine excess, pseudo-first-order rate coefficients (k_{obsd}) are found. Plots of k_{obsd} vs [N] (N is the free substituted quinuclidine) are linear and pH independent, with slope k_N. The Brönsted-type plots (log k_N vs pK_a of quinuclidinium ions) are linear, with slope $\beta = 0.85$ for NPTC, in agreement with a stepwise mechanism where the breakdown of a tetrahedral addition intermediate ($T^{\pm}$) is rate determining, and $\beta = 0.54$ and 0.47 for DNPTC and TNPTC, respectively, consistent with a concerted mechanism. By comparison of the reactions under investigation among them and with similar aminolyses, the following conclusions can be drawn: (i) Substitution of the 4-nitrobenzenethio group in $T^{\pm}$ by 2,4-dinitrobenzenethio or 2,4,6-trinitrobenzenethio destabilizes the tetrahedral intermediate. (ii) Quinuclidines destabilize the tetrahedral intermediate relative to secondary alicyclic amines, anilines, and pyridines. The leaving abilities of isobasic amines from $T^{\pm}$ follow the sequence pyridines < anilines < secondary alicyclic amines < quinuclidines. (iii) Quinuclidines are more reactive toward the carbonyl group of phenyl 4-nitrophenyl carbonate than that of NPTC.

Introduction

It has been described that secondary alicyclic amines are better nucleofuges from a zwitterionic tetrahedral intermediate ($T^{\pm}$) than isobasic pyridines; this has been deduced from the pK_a values at the center of the break (p$K_a°$) of nonlinear Brönsted plots found for the reactions of the above two series of amines with 2,4-dinitrophenyl acetate,[1] 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates,[2] and 2,4-dinitrophenyl and 2,4,6-trinitrophenyl dithiocarbonates.[3]

On the other hand, in the reactions of ethyl *S*-(2,4-dinitrophenyl) thiolcarbonate[4a] (DNPTC) and ethyl *S*-(2,4,6-trinitrophenyl) thiolcarbonate[4b] (TNPTC) with secondary alicyclic amines it has been found that the mechanism is concerted, whereas the pyridinolysis of the above substrates proceeds by a stepwise mechanism, i.e., in the latter reactions a tetrahedral $T^{\pm}$ intermediate is formed on the reaction path.[5] The concerted mechanism with the alicyclic amines was attributed to a substantial destabilization of $T^{\pm}$ due to the substitution of a pyridine by a secondary alicyclic amine. This destabilization is caused by the larger nucleofugality from $T^{\pm}$ of the latter amines compared to isobasic pyridines.[5]

Recently, we have studied the reactions of anilines with DNPTC and TNPTC, and found that the former reactions are stepwise whereas the latter are concerted.[6] Comparison of these reactions with those of the same substrates with alicyclic amines and pyridines shows that the stability of the intermediate $T^{\pm}$ formed with these amines increases in the sequence: secondary alicyclic amines < anilines < pyridines.[6] Again, the high stability of $T^{\pm}$ for pyridines was attributed to a lower nucleofugality from $T^{\pm}$ than that for the other amines.[6]

It has also been found that pyridines are expelled more slowly than isobasic quinuclidines (tertiary alicyclic amines) from the zwitterionic tetrahedral intermediate formed in the aminolysis of phenyl 4-nitrophenyl carbonate.[7] Nevertheless, there is no information on the relative nucleofugalities from $T^{\pm}$ of isobasic quinuclidines, anilines, and secondary alicyclic amines.

In the present work we undertake a mechanistic study of the reactions of ethyl *S*-(4-nitrophenyl) thiolcarbonate (NPTC), and those of DNPTC and TNPTC with quinuclidines with the aim to (i) shed more light on the reaction mechanism of thiolcarbonates, (ii) assess the nucleofugality of quinuclidines from $T^{\pm}$, and the relative kinetic stability of tetrahedral intermediates by comparison of the title reactions with those of the same substrates with pyridines,[5] anilines,[6] and secondary alicyclic amines,[4,8] and (iii) examine the influence of the leaving group on the kinetics and mechanism, by a comparison of the title reactions among them.

Experimental Section

Materials. The quinuclidines or their hydrochlorides (Aldrich) were purified by recrystallization. The substrates,

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10.1021/jo991036g CCC: $18.00

Table 1. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-(4-Nitrophenyl) Thiolcarbonate (NPTC)[a]

amine	pH	10^2[N]$_{tot}$,[b] M	$10^3 k_{obsd}$, s^{-1}	no. of runs
quinuclidine[c]	8.5	2.0−12	0.101−0.458	6
	8.8	2.0−12	0.206−1.07	6
	9.0	2.0−12	0.364−1.96	6
3-quinuclinidol	9.4	2.0−12	1.57−9.47	6
	9.7	2.0−12	1.74−14.3	6
	10.0	2.0−12	3.67−19.3	6
3-chloroquinuclidine	8.4	4.0−12	0.349−1.03	5
	8.7	2.0−12	0.157−2.17	6
	9.0	2.0−12	0.662−3.34	6
3-quinuclidinone	7.5	2.0−12	0.0243−0.118	6
	7.8	2.0−12	0.0311−0.171	6
	8.0	2.0−12	0.0321−0.179	6

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Concentration of total amine (free base plus protonated forms). [c] In borate buffer (0.005 M).

Table 2. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-(2,4-Dinitrophenyl) Thiolcarbonate (DNPTC)[a]

amine	pH	10^2[N]$_{tot}$,[b] M	$10^3 k_{obsd}$, s^{-1}	no. of runs
quinuclidine[c]	8.5	2.0−12	0.559−2.99	6
	8.8	2.0−12	1.18−7.13	6
	9.0	2.0−12	2.24−12.5	6
3-quinuclinidol	9.4	2.0−12	16.8−94.9	6
	9.7	2.0−12	23.1−140	6
	10.0	2.0−12	30.8−211	6
3-chloroquinuclidine	8.4	2.0−12	4.37−22.1	6
	8.7	2.0−12	8.21−45.0	6
	9.0	2.0−12	12.0−68.8	6
3-quinuclidinone	7.5	2.0−12	1.02−5.30	6
	7.8	2.0−12	1.44−6.99	6
	8.0	2.0−12	1.37−8.29	6

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Concentration of total amine (free base plus protonated forms). [c] In borate buffer (0.005 M).

Table 3. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-(2,4,6-Trinitrophenyl) Thiolcarbonate (TNPTC)[a]

amine	pH	10^2[N]$_{tot}$,[b] M	$10^3 k_{obsd}$, s^{-1}	no. of runs
quinuclidine	7.2[c]	2.0−15	0.300−1.02	6
	8.0[d]	2.0−15	0.867−3.96	6
	8.2[d]	2.0−15	1.40−7.26	6
3-quinuclinidol	9.4	2.0−12	63.4−347	6
	9.7	2.0−12	104−470	6
	10.0	0.5−6.0	41.5−344	6
3-chloroquinuclidine	8.4	2.0−12	29.7−203	6
	8.7	2.0−12	25.2−283	6
	9.0	0.2−6.0	7.82−240	6
3-quinuclidinone	7.5	2.0−12	9.34−51.4	6
	7.8	2.0−12	12.9−71.2	6
	8.0	2.0−12	14.3−79.8	6

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Concentration of total amine (free base plus protonated forms). [c] In phosphate buffer (0.005 M). [d] In borate buffer (0.005 M).

Table 4. Values of pK_a for Amines and k_N for the Aminolysis of Ethyl *S*-Aryl Thiolcarbonates[a]

amine	pK_a	$10^2 k_N$, s^{-1} M^{-1} NPTC	DNPTC	TNPTC
quinuclidine	11.4	412	2680	6800
3-quinuclidinol	9.8	27.7	287	920
3-chloroquinuclidine	9.0	5.9	112	840
3-quinuclidinone	7.5	0.197	8.8	84

[a] Both pK_a and k_N values in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl).

NPTC, DNPTC, and TNPTC, were synthesized as previously reported.[4,8]

Determination of pK_a. The pK_a values of the different quinuclidines were determined spectrophotometrically in the 200−220 nm range, in water, 25.0 ± 0.1 °C, ionic strength 0.2 M (maintained with KCl).

Kinetic Measurements. These were carried out by means of a Hewlett-Packard 8453 diode array spectrophotometer, in water, at 25.0 ± 0.1 °C, ionic strength 0.2 M (KCl); in some reactions borate or phosphate buffer (0.005 M) was used. The reactions were followed at 400 nm (formation of the substituted benzenethiolate anions).

All reactions were studied under excess of the amine over the substrate (20-fold at least). The initial substrate concentration was 5×10^{-5} M.

Pseudo-first-order rate coefficients (k_{obsd}) were found for all reactions; for most of them k_{obsd} was determined by means of the "infinity" method. Only in the slowest reactions (those of NPTC with 3-quinuclidinone) the initial rate method was used.[9] The experimental conditions of the reactions and the k_{obsd} values obtained are shown in Tables 1−3.

Product Studies. One of the products the title reactions was identified as the corresponding benzenethiolate; this was achieved by comparison of the UV−vis spectra after completion of the reactions with those of authentic samples of the above products under the same experimental conditions.

Results and Discussion

The general rate law obtained in the present reactions is given by eqs 1 and 2, where Ar is 4-nitrophenyl, 2,4-dinitrophenyl, or 2,4,6-trinitrophenyl, k_o and k_N are the rate constants for hydrolysis and aminolysis of the substrates, respectively, and N represents the substituted quinuclidine free base. In most cases the hydrolysis term in eq 2 was negligible compared to that for the aminolysis.

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

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

The second-order rate coefficients for aminolysis (k_N) were obtained as the slopes of plots of eq 2 at constant pH and were pH independent. These values, together with those of the pK_a of the conjugate acids of the quinuclidines, are shown in Table 4.

With the data of Table 4 the Brönsted-type plots of Figure 1 were obtained. The plots are linear, with slopes $\beta_{nuc} = 0.85 \pm 0.1$, $\beta_{nuc} = 0.54 \pm 0.05$, and $\beta_{nuc} = 0.47 \pm 0.05$ for the reactions of NPTC, DNPTC, and TNPTC, respectively.

The magnitude of β_{nuc} for the reaction of NPTC is in agreement with the values of the Brönsted slopes found in the stepwise aminolysis of similar substrates when the breakdown to products of the zwitterionic tetrahedral intermediate ($T^\pm$) is the rate-determining step.[1−3,5,7,8,10−15] The mechanism for this reaction is shown in Scheme 1, where NP is 4-nitrophenyl. The step k_2 should be rate determining for these reactions, and the formation of $T^\pm$ should be an equilibrium step. The aminolysis rate constant is in this case: $k_N = k_1k_2/k_{-1} = K_1k_2$, where K_1 is the equilibrium constant for the formation of $T^\pm$.

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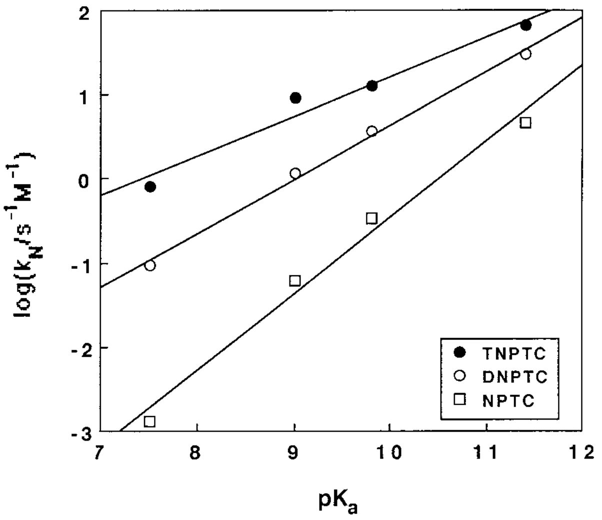
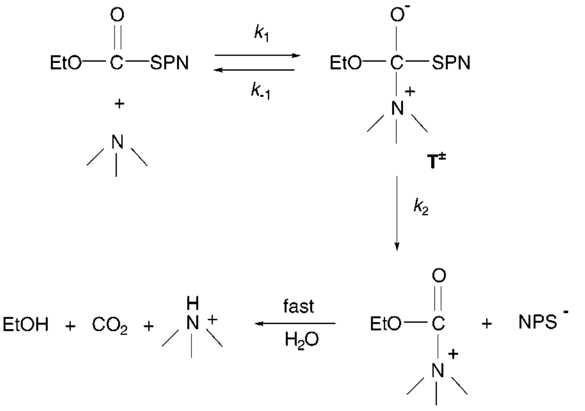
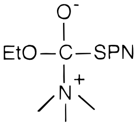


Figure 1. Brönsted-type plots obtained in the reactions of quinuclidines with ethyl *S*-(4-nitrophenyl) thiolcarbonate (NPTC), ethyl *S*-(2,4-dinitrophenyl) thiolcarbonate (DNPTC), and ethyl *S*-(2,4,6-trinitrophenyl) thiolcarbonate (TNPTC), in aqueous solution, 25.0 °C, ionic strength 0.2.

Scheme 1



A similar result was found by Gresser and Jencks for the reactions of phenyl 4-nitrophenyl carbonate (PNPC) with quinuclidines.[7] A comparison between the reactions on NPTC and PNPC with quinuclidines shows that the k_N values for PNPC are about 1 order of magnitude greater than those for NPTC. On the other hand, a comparison between the zwitterionic tetrahedral intermediates **1** and **2** formed in the reactions of quinuclidines with NPTC and PNPC, respectively, suggests that the nucleofuge is expelled faster in **1** (greater k_2) because 4-nitrobenzenethiolate anion is less basic than 4-nitrophenoxide anion (pK_a = 4.6 and 7.1, respectively),[7,8] and furthermore, the push provided by EtO in **1** to expel the leaving group is greater than that exerted by PhO in **2**.[14a] Therefore, if the k_2 value is larger for **1** and the k_N value ($= K_1k_2$) is larger for the reactions of PNPC, it follows that the equilibrium constant K_1 ($= k_1/k_{-1}$) is greater for the formation of **2** than that of **1**. It is difficult to evaluate the relative values of k_{-1} (rate constant for expulsion of quinuclidines) for **1** and **2** since the larger push provided by NPO in **2** than that by NPS in **1**[2] should be compensated by the stronger push exerted by EtO in **1** than that by PhO in **2**.[14a]



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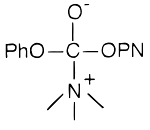

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On the other hand, the values of $\beta_{nuc} = 0.54$ and 0.47 found for the reactions of DNPTC and TNPTC (Figure 1) are in accord with a concerted process where the structure of the transition state remains constant with the variation of the nucleophile basicity.[16] These β_{nuc} values are in agreement with those found in the concerted reactions of secondary alicyclic amines with DNPTC and TNPTC, as indicated by the linear Brönsted plots ontained, with slopes $\beta = 0.56$ and 0.48, respectively,[4] together with the fact that the predicted Brönsted breaks, had these reactions been stepwise, were not observed.[4] The above β_{nuc} values are also in accordance with the value $\beta_{nuc} = 0.54$ found in the concerted reactions of TNPTC with anilines.[6]

The β value alone is not sufficient to prove that a reaction is concerted; one must be sure that the hypothetical break (pK_a°) of the Brönsted-type plot (due to the change in the rate determining step of a stepwise process) is located at a pK_a value within the pK_a range of the nucleophiles used in the plot.[16] Unfortunately, there are no studies on stepwise reactions of quinuclidines with thiolcarbonates where pK_a° values have been reported, to estimate an hypothetical Brönsted break for the reactions of DNPTC and TNPTC with quinuclidines. Gresser and Jencks have found a biphasic Bronsted plot with pK_a° = 7.5 in the reactions of quinuclidines with phenyl 2,4-dinitrophenyl carbonate (PDNPC).[7] Considering the increase of the pK_a° value of 0.8 pK_a unit by the change of nucleofuge from 2,4-dinitrophenoxide to 2,4-dinitrobenzenethiolate in the pyridinolysis of methyl 2,4-dinitrophenyl carbonate[11b] and DNPTC,[5] and taking into account the fact that for the reactions of quinuclidines with PNPC[7] pK_a° = 10.7, while for those with NPTC pK_a° > 11.5 (this work), it is possible to expect a value of pK_a° > 7.5 for the reactions of DNPTC with quinuclidines. No curvature is observed in Figure 1 for DNPTC at pK_a > 7.5. This argument and the great difference found in the Brönsted slopes for the reactions of DNPTC and TNPTC compared to that for NPTC (Figure 1), suggests that the mechanisms of the reactions of DNPTC and TNPTC with quinuclidines are concerted.

It has been reported that the reactions of DNPTC and TNPTC with pyridines[5] and the former with anilines[6]

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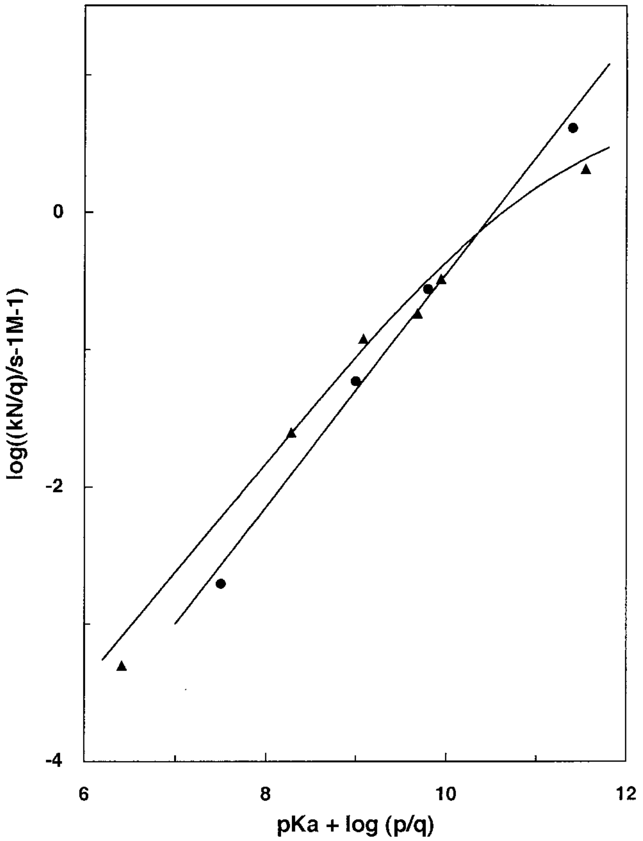

Figure 2. Brönsted-type plots (statistically corrected)[2] obtained in the reactions of ethyl *S*-(4-nitrophenyl) thiolcarbonate (NPTC) with quinuclidines (●, this work) and secondary alicyclic amines (▲, ref 8), in aqueous solution, 25.0 °C, ionic strength 0.2.

proceed through the formation of a tetrahedral intermediate ($T^{\pm}$). The fact that the reactions of the same substrates with quinuclidines are concerted (this work) can be explained by a faster expulsion rate from $T^{\pm}$ of the latter amines than isobasic pyridines and anilines. Namely, quinuclidines destabilize kinetically the tetrahedral intermediate relative to pyridines and anilines.

Figure 2 shows the Bronsted-type plots for the reactions of NPTC with quinuclidines (this work) and secondary alicyclic amines.[8] Three observations can be made: (i) In the pK_a range where the second step is rate determining the k_N ($= k_1k_2/k_{-1}$) values are greater for secondary alicyclic amines than for isobasic quinuclidines. (ii) Comparison of the k_N values in the high pK_a region (where the k_1 step is rate limiting for the reactions of the secondary amines) allow us to conclude that the k_1 values for quinuclidines (which are beyond pK_a 11.4) should be greater than those for isobasic secondary alicyclic amines. (iii) In the reactions with quinuclidines, the center of curvature (pK_a of a quinuclidine for which $k_2 = k_{-1}$) it is not observed in the pK_a range studied and, therefore, it must be at pK_a > 11.4. Considering the first and second observations and taking into account that the value of k_2 must be the same for both amine series, since the amino moiety in $T^{\pm}$ cannot exert the "push" to expel the leaving group,[7] it is possible to conclude that quinuclidines are expelled faster from the $T^{\pm}$ intermediate than isobasic secondary alicyclic amines. Therefore, quinuclidines destabilize kinetically the tetrahedral intermediate relative to secondary alicyclic amines. In other words, the fact that the p$K_a°$ for the reactions of NPTC with quinuclidines is larger than that for secondary alicyclic amines (see Figure 2) means that the k_{-1}/k_2 ratio is greater for quinuclidines.[3b] Since k_2 should not change significantly either with the basicity or the nature of the amine,[7] the larger k_{-1}/k_2 ratio for quinuclidines implies a larger k_{-1} for these amines relative to isobasic secondary alicyclic amines.

In summary, we can conclude that quinuclidines destabilize kinetically the tetrahedral intermediate (due to a larger k_{-1}) relative to the other series of amines studied. Therefore, the sequence: quinuclidines > secondary alicyclic amines > anilines > pyridines seems to hold for the rate constants for amine expulsion (k_{-1}) from the zwitterionic tetrahedral intermediate.

By comparison of the concerted reactions of the series of quinuclidines with DNPTC and TNPTC with the stepwise mechanism for the reactions of the same amines with NPTC, it can be concluded that there is a remarkable destabilization of the tetrahedral intermediate by introducing a second and a third nitro group to the nucleofuge. This destabilization must arise from the lower basicity of TNPS and DNPS, relative to NPS (pK_a 1.4, 3.4, and 4.6, respectively)[2] which results in a larger nucleofugality of the former two groups from the intermediate $T^{\pm}$ and renders these species highly unstable kinetically. The intermediate either no longer exists and the concerted mechanism is enforced, or it is so unstable that the reaction bypasses it and proceeds through a lower energy path (the concerted route).[17]

Acknowledgment. We thank FONDECYT of Chile for financial assistance to this work.

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