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Mechanistic study on the substitution reactions of *O*-ethyl *S*-aryl dithiocarbonates with quinuclidines

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The quinuclidinolysis of 4-nitrophenyl, 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates (1, 2, and 3, respectively) are studied kinetically at 25.0 °C, ionic strength 0.2 M; the two former in water and the latter in 44 wt% ethanol–water. The Brønsted plots (log k_N vs. pK_a of quinuclidinium ions) for the reactions of 1 and 2 are linear with slopes $\beta = 0.94$ and 0.76, respectively, and that of 3 shows a smooth curvature. From these results and other arguments it can be concluded that the quinuclidinolysis of dithiocarbonate 1 in water is stepwise, in contrast to those of dithiocarbonates 2 in water and 3 in aqueous ethanol, which are concerted. The kinetics and mechanistic effects of the leaving and electrophilic groups and the amine nature are discussed. Copyright © 2008 John Wiley & Sons, Ltd.

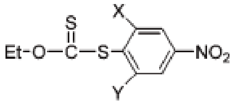
Keywords: kinetics; mechanism; Brønsted plots; aminolysis; dithiocarbonates

INTRODUCTION

The kinetics and mechanisms of the reactions of secondary alicyclic (SA) amines[1–5] and pyridines[6] with *O*-ethyl *S*-aryl dithiocarbonates have been subjected to investigation. Some of these reports involve the reactions of SA amines with 4-nitrophenyl 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates (**1**, **2**, and **3**, respectively)[1,2] and with a series of ethyl 4-X-phenyl dithiocarbonates (X = H, CH_3, CH_3O, and Cl),[2,3] and also those of pyridines with dithiocarbonates **2** and **3**,[6] all of them in water. All of these processes have been described as stepwise, proceeding through a zwitterionic tetrahedral intermediate ($T^{\pm}$).

Also, the reactions of **1** and **2** with SA amines in aqueous ethanol were found to be stepwise,[4] in contrast to the same aminolysis of **3** in this medium, which were claimed to be concerted.[5]

With the aim to determine the influence of the nucleofuge, amine nature and solvent on the mechanism of the aminolysis of dithiocarbonates, in the present work we carry out a kinetic study of the quinuclidinolysis of **1** and **2** in water and that of **3** in 44 wt% aqueous ethanol.



1 (X = Y = H)
2 (X = NO_2; Y = H)
3 (X = Y = NO_2)

RESULTS AND DISCUSSION

The kinetic law obtained under the reaction conditions is that described by Eqn (1), where ArS^- is the corresponding benzenethiolate anion, S is the substrate, and k_{obs} is the pseudo-first-order rate coefficient (under excess quinuclidine over the substrate).

$$\frac{d[ArS^-]}{dt} = k_{obs}[S] \qquad (1)$$

The experimental conditions of the reactions and the values of k_{obs} are shown in Tables 1–3.

Plots of k_{obs} against concentration of free quinuclidine at constant pH were linear, in accordance with Eqn (2), where k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrates, respectively. The values of k_0 and k_N were obtained as the intercept and slope, respectively, of plots of Eqn (2). The values of k_N were pH-independent. For some reactions the plots showed parallel lines for different pH values, indicating a dependence of k_0 with pH.

$$k_{obs} = k_0 + k_N[\text{free quinuclidine}] \qquad (2)$$

Tables 4 and 5 show the values of pK_a for the quinuclidinium ions and those of k_N for the reactions under study.

Figure 1 shows the Brønsted plots obtained for the reactions of the series of quinuclidines (QUI) with **1** and **2** in water (data in Table 4) and Fig. 2 exhibits the corresponding plot for the reactions with **3** in 44 wt% ethanol–water (data in Table 5). The plots in Fig. 1 are linear with slopes $\beta = 0.94$ and 0.76 for the reactions of **1** and **2**, respectively; but that in Fig. 2 presents a smooth curvature. The k_N values, as well as those of the pK_a of the conjugate acids of these amines, were statistically corrected[7] with $q = 2$ for DABCO ($q = 1$ for all the other amines) and $p = 1$ for all the conjugate acids of the amines. The parameter q is the

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Table 1. Experimental conditions and k_{obs} values for the reactions of quinuclidines with ethyl 4-nitrophenyl dithiocarbonate (**1**) in water[a]

Amine	pH	F_N[b]	$10^3[N]_{tot}/mol^{-1} dm^{-3}$[c]	$10^2k_{obs}/s^{-1}$	No. of runs
Quinuclidine	11.1	0.33	1.07–9.08	1.30–5.55	6
	11.4	0.50	1.09–9.23	2.39–8.51	6
	11.7	0.66	0.527–5.27	3.31–8.88	7
3-Hydroxyquinuclidine	9.6	0.33	5.39–53.9	0.162–1.44	7
	9.9	0.50	6.25–62.5	0.258–24.1	7
	10.2	0.66	2.35–23.5	0.245–1.42	6
3-Chloroquinuclidine	8.6	0.33	5.81–58.1	0.0207–0.171	7
	8.9	0.50	5.46–54.6	0.0304–0.258	7
	9.2	0.67	3.81–38.1	0.0332–0.261	7
DABCO	8.6	0.33	2.94–29.4	0.0147–0.104	7
	8.9	0.5	11.2–112	0.0709–0.575	7
3-Quinuclidinone	7.2	0.33	18.7–159	0.00357–0.0258	6
	7.5	0.50	19.1–191	0.00454–0.0319	7
	7.8	0.67	18.6–186	0.00554–0.0404	7

[a] At 25 °C, ionic strength 0.2 M (KCl).

[b] Free amine fraction.

[c] Concentration of total amine (free base plus protonated forms).

number of equivalent basic sites in the free amine and *p* is the number of equivalent dissociable protons in the conjugate acid of the amine.[7]

The Brønsted β value found for the reaction of **1** ($\beta = 0.94$) is in agreement with those obtained for other stepwise reactions where breakdown to products of the zwitterionic tetrahedral intermediate ($T^{\pm}$) is the rate-determining step (k_2 step in Scheme 1). Similar Brønsted slope values for the rate-determining k_2 step (β_2) have been obtained in some reactions showing biphasic Brønsted-type plots. Examples of these are the reactions of dithiocarbonate **1** with SA amines, both in water ($\beta_2 = 0.80$)[1] and in aqueous ethanol ($\beta_2 = 0.95$),[4] those of **2** and **3** with pyridines[6] ($\beta_2 = 1.0$ and 0.9, respectively) and SA amines in water ($\beta_2 = 0.8$ for both substrates)[2] and that of **2** with SA amines in aqueous ethanol ($\beta_2 = 0.8$).[4] Slope values in the same range have also been found for stepwise reactions exhibiting linear Brønsted-type plots, with slopes compatible with the k_2 step being rate-limiting. Among these are the reactions of

Table 2. Experimental conditions and k_{obs} values for the reactions of quinuclidines with *O*-ethyl 2,4-dinitrophenyl dithiocarbonate (**2**) in water[a]

Amine	pH	F_N[b]	$10^3[N]_{tot}/mol^{-1} dm^{-3}$[c]	$10^3k_{obs}/s^{-1}$	No. of runs
Quinuclidine	11.1	0.33	0.50–5.00	1.41–17.3	7
	11.4	0.50	0.50–5.00	2.39–30.1	6
	11.7	0.67	0.50–5.00	3.38–39.0	7
3-Hydroxyquinuclidine	9.5	0.33	2.00–20.0	0.794–6.68	6
	9.8	0.5	0.50–5.00	0.272–2.93	7
	10.1	0.67	2.00–20.0	1.36–14.4	6
3-Chloroquinuclidine	8.7	0.33	5.00–50.0	0.467–3.52	7
	9.0	0.50	5.00–50.0	0.740–5.17	7
	9.3	0.67	5.00–42.5	0.710–6.25	6
DABCO	7.5[d]	0.0457	5.00–50.0	0.185–0.582	7
	8.0[d]	0.131	5.00–50.0	0.303–1.37	7
3-Quinuclidinone	7.2	0.33	5.00–27.5	0.00396–0.168	4
	7.5	0.5	5.00–42.5	0.00569–0.343	6

[a] At 25 °C, ionic strength 0.2 M (KCl).

[b] Free amine fraction.

[c] Concentration of total amine (free base plus protonated forms).

[d] Phosphate buffer 0.01 M.

Table 3. Experimental conditions and k_{obs} values for the reactions of quinuclidines with *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate (**3**) in 44 wt% ethanol–water[a]

Amine	pH	F_N[b]	$10^3[N]_{tot}$/mol^{-1} dm^{-3}[c]	$10^3 k_{obs}$/s^{-1}	No. of runs
Quinuclidine	11.4	0.33	1.11–22.2	3.60–24.2	8
	11.7	0.50	2.17–10.9	11.1–26.5	6
	12.0	0.66	2.22–11.1	15.1–33.7	6
3-Hydroxyquinuclidine	9.7	0.50	1.11–11.1	1.45–8.86	7
	10.1	0.67	1.08–10.8	2.81–13.0	6
DABCO	8.0	0.33	2.25–9.02	0.546–1.55	5
	8.3	0.5	2.07–10.3	0.678–2.48	6
	8.6	0.67	1.10–8.79	0.649–2.91	6
3-Chloroquinuclidine	7.5	0.33	9.78–97.8	0.797–4.23	7
	7.8	0.50	10.3–103	0.915–7.95	7
	8.1	0.67	10.9–109	1.40–11.8	7
3-Quinuclidinone	6.8	0.33	10.2–102	0.308–1.42	7
	7.1	0.50	10.1–101	0.307–1.93	7
	7.4	0.67	10.1–101	0.418–2.34	7

[a] At 25 °C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).

Table 4. Values of pK_a for the conjugate acids of quinuclidines and k_N values for the reactions of these amines with *O*-ethyl 4-nitrophenyl dithiocarbonate (**1**) and *O*-ethyl 2,4-dinitrophenyl dithiocarbonate (**2**), both in water[a]

		k_N/s^{-1} M^{-1}	
Amine	pK_a	**1**	**2**
Quinuclidine	11.4	15.7 ± 0.4	12.8 ± 0.6
3-Hydroxyquinuclidine	9.8	0.78 ± 0.02	1.10 ± 0.02
3-Chloroquinuclidine	9.0	0.094 ± 0.004	0.193 ± 0.008
DABCO	8.9	0.101 ± 0.001	0.190 ± 0.007
3-Quinuclidinone	7.5	0.0034 ± 0.0001	0.0151 ± 0.0008

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

Table 5. Values of pK_a for the conjugate acids of quinuclidines and k_N values for the reactions of these amines with *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate (**3**) in 44 wt% ethanol–water[a]

Amine	pK_a	k_N/s^{-1} M^{-1}
Quinuclidine	10.7	3.1 ± 0.1
3-Hydroxyquinuclidine	9.7	1.54 ± 0.03
DABCO	8.3	0.45 ± 0.01
3-Chloroquinuclidine	7.8	0.15 ± 0.01
3-Quinuclidinone	7.1	0.0327 ± 0.0007

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

quinuclidines with 4-nitrophenyl methyl carbonate ($\beta = 0.86$)[8] and phenyl,[9] 4-methylphenyl[10], and 4-chlorophenyl[10] 4-nitrophenyl carbonates ($\beta = 1.0$, 0.88, and 0.87, respectively).

On the other hand, the β value found for the reaction of **2** ($\beta = 0.76$, Fig. 1) is in the borderline between stepwise and concerted mechanisms. In order to confirm one of these mechanisms it is necessary to check the presence or absence of the expected curvature center (pK_a^0 value, assuming a stepwise mechanism) in the pK_a range measured (in this case 7.5–11.4). It is known that the change of SA amines to QUI increases the pK_a^0 value.[10] Since in the stepwise reaction of SA amines with **2** in water the pK_a^0 is 9.2,[2] if the mechanism with QUI in water were stepwise the pK_a^0 value would be greater than 9.2. If the expected pK_a^0 value were between 9.2 and 11.4, the absence of curvature would confirm a concerted mechanism, but if the expected pK_a^0 value were greater than 11.4 we could not confirm the mechanism. Unfortunately, no pK_a^0 values have been reported

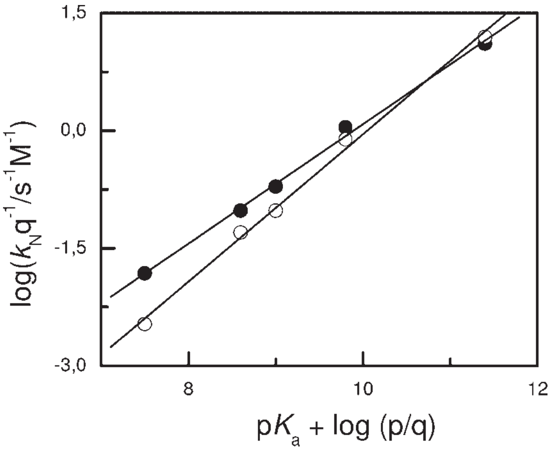


Figure 1. Brønsted-type plots obtained in the reactions of quinuclidines with *O*-ethyl 4-nitrophenyl dithiocarbonate (**1**, ○), and *O*-ethyl 2,4-dinitrophenyl dithiocarbonate (**2**, ●), in water, at 25.0 °C and an ionic strength of 0.2 M (KCl)

for quinuclidinolysis reactions; therefore, is not possible to predict the pK_a^0 value for a hypothetical stepwise mechanism for the quinuclidinolysis of **2**.

On the other hand, considering that: (i) the reactions of QUI with **1** are stepwise, with pK_a^0 value >11.4 (see above) and (ii) at pK_a values greater than 11.4 the rate-determining step is the formation of the zwitterionic tetrahedral intermediate ($T^{\pm}$),[1–6] if the reactions of QUI with **2** were stepwise, extrapolation of the two Brønsted lines in Fig. 1 to high pK_a shows that the k_1 values would be greater for the reactions of **1** compared to those of **2**. This is not reasonable because the thiocarbonyl group in the latter substrate is more positive and therefore more prone to nucleophilic attack. From this point of view the mechanism for the quinuclidinolysis of **2** should be concerted.

Scheme 2 shows the probable concerted quinuclidinolysis of **2** in aqueous solution.

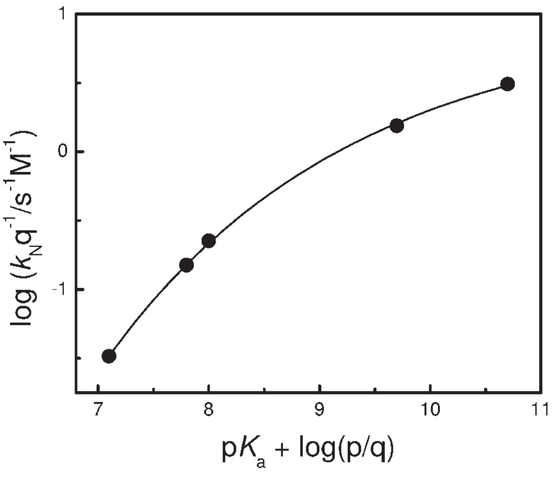
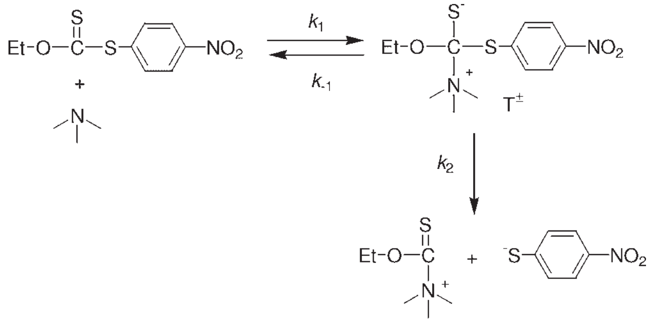


Figure 2. Brønsted-type plot obtained in the reactions of quinuclidines with *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate (**3**), in 44 wt% ethanol–water, at 25.0 °C and an ionic strength of 0.2 M (KCl)



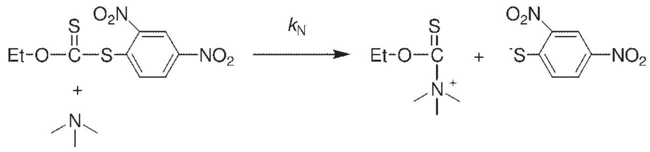
Scheme 1.

The quinuclidinolysis of dithiocarbonate **3** in aqueous ethanol shows a slightly curved Brønsted plot (Fig. 2). Although the curve could be fitted by a semiempirical equation derived for a stepwise mechanism with a change in the rate determining step,[1–6] we are more inclined towards a concerted mechanism for the following arguments: (i) the mechanism for the reactions of **3** with SA amines in aqueous ethanol is concerted[5] and it is known that QUIs are better nucleofuges than isobasic SA amines.[10] Therefore, tetrahedral intermediates derived from QUIs are more unstable than those derived from SA amines, and, consequently, the mechanism for the reactions with the former amines should be concerted. (ii) The change of 2,4-dinitrophenoxide by 2,4,6-trinitrophenoxide as nucleofuge destabilizes the putative tetrahedral intermediate;[4,5] the change of solvent, from water to aqueous ethanol, also destabilizes this intermediate.[5,11] Therefore, if the reactions of QUIs with **2** in water are concerted the quinuclidinolysis of **3** in aqueous ethanol should also be concerted.

Taking into account these arguments and in accordance with the Hammond postulate,[12] the smooth Brønsted curve for the reactions of QUIs with **3** in aqueous ethanol (Fig. 2) can be explained by a slight change in the transition state (TS) structure as the basicity of the amine varies in a reaction proceeding in a single step.[12] These plots show a slight decrease of the slope as the basicity of the amine increases, namely, a "late" TS for the less reactive amines (large β values) and an "early" TS for the more reactive amines (low β values).[12] These types of plots for concerted reactions have been obtained in the aminolysis of substituted benzoyl fluorides,[13] 4-methylphenyl 2,4-dinitrophenyl carbonate,[14] and bis(4-nitrophenyl) thionocarbonate.[15]

Effect of the electrophilic group

The quinuclidinolysis of ethyl *S*-2,4-dinitrophenyl thiolcarbonate (EDNPTC) in water is concerted.[16] On the other hand, it is known that the change of the electrophilic group from carbonyl to thiocarbonyl stabilizes the tetrahedral intermediate.[17] Since the quinuclidinolysis of **2** in water is also concerted (this study), it can be concluded that this stabilization is not sufficient to change the mechanism from concerted to stepwise.



Scheme 2.

The quinuclidinolysis of **3** in aqueous ethanol (this study) as well as that of ethyl *S*-2,4,6-trinitrophenyl thiolcarbonate (ETNPTC) in water[16] are concerted. The change of the electrophilic group from CO to CS should stabilize the tetrahedral intermediate (see above); in contrast, the change from water to aqueous ethanol as solvent should destabilize the tetrahedral intermediate.[5,11] The fact that both reactions are concerted means that these effects are totally or partially compensated and not sufficient to change the mechanism. On the other hand, the k_N values of the reactions of QUIs with EDNPTC and ETNPTC are greater than those with **2** and **3**, respectively.[16] This is in accordance with the HSAB principle.[18,19] QUIs are considered hard bases and these would prefer to bind to the harder carbonyl group rather than the softer thiocarbonyl.

Effect of the amine nature

The reactions of **1** with SA amines in water show a biphasic Brønsted-type plot ($\beta_1 = 0.2$, $\beta_2 = 0.8$, $pK_a^0 = 9.6$), in accordance with a stepwise mechanism.[1] The reactions of the same substrate with QUIs in the same solvent are also stepwise ($\beta = 0.97$, $pK_a^0 > 11.4$, this work). The difference is that the reactions of SA amines show a change in the rate determining step, from breakdown of the tetrahedral intermediate $T^{\pm}$ (for amines with $pK_a < 9.6$) to its formation (for amines with $pK_a > 9.6$), whereas for the reactions of QUIs the breakdown of the intermediate $T^{\pm}$ is rate determining for the whole pK_a range studied.

The greater pK_a^0 value for the quinuclidinolysis reaction is in accordance with the two following facts: (i) QUIs are better nucleofuges from the intermediate $T^{\pm}$ (greater k_{-1} values) than isobasic SA amines[10,16] and (ii) the amine moiety in $T^{\pm}$ does not possess an electron pair to exert its push to expel the nucleofuge (rate constant k_2); namely, k_2 is independent of the amine basicity and nature,[9,11] and, therefore, the k_2 value should be the same for SA amines and QUIs.

The above can be quantified by an equation derived from the hypothesis of the tetrahedral intermediate (Eqn 3).[6] This equation shows that the greater the pK_a^0 value the greater is the k_{-1}/k_2 ratio, assuming that ($\beta_2 - \beta_1$) does not change significantly. Since k_2 is independent of the amine, this means a greater k_{-1} value for QUIs, relative to that for isobasic SA amines.

$$\log(k_{-1}/k_2) = (\beta_2 - \beta_1)(pK_a^0 - pK_a) \tag{3}$$

The reactions of SA amines with **2** in water show a biphasic Brønsted-type plot ($\beta_1 = 0.2$, $\beta_2 = 0.8$, $pK_a^0 = 9.2$),[2] in accordance with a stepwise mechanism, in contrast to the reactions of QUIs with the same substrate in the same solvent, which are concerted (this work). This different behavior can be explained by a destabilization of the tetrahedral intermediate $T^{\pm}$ formed with the SA amines by the change to QUIs, since the latter amines are better nucleofuges than SA amines from the intermediate $T^{\pm}$.

CONCLUDING REMARKS

By comparing the reactions under investigation between each other and with similar aminolyses, the following conclusions can be drawn:

(i) The quinuclidinolysis of dithiocarbonate **1** in water is stepwise, in contrast to those of dithiocarbonates **2** in water and **3** in aqueous ethanol, which are concerted.

(ii) The change of SA amines to QUIs changes the mechanism of the reactions of **2** from stepwise to concerted.

(iii) The reactions of QUIs with dithiocarbonates **2** and **3** are concerted, as are the reactions of the same amines with the corresponding thiolcarbonates. Therefore, the stabilization of the putative tetrahedral intermediate by the change of CO to CS as electrophilic group is not sufficient to change the mechanism from concerted to stepwise.

EXPERIMENTAL

Materials

The dithiocarbonates, **1**,[1] **2**,[2] and **3**,[2] were prepared as described.

Kinetic measurements

These were carried out spectrophotometrically by means of a diode array at 25.0 ± 0.1 °C, ionic strength 0.2 M (KCl) by monitoring the appearance of the corresponding benzenethiolate anion.

All reactions were examined under excess amine over the substrate. The initial substrate concentration was 5×10^{-5} M, and the pH was maintained mainly by partial protonation of the quinuclidines (phosphate buffer was used only in one case).

Pseudo-first-order rate coefficients (k_{obs}) were found throughout and determined by means of the spectrophotometer kinetic software for first order reactions. The experimental conditions of the reactions and the values of k_{obs} are shown in Tables 1–3.

Product studies

One of the products of the reactions under scrutiny was identified as the corresponding benzenethiolate anion (the mononitro, dinitro, or trinitro derivative), as shown by comparison of the UV–vis spectra after completion of the reactions with those of authentic samples under the same experimental conditions.

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