

Reactions of aryl chlorothionoformates with quinuclidines. A kinetic study

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The reactions of quinuclidines with phenyl, 4-chlorophenyl, 4-cyanophenyl, and 4-nitrophenyl chlorothionoformates (1, 2, 3, and 4, respectively) are subjected to a kinetic study in aqueous solution, at 25.0 °C, and an ionic strength of 0.2 M (KCl). The reactions are studied by following spectrophotometrically the release of the corresponding phenoxide anion/phenol generated in the parallel hydrolysis of the substrates. Under amine excess, pseudo-first-order rate coefficients (k_{obs}) are found. Plots of k_{obs} versus [amine] are linear, with slope k_{N} . The Brønsted-type plots ($\log k_{\text{N}}$ vs. $\text{p}K_{\text{a}}$ of aminium ions) are linear, with slopes $\beta = 0.26, 0.22, 0.19$, and 0.28 for the reactions with 1, 2, 3, and 4, respectively. The magnitudes of the slopes indicate that these mechanisms are stepwise, with rate-determining formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$). A dual parametric equation with the $\text{p}K_{\text{a}}$ of the nucleophiles and non-leaving groups show $\beta_{\text{N}} = 0.26$ and $\beta_{\text{NLG}} = -0.16$, also in accordance with the proposed mechanism. On the other hand, the reactivity of these thiocarbonyl substrates and their carbonyl derivatives was studied using their hardness index and compared with their experimental parameters, confirming the proposed mechanisms. By comparison of the title reactions with similar aminolyses, the following conclusions arise: (i) The mechanism of the reactions under investigation is stepwise with rate-determining formation of $T^{\pm}$. (ii) The reactivity of the substrates toward quinuclidines follows the order $4 > 3 > 2 > 1$. (iii) Quinuclidines are more reactive than isobasic pyridines toward chlorothionoformates. (iv) Chlorothionoformates are less reactive than chloroformates towards quinuclidines in accordance with the HSAB principle. (v) The k_{N} values for phenyl chloroformate and 4 can be correlated with the $\text{p}K_{\text{a}}$ of quinuclidines and also with the hardness values calculated by the HF/3-21G level of theory.

Keywords: kinetics; mechanism; aminolysis; aryl chlorothionoformates; Brønsted plots

INTRODUCTION

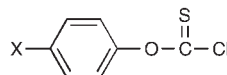
The kinetics of the aminolysis of thioesters and thiocarbonates have been extensively studied and their mechanisms are well established^[1]; nonetheless, the reactions of chlorothionoformates have been less investigated.^[1–4]

For the reactions of a series of aryl chlorothionoformates with anilines in acetonitrile a concerted mechanism, with a four-membered hydrogen bonded cyclic transition state, has been proposed.^[3]

On the other hand, the reactions of secondary alicyclic (SA) amines with phenyl chlorothionoformate (1) and 4-nitrophenyl chlorothionoformate (4) in water are governed by a stepwise mechanism, through a zwitterionic tetrahedral intermediate ($T^{\pm}$).^[4a] The low slope values ($\beta \approx 0.26$) of the linear Brønsted-type plots obtained indicate that the formation of $T^{\pm}$ is the rate-determining step.^[4a] Similarly, the reactions of pyridines with 1 and 4 in water also show linear Brønsted-type plots with small slopes ($\beta = 0.1$), in accordance to rate-determining $T^{\pm}$ formation.^[4b]

With the aim to shed some light on these mechanisms and to extend our kinetic studies on the aminolysis of chlorothionoformates, in the present work we investigate the reactions of quinuclidines with 1, 4, 4-chlorophenyl chlorothionoformate (2) and 4-cyanophenyl chlorothionoformate (3) in aqueous solution. A specific objective is to assess the influence of the amine nature and basicity, the electrophilic center (CO vs. CS) and the non-leaving group on the kinetics and mechanisms of these reactions. This will be achieved by a kinetic comparison of the

title reactions between them and with the aminolyses of similar compounds.



CHLOROTHIONOFORMATES

- 1 (X = H)
- 2 (X = Cl)
- 3 (X = CN)
- 4 (X = NO₂)



QUINUCLIDINES

- 5a X = CH; Y = CH₂
- 5b X = CH; Y = CHOH
- 5c X = CH; Y = CHCl
- 5d X = CH; Y = CO
- 5e X = N; Y = CH₂ (DABCO)
- 5f X = NH⁺; Y = CH₂ (DABCOH⁺)

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EXPERIMENTAL

Materials

The compounds **1**, **2**, and **4** were commercial samples and used as purchased. **3** was prepared as described.^[5]

Kinetics

Most of the kinetic measurements were carried out by means of a diode array spectrophotometer in aqueous solution, at $25.0 \pm 0.1^\circ\text{C}$ and an ionic strength of 0.2 M (KCl). The reactions were followed in the 220–500 nm range. Some fast reactions were measured using a stopped flow spectrophotometer.

The reactions were studied under excess of the amine over the substrate. Most of them were measured at a pH much lower than the pK_a of the conjugate acid of the quinuclidines, the pH being maintained by 0.005 M phosphate or acetate buffers. Some of the reactions were also carried out at pH near or equal to the pK_a of the conjugate acid of the quinuclidines. The initial substrate concentration was 5×10^{-5} M.

Pseudo-first-order rate coefficients (k_{obs}) were found for all reactions; these were determined by means of the spectropho-

tometer kinetic software for first-order reactions. The experimental conditions of the reactions and the k_{obs} values are shown in Tables 1–4.

Product studies

For the present reactions, one of the products was identified as the corresponding phenol/phenoxide anion; this was achieved by comparison of the UV–Vis spectra after completion of the reactions with an authentic sample under the same experimental conditions.

RESULTS AND DISCUSSION

Spectrophotometric study

The reactions of the title chlorothionoformates with the series of quinuclidines were followed spectrophotometrically (220–500 nm), showing in many cases a fast absorbance increase, followed by a further slower increase. This behavior is in agreement with a consecutive reaction model. The former increase is attributed to the formation of the corresponding phenol/phenoxide anion from the hydrolysis of the substrate (k_0 step in Scheme 1) and the latter to the slow hydrolysis of the corresponding cationic

Table 1. Experimental conditions and k_{obs} values for the reactions of quinuclidines with phenyl chlorothionoformate (**1**)^a

Amine	pH	F_N^b	$10^3[N]_{\text{tot}}/\text{M}^c$	$10^3 k_{\text{obs}}/\text{s}^{-1}$	No of runs
Quinuclidine	6.4 ^d	0.00001	4.00–40.0	0.602–2.26	6
	6.7 ^d	0.00002	4.00–40.0	0.954–4.56	6
	7.0 ^d	0.00004	6.00–40.0	2.09–9.00	5
3-Hydroxyquinuclidine	6.4 ^d	0.0004	4.00–40.0	2.87–17.9	6
	6.7 ^d	0.0008	4.00–20.0	5.10–22.6	5
	7.0 ^d	0.0016	4.00–40.0	9.60–70.9	9
	9.8	0.5	4.00–11.0	1270–6030	6
DABCO ^e + DABCOH ⁺ f	5.0 ^g	^h	0.275–2.75	12.3–86.8	6
	5.5 ^g	ⁱ	0.28–2.80	12.3–92.1	7
	6.0 ^d	^j	0.426–2.98	20.3–93.8	5
	6.2 ^d	^k	0.25–2.13	11.6–74.4	6
	6.5 ^d	^l	0.25–2.20	15.3–98.0	7
3-Chloroquinuclidine	6.4 ^d	0.0025	0.440–2.20	5.11–15.2	6
	6.7 ^d	0.005	0.420–4.20	5.32–41.6	6
	7.0 ^d	0.01	0.410–4.10	17.7–84.9	6
	9.0	0.5	4.00–16.0	875–3910	6
3-Quinuclidinone	4.7 ^g	0.00158	0.440–4.40	1.00–5.96	6
	5.0 ^g	0.0032	0.412–4.12	1.38–11.6	6
	5.3 ^g	0.0063	0.440–4.40	2.20–18.2	6
	7.5	0.5	2.00–5.00	335–1310	6

^a In 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 In the presence of 0.005 M phosphate buffer.

^e 1,4-diazabicyclo[2,2,2]octane.

^f Monoprotonated 1,4-diazabicyclo[2,2,2]octane.

^g In the presence of 0.005 M acetate buffer.

^h Free DABCO and DABCOH⁺ ion fractions are 0.00015 and 0.98995, respectively.

ⁱ Free DABCO and DABCOH⁺ ion fractions are 0.00048 and 0.99637, respectively.

^j Free DABCO and DABCOH⁺ ion fractions are 0.00151 and 0.99749, respectively.

^k Free DABCO and DABCOH⁺ ion fractions are 0.00239 and 0.99698, respectively.

^l Free DABCO and DABCOH⁺ ion fractions are 0.0048 and 0.99492, respectively.

Table 2. Experimental conditions and k_{obs} values for the reactions of quinuclidines with 4-chlorophenyl chlorothionoformate (**2**)^a

Amine	pH	F_N^b	$10^3 [N]_{\text{tot}}/M^c$	$10^3 k_{\text{obs}}/s^{-1}$	No. of runs
Quinuclidine	11.0	0.285	0.85–2.30	1210–7460	5
3-Hydroxyquinuclidine	9.8	0.5	4.0–11.0	1580–7880	6
3-Chloroquinuclidine	9.0	0.5	4.0–8.0	1170–5280	5
3-Quinuclidinone	7.5	0.5	4.0–10.0	597–2100	5

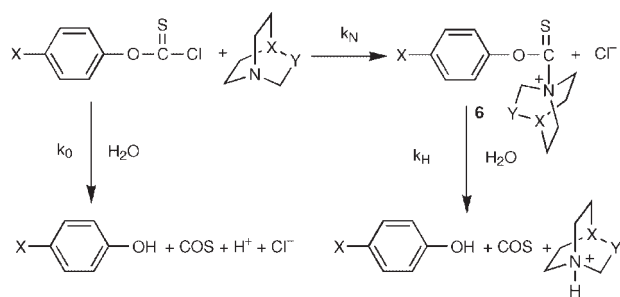
^a In water, at 25°C, ionic strength 0.2 M (KCl).^b Free amine fraction.^c Concentration of total amine (free base plus protonated forms).**Table 3.** Experimental conditions and k_{obs} values for the reactions of quinuclidines with 4-cyanophenyl chlorothionoformate (**3**)^a

Amine	pH	F_N^b	$10^3 [N]_{\text{tot}}/M^c$	$10^3 k_{\text{obs}}/s^{-1}$	No of runs
Quinuclidine	6.4 ^d	0.00001	4.00–40.0	1.34–7.16	6
	6.7 ^d	0.00002	4.00–40.0	1.81–6.80	4
	7.0 ^d	0.00004	4.00–40.0	2.87–19.0	6
3-Hydroxyquinuclidine	6.4 ^d	0.0004	4.00–10.0	16.67–44.9	4
	6.7 ^d	0.0008	4.00–20.0	10.3–42.1	5
	7.0 ^d	0.0016	4.00–40.0	17.8–41.	6
3-Chloroquinuclidine	9.8	0.5	4.00–40.0	4880–38000	6
	6.7 ^d	0.005	0.416–4.16	10.6–93.3	5
	7.0 ^d	0.01	0.412–4.12	24.3–187	6
3-Quinuclidinone	4.7 ^e	0.00158	0.440–4.40	2.17–14.1	6
	5.0 ^e	0.0032	0.412–4.12	2.75–23.0	6
	5.3 ^e	0.0063	0.440–3.08	6.80–33.2	5
	7.5	0.5	2.00–5.00	618–1810	4

^a In 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 In the presence of 0.005 M phosphate buffer.^e In the presence of 0.005 M acetate buffer.**Table 4.** Experimental conditions and k_{obs} values for the reactions of quinuclidines with 4-nitrophenyl chlorothionoformate (**4**)^a

Amine	pH	F_N^b	$10^3 [N]_{\text{tot}}/M^c$	$10^3 k_{\text{obs}}/s^{-1}$	No. of runs
Quinuclidine	6.4 ^d	0.00001	4.00–20.0	1.67–3.32	5
	6.7 ^d	0.00002	4.00–40.0	2.01–21.1	6
	7.0 ^d	0.00004	6.00–40.0	4.27–36.9	6
3-Hydroxyquinuclidine	6.4 ^d	0.0004	4.00–20.0	5.16–26.4	4
	6.7 ^d	0.0008	4.00–10.0	9.01–22.1	4
	7.0 ^d	0.0016	4.00–10.0	21.5–58.4	5
3-Chloroquinuclidine	6.4 ^d	0.0025	0.440–4.40	13.8–114	6
	6.7 ^d	0.005	0.416–4.16	15.2–229	6
	7.0 ^d	0.01	0.412–4.12	29.5–319	6
3-Quinuclidinone	4.7 ^e	0.00158	0.440–4.40	2.50–15.0	6
	5.3 ^e	0.0032	0.412–4.12	3.55–19.4	6
	5.5 ^e	0.0063	0.440–4.40	7.33–41.4	6

^a In 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 In the presence of 0.005 M phosphate buffer.^e In the presence of 0.005 M acetate buffer.



Scheme 1.

thionocarbamate **6** (k_H step in Scheme 1), which also produces the corresponding phenol/phenoxide anion.

It is noteworthy that the greater the amine concentration, the faster the initial absorbance increase, but the lower the final absorbance for the first reaction (k_0 step). This result permits to disregard an amine-catalyzed hydrolysis and is in accordance with Scheme 1. This is because a greater amine concentration favors the parallel aminolysis and a smaller fraction of substrate hydrolyzes, yielding a lower phenol/phenoxide product.

When the reactions were performed at very large amine concentration, only a slow increase of absorbance due to the phenol/phenoxide formation was observed. This result is attributed to the fact that at high amine concentration the aminolysis of the substrate is favored over its hydrolysis and the measured reaction corresponds only to the slow hydrolysis of thionocarbamate **6** (as in Scheme 1).

Quinuclidinolysis of chlorothionoformates

Despite the usual kinetic complications concerning consecutive reactions, as those depicted in Scheme 1, for most of the reactions studied in this work the kinetics were simple, showing pseudo-first-order behavior (amine excess was used throughout). This is because for most reactions very basic amines (except DABCOH⁺) were involved and, therefore, k_H was very small due to the strong N—C bond in thionocarbamate **6**. For the reactions with DABCOH⁺, k_H was large and the formation of thionocarbamate **6** was rate limiting. Therefore, this reaction also showed pseudo-first-order kinetics.

The kinetic law obtained under the reaction conditions is described by Eqn (1), where P is the corresponding substituted

phenol/phenoxide anion, S is the substrate, and k_{obs} is the pseudo-first-order rate coefficient (excess of amine).

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

Plots of k_{obs} against [amine] at constant pH were linear in accordance with Eqn (2), where k_0 and k_N are the rate coefficients for solvolysis and aminolysis of the substrates, respectively. The values of k_0 and k_N were pH independent.

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

The k_0 values obtained, as the intercept of plots of Eqn (2), were very similar to those measured in the absence of amine at the same pH. The k_0 values obtained at pH 7.0 for **1**, **3**, and **4** were 0.0005, 0.0008, and 0.001 s⁻¹, respectively.

The values of k_N obtained, as the slopes of plots of Eqn (2), for the reactions of quinuclidines with the chlorothionoformates studied and the pK_a values of the conjugate acids of these amines are summarized in Table 5.

The values of k_N for the reactions of DABCO and DABCOH⁺ cation with phenyl chlorothionoformate (**1**), as well as those of the pK_a of their conjugate acids, were statistically corrected with $q = 2$ and $p = 2$, respectively.^[6] The reactions with the other quinuclidines were not corrected statistically ($q = 1$ and $p = 1$). The statistical parameter q is the number of equivalent basic sites on the amine and p is the number of equivalent protons of the conjugate acid of the amine.^[6]

With the k_N and pK_a corrected values, the Brønsted-type plots (log k_N vs. pK_a of aminium ions) shown in Fig. 1 were obtained. These plots are linear, with slopes $\beta = 0.26, 0.22, 0.19$, and 0.28 for the reactions of **1**, **2**, **3**, and **4**, respectively.

It is noteworthy that quinuclidine **5b** (Y = CHOH) is less reactive than **5c** (Y = CHCl) toward chlorothionoformates (as in Table 5 and Fig. 1) despite the fact that the former amine is more basic than the latter. This is in contrast to the results found in the reactions of these two amines with aryl chloroformates,^[7] and diaryl carbonates,^[8] where **5b** is more reactive than **5c**. The reason for the abnormal results for the reactions of these two quinuclidines with chlorothionoformates is unknown.

The values of β found for the reactions of this study are in agreement with those obtained in the reactions of **1** and **4** with secondary alicyclic (SA) amines^[4a] and pyridines^[4b] in water, and in the reactions of aryl chloroformates with quinuclidines^[7] and SA amines,^[9] in water. In all these reactions, the formation of a

Table 5. Values of pK_a of the conjugate acids of quinuclidines and k_N values for the reactions of these amines with phenyl chlorothionoformate (**1**), 4-chlorophenyl chlorothionoformate (**2**), 4-cyanophenyl chlorothionoformate (**3**), and 4-nitrophenyl chlorothionoformate (**4**)^a

Amine	pK_a	$10^{-3}k_N/s^{-1}M^{-1}$			
		1	2	3	4
Quinuclidine	11.4	5.4 ± 0.1	9.2 ± 0.6	11.5 ± 0.3	23.4 ± 0.8
3-Hydroxyquinuclidine	9.8	1.10 ± 0.07	3.6 ± 0.3	2.2 ± 0.1	3.6 ± 0.2
3-Chloroquinuclidine	9.0	2.00 ± 0.08	4.1 ± 0.2	4.5 ± 0.1	7.6 ± 0.3
DABCO	8.9	1.9 ± 0.3			
3-Quinuclidinone	7.5	0.70 ± 0.02	1.10 ± 0.04	1.70 ± 0.06	1.40 ± 0.04
DABCOH ⁺	2.9	0.030 ± 0.001			

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

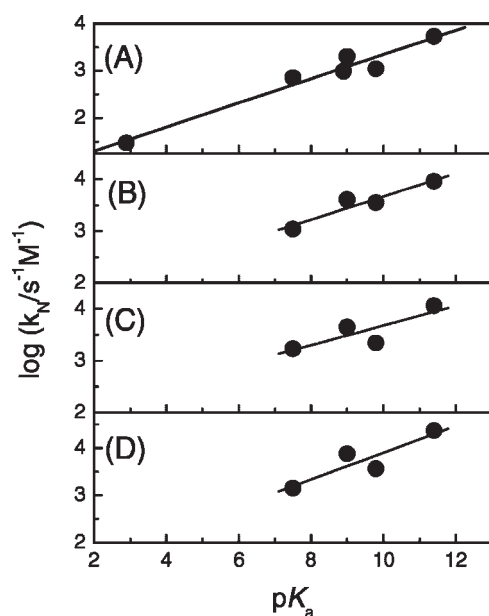


Figure 1. Brønsted-type plot obtained for the reactions of quinuclidines with: (A) phenyl chlorothionoformate (**1**), (B) 4-chlorophenyl chlorothionoformate (**2**), (C) 4-cyanophenyl chlorothionoformate (**3**), and (D) 4-nitrophenyl chlorothionoformate (**4**), in water, at 25.0°C and ionic strength 0.2 M

zwitterionic tetrahedral intermediate ($T^\pm$) is the rate-determining step. Therefore, the mechanism that we propose for the reactions of quinuclidines with the chlorothionoformates **1–4** is shown in Scheme 2, where Ar is 4-X-phenyl (X = H, Cl, CN, NO₂).

The reactivity of aryl chlorothionoformates with quinuclidines increases in the sequence **4** > **3** > **2** > **1**; this order is the reverse of that followed by the pK_a of the conjugate acid of the non-leaving groups. This result is in agreement with the greatest electron withdrawing ability of nitro in the non-leaving group of the substrate, which leaves the thiocarbonyl carbon of **4** the most positive and therefore, the most prone to amine attack.

With the k_N values found (Table 5), the corrected pK_a values of the nucleophiles^[6] and the pK_a values of the non-leaving groups (9.9, 9.4, 7.8, and 7.2 for phenol, 4-chlorophenol, 4-cyanophenol, and 4-nitrophenol, respectively),^[10] Eqn (3) can be deduced by regression analysis ($n = 18$, $R^2 = 0.898$). In this expression, N and nlg refer to the nucleophile and the non-leaving group, respectively; the coefficients of pK_a (N) and pK_a (nlg) (β_N and

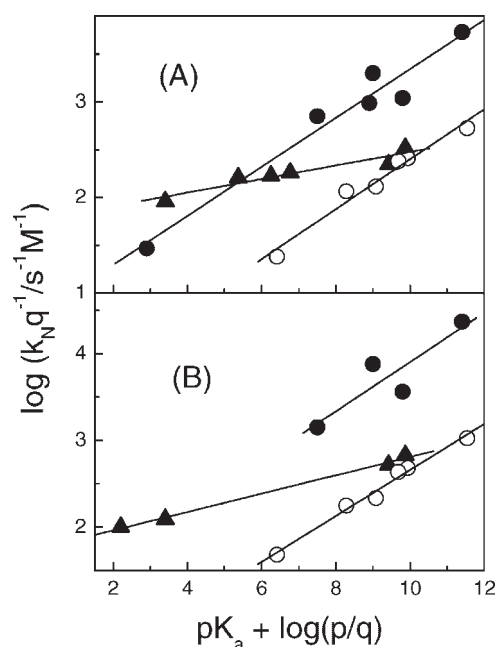


Figure 2. Brønsted-type plots for the reactions of phenyl chlorothionoformate (**1**) (A) and 4-nitrophenyl chlorothionoformate (**4**) (B) with quinuclidines (●, this work), SA amines (○, Reference [4a]) and pyridines (▲, Reference [4b]) in water, at 25.0°C and an ionic strength of 0.2 M

β_{nlg}) are subjected to an error of ± 0.03 and ± 0.05 , respectively.

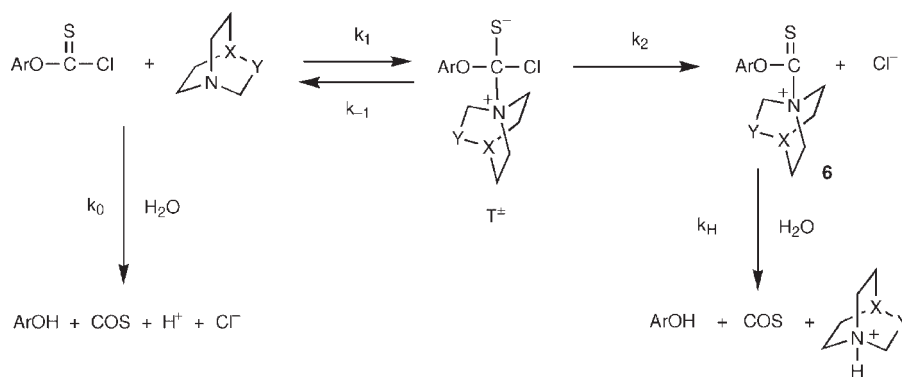
$$\log k_N = 2.46 + 0.26 pK_a(N) - 0.16 pK_a(nlg) \quad (3)$$

A logarithmic plot (not shown) of the experimental k_N versus the calculated one through Eqn (3) is linear through the origin, with unity slope.

The β_{nlg} value of -0.16 is in accordance with those expected for a stepwise mechanism with the tetrahedral intermediate formation as the rate-determining step. This is the case of the reactions of a series of aryl chloroformates with quinuclidines^[7] and SA amines,^[9] which show β_{nlg} values of -0.16 and -0.2 , respectively.

Effect of the amine nature

Figure 2 shows a comparison between the Brønsted-type plots obtained for the reactions of **1** and **4** with quinuclidines (this work) and those for the reactions of the same substrates with SA



Scheme 2.

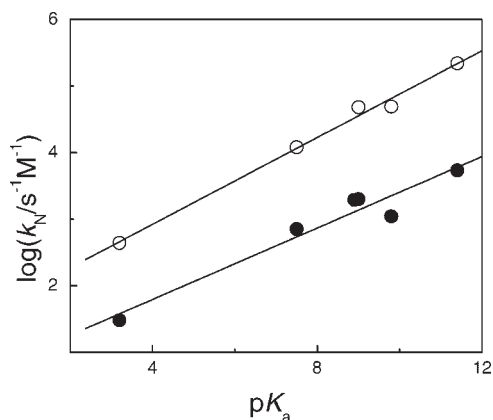


Figure 3. Brønsted-type plots for the reactions of quinuclidines with phenyl chloroformate (**7**, ○, Reference [7]) and phenyl chlorothionoformate (**1**, ●, this work), in water, at 25.0°C and an ionic strength of 0.2 M

amines^[4a] and pyridines,^[4b] under the same experimental conditions.

For all the reactions shown in Fig. 2, the rate-limiting step is the formation of the zwitterionic tetrahedral intermediate ($T^\pm$); therefore, the k_N values are those of k_1 in Scheme 2. The k_1 values found for the reactions of quinuclidines with **1** and **4** are about 10-fold larger than those obtained for the reactions of the same substrates with isobasic SA amines.^[4a] The same results were found for the reactions of the corresponding chloroformates with both amine series: quinuclidines are more reactive than isobasic SA amines toward chloroformates.^[7,11]

As seen in Fig. 2, most of the quinuclidines are more reactive than isobasic pyridines toward chlorothionoformates.^[4b] The exception occurs for amines of very low basicity (Fig. 2A), due to the fact that the Brønsted slope for quinuclidines is larger than that for pyridines.

Chloroformates versus chlorothionoformates

Figure 3 shows the Brønsted-type plots obtained for the quinuclidinolysis of **1** (this work) and phenyl chloroformate (**7**).^[7] For both reaction series, the tetrahedral intermediate formation is the rate-determining step, that is, $k_N = k_1$. It can be observed from this figure that the k_1 values for **7** are more than 10-fold greater than those for **1**, showing a greater reactivity of quinuclidines toward the carbonyl than the thiocarbonyl group. An explanation can be found in Pearson's hard-soft acid-base (HSAB) principle,^[12] which suggests that hard-hard and soft-soft interactions are favorable over hard-soft interactions.^[13] Therefore, quinuclidines, considered as hard bases, are more suitable to react faster with the hard carbonyl group than the softer thiocarbonyl moiety.

In order to confirm this explanation, Hartree-Fock (HF/3-21G) calculations were performed using the GAUSSIAN 98 suite of programs^[14] in order to evaluate the electronic quantities required to calculate the ground state for **7** and **1**. The chemical hardness, η , is obtained from a finite difference method, together with Koopman's theorem, in terms of the one electron energy

level of frontier molecular orbitals HOMO and LUMO,^[15] described by Eqn (4).

$$\eta \cong \varepsilon_L - \varepsilon_H \quad (4)$$

The hardness values found for **7** and **1** are 12.84 and 10.71, respectively. With these values and those for the pK_a of the conjugate acid of the nucleophiles, Eqn (5) can be deduced by regression analysis ($n = 11$, $R^2 = 0.977$). In this expression, N and η refer to the nucleophile and substrate hardness, respectively.

$$\log k_N = -6.4 + 0.3 pK_a(N) + 0.645 \eta \quad (5)$$

A logarithmic plot (not shown) of the experimental k_N versus the calculated one through Eqn (5) is linear through the origin, with unity slope. It should be noted that the hardness is the inverse of the chemical softness, which is directly related to the polarizability of the CO and CS groups. Experimentally, **7** is more reactive than **1** toward quinuclidines. A possible explanation for this result is the greater electronegativity of the oxygen as compared to that of the sulfur atom, which makes the carbonyl carbon more positive than the thiocarbonyl carbon, improving the nucleophilic attack of the amine.

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