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Kinetic and mechanistic study of the reactions of aryl chloroformates with quinuclidines

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ABSTRACT: The reactions of quinuclidines with phenyl, 4-methoxyphenyl, 4-chlorophenyl, and 4-nitrophenyl chloroformates (PClF, MOPClF, ClPClF, and NPClF, respectively) in aqueous solution (25 °C, ionic strength 0.2 M KCl) are followed spectrophotometrically and evaluated kinetically. Under amine excess, pseudo-first-order rate coefficients (k_{obsd}) are found. Plots of k_{obsd}*versus* [quinuclidine] are linear, with the pH-independent slope (k_N). The Brønsted-type plots (log k_N*vs*. pK_a of quinuclidinium ions) are linear with slopes (β) of 0.32, 0.34, 0.31, and 0.23 for the reactions of PClF, MOPClF, ClPClF, and NPClF, respectively. The magnitude of the slopes suggests that these mechanisms are stepwise, with the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) being the rate-determining step. The sensitivity of log k_N to the basicity of the nonleaving group (β_{nlg}) is −0.16. By comparing the reactions under investigation between each other and with similar aminolyses, the following conclusions can be drawn: (i) the mechanisms for the quinuclidinolysis of the four chloroformates studied are stepwise. (ii) The reactivity increases in the sequence MOPClF < PClF < ClPClF < NPClF. (iii) The change of the leaving group from 2,4-dinitrophenoxide to chloro changes the mechanism from concerted to stepwise. (iv) Quinuclidines are more reactive toward aryl chloroformates than isobasic secondary alicyclic amines. Copyright © 2006 John Wiley & Sons, Ltd. *Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/0894-3230/suppmat/*

KEYWORDS: kinetics; aminolysis; aryl chloroformates; Brønsted plots

INTRODUCTION

Although there have been several reports on the kinetics and mechanisms of the aminolyses (various types of amines) of alkyl and aryl chloroformates,[1] some aspects of their mechanisms have not been clarified. The pyridinolyses of phenyl and 4-nitrophenyl chloroformates in acetonitrile show linear Brønsted-type plots with slopes (β) of ca. 0.3, which were explained by stepwise mechanisms where the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) is the rate-determining step.[1d] The reactions of secondary alicyclic (SA) amines with a series of aryl chloroformates in water also show linear Brønsted-type plots (β ca. 0.3) consistent with rate limiting formation of the intermediate $T^{\pm}$.[1e,f] Recently, we undertook a kinetic and mechanistic study of the reactions of pyridines and SA amines with *S*-methyl chlorothiolformate (SMClTF).[2]

With both amines series, the mechanism is stepwise, with formation of the intermediate $T^{\pm}$ being rate determining for all the SA amines and also for the more basic pyridines. Nevertheless, for the less basic pyridines, breakdown to products of the tetrahedral intermediate is the rate-determining step.[2] The results obtained for the reactions of SMClTF with pyridines are in accordance with the biphasic Brønsted-type plot ($\beta = 0.2$ at high pK_a and $\beta = 0.9$ at low pK_a) found for the pyridinolysis of methyl chloroformate.[1b]

In order to further extend our investigations on the kinetics of the aminolyses of chloroformates and in order to clarify their mechanisms, in this work we report kinetic results for the quinuclidinolysis of a series of 4-X-phenyl chloroformates (4—X—C_6H_4—O—CO—Cl), with X = H, MeO, Cl, and NO_2 (PClF, MOPClF, ClPClF, and NPClF, respectively). By comparing these reactions between them, with the aminolysis (SA amines) of some of the above chloroformates and with the

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quinuclidinolysis of diaryl carbonates,[3,4] the effect of the amine nature and that of the leaving and nonleaving groups on the mechanism will be evaluated.

RESULTS AND DISCUSSION

Spectrophotometric study of intermediates and products

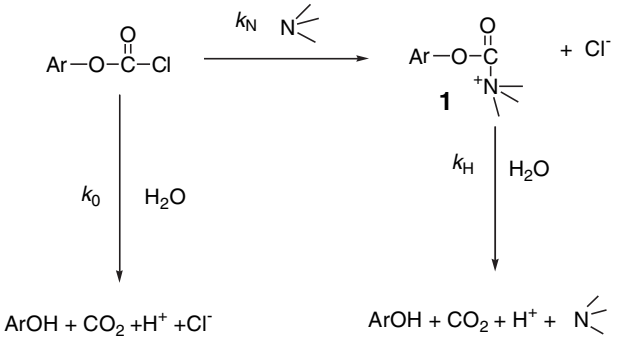
This study was performed for some reactions. As an example, we now describe the reactions of NPClF with 3-hydroxyquinuclidine (in excess), at $pH = pK_a = 9.8$, by means of conventional spectrophotometry.

1 When the reactants are mixed, the 'instantaneous' formation of a band centered at 400 nm is observed, due to 4-nitrophenoxide. Later, a much slower increase of the same band occurs until 100% of 4-nitrophenoxide is reached and at the same time, the absorbance of two bands centered at 260 and 290 nm decreases until disappearance.
2 As the concentration of the amine increases, the absorbance value reached by the 'instantaneous' process diminishes; nevertheless, the absorbance continues to grow until that corresponding to 100% phenoxide anion.

These results can be explained by the reactions shown in Scheme 1.

At very low amine concentration, the reaction occurs by the hydrolysis path (k_0). If it is assumed that this process is very fast, the 'instantaneous' absorbance corresponds to 100%.

As the amine concentration increases, the aminolysis path, k_N[N], becomes faster and the values of k_0 and k_N[N] become comparable. In this case, not all of the substrate forms 4-nitrophenoxide ion since part of it suffers aminolysis, leading to the formation of the cationic carbamate **1**. This way only a fraction of the expected 4-nitrophenoxide is formed 'instantaneously.' The rest will be formed slowly by the hydrolysis of the cationic carbamate (k_H step) until the stoichiometric amount is reached. In order to confirm this, the same reactions were carried out by stopped-flow technique. In this case, the formation of 4-nitrophenoxide at a very fast rate is observed as soon as the reactants are mixed.



Scheme 1

On the other hand, it is reasonable to assume that the bands at 260 and 290 nm that disappear as the band at 400 nm increases, correspond to the cationic carbamate **1**. This assumption is supported by the facts that in several reactions of chloroformates with secondary amines, this type of compound has been isolated,[1e,f] and in the reactions of the same substrates with tertiary amines, amino intermediates, ascribed to cationic carbamates, have been detected spectrophotometrically.[1b,5]

For the reaction of NPClF with monoprotonated 1,4-diazabicyclo[2,2,2]octane ($DABCOH^+$) at $pH = pK_a = 2.9$, only the increase of a band at 330 nm, corresponding to 4-nitrophenol, is observed. This result can be explained assuming that the hydrolysis of the cationic carbamate intermediate is faster than its formation plus the hydrolysis of the substrate ($k_H \gg (k_0 + k_N[N])$). This is reasonable in view of the great instability of this dication intermediate due to the additional protonation in N-4.

Kinetic results

In order to study the title reactions kinetically, some of them were followed by stopped-flow techniques (without external buffer) and the others (most of them) by conventional spectrophotometry (with buffer).

The reactions followed by the stopped-flow were carried out at pH values similar to that of the pK_a of the conjugate acid of the quinuclidines, at amine fractions *ca.* 0.3–0.5. At these pH values both, k_0 and k_N[N] of Scheme 1 are large and the appearance of the phenoxide anion from the cationic intermediate (k_H in Scheme 1) is relatively very slow.

Most of the reactions were conducted under the presence of external buffer (acetate or phosphate), and the pH values were lower than the pK_a of the conjugate acids of quinuclidines, that is, at low amine fractions. For these reactions, the values of both k_0 and k_N[N] were much lower than the corresponding values at high pH. Therefore, for these reactions, the appearance of the corresponding phenol from the hydrolysis of the substrate (k_O in Scheme 1) is no longer 'instantaneous,' as observed at higher pH values (see Spectrophotometric Study). Similarly, the aminolysis reaction, k_N[N], becomes much slower than that at larger amine fraction (as in the stopped-flow studies).

For the above reactions, the kinetics were measured by following the appearance of the corresponding phenol coming from the substrate (k_O in Scheme 1), up to the time where deviations from first-order kinetics occurred. These deviations were caused by the slow appearance of the corresponding phenol from the hydrolysis of the

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cationic carbamate (k_H in Scheme 1). Under these circumstances, pseudo-first-order kinetics were found.

For the reactions of the title chloroformates with $DABCOH^+$, k_H in Scheme 1 is very large and the aminolysis of the substrate (k_N[N] in Scheme 1) is the rate-limiting step.

For all the reactions, followed as described in this section, pseudo-first-order coefficients (k_{obsd}) were obtained (under amine excess). These were determined by means of the kinetics software for first-order reactions of the spectrophotometer. The experimental conditions of the reactions and the values of k_{obsd} are summarized in Tables S1–S4 in the Supplementary Material.

The kinetic law obtained under the reaction conditions is that described by Eqn (1), where P is the corresponding phenol and/or phenoxide anion, S is the substrate, and k_{obsd} is the pseudo-first-order rate coefficient (under excess amine).

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

Plots of k_{obsd} 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 at each pH were obtained as the intercept and slope, respectively, of plots of Eqn (2). These k_N values were pH independent within experimental error. The definitive k_N values were found as the average of those at each pH.

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

The fact that the value of k_{obsd} increases with the amine concentration rules out a S_N1 mechanism, which has been found to operate in some solvolysis (highly polar solvents) of chloroformates and chlorothioformates.[6]

Table 1 shows the values of pK_a of the quinuclidinium ions and those of k_N for the reactions under study. The pK_a of the conjugate acid of DABCOH+ ion was statistically corrected ($pK_a + \log p/q$) with $p = 2$. Neither the pK_a of the conjugate acid of the other quinuclidines nor the k_N values need statistical correction because for these $q = 1$ and $p = 1$. The statistical parameter q is the number of equivalent basic sites of the amine and p is the number of equivalent protons of the conjugate acid of the amine.[7]

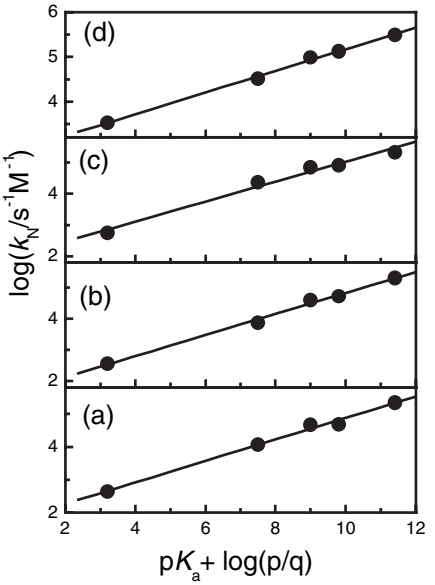

Figure 1. Brønsted-type plots (pK_a of $DABCOH^+$ statistically corrected) obtained in the reactions of quinuclidines with: (a) phenyl (PClF), (b) 4-methoxyphenyl (MOPClF), (c) 4-chlorophenyl (ClPClF), and (d) 4-nitrophenyl (NPClF) chloroformates, in water at 25.0°C and an ionic strength of 0.2 M

With the pK_a and k_N values in Table 1, the Brønsted-type plots (shown in Fig. 1) were obtained. These plots are linear with slopes (β) of 0.32, 0.34, 0.31, and 0.24 for the reactions of PClF, MOPClF, ClPClF, and NPClF, respectively.

The values of β found for the reactions of quinuclidines with aryl chloroformates (Fig. 1) are in agreement with those obtained in the following stepwise aminolyses in water, where the attack of the amine to the carbonyl group is the rate determining step: (i) aryl chloroformates with SA amines,[1e,f] (ii) aryl acetates with various types of basic amines,[8] (iii) methyl chloroformate with pyridines,[1b] (iv) *S*-methyl chlorothioformate with SA amines,[2] (v) methyl 4-nitrophenyl carbonates with basic SA amines,[9] and (vi) diaryl carbonates with basic quinuclidines.[3]

Table 1. Values of pK_a for the conjugate acids of quinuclidines (that of $DABCOH^+$ statistically corrected) and k_N values for the reactions of these amines with phenyl (PClF), 4-methoxyphenyl (MOPClF), 4-chlorophenyl (ClPClF), and 4-nitrophenyl (NPClF) chloroformates[a]

		$10^{-3}\,k_N$ ($s^{-1}\,M^{-1}$)			
Amine	$pK_a + \log(p/q)$	MOPClF	PClF	ClPClF	NPClF
Quinuclidine	11.4	200 ± 20	220 ± 20	210 ± 20	310 ± 30
3-hydroxyquinuclidine	9.8	50 ± 10	49 ± 6	80 ± 10	130 ± 10
3-chloroquinuclidine	9.0	39 ± 6	48 ± 4	70 ± 10	100 ± 10
3-quinuclidinone	7.5	7 ± 1	12 ± 1	24 ± 5	33 ± 3
$DABCOH^+$	3.2	0.36 ± 0.05	0.44 ± 0.01	0.57 ± 0.05	3.4 ± 0.5

[a] Both the pK_a and k_N values were determined in aqueous solution, at 25.0 °C, ionic strength 0.2 M (KCl), except the pK_a of $DABCOH^+$, which was obtained from the literature without specification of ionic strength.

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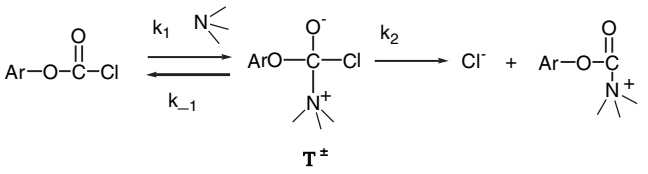

Scheme 2

Taking into account the slopes of the Brønsted plots obtained, the discussion above, the kinetic law, and product studies, the most likely mechanism for the reactions under scrutiny is the stepwise process shown Scheme 2, with $k_2 \gg k_{-1}$. Namely, the rate-determining step is the formation of the zwitterionic tetrahedral intermediate ($T^{\pm}$). In this Scheme, Ar is 4-X-phenyl (X = H, MeO, Cl, NO_2) and N represents a quinuclidine.

Those reactions that were measured in the absence of external buffer, by stopped-flow, show the same values of k_N as those measured under the presence of external buffer, at low free amine fractions. This means that the amine-catalyzed nucleophilic attack of the external buffer to the chloroformate can be ruled out.

On the other hand, at very large amine concentrations, aminolysis is favored, relative to hydrolysis, and carbamate is formed almost quantitatively. This fact indicates that the amine-catalyzed hydrolysis of chloroformates is much slower than the direct nucleophilic attack of the amine on the chloroformate.

Effect of the nonleaving group

In order to evaluate the influence of the nonleaving group of the substrate on the kinetics and mechanism of the aminolysis reaction, the Brønsted plots of Fig. 2 were obtained. These plots were drawn with the k_N values found in this work (Table 1) and the pK_a values of the conjugate acids of the nonleaving groups (the latter are 10.3, 9.9, 9.4, and 7.1, for 4-methoxylphenol, phenol, 4-chlorophenol, and 4-nitrophenol, respectively).[10]

It can be observed that the β_{nlg} values are negative for all the quinuclidines, ranging from −0.06 to −0.3, with a mean value −0.16. The sequence of reactivities of aryl chloroformates (Table 1) may be traced to the negative value of β_{nlg} and value of the pK_a of the phenols.

A multiparametric equation can be derived using the k_N values obtained in the quinuclidinolysis, together with the pK_a values of the conjugate acids of the nucleophiles and nonleaving groups. This equation (statistically corrected for the pK_a of $DABCOH^+$) is shown in Eqn (3) ($n = 20$, $R^2 = 0.972$). In this equation, N and nlg correspond to the nucleophile and nonleaving group, respectively, pK_a(N)-corr is pK_a(N) + log p/q; and the indicated errors are the standard errors.

$$\log k_N = (3.4 \pm 0.3) + (0.31 \pm 0.01)\mathrm{p}K_a(\mathrm{N})\mathrm{corr} - (0.16 \pm 0.02)\mathrm{p}K_a\,(\mathrm{nlg}) \quad (3)$$

A plot of experimental log k_N against calculated (through Eqn (3)) log k_N (not shown) is linear with unity slope and zero intercept.

Effect of the amine structure

Fig. 3 shows a comparison of the Brønsted-type plots obtained for the reactions of aryl chloroformates with quinuclidines (this work) and SA amines,[1e,f] both in aqueous solution. It can be observed that the k_N values found for the reactions of quinuclidines are larger (about 10 times) than those obtained for the reactions of isobasic

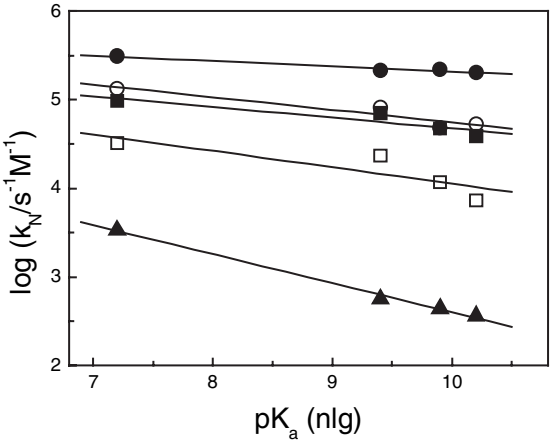

Figure 2. Logarithmic plot of experimental k_N *versus* pK_{nlg} for the reactions of MOPClF, PClF, ClPClF, and NPClF with quinuclidine (●), 3-hydroxyquinuclidine (○), 3-chloroquinuclidine (■), 3-quinuclidinone (□), and $DABCOH^+$ (▲) in water, at 25.0°C and an ionic strength of 0.2 (KCl)

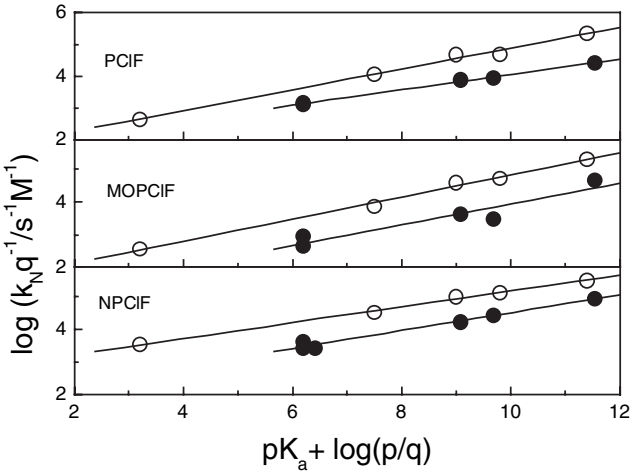

Figure 3. Brønsted-type plots (statistically corrected) for the reactions of aryl chloroformates with quinuclidines (○, this work) and SA amines (●, Ref. 1e,f), in water, at 25.0 °C and an ionic strength of 0.2 M

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Table 2. Experimental conditions and values of k_H and of hydrolysis rate constants (k) for the reaction of the carbamate cation **1**, formed '*in situ*' by the reactions of NPClF with quinuclidines[a]

Quinuclidine substituent	pH	$10^2[N]_{tot}/M$[b]	k_H (s^{-1})	No. of runs	k ($s^{-1}M^{-1}$)
H	11.4	0.24–7.2	1.27–40.2	5	1090 ± 50
3-hydroxy	9.8	0.24–18.0	3.61–66.0	10	770 ± 30
3-Chloro	9.0	27.4–66.2	0.18–0.85	5	3.8 ± 0.5
3-One	7.5	72.2–242	0.017–0.123	5	0.13 ± 0.01

[a] In water, at 25°C, ionic strength 0.2 M (KCl).
[b] Concentration of total amine (free base plus protonated forms).

SA amines with the same chloroformates.[1e,f] This result is in agreement with the greater reactivity toward aryl 2,4-dinitrophenyl carbonates shown by quinuclidines[3] as compared with isobasic SA amines.[9]

Comparison with carbonates

The reactions of quinuclidines with aryl chloroformates (this work) and those with 4-X-phenyl 4-nitrophenyl carbonates (X═Me, H, Cl) are stepwise.[3,4a] For the reactions of chloroformates, formation of the intermediate $T^{\pm}$ is rate determining (β about 0.3), whereas for the reactions with 4-X-phenyl 4-nitrophenyl carbonates breakdown of $T^{\pm}$ to products is the rate determining step ($\beta = 1.0$, 0.87, and 0.88 for X═H in water[3] and X═Cl and Me in aqueous ethanol,[4a] respectively). This difference in the rate-determining step is due to the much greater nucleofugality of Cl than 4-nitrophenoxy from the corresponding $T^{\pm}$. In fact, for the quinuclidinolysis of aryl chloroformates, Cl is expelled faster from the tetrahedral intermediate than all the quinuclidines of the series, whereas for the reactions of aryl 4-nitrophenyl carbonates all the quinuclidines are expelled faster than 4-nitrophenoxy from the corresponding $T^{\pm}$ intermediate.

The reactions of 4-X-phenyl 2,4-dinitrophenyl carbonates (X═Me, H, Cl) with quinuclidines are concerted,[4b] as shown by the linear Brønsted-type plots of slopes β ca. 0.57 found.[4b] This is in contrast with the reactions of the same amines with aryl chloroformates, which are stepwise (this work). This is in agreement with the fact that the reactions of SA amines with 4-methylphenyl chloroformate are stepwise,[1f] in contrast to their reactions with 4-methylphenyl 2,4-dinitrophenyl carbonate, which are concerted.[11]

The above means that 2,4-dinitrophenoxy destabilizes the corresponding $T^{\pm}$ relative to chloro. Recently, we have described the same behavior for the reactions of SA amines with *S*-methyl chlorothiolformate[2] and *S*-methyl 2,4-dinitrophenyl thiolcarbonate.[12] An explanation to this behavior would be that the $T^{\pm}$ intermediate possessing 2,4-dinitrophenoxy would be much more crowded (and, therefore, more unstable) compared to that with chloro.[12]

Hydrolysis of the cationic carbamate

In order to determine the influence of the amine on the hydrolysis of the 1-(4-nitrophenoxycarbonyl)quinuclidinium (**1** in Scheme 1), product of the aminolysis reaction, we studied the decomposition of **1** by water in the presence of the corresponding quinuclidine. The reactions were carried out at high quinuclidine concentration in order to minimize the hydrolysis of NPClF relative to its aminolysis and therefore to obtain the highest initial concentration of the cationic carbamate 1 in the reaction media.

Table 2 shows the values of the pseudo-first-order rate constants (k_H) obtained. The rate constants for decomposition of this cationic carbamate show a linear dependence on the corresponding free quinuclidine concentration. The slope value of the linear plots of k_H *versus* free amine concentration is the hydrolysis rate constant k, also shown in Table 2.

It can be noticed that the value of k_H for each amine increases with its concentration and also that k increases with the quinuclidine basicity. This indicates that the hydrolysis of **1** is general base catalyzed by the amine. Taking into account that the carbamates studied are obtained '*in situ*,' the kinetic study corresponds to a simultaneous change of the quinuclidine group of the carbamate and the quinuclidine catalyst. Nevertheless, the increased value of k with the pK_a of quinuclidines means that as pK_a increases the effect of a better quinuclidine catalyst is greater than the negative effect due to a worse leaving quinuclidine from the corresponding carbamate.

CONCLUSIONS

The Brønsted-type plots (log k_N *vs.* pK_a of quinuclidinium ions) of the reactions of quinuclidines with PClF, MOPClF, ClPClF, and NPClF are linear with slopes (β) of 0.32, 0.34,

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0.31, and 0.23, respectively. By comparing the reactions under investigation between each other and with similar aminolyses, the following conclusions can be drawn: (i) The magnitude of the slopes suggests that these mechanisms are stepwise, with the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) being the rate-determining step; (ii) The reactivity increases in the sequence MOPClF < PClF < ClPClF < NPClF; (iii) The change of the leaving group from 2,4-dinitrophenoxide to chloro changes the reaction mechanism from concerted to stepwise; (iv) Quinuclidines are more reactive toward aryl chloroformates than isobasic SA amines.

EXPERIMENTAL SECTION

Materials

The series of quinuclidines were purified as reported.[3] PClF, MOPClF, ClPClF, and NPClF are from Sigma and were used as purchased.

Kinetic measurements

These were carried out by means of either a Hewlett--Packard HP-8453 diode array or an Applied Photophysics DX17MV stopped-flow spectrophotometer in aqueous solution, at $25.0 \pm 0.1\,^{\circ}C$ and an ionic strength 0.2 M (KCl). The reactions were studied spectrophotometrically by following the corresponding phenol and/or its phenoxide anion (generated in the parallel hydrolysis reaction) at the wavelength where the absorbance change was the greatest during the reaction course.

The reactions studied by diode array spectroscopy (under external buffer) were initiated by the addition of 10 μL of a stock solution of the substrate in acetonitrile into 2.5 mL of the amine aqueous solution.

The reactions in the stopped-flow spectrophotometer were carried out with unequal mixing. The corresponding chloroformate dissolved in dry acetonitrile was placed in the smaller syringe (0.1 mL) and the larger syringe (2.5 mL) was filled with the amine aqueous solution.

All the reactions were studied under excess amine over the substrate. The initial substrate concentration was ca. 5×10^{-5} M, and the pH was maintained either by partial protonation of the quinuclidines (stopped-flow studies) or by external buffer (acetate or phosphate 0.01 M).

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