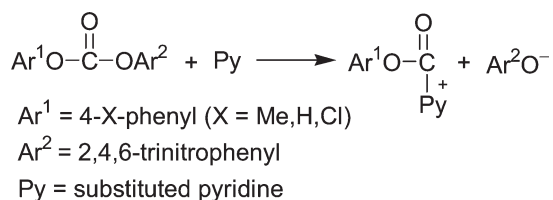# Concerted Pyridinolysis of Aryl 2,4,6-Trinitrophenyl Carbonates

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$$Ar^1O-\overset{\overset{\textstyle O}{\|}}{C}-OAr^2 + Py \longrightarrow Ar^1O-\overset{\overset{\textstyle O}{\|}}{\underset{\underset{\textstyle Py}{+}}{C}} + Ar^2O^-$$

Ar^1 = 4-X-phenyl (X = Me,H,Cl)
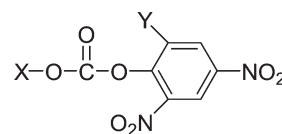
Ar^2 = 2,4,6-trinitrophenyl

Py = substituted pyridine

The Brønsted plots for the title reactions are linear with slopes of 0.53−0.56. The magnitude of the slopes and the fact that there are no breaks at the predicted pK_a for stepwise mechanisms indicate that these reactions are concerted. This finding is in great contrast to the stepwise mechanisms found for the pyridinolysis of other carbonates. The concerted mechanism is attributed to the fact that the title carbonates possess two O-aryl groups, one of them being an exceptionally good nucleofuge.

The kinetics of the reactions of primary and secondary amines and quinuclidines with reactive carbonates has been investigated to some extent.[1−6] On the other hand, the pyridinolysis of these compounds has received little attention.[7−10] Most of the above aminolysis reactions are governed by a stepwise mechanism, with a zwitterionic tetrahedral intermediate (T$^\pm$) on the reaction pathway. On the other hand, those aminolysis reactions (except pyridinolysis) involving very reactive carbonates are driven by a concerted mechanism; namely, these reactions occur in a single step with no T$^\pm$ intermediate.[6] Among such very reactive substrates are 2,4-dinitrophenyl and 2,4,6-trinitrophenyl methyl carbonates (**1** and **2**, respectively) and 4-X-phenyl 2,4-dinitrophenyl carbonates, with X = H, Me, and Cl (**3−5**).[6]

In contrast, the pyridinolysis reactions of all the above very reactive carbonates (**1−5**) are stepwise.[9,10] The change in mechanism, from stepwise for pyridines to concerted for the other amines, has been explained by the greater nucleofugality from T$^\pm$ of the other amines relative to isobasic pyridines.[4,9−11] This destabilizes T$^\pm$, and the mechanism changes to concerted.

To extend our investigations on the pyridinolysis of very reactive carbonates and with the aim to find out whether the pyridinolysis of some very reactive carbonates can be concerted, we decided to study the reactions of 4-X-phenyl 2,4,6-trinitrophenyl carbonates (X = H, Me, and Cl, carbonates **6**, **7**, and **8**) with a series of pyridines in aqueous ethanol. We found that these reactions are concerted. To our knowledge, this is the first time a concerted pyridinolysis of carbonates in water or mixed aqueous solvents is reported.

$$X-O-\overset{\overset{\textstyle O}{\|}}{C}-O-\underset{\underset{\textstyle O_2N}{}}{\overset{\overset{\textstyle Y}{}}{\bigcirc}}-NO_2$$

1: X = Me ; Y = H
2: X = Me ; Y = NO$_2$
3: X = Ph ; Y = H
4: X = 4-MePh ; Y = H
5: X = 4-ClPh ; Y = H
6: X = Ph ; Y = NO$_2$
7: X = 4-MePh ; Y = NO$_2$
8: X = 4-ClPh ; Y = NO$_2$

The rate law obtained for the pyridinolysis of the title carbonates (under excess amine) is shown in eq 1, where TNP$^-$ and S represent 2,4,6-trinitrophenoxide anion and the substrate, respectively, and k_{obsd} is the pseudo-first-order rate constant. For the reactions of these substrates with the series of pyridines, linear plots of k_{obsd} against concentration of free amine ([N]) were found, as depicted by eq 2, where k_0 and k_N are the rate constants for solvolysis and pyridinolysis of the substrates, respectively. The k_0 values were much smaller than those of $k_N[N]$ in eq 2. The slopes (k_N) were independent of pH for the reactions of all pyridines, with the exception of 4-oxypyridine.

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

$$k_{obsd} = k_0 + k_N[N] \qquad (2)$$

For the reactions with 4-oxypyridine, the values of k_N were pH-dependent. We attribute this to the fact that pH values

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(8) Bond, P. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 679.
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SCHEME 1
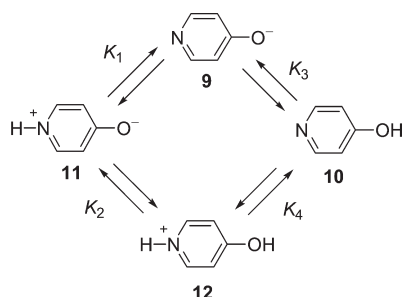
much lower than the pK_a of its conjugate acid had to be used, due to the high reactivity of this pyridine. At these low pH values, there is a competition between 4-oxypyridine (species **9**) and 4-hydroxypyridine (species **10**) to attack the substrate by their pyridinic nitrogen atoms (see Scheme 1).[12]

The values of K_1 and K_2 were determined experimentally in 44 wt % ethanol−water; the corresponding pK_a values are 11.5 and 3.2, respectively.[13] We have estimated the pK_3 value as follows: The pK_a of a phenol is given by pK_a = 9.92 − 2.23σ, where σ is the Hammett substituent constant.[14] Since the σ_P value for a ring N is 0.83,[14] this equation gives a pK_a (pK_3) value of 8.07 for species **10**. The pK_4 value can be deduced from pK_4 = pK_1 + pK_2 − pK_3, which yields pK_4 = 6.6. According to these pK_a values, the main competition for attack to a carbonate is between species **9** and **10**, by their N atoms.

Therefore, these reactions can be depicted by eq 3, where k_9 and k_{10} are the nucleophilic rate constants (k_N) of species **9** and **10**; F_9 and F_{10} are their corresponding amine fractions, and [N]$_{tot}$ is the concentration of total amine.

$$k_{obsd} = k_0 + (k_9 F_9 + k_{10} F_{10})[\text{N}]_{tot} \qquad (3)$$

Plots of k_{obsd} against [N]$_{tot}$ at constant pH were linear, with the slopes ($k_{N,obsd}$) pH-dependent. Equation 3 can be rearranged to give eq 4. Plots of $k_{N,obsd}/F_{10}$ versus F_9/F_{10} were linear, with intercept k_{10} and slope k_9 (see Figure 1).

$$k_{N,obsd} F_{10} = k_{10} + k_9 F_9/F_{10} \qquad (4)$$

The values of F_9 and F_{10} were calculated from eqs 5 and 6.[15]

$$1/F_9 = 1 + [\text{H}^+]/K_1 + [\text{H}^+]/K_3 + [\text{H}^+]^2/K_1 K_2 \qquad (5)$$

$$F_{10} = F_9 [\text{H}^+]/K_3 \qquad (6)$$

The k_N values obtained for the reactions of all the pyridines with the title carbonates, either through eq 2 or eq 4 (k_9 for 4-oxypyridine),[16] are shown in Table 1.

According to the k_N values in Table 1, the order of reactivities of these carbonates is **8** > **6** > **7**. This sequence is

(12) Although there is prototropy between species **10** and 4-pyridone, this was not included in Scheme 1 for clarity reasons (see Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981; p 55). The existence of this prototropy does not affect the kinetic results.
(13) Castro, E. A.; Aguayo, R.; Bessolo, J.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 3530.
(14) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981, p 56; p 139.
(15) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 63.
(16) The k_N value for 4-hydroxypyridine (k_{10}) was not included in Table 1 due to the large error involved in its determination.
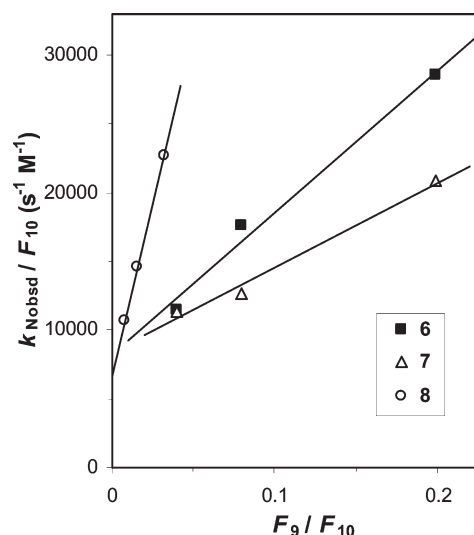

FIGURE 1. Plots of $k_{N,obsd}/F_{10}$ against F_9/F_{10} for the pyridinolysis of carbonates **6**–**8** in 44 wt % ethanol−water, at 25.0 °C, and an ionic strength of 0.2 M (KCl).

the same as that of the Hammett *p*-substituent constants in the nonleaving group of the substrates: σ_P values in water for Cl, H, and Me are +0.23, 0.0, and −0.17, respectively.[17] A Hammett plot (log k_N vs σ_P, not shown) for the reactions of carbonates **6**−**8** with different pyridines shows a reaction constant ρ of ca. 1.0. The positive value of this parameter is in accordance with the fact that the greater the electron-withdrawing effect from the nonleaving group of the carbonate, the more positive the carbonyl carbon and, therefore, the more prone it becomes to nucleophilic attack.

The Brønsted plots for the pyridinolysis of carbonates **6**−**8**, obtained with the data in Table 1, are shown in Figure 2. The slopes (β) of the linear Brønsted plots are 0.53 ± 0.02, 0.53 ± 0.02, and 0.56 ± 0.02 for the reactions of carbonates **6**, **7**, and **8**, respectively. The magnitude of the slopes is in accordance with a concerted mechanism. In fact, the concerted reactions of secondary alicyclic amines, quinuclidines, anilines, and other primary amines with very reactive carbonates (such as **1**−**5**) in aqueous solutions show linear Brønsted plots with slopes in the range of 0.4−0.7.[6] Nevertheless, the pyridinolysis of these very reactive carbonates (**1**−**5**) either in water or in aqueous ethanol solution is governed by a stepwise mechanism, as judged by the biphasic (two linear portions and a curvature between) Brønsted plots found.[9,10]

In order to confirm that the pyridinolyses of the title carbonates are concerted, it is necessary to estimate the pK_a position at the center of the curvature (pK_a^0) of the biphasic Brønsted plot for a hypothetical stepwise mechanism.[18,19] The stepwise pyridinolysis of carbonate **1** shows a biphasic Brønsted plot with pK_a^0 = 7.8, whereas the same aminolysis of carbonate **2** shows pK_a^0 = 6.5. Namely, for stepwise mechanisms, the change of 2,4-dinitrophenoxide by 2,4,6-trinitrophenoxide as the leaving group lowers the Brønsted break by 1.3 pK_a units. If this shift can be extended

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(18) (a) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040. (b) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387.
(19) Williams, A. *Free Energy Relationships in Organic and Bio-Organic Chemistry*; The Royal Society of Chemistry: Cambridge, 2003; p 171.

TABLE 1. Values of pK_a for the Conjugate Acids of Pyridines and k_N Values for the Pyridinolysis of Carbonates 6, 7, and 8[a]

pyridine substituent	pK_a	$k_N/s^{-1}M^{-1}$		
		6	7	8
4-O^{-b}	11.5	$(1.0 \pm 0.2) \times 10^5$	$(6.1 \pm 0.4) \times 10^4$	$(5.1 \pm 0.3) \times 10^5$
4-NH$_2$	8.98	5100 ± 100	4340 ± 140	10300 ± 300
none	4.63	51 ± 1	34 ± 1	90 ± 3
3-CONH$_2$	2.67	2.4 ± 0.1	1.5 ± 0.1	3.8 ± 0.2
4-CN	0.80	0.15 ± 0.02	0.12 ± 0.01	0.40 ± 0.02

[a]Both the pK_a and k_N values were determined in 44 wt % ethanol–water, at 25.0 °C, and an ionic strength of 0.2 M (KCl). [b]For this pyridine, the k_N values are those of k_9 in eqs 3 and 4.
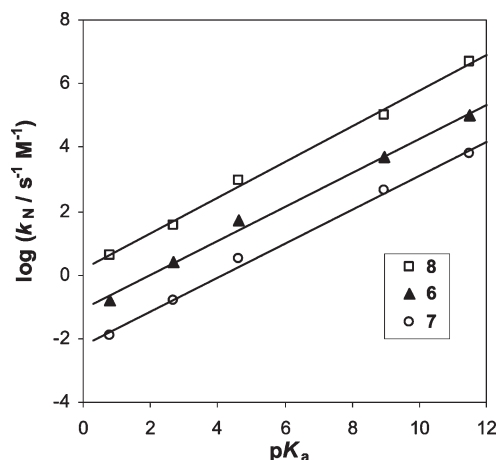

FIGURE 2. Brønsted plots obtained for the pyridinolysis of carbonates 6–8 in 44 wt % ethanol–water, at 25.0 °C, and an ionic strength of 0.2 M (KCl). For reasons of clarity, the points for 8 were shifted one log unit upward and those for 7 were shifted one log unit downward.

to diaryl carbonates, and knowing that the Brønsted break for the stepwise pyridinolysis of carbonate 3 is pK_a^0 = 8.0,[10] one can predict a pK_a^0 value of 8.0 − 1.3 = 6.7 for the hypothetical stepwise pyridinolysis of carbonate 6. Similarly, since the same aminolyses of carbonates 4 and 5 show pK_a^0 values of 8.3,[10] a pK_a^0 value of 7.0 can be estimated for the hypothetical stepwise pyridinolyses of carbonates 7 and 8. Perusal of the Brønsted plots in Figure 2 shows that there are no breaks at pK_a 6.7–7.0. Therefore, the stepwise mechanism can be safely discarded for the pyridinolysis of the title carbonates. Namely, the concerted mechanism can be confirmed for these reactions (Scheme 2).

To our knowledge, this is the first time that a *concerted* pyridinolysis of a carbonate in water or in its mixtures with other solvents is reported. Even very reactive carbonates such as 4-nitrophenyl 2,4-dinitrophenyl and bis(2,4-dinitrophenyl) carbonates exhibit stepwise pyridinolysis in aqueous ethanol.[10] The concerted mechanism for the title reactions can be attributed to the great destabilization of the zwitterionic tetrahedral intermediate (T$^{\pm}$) formed in the above stepwise pyridinolyses by the change of the leaving group to 2,4,6-trinitrophenoxide. This means that the intermediate T$^{\pm}$ is so unstable that either it does not exist (enforced concerted mechanism) or the intermediate still exists but the concerted pathway has lower energy.[20]

Not only the change of leaving group can cause a change in mechanism. The substitution of the nonleaving group can

SCHEME 2
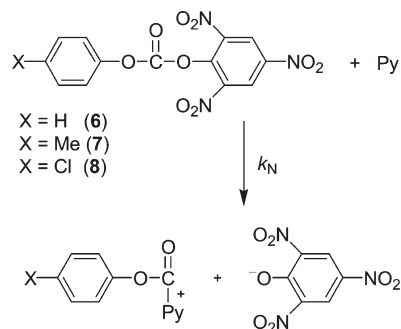
also produce such a change. For instance, the pyridinolysis of carbonate 2 in water is stepwise.[9b] Substitution of MeO by PhO as the nonleaving group (to yield carbonate 6) and water to aqueous ethanol as solvent changes the mechanism from stepwise to concerted. It is unlikely that this change in mechanism is due to the change of solvent, in view of the similar polarity of both solvents. On the other hand, substitution of Me by PhO also changes the mechanism, as shown by the fact that the pyridinolysis of 2,4,6-trinitrophenyl acetate in water is stepwise,[9b] in comparison with the concerted pyridinolysis of carbonate 6. This is in agreement with the fact that the aminolysis (secondary alicyclic amines) of 2,4-dinitrophenyl acetate in water is stepwise,[21] whereas the same aminolysis of 2,4-dinitrophenyl phenyl carbonate (3) in the same solvent is concerted.[6b]

The fact that the pyridinolyses of carbonates 1−5 are governed by stepwise mechanisms, whereas the reactions of the same carbonates with secondary alicyclic amines,[6a,6b] anilines,[6b,6c] and quinuclidines[22] are concerted, can be explained by the poorer nucleofugality of pyridines from the intermediate T$^{\pm}$ compared with the other isobasic amines.[4,15,23] This stabilizes the intermediate T$^{\pm}$ formed with pyridines, and the stepwise pathway becomes of lower free energy relative to the concerted mechanism for the other aminolyses.

In conclusion, we have found in this work that the pyridinolysis reactions of carbonates 6−8 in aqueous ethanol are ruled by a concerted mechanism. To our knowledge, this is the first report of a concerted pyridinolysis of any ester or carbonate in water or mixed aqueous solvents. We attribute this to the fact that the title carbonates are very

(20) (a) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161. (b) Jencks, W. P. *Chem. Soc Rev.* **1981**, *10*, 345. (c) Williams, A. *Chem. Soc. Rev.* **1994**, *23*, 93.

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(22) Castro, E. A.; Campodonico, P. R.; Contreras, R.; Fuentealba, P.; Santos, J. G.; Leis, J. R.; Garcia-Rio, L.; Saez, J. A.; Domingo, L. R. *Tetrahedron* **2006**, *62*, 2555.
(23) (a) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505. (b) Castro, E. A. *J. Sulfur Chem.* **2007**, *28*, 401.

reactive due to their diaryl nature and the very large nucleofugality of the leaving group. Therefore, the hypothetical tetrahedral intermediate should be extremely unstable or nonexistent. This makes the stepwise pathway highly energetic, and the concerted mechanism takes over.

Experimental Section

Materials. Pyridines were distilled or crystallized before use. To our knowledge, carbonates **6**–**8** have not been synthesized. These were prepared by a modification of the general method described.[3] Equimolar quantities of anhydrous picric acid and the corresponding chloroformate, both in dry dichloromethane solution and in the presence of pyridine, were reacted under nitrogen for 4 h at room temperature. The solid phase was disregarded and the liquid phase washed three times with cold water, dried with magnesium sulfate, and the solvent eliminated. The products were obtained by crystallization of the solids in hexane. These were identified by the following properties.

Phenyl 2,4,6-trinitrophenyl carbonate (**6**): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31–7.37 (m, 3H), 7.47 (t, 2H), 9.21 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 120.8, 125.4, 127.6, 130.2, 142.9, 143.9, 144.8, 149.0, 150.9; HRMS calcd for C$_{13}$H$_7$N$_3$O$_8$ 349.01823, found 349.01818.

4-Methylphenyl 2,4,6-trinitrophenyl carbonate (**7**): [1]H MNR (400 MHz, acetone-d_6) δ 7.23 (d, 2H), 7.34 (d, 2H), 9.35 (s, 2H), 2.37 (s, 3H); ^{13}C MNR (100 MHz, acetone-d_6) δ 19.9, 120.3, 125.8, 130.4, 137.2, 141.8, 143.4, 145.2, 148.8, 149.1; HRMS calcd for C$_{14}$H$_9$N$_3$O$_9$ 363.03388, found 363.0332.

4-Chlorophenyl 2,4,6-trinitrophenyl carbonate (**8**): [1]H MNR (400 MHz, acetone-d_6) δ 7.43 (d, 2H), 7.59 (d, 2H), 9.36 (s, 2H); ^{13}C MNR (100 MHz, acetone-d_6) δ 122.5, 125.9, 130.1, 132.3, 141.6, 143.4, 145.2, 148.8, 149.5; HRMS calcd for C$_{13}$H$_6$ClN$_3$O$_9$ 382.97926, found 382.97911.

(24) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 2nd ed.; Champman and Hall: London, 1971; p 44.

Kinetic Measurements. These were carried out by means of a diode array spectrophotometer in 44 wt % ethanol aqueous solution at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (KCl). The reactions were studied by monitoring the appearance of 2,4,6-trinitrophenoxide anion.

All of the reactions were examined under excess amine over the substrate. The initial substrate concentration was about 5 × 10^{-5} M, and in most cases, the pH was maintained by using external buffer (0.01 M phosphate or 0.01 M acetate buffer).

Pseudo-first-order rate coefficients (k_{obsd}) were found throughout and determined by means of the spectrophotometer kinetics software for first-order reactions. The experimental conditions of the reactions and the values of k_{obsd} and amine concentrations, together with their corresponding plots, are shown in Tables S1–S3 in Supporting Information.

Determination of pK_a. The pK_a value for the conjugate acid of 4-cyanopyridine was determined spectrophotometrically at 276 nm, by the reported method.[24] The experimental conditions used were the same as those for the kinetic measurements (44 wt % ethanol–water, 25.0 ± 0.1 °C, ionic strength 0.2 M). Under these conditions, the pK_a obtained for the conjugate acid of 4-cyanopyridine was 0.8.

Product Studies. One of the products of the reactions under scrutiny was identified as 2,4,6-trinitrophenoxide anion, as shown by a comparison of the UV–vis spectra after completion of the reactions with that of an authentic sample under the same experimental conditions.

Supporting Information Available: Tables S1–S3 containing [amine], k_{obsd}, and pH data for the title reactions, and ^{1}H NMR and ^{13}C NMR spectra of carbonates **6**–**8**. This material is available free of charge via the Internet at http://pubs.acs.org.