

## Solvent Effect on the Relative Nucleofugalities of Pyridines and Phenoxide Ions: Brønsted-Type Plots in the Pyridinolysis of 2,4-Dinitrophenyl Methyl Carbonate and 2,4-Dinitrophenyl Acetate in Aqueous Ethanol

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Curved Brønsted-type plots ( $\log k_N$  vs.  $pK_a$ ) are obtained for the nucleophilic reactions of the title in 44 wt % aqueous ethanol, at 25 °C, ionic strength 0.2 M (KCl). The curves are described by a semiempirical equation based on the existence of a tetrahedral intermediate ( $T^\ddagger$ ) in the reaction path and a change of the rate-determining step from breakdown to formation of  $T^\ddagger$  as the pyridine is more basic. The  $pK_a$  value at the center of curvature ( $pK_a^0$ ) increases with increasing inductive electron withdrawal from the nonleaving group of the substrate ( $pK_a^0$  7.6 and 8.0 for the acetate and carbonate esters, respectively), favoring amine expulsion, relative to that of 2,4-dinitrophenoxide ion, from  $T^\ddagger$ . The  $pK_a^0$  values for the present reactions are larger than those for the same reactions in water, which shows that amine expulsion from  $T^\ddagger$  is favored over 2,4-dinitrophenoxide expulsion by the change to a less polar solvent. Specific acid catalysis of aminolysis is found in the reactions of both substrates with 4-cyanopyridine at low pH. The most likely mechanism involves amine attack to the substrate to form  $T^\ddagger$ , followed by protonation equilibrium with  $T^\ddagger$  and breakdown to products of  $T^\ddagger$  and  $T^+$ .

The Brønsted-type equation is one of the linear free energy relationships that has been most widely used in clarifying the mechanism of the reactions of a series of nucleophiles with reactive carbonyl compounds.<sup>1</sup> In logarithmic terms it has the form  $\log k_N = \log G + \beta pK_a$ , where  $k_N$  is the rate constant for the nucleophilic reaction,  $K_a$  is the ionization constant of the conjugate acid of the nucleophile, and  $G$  and  $\beta$  are constants.

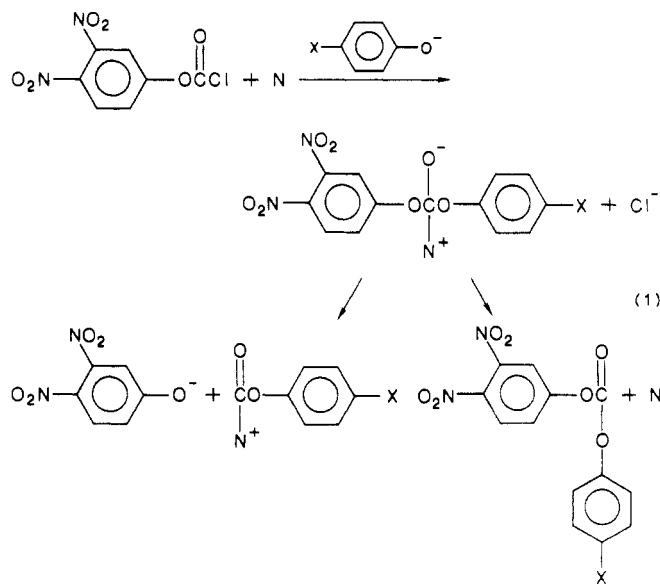
Brønsted-type plots ( $\log k_N$  against  $pK_a$ ) which are linear have been found in the aminolysis of carboxylic acid derivatives (RCOL, where L is the leaving group), when  $L^-$  is relatively basic, e.g., phenyl and *p*-nitrophenyl acetates<sup>2</sup> and phenyl<sup>3</sup> and *p*-nitrophenyl methyl carbonates.<sup>4</sup> When  $L^-$  is less basic the plots are curved, as in the aminolysis and pyridinolysis of 2,4-dinitrophenyl acetate in water<sup>2,3</sup> and the pyridinolyses of 2,4-dinitrophenyl methyl carbonate,<sup>5</sup> acetyl chloride,<sup>6</sup> and methyl chloroformate<sup>7</sup> in aqueous solution.

The results above show that as the basicity of the leaving group of the substrate becomes less basic the center of the Brønsted-type curvature ( $pK_a^0$ ) appears earlier on the  $pK_a$  axis (smaller  $pK_a^0$  value). This was confirmed by Gresser and Jencks in the reactions of quinuclidines with aryl phenyl carbonates.<sup>8a</sup>

In order to assess the influence of the permanent group of the substrate (R) on the  $pK_a^0$  value Gresser and Jencks obtained the Brønsted-type plots for the reactions of quinuclidines with substituted phenyl 3,4-dinitrophenyl carbonates.<sup>8b</sup> They found that  $pK_a^0$  increases with the increasing electron-withdrawing effect of the R group. Confirmation of this can be found by comparing the Brønsted-type plots obtained in the pyridinolyses of 2,4-dinitrophenyl benzoates in 44 wt % aqueous ethanol. The plots for the *p*-nitro- and *p*-chlorobenzoate derivatives are straight ( $pK_a^0 > 9.5$ ),<sup>9</sup> while that for the unsubstituted

benzoate ester is curved ( $pK_a^0 = 9.5$ ).<sup>10</sup>

Little is known, however, on the influence of the solvent on the  $pK_a^0$  value. It was found in the reactions of 3,4-dinitrophenyl chloroformate with quinuclidines in the presence of phenoxide anions, that partitioning of the tetrahedral intermediate formed in the reactions (eq 1, N



is a quinuclidine) favors amine repulsion relative to 3,4-dinitrophenoxide ion by the addition of acetonitrile to the aqueous solution.<sup>8b</sup> This is an indication that for a given aminolysis reaction the value of  $pK_a^0$  increases as the polarity of the solution decreases (see below).

The curved Brønsted-type plots described above have been explained by the presence of a tetrahedral intermediate ( $T^\ddagger$ ) in the reaction pathway and a change in the rate-determining step, from its breakdown (to products) to its formation as the amine becomes more basic.<sup>3,5-8,10</sup> At the center of the curvature ( $pK_a^0$ ) the nucleofugalities from  $T^\ddagger$  of an amine of  $pK_a = pK_a^0$  and the leaving group of the substrate are the same. It follows from this that if expulsion of a given amine from  $T^\ddagger$  relative to phenoxide

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ion increases for some reason (change of R, L or solvent), the new Brønsted-type plot will have a larger  $pK_a^0$  value.<sup>3,5-8,10</sup> This fact underlies the importance of the  $pK_a^0$  values.

In order to clarify the solvent effect on the relative nucleofugalities of amines and aryloxy ions from  $T^+$ , we report in this paper the Brønsted-type plots found in the pyridinolysis of 2,4-dinitrophenyl acetate and 2,4-dinitrophenyl methyl carbonate in 44 wt % aqueous ethanol, and we compare their  $pK_a^0$  values with those found in the same reactions in aqueous solution.<sup>3,5</sup>

### Experimental Section

**Materials.** Absolute ethanol, analytical grade, was used in the preparation of the solutions. Acetonitrile (solvent for the stock solution of the substrate) was spectrophotometric grade. Potassium chloride and sodium dihydrogen phosphate (used as additional buffer in some reactions) were analytical grade. The substituted pyridines were purified as previously described.<sup>10</sup> 2,4-Dinitrophenyl acetate<sup>3</sup> and 2,4-dinitrophenyl methyl carbonate<sup>11</sup> were prepared by standard procedures.

**Determination of the  $pK_a$  Values of 4-Cyanopyridinium Ion.** It was carried out spectrophotometrically (Perkin-Elmer Lambda 3), in the same experimental conditions as the kinetics, i.e., in 44 wt % aqueous ethanol, at  $25 \pm 0.1$  °C, ionic strength 0.2 M (maintained with KCl). The absorbance measurements were performed at two wavelengths (230 and 276 nm), and in each case the same  $pK_a$  value was obtained, within experimental error. A Radiometer PHM-62 pH meter, provided with Radiometer G-2040C (glass) and K-4040 (calomel) electrodes, was employed for the pH readings. The  $pK_a$  values of the other pyridinium ions studied in this work were determined previously in the same experimental conditions as above.<sup>10</sup>

**Kinetic Measurements.** The reactions were followed spectrophotometrically by monitoring the absorbance increase of 2,4-dinitrophenoxide ion (400 nm) and/or its conjugate acid (350 nm) by means of a Perkin-Elmer Lambda 3 spectrophotometer. Sample solutions (3 mL) of the appropriate pyridine in the kinetic conditions (Table I) were poured into 1-cm cells and placed in the thermostated cell holder of the instrument. After thermal equilibration ( $25 \pm 0.1$  °C) a stock solution of the substrate in acetonitrile (1–10  $\mu$ L) was injected into the solutions and the recordings started. The acetonitrile concentration in the kinetic solutions never exceeded 0.3%. The initial substrate concentration was  $(0.1\text{--}5.0) \times 10^{-4}$  M.

The reactions were buffered either by the pyridines or by an external buffer ( $H_2PO_4^- + HPO_4^{2-}$  in the case of the reactions of the two aminopyridines). The preparation of the buffers have been previously described.<sup>10</sup>

Pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) were found throughout (the total pyridine concentration was at least 10-fold in excess over that of the substrates) by the "infinity" method.<sup>12</sup>

The values of  $k_{\text{obsd}}$  together with the experimental conditions of the reactions are shown in Table I.

**Product Studies.** 2,4-Dinitrophenoxide anion and its conjugate acid were one of the final products of the reactions of both substrates with 4-(dimethylamino)pyridine (pH ca. 7) and nicotinamide (pH ca. 3), respectively. Identification of these products was achieved by comparison of the solutions spectra (220–500 nm) after completion of the reactions with those of authentic samples in the same experimental conditions.

Accumulation and decomposition of an intermediate was spectrophotometrically observed (310 nm) in the reaction of 2,4-dinitrophenyl methyl carbonate with 4-(dimethylamino)pyridine at the same experimental conditions of the kinetics. It is reasonable to assume that this intermediate is 1-(methoxycarbonyl)-4-(dimethylamino)pyridinium ion since it has also been spectrophotometrically observed at similar experimental condi-

tions in aqueous solution<sup>5,7,13</sup> and the values of  $\lambda_{\text{max}}$  shown in 44 wt % aqueous ethanol (310 nm, this work) are similar to those exhibited by an authentic sample in water<sup>14</sup> and by 1-acetyl-4-(dimethylamino)pyridinium ion in various solvents.<sup>15</sup>

### Results

The kinetic law obtained for all the reactions studied in the presented work obeys eq 2, where DNP represents 2,4-dinitrophenoxide ion and/or its conjugate acid, S is the substrate 2,4-dinitrophenyl methyl carbonate or 2,4-dinitrophenyl acetate, and  $k_{\text{obsd}}$  is the pseudo-first-order rate constant observed.

$$\frac{d[\text{DNP}]}{dt} = k_{\text{obsd}}[S] \quad (2)$$

For the reactions of the substrate with all the amines, except 4-cyanopyridine, the rate equation found for  $k_{\text{obsd}}$  is given by eq 3, where  $k_N$  is the second-order rate constant

$$k_{\text{obsd}} = k_N F_N [N]_T \quad (3)$$

for the nucleophilic reaction,  $[N]_T$  is the concentration of total amine ( $[N] + [NH^+]$ ), where N and  $NH^+$  represent the basic and acidic forms of the pyridine, and  $F_N$  is the free-amine fraction ( $[N]/[N]_T$ ). The rate constants for solvolysis of the substrates ( $k_0$ ) were not observed for these reactions, since the pyridinolysis was much faster. The value of  $k_0$  was determined in the reactions with the least basic pyridine studied, 4-cyanopyridine (see below).

The values of  $k_N$  were obtained from the slopes of straight plots of  $k_{\text{obsd}}$  against  $[N]_T$  at constant  $F_N$ . Three different  $F_N$  values were used for the reactions with each amine (Table I) and no dependence of  $k_N$  on  $F_N$  was observed. The final values of  $k_N$  (average of the values at each  $F_N$ ) are shown in Table II.

The rate equation for  $k_{\text{obsd}}$  found in the reactions of both substrates with 4-cyanopyridine is given by eq 4, where  $k_0$  and  $k'$  are the rate constants for solvolysis of the substrate and for specific acid catalysis, respectively. The value of

$$k_{\text{obsd}} = k_0 + (k_N + k[H^+])F_N[N]_T \quad (4)$$

$k_0$  was obtained as the intercept of linear plots of  $k_{\text{obsd}}$  against  $[N]_T$  at constant  $F_N$ . The slopes of these plots ( $k_{N \text{ obsd}}$ ) showed a linear dependence on  $[H^+]$ . The values of  $k_N$  and  $k'$  for the reactions of the two substrates with 4-cyanopyridine were obtained as the intercept and slope, respectively, of  $k_{N \text{ obsd}}$  against  $[H^+]$  plots. Actually, these plots could be either linear or parabolic within experimental error, but for reasons stated in Discussion the plots are more likely to be straight.

Table II shows the  $k_N$  values, and Table III gathers the  $k_{N \text{ obsd}}$ ,  $k'$ , and  $k_0$  values found for the reactions of both substrates with 4-cyanopyridine.

The  $pK_a$  value obtained for 4-cyanopyridinium ion (Table II) shows the expected decrease compared to its value in aqueous solution at the same temperature and ionic strength.<sup>7</sup> The  $k_N$  values obtained for the reactions of the two substrates (Table II) are in accord to the higher nucleophilic reactivity expected for 2,4-dinitrophenyl acetate, in view of the larger electron-donating effect of the methoxy group of 2,4-dinitrophenyl methyl carbonate compared to the methyl group of the acetate ester. This fact should render the carbonyl carbon of the carbonate

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(12) In some reactions the free amine was not in excess over the substrate, but since the total amine (protonated plus free forms) was in excess, the free amine concentration is effectively held constant during the reaction by displacement of the equilibrium between the protonated and free amine species.

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**Table I. Experimental Conditions and Pseudo-First-Order Rate Constants ( $k_{\text{obsd}}$ ) for the Pyridinolyses of 2,4-Dinitrophenyl Methyl Carbonate and 2,4-Dinitrophenyl Acetate<sup>a</sup>**

pyridine substituent	[N] <sub>T</sub> , M <sup>b</sup>	F <sub>N</sub> <sup>c</sup>	$k_{\text{obsd}}$ , s <sup>-1</sup>	no. of runs
2,4-Dinitrophenyl Methyl Carbonate				
4-cyano	0.03-0.27	0.51	$(0.7-3.7) \times 10^{-5}$	9
	0.05-0.50	0.65	$(1.0-5.8) \times 10^{-5}$	9
	0.05-0.50	0.90	$(1.8-6.7) \times 10^{-5}$	10
3-carbamoyl	0.03-0.24	0.49	$(0.8-4.6) \times 10^{-4}$	8
	0.05-0.50	0.67	$(0.9-12.6) \times 10^{-4}$	10
	0.05-0.50	0.91	$(2.8-17.9) \times 10^{-4}$	10
none	$(2.6-26.3) \times 10^{-2}$	0.30	$(1.5-13.7) \times 10^{-3}$	10
	$(1.3-13.1) \times 10^{-2}$	0.49	$(1.3-11.1) \times 10^{-3}$	10
	$(1.3-13.1) \times 10^{-2}$	0.68	$(1.5-13.6) \times 10^{-3}$	10
3-methyl	$(0.7-6.6) \times 10^{-2}$	0.38	$(0.9-8.2) \times 10^{-3}$	10
	$(0.7-6.6) \times 10^{-2}$	0.56	$(1.2-11.8) \times 10^{-3}$	10
	$(0.3-3.3) \times 10^{-2}$	0.72	$(0.8-7.2) \times 10^{-3}$	10
4-methyl	$(3.3-33.0) \times 10^{-3}$	0.37	$(0.8-7.7) \times 10^{-3}$	10
	$(3.3-33.0) \times 10^{-3}$	0.52	$(1.0-11.6) \times 10^{-3}$	10
	$(1.7-16.5) \times 10^{-3}$	0.68	$(0.8-7.5) \times 10^{-3}$	10
3,4-dimethyl	$(1.6-16.1) \times 10^{-3}$	0.37	$(0.8-8.2) \times 10^{-3}$	10
	$(0.8-8.0) \times 10^{-3}$	0.57	$(0.8-7.0) \times 10^{-3}$	10
	$(0.8-8.0) \times 10^{-3}$	0.70	$(0.9-9.0) \times 10^{-3}$	10
4-amino <sup>d</sup>	$(0.4-4.0) \times 10^{-3}$	0.0055	$(0.3-2.9) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-3}$	0.014	$(0.4-3.5) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-3}$	0.032	$(0.8-7.5) \times 10^{-3}$	10
4-dimethylamino <sup>d</sup>	$(0.4-4.0) \times 10^{-3}$	0.0083	$(0.7-6.5) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-3}$	0.012	$(0.6-4.7) \times 10^{-3}$	10
	$(0.1-1.0) \times 10^{-3}$	0.026	$(0.5-4.4) \times 10^{-3}$	10
2,4-Dinitrophenyl Acetate				
4-cyano	0.03-0.30	0.50	$(1.3-9.3) \times 10^{-5}$	10
	0.05-0.45	0.70	$(2.5-15.1) \times 10^{-5}$	9
	0.06-0.60	0.90	$(3.3-22.8) \times 10^{-5}$	10
3-chloro	0.04-0.40	0.50	$(0.7-5.3) \times 10^{-4}$	10
	0.04-0.40	0.67	$(0.8-6.9) \times 10^{-4}$	10
	0.08-0.40	0.90	$(2.1-10.9) \times 10^{-4}$	5
3-carbamoyl	0.03-0.30	0.33	$(0.9-9.1) \times 10^{-4}$	10
	0.04-0.36	0.50	$(1.8-17.1) \times 10^{-4}$	8
	0.04-0.40	0.67	$(2.4-23.7) \times 10^{-4}$	10
none	$(0.3-3.0) \times 10^{-2}$	0.33	$(0.4-3.1) \times 10^{-3}$	10
	$(0.3-3.0) \times 10^{-2}$	0.50	$(0.5-4.9) \times 10^{-3}$	10
	$(0.3-3.0) \times 10^{-2}$	0.67	$(0.7-6.4) \times 10^{-3}$	10
3-methyl	$(0.2-2.0) \times 10^{-2}$	0.33	$(0.4-4.5) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-2}$	0.50	$(0.7-6.8) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-2}$	0.74	$(1.1-10.1) \times 10^{-3}$	10
4-methyl	$(0.2-2.0) \times 10^{-2}$	0.31	$(0.8-7.1) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-2}$	0.50	$(1.3-12.2) \times 10^{-3}$	10
	$(0.2-2.0) \times 10^{-2}$	0.67	$(1.7-16.6) \times 10^{-3}$	10
3,4-dimethyl	$(0.1-1.0) \times 10^{-2}$	0.33	$(0.7-7.7) \times 10^{-3}$	10
	$(0.1-1.0) \times 10^{-2}$	0.50	$(1.2-12.2) \times 10^{-3}$	10
	$(0.1-1.0) \times 10^{-2}$	0.67	$(1.7-18.4) \times 10^{-3}$	10
4-amino <sup>d</sup>	$(0.2-2.0) \times 10^{-3}$	0.015	$(0.7-5.5) \times 10^{-3}$	10
	$(0.2-1.8) \times 10^{-3}$	0.033	$(1.4-12.0) \times 10^{-3}$	9
	$(0.2-2.0) \times 10^{-3}$	0.071	$(2.9-26.5) \times 10^{-3}$	8
4-dimethylamino <sup>d</sup>	$(0.2-2.0) \times 10^{-3}$	0.011	$(0.7-6.0) \times 10^{-3}$	10
	$(0.1-1.0) \times 10^{-3}$	0.023	$(0.7-6.5) \times 10^{-3}$	10
	$(0.2-1.8) \times 10^{-3}$	0.052	$(3.1-27.3) \times 10^{-3}$	8

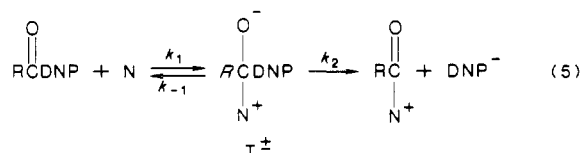
<sup>a</sup> In 44 wt % aqueous ethanol, at  $25 \pm 0.1$  °C, ionic strength 0.2 M (maintained with KCl). <sup>b</sup> Concentration of total pyridine.  $[N]_T = [N] + [NH^+]$ , where N and  $NH^+$  are the free base and protonated forms of the pyridine. <sup>c</sup> Free amine fraction of the pyridine.  $F_N = [N]/[N]_T$ . <sup>d</sup> In the presence of phosphate buffer ( $H_2PO_4^- + HPO_4^{2-}$ ). Concentration of total phosphate buffer 0.02 M.

ester less positive than that of the acetate, and therefore, less susceptible to nucleophilic attack. This is in agreement with the lower  $k_N$  values found in the pyridinolysis of methyl chloroformate<sup>7</sup> compared to the same reaction of acetyl chloride.<sup>6</sup>

### Discussion

Figure 1 shows the Brønsted-type plots obtained in the reactions under study in the present work (data from Table II). The inclusion of 3,4-dimethylpyridine in this plot, the only disubstituted pyridine of the series, is justified since this amine correlates well with the monosubstituted pyridines in Brønsted-type plots obtained in analogous reaction.<sup>6,9b,10,16</sup>

The curved Brønsted-type plots can be explained in terms of a zwitterionic tetrahedral intermediate ( $T^\ddagger$ ) in the reaction pathway and a change in the rate-determining step from  $k_2$  to  $k_1$  (eq 5,  $DNP^-$  and N represent 2,4-di-



**Table II.  $pK_a$  Values of Substituted Pyridinium Ions and  $k_N$  Values for the Pyridinolyses of 2,4-Dinitrophenyl Methyl Carbonate (DNPMC) and 2,4-Dinitrophenyl Acetate (DNPA)<sup>a</sup>**

pyridine subst	$pK_a^b$	$k_N \text{ s}^{-1} \text{ M}^{-1c}$	
		DNPMC	DNPA
4-cyano	1.39	$(1.1 \pm 0.2) \times 10^{-4}$	$(3.6 \pm 0.4) \times 10^{-4}$
3-chloro	2.17		$(2.7 \pm 0.3) \times 10^{-3}$
3-carbamoyl	2.67	$(3.7 \pm 0.3) \times 10^{-3}$	$(9.0 \pm 0.7) \times 10^{-3}$
none	4.63	$0.16 \pm 0.01$	$0.32 \pm 0.01$
3-methyl	4.92	$0.31 \pm 0.02$	$0.68 \pm 0.03$
4-methyl	5.35	$0.67 \pm 0.03$	$1.20 \pm 0.07$
3,4-dimethyl	5.68	$1.5 \pm 0.4$	$2.5 \pm 0.2$
4-amino	8.98	$126 \pm 10$	$188 \pm 14$
4-dimethylamino	9.14	$184 \pm 16$	$281 \pm 20$

<sup>a</sup> In 44 wt % aqueous ethanol, at  $25 \pm 0.1$  °C, ionic strength 0.2 M (maintained with KCl). <sup>b</sup> The standard deviations are 0.02 unit in all cases. The value of the 4-cyano derivative was obtained in this work. The values of the other pyridinium ions are taken from ref 10. <sup>c</sup> Errors shown are standard deviations.

**Table III. Experimental Conditions and Rate Constants Values for the Reactions of 2,4-Dinitrophenyl Methyl Carbonate and 2,4-Dinitrophenyl Acetate with 4-Cyanopyridine<sup>a</sup>**

$F_N$	$10^2[\text{H}^+], \text{M}$	$10^4 k_{N \text{ obsd}}^b, \text{s}^{-1} \text{ M}^{-1}$	$10^6 k_0^c, \text{s}^{-1}$	$10^8 k_1^d, \text{s}^{-1} \text{ M}^{-2}$
2,4-Dinitrophenyl Methyl Carbonate				
0.90	0.45	$1.3 \pm 0.1$		
0.65	2.19	$1.6 \pm 0.2$	$7 \pm 3$	$3 \pm 1$
0.51	3.85	$2.3 \pm 0.2$		
2,4-Dinitrophenyl Acetate				
0.90	0.45	$4.0 \pm 0.2$		
0.70	1.75	$4.5 \pm 0.2$	$9 \pm 4$	$6 \pm 2$
0.50	4.07	$6.1 \pm 0.3$		

<sup>a</sup> In 44 wt % aqueous ethanol, at  $25 \pm 0.1$  °C, ionic strength 0.2 M (maintained with KCl). Errors shown are standard deviations. <sup>b</sup> Values obtained by dividing by  $F_N$  the slopes of  $k_{\text{obsd}}$  against  $[\text{N}]_T$  plots. <sup>c</sup> Average value of intercepts of  $k_{\text{obsd}}$  against  $[\text{N}]_T$  plots. <sup>d</sup> Value of the slope of the  $k_{N \text{ obsd}}$  against  $[\text{H}^+]$  plot.

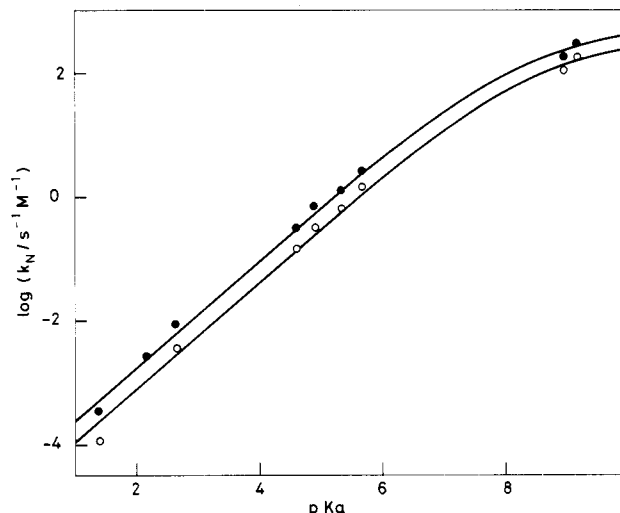
nitrophenoxide ion and a substituted pyridine, respectively) as the nucleophile becomes more basic.<sup>3,5-8,10</sup> At the  $pK_a$  of the center of the Brønsted-type curve ( $pK_a^0$ ),  $k_{-1} = k_2$ , i.e., a pyridine of basicity  $pK_a^0$  has the same nucleofugality from  $\text{T}^\pm$  as  $\text{DNP}^-$ . For pyridines of  $pK_a < pK_a^0$ ,  $k_{-1} > k_2$ , and  $k_N = K_1 k_2$ , where  $K_1$  is the equilibrium constant for the first step of eq 5. The  $k_2$  step is rate-limiting. For pyridines of higher basicities than  $pK_a^0$ ,  $k_{-1} < k_2$ , and  $k_N = k_1$ . In this case the first step of eq 5 is rate-determining.

A semiempirical equation based on the hypothesis of the tetrahedral intermediate and the change of the rate-determining step can be derived. This is shown in eq 6,

$$\log(k_N/k_N^0) = \beta_2(pK_a - pK_a^0) - \log \frac{1+a}{2} \quad (6)$$

$$\log a = (\beta_2 - \beta_1)(pK_a - pK_a^0)$$

where  $k_N^0$  is the rate constant corresponding to  $pK_a^0$  and  $\beta_1$  and  $\beta_2$  are the Brønsted-type slopes at high ( $k_1$  rate-determining step) and low ( $k_2$  rate-determining step) basicities. The Brønsted-type curves of Figure 1 were calculated by means of eq 6 using the following values:  $\log k_N^0 = 1.80$ ,  $pK_a^0 = 7.6$ ,  $\beta_1 = 0.20$ , and  $\beta_2 = 0.87$  for 2,4-dinitrophenyl acetate;  $\log k_N^0 = 1.75$ ,  $pK_a^0 = 8.0$ ,  $\beta_1 = 0.20$ , and  $\beta_2 = 0.85$  for 2,4-dinitrophenyl methyl carbonate. Equation 6 has successfully described the Brønsted-type plots found in the pyridinolyses of methyl chloroformate,<sup>7</sup> 2,4-dinitrophenyl acetate,<sup>3</sup> 2,4-dinitrophenyl methyl carbonate,<sup>5</sup> and acetic anhydride<sup>17</sup> in aqueous solution and



**Figure 1.** Brønsted-type plots obtained in the pyridinolyses of 2,4-dinitrophenyl acetate (●) and 2,4-dinitrophenyl methyl carbonate (○) in 44 wt % aqueous ethanol at 25 °C, ionic strength 0.2 M (KCl). The points are experimental, and the lines were calculated by means of eq 6.

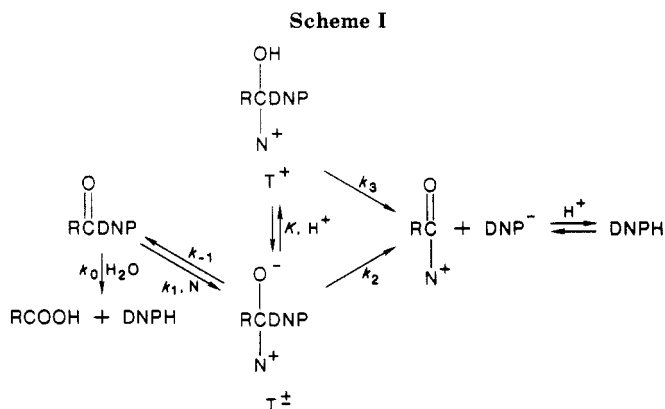
2,4-dinitrophenyl benzoate in aqueous ethanol.<sup>10</sup> Similar equations to eq 6 which account for Brønsted-type curvatures, have been reported in aminolyses<sup>6,8a,18</sup> as well as in other reactions.<sup>19</sup>

Comparison of the Brønsted-type plots shown in Figure 1 indicates that in aqueous ethanol solution the larger the inductive electron-withdrawing effect of the R group of the substrate<sup>20</sup> (eq 5) the larger the  $pK_a^0$  value ( $pK_a^0 = 7.6 \pm 0.1$  and  $8.0 \pm 0.1$  for R = Me and MeO, respectively), and, therefore, the larger the  $k_{-1}/k_2$  ratio (eq 5) for a given pyridine. The same result was found in the pyridinolyses of both substrates in water.<sup>3,5</sup>

The above findings can be explained on the basis of the two mechanisms involved in the nucleofugalities of N and  $\text{L}^-$  from  $\text{T}^\pm$  (eq 5). These are the *pull* or ability of a group to withdraw the electrons of the bond and leave and the *push* or ability of a group to donate an electron pair to help the expulsion of other groups. The group DNP (eq 5) has two electron pairs to exert the *push*, whereas the group  $\text{N}^+$  has none. Electron-withdrawal from R of  $\text{T}^\pm$  will enlarge the *push* provided by DNP, helping the leaving of N and disfavoring the  $\text{DNP}^-$  leaving from  $\text{T}^\pm$ . This means that the larger the inductive electron-withdrawing effect of R (since the electronic effects of a group attached to a tetrahedral carbon are mainly inductive<sup>21</sup>) the larger the  $k_{-1}/k_2$  ratio. Since MeO has an inductive effect more electron-withdrawing than Me,<sup>20</sup> it follows that the  $pK_a^0$  value for the pyridinolysis of 2,4-dinitrophenyl methyl carbonate should be larger than that for 2,4-dinitrophenyl acetate, as observed.

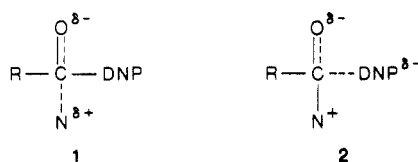
The  $pK_a^0$  values for the reactions reported in this work are larger than those for the same reactions in water.<sup>3,5</sup> For the pyridinolysis of the acetate ester an increase of 0.3  $pK_a$  unit is observed (from  $pK_a^0$  7.3 to 7.6) in going from water to 44 wt % aqueous ethanol. The increment is 0.2  $pK_a$  unit for the reaction of the carbonate (from  $pK_a^0$  7.8 to 8.0). Gresser and Jencks also found an increase of the  $pK_a^0$  value

- (17) Castro, C.; Castro, E. A. *J. Org. Chem.* 1981, 46, 2939.  
 (18) Kluger, R.; Hunt, J. C. *J. Am. Chem. Soc.* 1984, 106, 5667.  
 (19) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* 1977, 99, 451. Pohl, E. R.; Wu, D.; Hupe, D. J. *J. Am. Chem. Soc.* 1980, 102, 2759.  
 (20) Charton, M. *J. Org. Chem.* 1964, 29, 1222.  
 (21) (a) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* 1973, 95, 5637.  
 (b) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* 1974, 96, 1436. (c) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* 1981, 103, 572.



with the decrease of solvent polarity in aminolysis reactions.<sup>8b</sup>

The above results can be rationalized on the basis of the structures of the two transition states involved in eq 5. The structure for the first step (1) is less polar than that for the second step (2). On one hand the rate constant  $k_{-1}$



should increase with the decrease of the solvent polarity, since 1 is less polar than  $T^\pm$ . On the other hand,  $k_2$  is not expected to vary significantly in view of the similar polarities of 2 and  $T^\pm$ . The decrease of the solvent polarity should increase, therefore, the value of  $k_{-1}/k_2$  and, hence, the  $pK_a^0$  value.

As stated in Results, for the reactions of both substrates with 4-cyanopyridine acid catalysis was found in the aminolysis reaction (see eq 4). Although the relationship shown by the slopes of  $k_{\text{obsd}}$  vs.  $[N]_T$  plot at constant  $F_N$  ( $k_{N \text{ obsd}}$ ) and  $[H^+]$  could be either linear or parabolic, we believe the relation is linear for the following reasons. Rearrangement of the possible parabolic dependence shown by eq 7 gives eq 8. Giving reasonable estimates

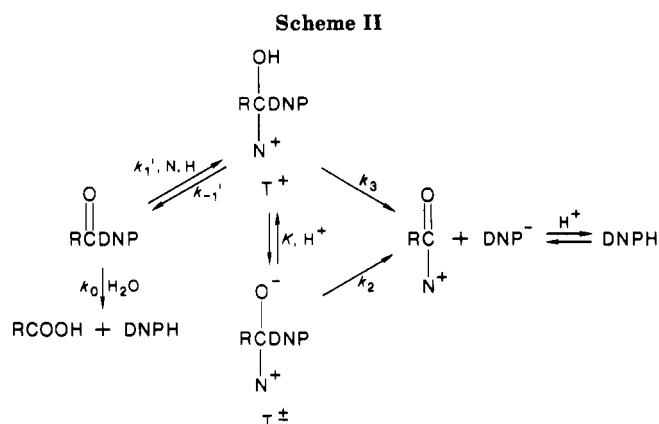
$$k_{N \text{ obsd}} = k_N + k[H^+] + k''[H^+]^2 \quad (7)$$

$$\frac{k_{N \text{ obsd}} - k_N}{[H^+]} = k' + k''[H^+] \quad (8)$$

for the  $k_N$  values (obtained as reasonable intercepts of the  $k_{N \text{ obsd}}$  against  $[H^+]$  plot, assuming a parabolic relation) plots of the left-hand side of eq 8 against  $[H^+]$  are not linear. Moreover, the plots show a minimum. Although there are only three points in each plot, there is, nevertheless, some ground to believe that the relation between  $k_{N \text{ obsd}}$  and  $[H^+]$  is not parabolic. Another reason to support that this relation is linear is given below.

Two simple mechanisms of nucleophilic acid catalysis, compatible with the kinetic law depicted by eq 4 for the reactions of the title substrates with 4-cyanopyridine, are shown in Schemes I and II, where N represents 4-cyanopyridine. In Scheme II the  $k_1'$  step is a nucleophilic attack by the amine concerted with protonation by  $H_3O^+$  (and/or  $EtOH_2^+$ ). Ethanol was omitted from both schemes since the water concentration was more than 3-fold larger than that of ethanol and the basicity of the former is higher.<sup>22</sup>

Applying the steady state treatment to the tetrahedral intermediates  $T^+$  and  $T^\pm$  in both schemes, and assuming



$k_{-1} \gg k_2 + k_3K[H^+]$  for Scheme I and  $k_{-1}' \gg k_3 + (k_2/K[H^+])$  for Scheme II, eq 9 and 10 result from Schemes I and II, respectively. In these equations  $K_1$  and  $K_1'$  are

$$k_{\text{obsd}} = k_0 + \left[ K_1k_2 + K_1k_3K[H^+] \right] [N] \quad (9)$$

$$k_{\text{obsd}} = k_0 + \left[ K_1' \frac{k_2}{K} + K_1'k_3[H^+] \right] [N] \quad (10)$$

the equilibrium constants for the first step leading to a tetrahedral intermediate of Scheme I and II, respectively. It can be seen that both schemes are kinetically indistinguishable and can account for the kinetic law (eq 4). The inequalities assumed for both schemes are justified in view of (1) the weak C-N bond of  $T^\pm$  (Scheme I) and  $T^+$  (Scheme II) when N is 4-cyanopyridine, which is the weakest base of the series of pyridines studied, and (2) the fact that the value of  $k_3K[H^+]$  is not very large in the experimental conditions, as will be shown next.

The  $pK_a$  of  $T^\pm$  for  $R = \text{Me}$  in the schemes can be estimated, following the procedure of Jencks and co-workers,<sup>21</sup> on the basis of  $pK_a = 9.98$  for the hydroxyl group of  $\text{MeNH}_2^+\text{CH}_2\text{OH}$ ,<sup>23</sup>  $\sigma_1 = -0.05$  for Me,<sup>20</sup> and  $\rho_1 = 8.4$  for the dissociation constants of substituted alcohols,<sup>21b</sup> which give a  $pK_a = 10.4$  for  $\text{MeNH}_2^+\text{CH}(\text{Me})\text{OH}$ .  $\alpha$ -Phenyl substitution for hydrogen lowers the  $pK_a$  of an aldehyde hydrate by 0.2 unit,<sup>24</sup> and 2,4-dinitro substitution should further decrease the  $pK_a$  in 3.1 units, based on  $\rho = 1.1$  for the ionization of trifluoroacetophenone hydrates<sup>25</sup> and  $\text{ArCR}_2\text{OH}$ <sup>26</sup> and "effective"  $\sigma = 2.8$  for 2,4-dinitro.<sup>27,28</sup> This gives a  $pK_a = 7.1$  for the hydroxyl group of compound 3. Insertion of an oxygen atom between the central tetrahedral carbon and the aryl group of 3 should lower the  $pK_a$  by ca. 3 units,<sup>29</sup> giving a  $pK_a$  of ca. 4 for the hydroxyl group of compound 4. Considering  $\sigma_1 = 0.1$  for  $\text{CH}_3\text{NH}_2^+$ ,<sup>21b</sup> an estimate of  $\sigma_1 = 0.22$  for the 4-cyanopyridino group,<sup>30</sup> and

(23) Hine, J.; Craig, J. C., Jr.; Underwood, J. G., II; Via, F. A. *J. Am. Chem. Soc.* 1970, 92, 5194.

(24) Hine, J.; Koser, G. F. *J. Org. Chem.* 1971, 36, 1348.

(25) Stewart, R.; Van der Linden, R. *Can. J. Chem.* 1960, 38, 399.

(26) McClelland, R. A.; Coe, M. *J. Am. Chem. Soc.* 1983, 105, 2718.

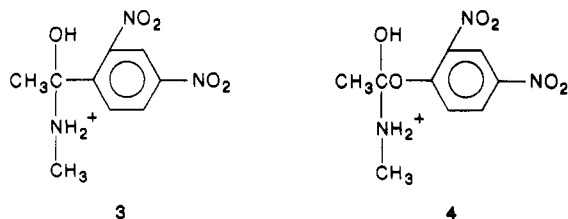
(27) This  $\sigma$  value was determined on the basis of the Hammett line for the dissociation of substituted benzoic acids ( $\rho = 1.0$ ), using a  $pK_a$  1.43 for 2,4-dinitrophenylbenzoic acid at 25 °C.<sup>28</sup>

(28) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971; p 85.

(29) This is the  $pK_a$  lowering for the hydroxyl group in going from  $\text{MeNH}_2^+\text{CH}(\text{OH})\text{Ph}$  ( $pK_a$  9.78) to  $\text{MeNH}_2^+\text{CH}(\text{OH})\text{OPh}$  ( $pK_a$  6.78). This values can be obtained based on the  $pK_a$  9.98 for the hydroxyl group of  $\text{MeNH}_2^+\text{CH}_2\text{OH}$ ,<sup>23</sup> the  $pK_a$  lowering of 0.2 unit by  $\alpha$ -phenyl substitution,<sup>24</sup>  $\sigma_1 = 0.38$  for  $\text{OPh}$ ,<sup>20</sup> and  $\sigma_1 = 8.4$  for the dissociation constants of substituted alcohols,<sup>21b</sup> following the procedure of Jencks and co-workers.<sup>21a,c</sup>

The  $pK_a$  lowering when going from 3 to 4 should be larger than 3 units in view of the enhanced electron-withdrawing effect of the nitro groups attached to phenoxy compared to a phenyl group.

(22) Newall, C. E.; Eastham, A. M. *Can. J. Chem.* 1961, 39, 1752. Deno, N. C.; Wisotsky, M. J. *J. Am. Chem. Soc.* 1963, 85, 1735.



$\rho_1 = 8.4$  for the dissociation constants of substituted alcohols,<sup>21b</sup> the  $pK_a$  decrease from 4 to  $T^\pm$  (Scheme I and II, R = Me) can be estimated as  $\Delta pK_a = (0.22 - 0.1) \times 8.4 = 1$ , giving a  $pK_a$  of ca. 3 for  $T^+$  (R = Me). Obviously, this is a rough estimation subject to an error of 1–2 units. The  $pK_a$  value for  $T^+$  (R = MeO) should be ca. 0.5, on the basis of the  $pK_a$  of  $T^+$  (R = Me),  $\sigma_1 = 0.25$  and  $-0.05$  for MeO and Me,<sup>20</sup> respectively, and  $\rho_1 = 8.4$ .<sup>21b</sup>

If the  $pK_a$  of  $T^+$  (R = Me) is ca. 3, it follows that  $K = 10^3$  (Schemes I and II, R = Me). The range of hydrogen ion concentration employed in the reactions of 4-cyanopyridine with both substrates was  $(4-40) \times 10^{-3}$  M (Table III), which gives a range of values of 4–40 for  $K[H^+]$ . It is reasonable, therefore, to assume that  $k_{-1} \gg k_2 + k_3K[H^+]$  (Scheme I) for the reactions with 2,4-dinitrophenyl acetate since (1) the term  $k_3K[H^+]$  should be similar to  $k_2$  within an order of magnitude (assuming  $k_2 > k_3$ , which is reasonable in view of the larger push provided by  $O^-$  of  $T^\pm$  compared to that exerted by OH of  $T^+$ ), and (2)  $k_{-1} \gg k_2$ .<sup>31</sup>

For Scheme II, also  $k_{-1}' \gg k_3 + (k_2/K[H^+])$  seems justified for the reasons stated above, although  $k_{-1}'$  should be smaller than  $k_{-1}$  since the first process involves amine expulsion concerted with solvent deprotonation from  $T^+$ .

For the reaction of 4-cyanopyridine with 2,4-dinitrophenyl methyl carbonate,  $K = 3$  (Schemes I and II, R = MeO) since  $pK_a = 0.5$  for  $T^+$  (R = MeO), which gives  $K[H^+] = 0.012-0.12$  for the pH range used. The term  $k_3K[H^+]$  is therefore, even smaller for R = MeO than R = Me, and  $k_{-1}/k_2$  should be larger for R = MeO ( $pK_a^0 = 8$ ), which makes the inequality  $k_{-1} \gg k_2 + k_3K[H^+]$  (Scheme I) even more certain for R = MeO compared to R = Me.

If Scheme II holds for R = MeO the value for  $k_2/(K[H^+])$  is  $(8-80)k_2$  in the pH range used, but since  $k_{-1}' \gg k_2$ ,  $k_{-1}' \gg k_3 + k_2/(K[H^+])$  seems justified.

A third scheme for the reactions of 4-cyanopyridine with both substrates (Scheme III, not shown) can be envisaged,

(30) Obtained from a plot of  $pK_a$  against  $\sigma_1$  for  $MeNH_2^+$  and  $MeONH_2^+$ , by extrapolation to the  $pK_a$  of 4-cyanopyridinium ion. The  $\sigma_1$  values for  $MeNH_2^+$  are 0.1 and 0.18, respectively.<sup>21b</sup> The  $\sigma_1$  value for the 4-cyanopyridino group is a rough estimate in view of the different nature of alkylamines and pyridines, which makes the linear correlation of their  $pK_a$  against  $\sigma_1$  dubious.

(31) For the pyridinolysis of 2,4-dinitrophenyl acetate,  $pK_a^0 = 7.6$  (Figure 1). With this value and  $pK_a = 1.39$  for 4-cyanopyridinium ion a value of  $k_{-1}/k_2$  ca.  $10^6$  can be derived with the aid of eq 6.

whereby Schemes I and II operate simultaneously, i.e., there are two parallel reversible paths joining the substrate to  $T^+$  and  $T^\pm$ . Application of the steady state to  $T^+$  and  $T^\pm$ , and assuming  $k_{-1} \gg k_2 + k_3K[H^+] + k_{-1}'K[H^+]$ , the parabolic eq 11 obtains, which does not account for the most likely kinetic law observed (eq 4).

$$k_{\text{obsd}} = k_0 + \left[ \frac{k_1'k_3K}{k_{-1}} [H^+]^2 + \frac{k_1k_3K + k_1'k_2}{k_{-1}} [H^+] + \frac{k_1k_2}{k_{-1}} \right] [N] \quad (11)$$

Of the three schemes, Scheme I seems the most probable because of the following reasons: (1) It is unlikely that the  $k_1'$  step be much faster (Scheme II) or of similar rate (Scheme III) compared to step  $k_1$  in view of the three-body collision involved in the former. (2) In the reaction of 2,4-dinitrophenyl acetate with 3-chloropyridine the  $k_1'$  step did not occur (nor in the reactions of both substrates with the other more basic pyridines); therefore, it seems unlikely that in the reactions with 4-cyanopyridine, which is only slightly less basic than 3-chloropyridine, the  $k_1'$  step should occur exclusively, as in Scheme II, involving a drastic change in mechanism. (3) The values of  $k_N$  for the reactions of both substrates with 4-cyanopyridine were obtained as intercepts of  $k_{N\text{obsd}}$  against  $[H^+]$  plots, and they correlate nicely with the  $k_N$  values for the reactions with the other pyridines in the Brønsted-type plots (Figure 1). As seen in eq 9 (based on Scheme I), the intercepts of  $k_{N\text{obsd}}$  against  $[H^+]$  plots, ( $k_{N\text{obsd}}$  corresponds to the terms enclosed in parentheses) are  $K_1k_2$ , which have the same form as  $k_N$  for all the other pyridines of  $pK_a < pK_a^0$ . The corresponding intercepts for eq 10 (based on Scheme II) are  $K_1'k_2/K$ , which should not correlate well with  $K_1k_2$  for the other pyridines. (4) For reactions similar to the ones reported in this work there are precedents supporting Scheme I for the nucleophilic-specific acid-catalyzed mechanism,<sup>21a,32</sup> but, to our knowledge, no mechanisms such as those described by Schemes II and III have been reported.

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**Registry No.** 2,4-Dinitrophenyl methyl carbonate, 6099-87-2; 2,4-dinitrophenyl acetate, 4232-27-3; 4-cyanopyridine, 100-48-1; 3-carbamoylpyridine, 98-92-0; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; 3-chloropyridine, 626-60-8.

(32) See, for example: Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7031. Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5956.