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Kinetics and Mechanism of Aminolysis of Phenyl Acetates in Aqueous Solutions of Poly(ethylenimine)

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Second-order rate constants (k_n) for the aminolysis of some phenyl acetates with poly(ethylenimine) (PEI) were obtained in a pH range 4.36−11.20 at 25 °C in 1 M KCl. Linear Bronsted-type plots (log k_n vs pK_N of PEI) were found for less reactive esters 2-nitrophenyl acetate, 4-acetoxy-3-chlorobenzoic acid, and 4-acetoxybenzenesulfonate with slopes of 0.92, 0.99, and 0.82, respectively. Curved plots were obtained for 3-acetoxy-2,6-dinitrobenzoic acid and 4-acetoxy-3-nitrobenzenesulfonate, which are consistent with a stepwise reaction. The most likely mechanism involves the existence of a tetrahedral intermediate ($T^{\pm}$) and a change in the rate-determining step from its breakdown to its formation when the basicity of the polyamine increases. A semiempirical equation was used to calculate the values of limiting slopes of the plots (0.9 and 0.1 for both esters) and pK_N at the center of the curvature of the plots (pK_{N° = 7.94 and 9.02, respectively). The values of pK_{N° are lower than those estimated for the aminolysis of the same esters with simple monomeric amines (pK_{n° > 11) because of a better leaving ability of the aryl oxide ion from the tetrahedral intermediate when amino groups of PEI instead of simple amines are involved. Estimation of the p*K*'s of the reactive intermediates and of the microscopic rate constants for the proton transfer from $T^{\pm}$ to PEI or from $PEIH^+$ to $T^{\pm}$ indicates that either base or acid catalysis is unimportant in the aminolysis of these esters by PEI.

Introduction

The mechanism of acetyl-transfer reactions involving small molecules has been subject to extensive investigation owing to the importance of these reactions in chemistry as well as in biochemistry.[1,2] Structure−reactivity correlations such as Hammett or Bronsted-type relationships help to clarify the rate-determining steps and to determine whether the reaction proceeds stepwise or by a concerted pathway.[3] Indeed, only a few papers have been published which deal with these subjects in systems involving esters of low molecular weight and polyelectrolytes which have reactive nucleophilic groups in the chain.[4,5a−c] Substrate−polyelectrolyte interactions create inhomogeneity in the solution; the local concentration of the reagents, the basicity of the nucleophilic groups, or even the solvent properties in the polyelectrolyte microenvironment cannot be determined quantitatively, so it is difficult to investigate the reaction mechanism in detail.[6] However, when the ionic strength is largely increased by addition of strong electrolytes such as KCl, the substrate−polyelectrolyte interactions are suppressed and accurate selective rate constants can be measured.[5a]

A rather well known polyelectrolyte is poly(ethylenimine) (PEI) (Chart 1) which has a branched, very compact structure and only a limited expansion possibility.[7a,8] It contains 25% primary, 50% secondary, and 25% tertiary amino groups. Unlike simple amines, the basicity of PEI changes with the ionization degree (i.e., the pH) because of the strong interactions between vicinal charged and uncharged amino groups along the polymeric chain.[7a,b] This peculiarity leads to a large interval of basicity of the nucleophilic groups without a change in the structure as generally occurs with different amines. In a continuation of our studies on the aminolysis of phenyl acetates by PEI,[5a] we investigated the dependence of the rate of aminolysis in 1 M KCl on the basicity of PEI and on the leaving group ability, with the aim of identifying structure−reactivity relationships useful to the elucidation of the reaction mechanism. The final purpose is to extend this approach in order to analyze the behavior of the said substrates with PEI in the absence of added electrolytes, when the polyamine causes a 10^5-fold rate enhancement, but association and/or inhibition phenomena result in a complex kinetic behavior.[9] One of the esters examined was also reacted with a set of monomeric amines in order to compare the behavior of the two kinds of nucleophiles.

Experimental Section

Materials. 3-Chlorophenyl acetate, 2-nitrophenyl acetate, 3-acetoxy-2,6-dinitrobenzoic acid, 4-acetoxy-3-nitrobenzenesulfonate (natrium salt), 4-nitrophenyl acetate; 4-acetoxybenzoic acid, 4-acetoxy-3-nitrobenzoic acid, 4-acetoxybenzenesulfonate (natrium salt), and 4-acetoxy-3-chlorobenzoic acid were synthesized and purified according to ref 5a.

Poly(ethylenimine) (PEI) was "Polymin P" 47.6% by weight from B.D.H. A monomer molecular weight of 59 was determined by titration with HCl.[5b] Amine hydrochlorides were recrystallized before use. All other reagents were of analytical grade. Water was deionized and then redistilled from $KMnO_4$.

Buffer solutions of amines were prepared from amine hydrochlorides with the pH adjusted with 0.1−1 M NaOH or

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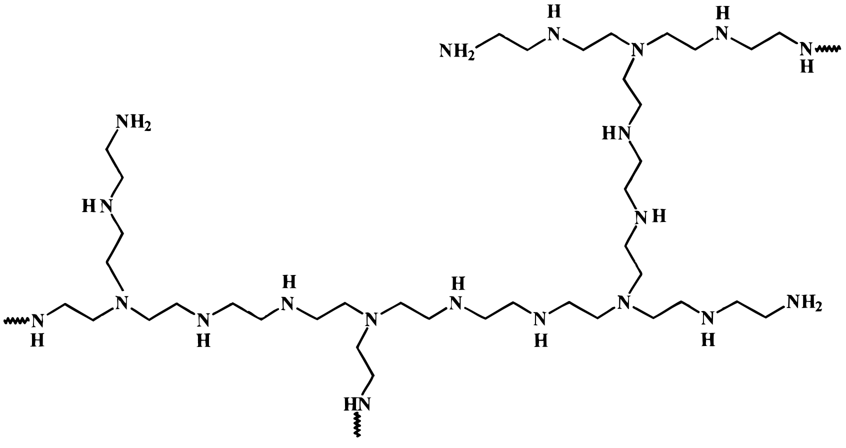
Chart 1



PEI

in 0.05 M KH_2PO_4/Na_2HPO_4 or 0.05 M $NaHCO_3$−NaOH buffer carrier. Ionic strength was maintained at 1.0 M with added KCl. PEI buffers were prepared from a stock solution (0.5 monomer mol L^{-1}) at 1.0 M KCl final concentration, with the pH adjusted with 0.1−5 M HCl. Solutions were prepared and kept under nitrogen atmosphere and used within 1 day.

Potentiometric Titrations. pH measurements and potentiometric titrations were performed with a Knick 802 pH-meter and an Ingold HA 405 combined glass electrode standardized according to ref 10. The apparent p*K* of the conjugate acid of the amino groups of PEI (pK_N) at each pH was determined at 25 °C in 1.0 M KCl in a nitrogen atmosphere by the equation

$$pK_N = pH - \log[(1-\alpha)/\alpha]$$

where $\alpha = [NH^+]/[N_{tot}]$ is the ionization degree calculated by the equation

$$\alpha = ([H^+]_{add} - [H^+]_f + [OH^-]_f)/[N_{tot}]^{7b}$$

Here, $[H^+]_{add}$ is the proton concentration as resulting from added HCl, $[H^+]_f$ and $[OH^-]_f$ are the concentrations of free protons and hydroxyl ions, as determined from titrations of strong acid and base, respectively, at the same ionic strength with respect to added salt, $[N_{tot}]$ is the total PEI concentration, and pK_N values are reported in Table 1.

Identification of the Reaction Products. The identification and the quantitative determination of the phenolic moiety at the end of reaction was performed by comparison of UV spectra with authentic samples. Aryl acetates acetylate the primary and secondary amino groups of PEI,[5c] while they could give free acetic acid when reacted with tertiary amino groups. To verify this possibility, a 0.02−0.04 M solution of each ester was reacted with 5 mL of a 0.4 monomer mol L^{-1} PEI buffer solution at pH 10.7 at 60 °C. At the end of the reaction the solutions were acidified to pH 2 with concd HCl. Acetic acid was analyzed by a Carlo Erba HRGC 5300 mega series gas chromatograph using a capillary column (Megaacid 15 m × 0.32 mm). Comparative experiments with added acetic acid to PEI buffers gave a quantitative recovery of the acid, assuring the effectiveness of the procedure. For 3-acetoxy-2,6-dinitrobenzoic acid and 4-acetoxy-3-nitrobenzenesulfonate, the presence of acetic acid was also tested after aminolysis at pH 4.0 at 25 °C. The presence of free acetic acid at the end of the reactions (2−5%) also suggested that tertiary amino groups of PEI were involved in the reaction.

Kinetic Methods. Reactions were followed on a Perkin-Elmer Lambda 6 UV/vis spectrophotometer equipped with a thermostated cell holder, measuring at suitable wavelengths the release of phenol or phenolate ion. Thirty μL of a 0.01−0.03 M stock solution of the ester in dioxane or in 50% v/v water−dioxane was injected by a Hamilton syringe into a cuvette containing 3 mL of buffer solution thermally equilibrated at 25 ± 0.1 °C. The pseudo-first-order rate constants (k_{obs}) were calculated by least-squares analysis of plots of $\ln(O.D._\infty - O.D._0)/(O.D._\infty - O.D._t)$ vs time and followed for 3−4 half-lives. Very slow kinetics were followed by the initial rate method; the optical density at infinite time was determined independently on a solution of phenol in the same buffer. Fast kinetics were followed by a Sigma WZS-II (Biochem) dual-wavelength spectrophotometer equipped with a thermostated stopped-flow unit and digital data storage, interfaced with an Apple IIe PC. The solutions of ester and of nucleophile were mixed in the observation chamber in a 1:10 ratio. Ester concentration after mixing was between 2×10^{-4} and 1×10^{-5} M. The change of pH at the end of all the kinetics never exceeded 0.05 units. The pseudo-first-order k_{obs} was determined by the method of Guggenheim.[11] Other calculations and plots of the curves were performed by FigP program by Biosoft. Experimental details and values of rate constants are reported in Tables 1 and 2.

Results

The experimental pseudo-first-order rate constants (k_{obs}) for the aminolysis by PEI of anionic and neutral phenyl acetates were determined at 25 °C in 1.0 M KCl at a fixed pH (4.36 − 11.20) in an excess of PEI (0.09−0.4 monomer mol L^{-1}). A linear dependence of rate constants on the concentration of the polyamine was observed which can be expressed by eq 1

$$k_{obs} = k_0 + (k_n + k'_{OH}[OH^-])\,[PEI]\,(1-\alpha) \quad (1)$$

where k_0 represents the spontaneous hydrolysis, k_n is the nucleophilic second-order rate constant, $k'_{OH}[OH^-]$ is the rate of the hydroxide ion-catalyzed aminolysis, [PEI] is the concentration of the polyamine in monomer mol L^{-1}, and α is its ionization degree at each pH. k_0 was always negligible even at basic pH as is shown also by the low values of the rates of the alkaline hydrolysis (k_{OH^-} in Table 1). $k'_{OH}[OH^-]$, which cannot be calculated, was considered unimportant because of the relatively low values of pH used. The linearity of the function (1) in the large concentration range of PEI excludes second-order terms in amine due to intermolecular general base or general acid catalysis. With 3-acetoxy-2,6-dinitrobenzoic acid at pH > 8.75, a downward curvature of the plot was observed, suggesting the presence of a substrate−

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Table 1. Experimental Conditions and Kinetic Parameters for the Aminolysis of Phenyl Acetates by Poly(ethyleneimine) in 1 M KCl at 25 °C

$R^1R^2R^3C_6H_2OCOCH_3$										
R^1	R^2	R^3	λ[a]/nm	pH	pK_N[b]	concn range/ monomer[c]/mol L^{-1}	no. of runs	k_{obs}[d]/s^{-1}	k_n/s^{-1} M^{-1}	k_{OH}[e]/ s^{-1} M^{-1}
4-SO_3^-	H	H	252	7.20	7.62	0.1−0.4	8	$(1.34-4.64) \times 10^{-4}$	$(3.45 \pm 0.05) \times 10$	4.54 ± 0.35
				8.40	8.53				$(1.86 \pm 0.06) \times 10^{-2}$ [f]	
			252	10.00	9.42	0.1−0.4	12	0.01−0.0367	0.112 ± 0.0009	
			256	10.70	9.54	0.091−0.364	14	0.0139−0.0474	0.119 ± 0.02	
			265−350	11.20[g]	9.88	1.30−2.20	10	0.196−0.323	0.139 ± 0.013	
2-Cl	4-CO_2H	H	250	4.36	5.54	0.1−0.4	8	$(3.64-9.57) \times 10^{-6}$	$(7.87 \pm 0.18) \times 10^{-5}$ [h]	4.89 ± 0.30
			250	6.00	6.68	0.1−0.4	9	$(1.13-2.39) \times 10^{-4}$	$(2.92 \pm 0.03) \times 10^{-3}$	
			280−350	8.40					1.6 ± 0.1[f]	
			280−350	10.00		0.1−0.4	15	0.048−0.181	0.566 ± 0.023	
			280−350	11.20[g]		0.863−1.72	16	0.631−1.26	0.749 ± 0.073	
2-NO_2	4-SO_3^-	H	345	4.36		0.1−0.4	8	$(0.771-2.61) \times 10^{-4}$	$(4.87 \pm 0.34) \times 10^{-3}$	25.2 ± 1.5
			345	4.00	5.22	0.1−0.4	8	$(0.364-1.21) \times 10^{-4}$	$(2.72 \pm 0.2) \times 10^{-3}$	
			400	5.00	5.92	0.1−0.4	8	$(3.22-8.51) \times 10^{-4}$	$(1.1 \pm 0.1) \times 10^{-2}$	
			400	6.00	6.68	0.1−0.4	12	$(2.34-6.62) \times 10^{-3}$	$(7.0 \pm 1) \times 10^{-2}$	
			400−650	7.92	8.17	0.091−0.364	12	0.0534−0.157	1.05 ± 0.13	
				8.40					2.43 ± 0.12[f]	
			400−650	9.21	9.05	0.091−0.364	13	0.408−1.24	5.05 ± 0.53	
			400−650	10.00		0.091−0.364	15	0.691−2.5	7.72 ± 0.67	
			400−650	10.70	9.54	0.091−0.364	16	0.917−2.88	7.81 ± 0.47	
			400−650	11.20[g]	9.88	0.804−2.29	14	8.23−22.8	10.0 ± 0.6	
4-CO_2H	H	H	250	4.36		0.1−0.4	8	$(0.327-1.19) \times 10^{-6}$	$(7.17 \pm 0.19) \times 10^{-6}$ [h]	
			250	6.00		0.1−0.4	8	$(0.397-1.45) \times 10^{-5}$	$(1.7 \pm 0.28) \times 10^{-4}$	
			280	10.00		0.1−0.4	12	$(0.399-1.44) \times 10^{-2}$	$(4.36 \pm 0.04) \times 10^{-2}$	
2-NO_2	4-CO_2H	H	350	4.36		0.1−0.4	8	$(0.443-1.44) \times 10^{-4}$	$(1.75 \pm 0.5) \times 10^{-3}$	
			410	6.00		0.1−0.4	8	$(0.988-3.31) \times 10^{-3}$	$(3.71 \pm 0.3) \times 10^{-2}$	
				8.40					0.758 ± 0.03[f]	
2-NO_2	4-NO_2	3-CO_2H	380	4.36	5.54	0.1−0.4	8	$(0.785-2.4) \times 10^{-3}$	$(4.26 \pm 0.069) \times 10^{-2}$	109 ± 8
			380	5.40	6.22	0.1−0.4	8	$(0.484-1.64) \times 10^{-2}$	0.216 ± 0.02	
			377	6.00		0.1−0.4	14	0.015−0.0524	0.599 ± 0.07	
			377−570	6.55	7.11	0.095−0.364	14	0.048−0.11	1.05 ± 0.08	
			377−570	7.25	7.62	0.095−0.364	16	0.105−0.405	3.5 ± 0.06	
			377−570	8.01	8.23	0.091−0.364	16	0.268−0.876	5.55 ± 0.18	
			377−570	8.33	8.48	0.091−0.367	15	0.523−1.29	6.42 ± 0.46	
			377−570	8.40					6.14 ± 1[f]	
			377−570	8.75	8.78	0.0545−0.227	18	0.607−1.34		
			377−570	10.00	9.42	0.0727−0.294	22	2.27−8.59	29.8 ± 0.5[i]	
4-NO_2	H	H	318	4.36		0.1−0.4	8	$(0.295-1.2) \times 10^{-5}$	$(1.96 \pm 0.19) \times 10^{-4}$	
			420−550	10.00		0.091−0.364	8	0.095−0.33	1.1 ± 0.009	
2-NO_2	H	H	350	5.14	6.04	0.1−0.4	8	$(1.56-6.56) \times 10^{-5}$	$(1.05 \pm 0.07) \times 10^{-3}$	10.5 ± 0.73
			420	6.13	6.79	0.1−0.4	9	$(1.40-4.80) \times 10^{-4}$	$(5.17 \pm 0.4) \times 10^{-3}$	
			420	7.23	7.62	0.1−0.4	8	$(1.13-4.30) \times 10^{-3}$	$(3.35 \pm 0.08) \times 10^{-2}$	
				8.40					0.216 ± 0.02[f]	
			420−550	9.44	9.18	0.091−0.364	12	0.0567−0.255	1.01 ± 0.05	
			420−550	9.93	9.38	0.1−0.3	14	0.118−0.313	1.26 ± 0.07	
			420−550	11.20[g]	9.88	1.30−2.17	12	4.03−6.63	2.98 ± 0.67	
3-Cl	H	H	273	4.36	5.54	0.1−0.4	8	$(1.71-4.83) \times 10^{-7}$	$(8.34 \pm 0.53) \times 10^{-6}$	

[a] Analytical wavelength for phenol or phenolate release. The second value reported was used for dual wavelength spectroscopy. [b] Calculated from $pK_N = pH - \log[(1 - a)/a]$ were a is the ionization degree (see text). The accuracy was within ±0.05 pK units. [c] Total polyamine concentration. [d] Calculated from eq 1. Standard errors are reported. [e] From $k_{obs} = k_{OH}[OH^-]$ at pH = 11.30 in 0.05 M $NaHCO_3$/NaOH buffer. [f] From ref 5a. [g] In 2 M KCl. [h] Values corrected for the contribution of the protonated form by eq 2. [i] Uncertain value due to a probable substrate−polyamine association.

Table 2. Experimental Conditions and Rate Constants for the Aminolysis of 4-Acetoxy-3-nitrobenzenesulfonate by Primary Amines at 25 °C and 1.0 M Ionic Strength[a]

amine	pK_N[b]	pH	$10^2[N]tot$[c]/M	no. of runs	$10^3k_{obs}/s^{-1}$	10^2 k_n[d]/s^{-1} M^{-1}
aniline	4.85	6.45[e]	3.9−19.1	6	0.558−2.31	1.14 ± 0.05
trifluoroethylamine	5.84	7.00[e]	3.8−14.7	6	1.15−4.22	2.82 ± 0.04
ethylenediamine	7.42	7.50	4.8−24.0	8	35−191	
		6.95	7.94−31.7	8	51.1−105	113 ± 2
glycylglycine	8.25					204 ± 12[f]
glycine	9.76	9.70	1.8−7.2	10	184−736	
		9.22	3.6−9.0	8	203−459	$(2.07 \pm 0.21) \times 10^3$ [g]
methylamine	10.66	11.42	3.6−14.5	12	$(5.92-20.7) \times 10^3$	
		10.51	3.6−14.5	12	$(1.61-7.17) \times 10^3$	$(1.25 \pm 0.12) \times 10^4$ [g]

[a] Kinetics were followed at λ 400 nm. Standard errors of estimate are reported. [b] From refs 12a and 13. [c] Total amine concentration. [d] In 0.05 M KH_2PO_4/Na_2HPO_4 buffer carrier. [e] Calculated from $k_{obs} = k_o + k_n [N]_f$. [f] From lit. 5a. [g] Calculated from the plots of $k_{obs} = k_o + (k_n + k'_{OH^-}[OH^-])[N]_f$ vs $[N]_f$ at two pHs and then from the intercept of the plot $(k_n + k'_{OH^-}[OH^-])$ vs $[OH^-]$.

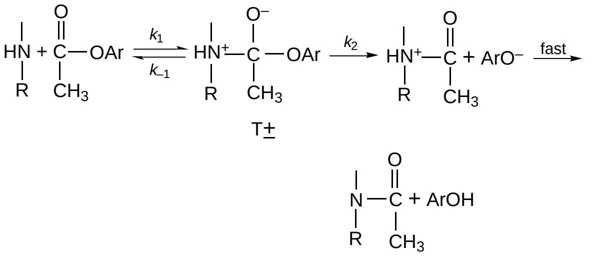
polyelectrolyte association. Protogenic esters react in the anionic form in all the pH ranges except for 4-acetoxy-3-nitrobenzoic acid (pK_a 3.15), 4-acetoxy-3-chlorobenzoic acid (pK_a 3.52), and 4-acetoxybenzoic acid (pK_a 3.89) for which at pH 4.36 the contribution of the protonated form must also be considered. The rate constants k_{nCOOH} and k_{nCOO^-}, for the aminolysis of the acid and anionic forms, were obtained by eq 2

$$k_{\mathrm{obs}} - k_0 = \left[k_{\mathrm{nCOO^-}}\left(\frac{K_\mathrm{a}}{a_\mathrm{H} + K_\mathrm{a}}\right) + k_{\mathrm{nCOOH}}\left(\frac{a_{\mathrm{H^+}}}{a_{\mathrm{H^+}} + K_\mathrm{a}}\right)\right][\mathrm{PEI}](1 - \alpha) \quad (2)$$

where K_a is the dissociation constant of the carboxylic group calculated according to ref 12b. Due to the pH dependence of pK_N of PEI, k_{nCOO^-} could not be calculated the same way as simple amines.[14] It was obtained from the slope of eq 2 and from the ratio k_{nCOOH}/k_{nCOO^-} 9.5 calculated by the Hammett relationship $\log(k_{nCOOH}/k_{nCOO^-}) = \rho(\sigma_{p-COOH} - \sigma_{p-COO^-})$ taking $\rho = 2$ for simple amines[14] and $\sigma_{p-COOH} = 0.44$ and $\sigma_{p-COO^-} = -0.05$.[12b] The values of the second-order rate constants k_n for the aminolysis by PEI of the neutral and anionic phenyl acetates are reported in Table 1. The aminolysis of 4-acetoxy-3-nitrobenzenesulfonate was also performed with a set of primary amines. Under our experimental conditions, the spontaneous hydrolysis was negligible, and only the first-order term in amine was highlighted according to the eq $k_{obs} = (k_n + k'_{OH}[OH^-])[N]_f$, where $[N]_f$ is the free base amine concentration (results are listed in Table 2).

Discussion

It is generally accepted that the aminolysis of a phenyl acetate occurs through a zwitterionic tetrahedral intermediate ($T^{\pm}$) produced by the primary or secondary amine attack on the carbonyl carbon:



(3)

From steady state treatment the rate constant for such a reaction scheme gives $k_n = k_2k_1(k_{-1} + k_2)$. The rate constant reduces to $k_n = k_2k_1/k_{-1}$ when $k_{-1} \gg k_2$; i.e., when the rate-determining step is the decomposition of the $T^{\pm}$ intermediate (less basic nucleophiles and esters with poor leaving groups), and to $k_n = k_1$ when $k_{-1} \ll k_2$, i.e., when the rate-determining step is the formation of the $T^{\pm}$ intermediate (more basic nucleophiles and esters with good leaving groups).[15a,b,16a,b,17a] Nonlinear Bronsted-type plots (log k_n vs pK_N of the nucleophile) are observed when there is a change from one to the other rate-determining step on increasing pK_N. In this case, eq 4 was proposed

$$\log(k_n/k^\circ_n) = \beta_2(\mathrm{p}K_N - \mathrm{p}K_{N^\circ}) + \log 2 - \log[1 + 10^{(\beta_2 - \beta_1)(\mathrm{p}K_N - \mathrm{p}K_{N^\circ})}] \quad (4)$$

by Castro[16b] for structurally homogeneous nucleophiles where β_2 and β_1 are the slopes of the Bronsted plot when k_2 or k_1 are rate determining and log k°_n and pK_{N° are the values of log k_n and of pK_n at the center of the inflection of the plot. In the aminolysis of phenyl acetates, nitrogen nucleophiles and leaving aryl oxide ions have the same nucleofugality from the $T^{\pm}$ intermediate ($k_{-1} = k_2$) when the difference between the pK of the nucleophile and that of the conjugate acid of the leaving group (pK_{lg}) is 4−5 pK units.[17a]

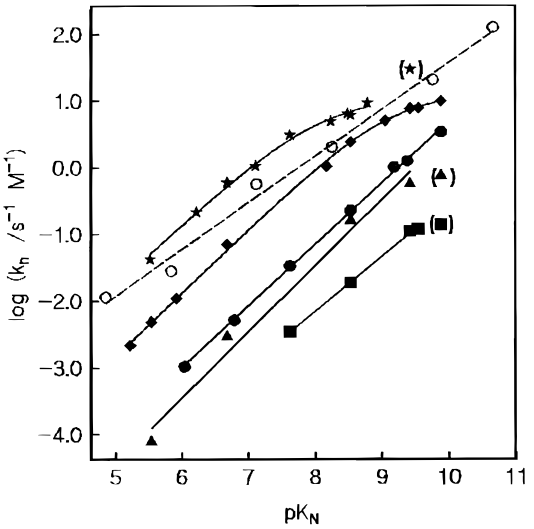


Figure 1. Bronsted-type plots for the aminolysis by poly(ethylenimine) in 1.0 M KCl at 25 °C of 4-acetoxy-2,6-dinitrobenzoic acid (*); 4-acetoxy-3-nitrobenzensulfonate (◆); 2-nitrophenyl acetate (●); 4-acetoxy-3-chlorobenzoic acid (▲); and 4-acetoxybenzenesulfonate (■) (cf. Table 1). Aminolysis of 4-acetoxy-3-nitrobenzenesulfonate by primary amines (○) at ionic strength 1.0 M with added KCl (cf. Table 2). Points are experimental, and curves were calculated according to eq 4 or by linear least-squares method excluding points in parentheses.

In the aminolysis of 4-acetoxy-3-nitrobenzenesulfonate with simple amines in the range of pK_N 4.85−10.66 we found a linear Bronsted-type plot with slope 0.70 (Figure 1). The value of the slope is still comparable with that reported for the aminolysis of most phenyl acetates with monomeric amines (β_{nuc} 0.8−0.9 ± 0.1[13,18,19]). Since the pK of the leaving group of the ester is 6.08,[5d] an inflection of the plot for an amine of pK_N 4−5 pK units higher was expected, beyond the range of basicity examined by us. Linear Bronsted-type plots were also found for the aminolysis by PEI of 2-nitrophenyl acetate (pK_{lg} 7.23[5d]), 4-acetoxybenzenesulfonate (pK_{lg} 9.06[5d]), and 4-acetoxy-3-chlorobenzoic acid (pK_{lg} 7.89[5d]) with slopes of 0.92, 0.99, and 0.82 (Figure 1). The small negative deviation from the linearity of the values of k_n at pK_N 9.54−9.88 (points not computed in the plots) could indicate an incipient inflection of the plots which should be centered at higher values of pK_N unattainable with PEI. The values of k_n and of pK_N were not statistically corrected because the number of equivalent protons which can be transferred from PEI and that of the sites on the polyamine which can accept protons are unknown.

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(12) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK$_a$ Prediction For Organic Acids and Bases*; Chapman and Hall: London, 1981; (a) p 22; (b) p 104; (c) p 27.

(13) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

(14) St. Pierre, T.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 3817.

(15) (a) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1990**, *55*, 1676; (b) *J. Chem. Soc., Perkin Trans. 2* **1991**, 63; (c) *J. Chem. Res., Synop.* **1987**, 358.

(16) (a) Castro, E. A.; Ibanez, F.; Salas, M.; Santos, J. G.; Sepulveda, P. *J. Org. Chem.* **1977**, *42*, 459. (b) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1993**, *99*, 7611. (c) Castro, E. A.; Ibanez, F.; Santos, J. S.; Ureta, C. *J. Org. Chem.* **1992**, *57*, 7024.

(17) (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963; (b) 6970.

(18) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442.

(19) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.

In the aminolysis of 3-acetoxy-2,6-dinitrobenzoic acid and 4-acetoxy-3-nitrobenzenesulfonate by PEI-curved Bronsted-type plots were obtained (Figure 1). The values of the limiting slopes of the curves fitting the experimental points according to eq 4 and the values of the parameters at the inflection points were $\beta_1 = 0.1$, $\beta_2 = 0.90$, $pK_{N^\circ} = 7.94$, and $\log k_N{}^\circ = 0.618$ for the former ester and $\beta_1 = 0.1$, $\beta_2 = 0.9$ $pK_{N^\circ} = 9.02$, and $\log k^\circ{}_n = 0.687$ for the latter. Since the pK_{1g} of the two esters are 6.08[5a] and 4.40,[5d] respectively, the change of the rate-determining step occurs when the difference $pK_{N^\circ} - pK_{1g}$ is 3−3.5, about one pK unit lower than the value found for simple amines. A tentative explanation of this difference can result from the knowledge of the rate constants for the expulsion of the nucleophile and of the aryl oxide ion from the $T^\pm$ intermediate according to eqs 5 and 6, obtained as detailed in the Appendix.

$$\log k_{-1} = 14.4 + 0.5pK_{1g} - 0.8pK_N \quad (5)$$

$$\log k_2 = 10.69 - 0.1pK_{1g} \quad (6)$$

The value of pK_N at the center of the Bronsted-type plots in Figure 1, calculated by equating eq 5 and 6, results in 9.19 for 4-acetoxy-3-nitrobenzenesulfonate (pK_{1g} 6.08), in fair agreement with the value of 9.02 obtained from eq 4. Values of $pK_{N^\circ} > 10$ were obtained for esters giving linear plots.

In the comparison of the values of k_{-1} and k_2 calculated for PEI with those obtained for alicyclic amines by eqs 6 and 8 in ref 16a, the ratio $k_{2(\mathrm{PEI})}/k_{2(\mathrm{amines}}$ is 9 for 3-acetoxy-2,6-dinitrobenzoic acid and 41 for 4-acetoxy-3-nitrobenzenesulfonate, while the ratio $k_{-1(\mathrm{PEI})}/k_{-1(\mathrm{amines})}$ (calculated in the pK_N range 7−9) is about 0.5 for both esters. These findings support a better nucleofugality of the aryl oxide from the $T^\pm$ intermediate rather than a worse nucleofugality of PEI with respect to an isobasic amine. Electrostatic interactions and/or hydrogen bonds involving PEI and charged groups of the esters may perhaps facilitate the aryl oxide over the amine expulsion. The lower polarity in the microenvironment[20] of the polyion chain cannot be responsible for the lower value of pK_{N° found with PEI: an increase of just 0.2−0.3 units was reported for pK_{N° in the aminolysis of some esters when the polarity of the solvent decreases.[15c,17b] In addition, neither a pH-induced change of substrate−polyelectrolyte interactions nor the change of the conformation of the polyelectrolyte can be involved, taking into account that linear plots were observed with the other structurally similar phenyl esters under the same experimental conditions (Figure 1).

In agreement with the above results is the effect of the change of the leaving group of the esters on the rate of aminolysis by PEI at constant pH. Figure 2 shows the dependence of $\log k_n$ on the pK of the conjugate acid of the leaving aryl oxide ion (pK_{1g}). Solid curves are the least-squares fitting of experimental data according to an equation corresponding to (4), where pK_N and pK_{N° are substituted by pK_{1g} and pK_{1g°. The values of the optimized parameters pK_{1g°, $\log k_n{}^\circ$, and β_{1g2} were 4.98, 1.27, and −0.73 at pK_N 9.42, 5.95, 0.28, and −0.76 at pK_N 8.53, 5.06, −0.51, and −0.80 at pK_N 6.80, and 4.46, −1.37, and −0.85 at pK_N 5.52. Slopes β_{1g1} around −0.24 are estimated for the most reactive ester at all pK_N. The values of the slopes were comparable with those found for the aminolysis of a set of phenyl acetates with glycylglycine[5a] (slope −0.88 which becomes −0.28 for the most reactive ester) or with monomeric amines (slope −1 ± 0.1 changing to −0.2 ± 0.2).[18,19] The lower sensitivity of $\log k_n$ to the change of pK_{1g} (slope −0.73), observed with PEI at high basicity ($pK_N = 9.42$), could suggest a lower C−O bond breaking in the transition state in agreement with the Hammond postulate.

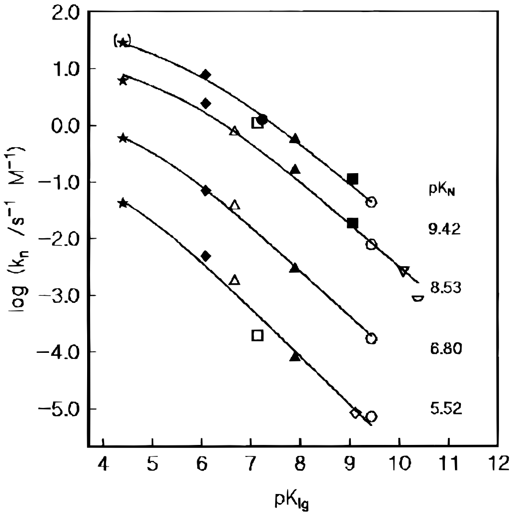

Figure 2. Bronsted-type plots for the aminolysis of some phenyl acetates of different leaving group acidity (pK_{1g} from ref 5a,d) by poly(ethylenimine) in 1 M KCl at 25 °C at various PEI basicity. Points are experimental, and lines were calculated according to eq 4 for each value of pK_{1g}. Uncertain values are in parentheses. Esters and respective symbols are the same as in Figure 1. Other esters are 4-acetoxy-3-nitrobenzoic acid (△), 4-nitrophenyl acetate (⊡); 3-chlorophenyl acetate (◇); 4-acetoxybenzoic acid (○); 3-acetoxybenzoic acid (▼) (ref 5a); and 4-acetoxyphenylacetic acid (half circle) (ref 5a).

The curvature of the Bronsted-type plots does not prove the presence of any intermediate in the reaction path,[16a,17a] but the existence of different inflection points for different esters agrees with the presence of a stepwise mechanism as reported for simple amines,[21] where the leaving group expulsion or the proton transfer in the tetrahedral intermediate decomposition is believed to be rate limiting.

Our results do not offer evidence for the contribution of an intermolecular base or acid catalysis in the range of used concentration of PEI. Such types of catalysis are also excluded by the comparison of the microscopic rate constants estimated for the two processes (k_3 and k_5) with the rate of decomposition of the $T^\pm$ intermediate (k_2) according to the paths shown in Scheme 1. To this purpose we first consider the aminolysis of 4-acetoxy-2,3-dinitrobenzoic acid. For the deprotonation step of $T^\pm$ to T^- by a base we calculate $pK_N(T^\pm)$, the acidity of the aminium ion in $T^\pm$. According to Castro,[16a] the introduction of the $CH_3CH(O^-)-$ group on the nitrogen atom of an amine increases the pK_N of the parent aminium ion by 2.2 pK units. We then assume the same increment of pK_N when going from PEI to **1**. Since ρ_I of pK_N-substituted aminium ions is −8.4,[22] from σ_I 0 for H and σ_I 0.52 for $-OC_6H_2\text{-}2,4\text{-}NO_2\text{-}3\text{-}COO^-$ (ref 23), a difference of $-8.4 \times 0.52 = -4.4$ units is expected for

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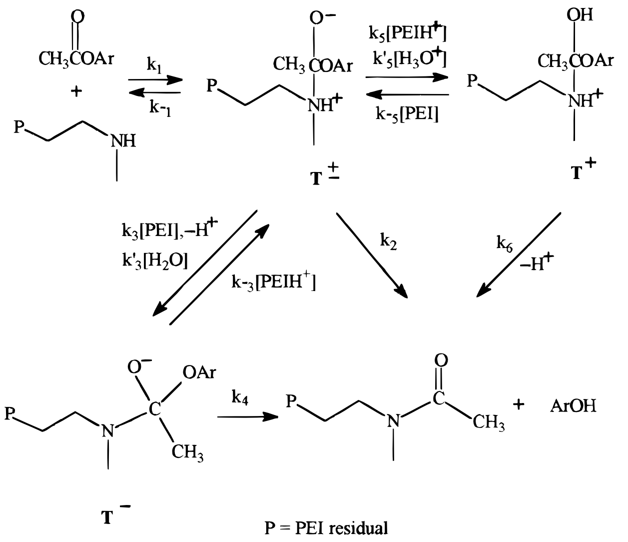
[20] Everaerts, A.; Samyn, C.; Smets, G. *Macromol. Chem.* **1984**, *185*, 1881.

[21] Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8479.

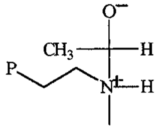
[22] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

Scheme 1



the pK_N of the aminium ion on going from **1** to T$^\pm$, and one obtains pK_N(T$^\pm$) = pK_N(PEI) −4.4 + 2.2 = pK_N(PEI) − 2.2. At the lowest and at the highest pH investigated for this ester (4.36 and 8.75), pK_N(PEI) is 5.52 and 8.78, respectively, and for pK_N(T$^\pm$) the values 3.3 and 6.6 are obtained. It follows that the proton transfer from T$^\pm$ to PEI is thermodynamically favored at both pH's, and according to Eigen,[26] the value 2 × 10^9 s^{-1} M^{-1} can be assumed for the rate constant k_3.[27] Consequently, under the best conditions for the proton transfer (pH 8.75), k_3[PEI] (1 − α) = (2 × 10^9)(0.23)(0.48) = 2.2 × 10^8 s^{-1}, lower than k_2 = 1.8 × 10^{10} s^{-1} calculated according to eq 6 for a pK_{1g} 4.40. The base catalysis by PEI on a tetrahedral intermediate can then be ignored. The proton transfer from T$^\pm$ to water is not favored even at pH 4.36 where the pK_N(T$^\pm$) has the lowest value. According to ref 26 one calculates log k'_3 = log k'_{-3} − pK_N(T$^\pm$) + p$K_{H_3O^+}$ = 9.3 − 3.3 − 1.75 = 4.25, i.e., k'_3 = 1.8 × 10^4 s^{-1} M^{-1}, and finally k'_3[H_2O] = 1 × 10^6 s^{-1}, a value still negligible in comparison with k_2.

To evaluate the contribution of the acid catalysis, i.e., the protonation of T$^\pm$ to give T$^+$, we first estimate pK_{OH}(T$^+$), the acidity of the −OH group in T$^+$ (Scheme 1). We consider only polar effects since the electrostatic potential in the environment of the polycation, which mainly contributes to decrease the pK_a of ionizable groups of covalently incorporated moieties, is considerably reduced even at low concentrations of added salt.[28] Structures **2** and **3** are chosen to simulate those of the intermediate T$^\pm$ at basic or acid pH, when the attacking amino group is primary or secondary because at low ionization degree of PEI the more basic primary amino groups (intrinsic pK_N 9.5[7a]) react preferentially over the less basic secondary amino groups (intrinsic pK_N 8.5[7a]). We estimate[29] pK_{OH}(T$^+$) 6.1 at pH 8.75 (for **2**) and pK_{OH}(T$^+$) 4.9 at pH 4.36 (for **3**). At both pH's the proton transfer from PEIH$^+$ to T$^\pm$ is unfavored even in the best conditions for the proton transfer. At pH 4.36, we assume for k_{-5} the value 10^9 s^{-1} M^{-1} (refs 15a and 26), obtaining log k_5 = log k_{-5} − pK_{OH}(T$^+$) = 9 − 4.9 = 4.1 and k_5[PEI]$^\alpha$ = 4.7 × 10^3 s^{-1}, lower than k_2. Also for the proton transfer from H_3O^+ to T$^\pm$, assuming for k'_5 the value 10^9 s^{-1} M^{-1} (refs 16a and 27), we obtain k'_5[H_3O^+] = 4.4 × 10^4 s^{-1}, negligible in comparison with k_2. Since the paths described do not appear to influence the spontaneous decomposition of T$^\pm$ to products, we did not evaluate k_4 and k_6, the rate constants of the subsequent steps of the catalyzed paths.



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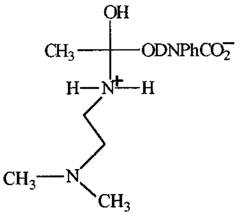

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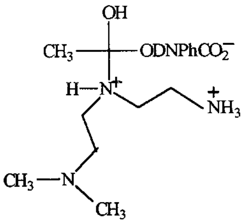

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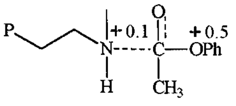

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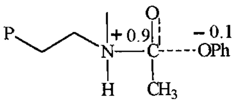

5

For the aminolysis of 4-acetoxy-3-nitrobenzenesulfonate the rate constants k_2, k_3, and k_5 are similarly obtained. In the best conditions for the proton transfer from T$^\pm$ intermediate to PEI (pH = 11.20, [PEI] = 2.3 monomer mol L^{-1}, a = 0.05, pK_N(PEI) = 9.88, pK_N(T$^\pm$) = 8.1), assuming k_3 = 2 × 10^9 s^{-1} M^{-1}, it gives k_3[PEI](1 − a) = 4.35 × 10^9 lower than k_2 = 1.2 × 10^{10} s^{-1}. For the proton transfer from PEIH$^+$ to T$^\pm$ to obtain T$^+$ (pH = 4.36, [PEI] = 0.4 monomer mol L^{-1}, pK_N(PEI) = 5.52, a = 0.9, pK_{OH}(T$^+$) = 5.2) one obtains k_5[PEI]a = 2.2 × 10^3 s^{-1}, again lower than k_2. Also, the rate constants for the proton transfer at pH 4.36 from T$^\pm$ to water (k'_3[H_2O] = 3.9 × 10^5 s^{-1}) and from H_3O^+ to T$^\pm$ (k'_5[H_3O^+] = 4.4 × 10^4 s^{-1}), are much lower than k_2. In the aminolysis at pH 11.20, the highest pH used with this ester, the proton

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[23] The value of σ_I of the group $-OC_6H_2$-2,4-NO_2-3-CO_2^- was obtained as in ref 24. From the pK_{OH} 4.40 of the phenolic group one calculates σ_{Ar}* 1.86 for $-C_6H_2$-2,4-NO_2-3-CO_2^-, and from the linear relationship of σ_{ArO}* vs σ_{Ar}* (from ref 12b), σ* = 3.27 was obtained which led to σ_I = 3.27/6.23 = 0.52, σ_I = σ*/6.23 in ref 25.

[24] Gurthrie, J. P.; Pike, D. C. *Can. J. Chem.* **1987**, *65*, 1951.

[25] Charton, M. J. *J. Org. Chem.* **1964**, *29*, 1222.

[26] Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

[27] The rate constant should be even lower than this value owing to the shielding effect of the high number of positive charges on the polycation. A decrease from 10^{10} to 2 × 10^9 s^{-1} M^{-1} of the rate constant is reported for the proton transfer from the T$^\pm$ intermediate, originating from 4-nitrophenyl dithioacetate and piperazine or piperazine cation, to the corresponding aminium ion.[16c]

[28] Morishima, Y.; Kobayashi, T.; Nozakura, S.-i. *Macromolecules*, **1988**, *21*, 101.

[29] Starting from pK_{OH} 7.7 of $CH_3NH_2^+C(CH_3)(OH)(OPh)$ calculated by Castro,[16a] taking σ_I = 0.39 for PhO^- and σ_I = 0.52 for $-OC_6H_2$-2,4-$(NO_2)_2$-3-COO^-, and considering that the sensitivity of alcohols to σ_I is expressed by ρ_I = −8.4,[22] one obtains for $CH_3NH_2^+C(CH_3)(OH)(ODNPhCO_2^-)$ pK_{OH} = 7.7 − 8.4 (0.52 − 0.39) = 6.60. From σ* $-N(CH_3)_2$ = 0.32, considering the interposition of the two methylenes,[12c] it results that σ_I $-CH_2CH_2N(CH_3)_2$ = 0.32 × 0.4^2/6.23 = 0.01. Since σ_I of CH_3 is −0.05[25] and ρ_I = −8.4, we obtained for **2** a pK_{OH}(T$^+$) = 6.6 − 8.4 (0.01 + 0.05) = 6.1, Similarly, for **3**, from a σ* 2.24 of $-CH_2NH_3^+$, we calculated σ_I of $-CH_2CH_2NH_3^+$ = 2.24 × 0.4/6.23 = 0.14 and pK_{OH}(T$^\pm$) = 6.60 − 8.4 (0.01) + 0.05 + 0.14) = 4.9.

transfer from $T^{\pm}$ to OH^- is also considered: since $k_3 = 10^{10}\ s^{-1}\ M^{-1}$ (ref 26), $k_3[OH^-] = 1.6 \times 10^7\ s^{-1}$ is calculated, also lower than k_2.

Similar calculations for the less reactive 4-acetoxybenzenesulfonate (pK_{1g} 9.06) give for the decomposition of the tetrahedral intermediate at pH 11.20, $a = 0.05$, $[PEI] = 2.2$ monomer mol L^{-1}, the rate constant $k_2 = 6 \times 10^9\ s^{-1}$, $pK_N(T^{\pm}) = 8.6$ and then $k_3[PEI](1 - a) = 4.2 \times 10^9\ s^{-1}$ not far from k_2, suggesting that the base-catalyzed path could be partially rate determining at least at these extreme concentrations of PEI.

We conclude that the intermolecular acid or base catalyses in the aminolysis of phenyl acetates by PEI are less important than the uncatalyzed decomposition of the $T^{\pm}$ intermediate to products. An undetectable intramolecular acid or base catalysis can also be considered improbable because in the aminolysis of 4-acetoxy-3-nitrobenzenesulfonate the poly(ethylenimine) was from two to five times less reactive than isobasic monofunctional amines.

Appendix

The parameters in eqs 5 and 6 were obtained according to eq 12 in ref 17a for aminolysis of phenyl acetates with simple amines were β_0 was the sensitivity of the rate constants of each reaction step in Scheme 1 to the acidity of the conjugate acid of the leaving aryl oxide ion and β_N the sensitivity of the rate constants to the pK_N of the nucleophile. We assumed in the reagents a charge of 0.7 for the oxygen atom of the leaving aryl oxide ion and 0 for the nitrogen atom of the nucleophile and charges 0 and 0.9 for the two atoms in the $T^{\pm}$ intermediate. The effective charges 0.5 on the leaving oxygen and 0.1 on the nucleophilic nitrogen in the transition state **4** (on the path from reagents to $T^{\pm}$) were obtained by adding to the charges that the atoms have in the reagents, respectively, the values β_0 -0.2 that is the slope of the left hand side of the plots in Figure 2 and β_N 0.1, the slope of the right hand side of the two curved plots in Figure 1. In both cases $k_n = k_1$. Charges of -0.1 for the oxygen atom and 0.9 for the nitrogen atom in the transition state **5**, on the path from $T^{\pm}$ to products, were obtained by adding to the charges in the reagents the mean values β_0 -0.8 found for the right hand side of the plots in Figure 2 and β_N $+0.9$ found for the left hand side of the plots in Figure 1, where $k_n = k_1k_2/k_{-}$.[1] Value β_0 -0.1 to be used in eq 6 was obtained from the difference of charges on the leaving oxygen in the transition state **5** and in $T^{\pm}$. Assuming that the basicity of PEI does not affect the rate of expulsion of the aryl oxide ion, as was reported for simple amines,[16a,17a] β_N is 0. Since the nucleofugality of the aryl oxide ion from $T^{\pm}$ formed in the reaction of phenyl acetates with PEI is unknown, the intercept 10.69 in eq 6 was obtained using for β_0 the value -0.1 obtained above and for k_2 the value $3 \times 10^{10}\ s^{-1}$ reported[19] for the aminolysis of 1-acetoxy-4-methoxypyridinium (pK_{1g} 2.1) by methylamine. Similarly, β_0 0.5 and β_N -0.8 to calculate k_{-1} in eq 5 were obtained by subtracting from the charges of oxygen and of nitrogen atoms in the transition state **4** the charges that the atoms have in $T^{\pm}$. Finally, the value 14.4 for the intercept of eq 5 was obtained by equating k_{-1} and k_2 using the values pK_{1g} 4.40 and pK_{N° 7.9 found for 3-acetoxy-2,6-dinitrobenzoic acid and the values of β_0 and β_N calculated above.

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