not observed due to the limited solubility of the block copolyester.

1,1,2,2-Tetrachloroethane–*o*-chlorophenol–phenol (60:25:15 v/v/v) solutions of poly[oxy-*trans*-1,4-cyclohexyleneoxycarbonyl-*trans*-1,4-cyclohexylenecarbonyl-*b*-oxy(2-methyl-1,4-phenylene)oxyterephthaloyl] depolarized plane-polarized light when thin layers of the solutions were viewed at 100× magnification. When the solutions were sheared by the movement of the cover slide, microdomains of oriented, extended-chain segments were observed to form on microscopic examination between crossed polarizers. This phenomenon is shown in Figure 2.

Conclusion

In summary, synthetic procedures have been developed for block copolyesters which contain cyclohexane and benzene rings. Three of these block copolyesters display mesomorphic properties in solution. In subsequent publications, the spectroscopic, mechanical, and thermal properties of these block copolyesters will be described in detail.

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pH-Dependent Esterolysis by Dodecylated Poly(ethylenimine)

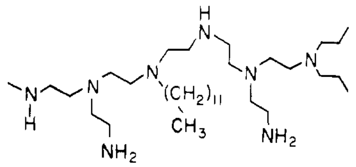
Curtis S. Lege and James A. Deyrup*

Center for Macromolecular Science, Department of Chemistry, University of Florida, Gainesville, Florida 32611. *Received May 12, 1981*

ABSTRACT: The esterolysis of *p*-nitrophenyl acetate (PNPA) and *p*-nitrophenyl caproate (PNPC) by partially dodecylated poly(ethylenimine) (PEI-D-NH_2-HCl) has been studied. The reactions proceed via nucleophilic attack of the pendent primary amino groups on the ester at a rate (k) which is dependent on the pH. The p$K_{a,app}$ of PEI-D-NH_2-HCl is also pH dependent. It was possible, therefore, to construct a Brønsted-type plot of log k (corrected for free amino groups) against the p$K_{a,app}$ of the polymeric amino groups for PNPA (β = 0.81). The pH dependence of PNPA esterolysis is thus accounted for by electrostatic effects on nucleophilicity. An additional pH dependence of PNPC was observed and attributed to pH effects on hydrophobic bonding.

The search for synthetic macromolecular catalysts continues and impressive developments in this area appear on a regular basis in the current literature.[1-6] At the same time many questions remain unanswered concerning the relative importance of those various factors which could contribute to catalytic activity. One such factor of particular concern relates to cooperative or bifunctional catalysis.[7] Such effects are important in many enzymatic reactions and involve the concerted interaction of two or more functional groups in the reaction with the substrate.

PEI [poly(ethylenimine)] modified by the attachment of dodecyl groups and imidazole substituents has shown remarkable esterolytic activity.[8-12] Klotz and co-workers attributed this activity to hydrophobic binding between the esters and the dodecyl groups. It occurred to us that a portion of this activity might be due to cooperative effects between the PEI backbone and the catalytically active imidazole groups. In order to address this question it became necessary to study first the esterolysis reactions of PEI substituted only by dodecyl groups. This polymer derivative (PEI-D-NH_2) contains primary amino groups but lacks heterocyclic substituents. The following paper deals with the question of cooperative catalysis in esterolyses which involve imidazole and related heterocyclic substituents. Our approach in both instances will be patterned on the work of others who have attempted to detect cooperative effects in small molecules via studies of the dependency of rate on pH.[13]


PEI-D-NH_2

Experimental Section

Melting points and boiling points are uncorrected unless otherwise noted. Nuclear magnetic resonance spectra were recorded

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on a Varian A60-A spectrometer. Chemical shift (δ) data were recorded in parts per million (ppm) from the appropriate internal reference, either tetramethylsilane (Me_4Si), 4,4-dimethyl-4-silapentanesulfonic acid (DSS), or water-*d* (HOD). Solvent evaporation was performed at reduced pressure with a Buchler Instruments flash evaporator. Lyophilization was carried out by using an apparatus and technique similar to that described by Vogel.[14] The aqueous dialyses were carried out in a 3-L filter flask connected to a deionized water tap and equipped with a stir bar. The polymer solutions to be dialyzed were transferred to dialysis bags prepared from Union Carbide (36/100 ft dialysis membrane) tubing according to the method of Gabbay et al.[15] In the case of dialysis against a stream of deionized water, the tap was opened to allow a moderate flow of water through the flask while stirring was maintained. Temperature control was provided by a Lauda K-2/R thermostat. All UV–visible spectrophotometric measurements were made on a Cary 17D spectrophotometer. The pH measurements were made with a Beckman research pH meter in conjunction with a Radiometer GK 2321C electrode. *p*-Nitrophenyl acetate[16] and *p*-nitrophenyl caproate[17] were prepared according to previous literature procedures.

Dodecyl-poly(ethylenimine) (PEI-D-NH_2). Dow PEI 600 poly(ethylenimine) solution (128 g) was freeze-dried for 8 h and then allowed to warm to room temperature while a vacuum (0.05 torr) was maintained for an additional 36 h. The viscous material (49 g, approximately 1.2 mol in ethylenimine units) was dissolved in 470 mL of argon-saturated anhydrous ethanol. Dodecyl iodide (35 g, 0.12 mol) in 5.0 mL of anhydrous ethanol was added to the polymer solution. The reaction flask was sealed and maintained at 45 °C for 120 h. The reaction mixture was quantitatively transferred to a 1-L volumetric flask and diluted to the mark with argon-saturated anhydrous ethanol. This solution was stored under argon and used as a stock solution in the following preparations (1.2 M in ethylenimine units).

Dodecyl-poly(ethylenimine) Hydrochloride (PEI-D-NH_2-HCl). A solution of dodecyl-poly(ethylenimine) (PEI-D) was prepared by diluting (25 mL, 0.030 mol) to 150 mL with absolute ethanol. This solution was added carefully to a 500-mL beaker containing 5 mL of concentrated hydrochloric acid in 50 mL of absolute ethanol at 0 °C. The resultant salt was filtered and washed with absolute ethanol.

Anal.: C, 42.17; H, 7.94; N, 14.66; Cl, 32.64.[18]

Dodecyl-isopropyl-poly(ethylenimine) Hydrochloride (PEI-D-Ip-HCl). A stock solution (ca. 30 mmol in 25 mL of H_2O) of PEI-D was combined with 3 g (52 mmol) of acetone in 25 mL of ethanol. After 2 h, 1 g of $NaBH_4$ (in 25 mL of ethanol) was added. The resultant mixture was stirred for 24 h and then dialyzed for 9 days. The resultant suspension was acidified with 6 N HCl, stirred for 24 h, and dialyzed for 24 h. The contents of the dialysis bag were lyophilized and then dried in vacuo at 45 °C. The resultant solid weighed 425 mg.

Anal.: C, 46.27; H, 9.64; N, 12.46; Cl, 27.18.[18]

Composition of PEI-D-HCl and PEI-D-Ip-HCl by Elemental Analysis. Elemental analysis data were used to calculate the values of D (fraction of CH_2CH_2N units dodecylated in PEI), Z (fraction of CH_2CH_2N units bearing an isopropyl unit in PEI-D-Ip-HCl), mole unit weight (average weight of a mole of CH_2CH_2N units after derivitization), and α_{init} (in the case of PEI-D-NH_2-HCl). The C/N ratio was used to calculate both D and Z. The carbon-to-nitrogen weight ratio is equal to the C/N ratio from elemental analysis. Therefore the number of carbons per unit (2 from the CH_2CH_2N unit, $12D$ from the dodecyl group, and $X = 3$ from the isosubstituent) divided by the number of nitrogens per unit (1 from the CH_2CH_2N unit) and multiplied by the C/N atomic weight ratio is equal to the C/N ratio from elemental analysis (eq 1). This equation is readily rearranged

$$C/N = \frac{2 + 12D}{1}\left(\frac{12.01}{14.01}\right)$$

$$D = \frac{1}{12}\left((C/N)\frac{14.01}{12.01} - 2\right)$$

$$Z = \left((C/N)\frac{14.01}{12.01} - 2 - 12D\right)\Big/3 \qquad (1)$$

to solve for either D or Z. In the case of PEI-D-NH_2-HCl the equation has a single unknown, D. For PEI-D-Ip-HCl the value of D calculated for PEI-D-NH_2-HCl was used. The error limits in these calculations are based on an assumed error of 0.2 in the elemental analysis. Values of C/N were calculated by using the relationships $C + 0.2/N - 0.2$ and $C - 0.2/N + 0.2$, which were substituted in the appropriate equations to calculate error limits. The mole unit weight was calculated from the relationship that the percent of an element in a compound is equal to the weight of that element in the compound divided by the formula (units) weight of the compounds multiplied by 100 (eq 2). In this way,

$$\%\ \text{elemental} = \frac{\text{weight of element} \times 100}{\text{formula weight (mole unit weight)}} \qquad (2)$$

values of 96 ± 1 and 115 ± 1 were determined for PEI-D-NH_2-HCl and PEI-D-Ip-HCl, respectively. The elemental analysis values for carbon and nitrogen together with the calculated values for D (0.113 ± 0.005) and Z (0.32 ± 0.04) were used for these calculations (eq 3). The error calculation for the unit mole weight

$$\text{mole unit weight} = \frac{(2 + 12D + ZX)12.01}{\%\ C \times 0.01} \qquad (3)$$

was based on the difference between the average from the carbon and nitrogen calculations and the highest possible value from the carbon-based calculation and lowest possible value for the nitrogen-based calculation consistent with the assumed error of ±0.2 in the elemental analysis data. A value of 0.15 ± 0.2 for α_{init} was calculated for the PEI-D-NH_2-HCl titration based on the assumption that all analyzed chlorine was present as the hydrochloride salt. The ratio of moles of chlorine to moles of nitrogen in the polymer represents the fraction of CH_2CH_2N units protonated, $1 - \alpha_{init}$ (eq 4). The error calculation for α_{init} was made

$$1 - \alpha_{init} = \frac{\%\ Cl/35.45}{\%\ N/14.01} \qquad (4)$$

assuming an error of 0.02 in the elemental analysis data.

Qualitative confirmation of these alkylation values were obtained via NMR spectroscopy.

Potentiometric Titration of PEI-D-NH_2-HCl. PEI-D-NH_2-HCl (0.0931 g) was dissolved in 50.0 mL of 0.100 M KCl after drying under vacuum for 10 days. The solution (0.0192 M in CH_2CH_2N units) was titrated with CO_2-free KOH (0.09977 N) at 25.0 ± 0.3 °C under a nitrogen atmosphere. After each addition of titrant the pH was recorded upon equilibration.

The values of $pK_{a,app}$ and α were calculated from the titration data. The value of α at each pH was determined by a modification of the method suggested by Albert and Serjeant[19] to calculate the ratio of nonprotonated species (eq 5). The value of KOH refers

$$\alpha = \frac{[KOH] + \alpha_{init}[CH_2CH_2N] - 10^{-pH} + 10^{pH-14.00}}{[CH_2CH_2N] + 10^{-pH} - 10^{pH-14.00}} \qquad (5)$$

to the initial concentration of potassium hydroxide, i.e., the total moles of titrant which were added to bring the pH to a given value divided by the volume of the solution. The value of α_{init} is the fraction of nonprotonated CH_2CH_2N units in PEI-D-NH_2-HCl as prepared and determined from the Cl/N ratio. The exponential terms in pH serve to correct the hydroxide ion concentration for water ionization. The value of $pK_{a,app}$ was calculated at each value of pH by use of the Henderson–Hasselbalch equation[20] (eq 6).

$$pK_{a,app} = pH + \log\frac{1 - \alpha}{\alpha} \qquad (6)$$

Kinetic Method. To a 4-mL cuvette were added polymer, either in solid form or as an aliquot of stock aolution, water, and acetonitrile. Amounts of water and acetonitrile were added such that the total volume of polymer stock solution and water was 0.100 mL and the total volume of acetonitrilic ester solution (added later) and acetonitrile was 0.050 mL. Buffer solution (3.00 mL, 0.100 M Tris, $I = 0.100$ M) was pipetted into the cuvette. The pH of the solution was recorded at room temperature, 25 ± 2 °C. The cuvette was placed in a spectrophotometer and equilibrated to 25.0 ± 0.3 °C, and absorbance data were collected. A_∞ was determined by following the increase in *p*-nitrophenoxide anion concentration at 400 nm until no further change in absorbance,

Table I
Primary Amine Content of PEI Derivatives Using TNBS

PEI derivative	absorbance	unit mole concn of PEI	% primary amine
PEI-D-NH$_2$-HCl	0.972 ± 0.013	4.08×10^{-4}	19.8 ± 0.4
PEI-D-Ip-HCl	0.058 ± 0.001	3.44×10^{-4}	1.4 ± 0.2
blank	0.007 ± 0.007		

A, was observed. The observed rate constants were calculated from values of $A_\infty - A_t$ and t (time) by a least-squares routine. These rate constants, K_Φ (i.e., the uncorrected rate constants), were then corrected for the background rate by subtraction of the value of the background rate constant (k_{BG}) at the appropriate pH. These corrected pseudo-first-order rates ($k = k_\Phi - k_{BG}$) were then divided by the concentration of CH_2CH_2N units, nucleophile concentration, or protonated nucleophile concentration (PEI-D-NH$_2$-HCl) to determine second-order rate constants k_{2GB} (see Results and Discussion), k_2, or k_2/α, respectively.

Background Rate. The rate of *p*-nitrophenyl acetate esterolysis without polymer was measured at seven pH values in the region of interest. The background rate constants (k_{BG}) were found to fit eq 7. The values of k_b[21] (7.0×10^{-2} M^{-1} min^{-1}), k_{OH}

$$k_{BG} = \frac{k_b[\mathrm{Tris}]_{total}}{1 + 10^{8.08-\mathrm{pH}}} + k_{OH}(10^{14-\mathrm{pH}}) + k_w[H_2O] \qquad (7)$$

(5.70×10^2 M^{-1} min^{-1}), and k_w[21] (6×10^{-7} M^{-1} min^{-1}) were available from the literature. The values from this equation were then used for the background rate.

Determination of Primary Content of PEI Derivatives Using Trinitrobenzenesulfonate (TNBS). 2,4,6-Trinitrobenzenesulfonate (TNBS) was used to determine the primary amine content of the PEI derivatives by a method similar to that used by Johnson and Klotz.[23] To a 25-mL volumetric flask were added 0.100 mL of an aqueous PEI solution (10^{-4} unit mol), 5 mL of a 4% aqueous sodium bicarbonate solution, and 1 mL of a 0.1% aqueous TNBS solution. The flask was heated for 0.5 h at 37 °C, cooled to room temperature, and filled to the mark with glacial acetic acid, and the absorbance was measured at 340 nm. The percentage of residual primary amine was calculated based on the extinction coefficient (12000 M^{-1} cm^{-1}) used by Johnson and Kotz (Table I).

Results and Discussion

PEI was partially dodecylated. This polymer derivative (PEI-D) was shown by analysis (see Experimental Section) to have dodecyl groups attached to 11% of its nitrogens and to consist of 20% primary amino groups. For control purposes (vide infra) a sample of PEI-D was reacted with acetone and $NaBH_4$ to give PEI-D-Ip. This derivative was shown to have 32% of its nitrogens isopropylated and approximately 1% of its nitrogen atoms still primary.

The acid-base properties of PEI-D-NH$_2$-HCl were determined by potentiometric titration. The values of α, the fraction of nonprotonated polymeric amine, after each addition of titrant were given by the concentration of added titrant divided by the concentration of polymeric amine units, CH_2CH_2N. The values of p$K_{a,app}$ at each value of α were calculated from the Henderson-Hasselbalch equation (eq 6).[20,24,25]

From the plot of p$K_{a,app}$ vs. α (Figure 1) it can be seen that the p$K_{a,app}$ is dependent on the fraction of polymeric amines unprotonated, α.

The pK_a values for ethylenediamine, diethylenetriamine, and triethylenetetramine can be determined discretely for each successive stage of ionization.[26] For comparison purposes, therefore, these pK_a-α values are also included in Figure 1.[27] The pK_a values for these systems qualitatively display the same sort of dependence on α as the polymer. The significance of these observations will be discussed later.

Rates of disappearance of substrate, *p*-nitrophenyl acetate (PNPA), or *p*-nitrophenyl caproate (PNPC), were monitored spectrophotometrically by observing the increase in *p*-nitrophenoxide absorbance. These reactions were studied under pseudo-first-order conditions (excess polymer) at pHs within the range 6.5–9.0. The second-order rate constants (k_2, M^{-1} min^{-1}) were calculated, after subtracting the background rate, by division by concentration of primary amine unless otherwise indicated.[29] Two different polymeric esterolysis processes may contribute to the pH dependence of *p*-nitrophenoxide formation, nucleophilic aminolysis, and/or general-base-catalyzed hydrolysis. The latter was eliminated by examining the rate data for PEI-D-Ip in which virtually all the primary amino groups had been eliminated. Rate constants from this system should estimate an upper limit for the general-base component. In order to compare the rate data for these two systems, we must calculate the second-order rate constants (k_{2GB}) based on the concentration of basic sites, CH_2CH_2N units (Figure 2). In comparing the rates for the PNPA reaction one can see (Figure 2) that the maximum contribution of the general-base reaction is less than 3%[30]

The pH-rate profiles (k_2 based on the primary amine concentration and divided by α) for reaction of PEI-D with both PNPA and PNPC are shown in Figure 3. In

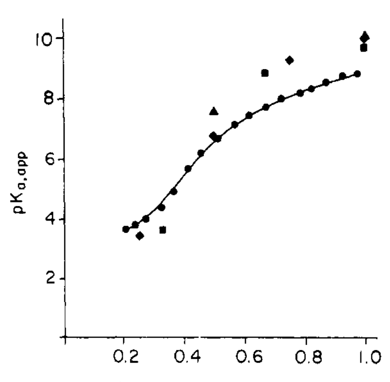

Figure 1. Comparison of p$K_{a,app}$ dependence on α for PEI-D-NH$_2$-HCl with low molecular weight polyamines:[26] (●) PEI-D-NH$_2$-HCl; (▲) ethylenediamine; (■) diethylenetriamine; (♦) triethylenetetramine.

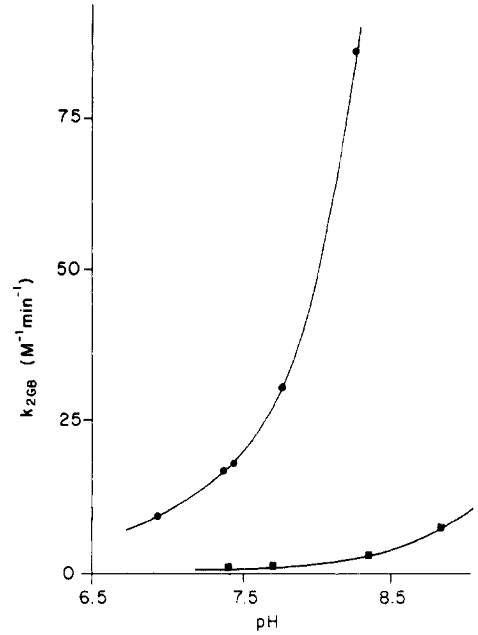

Figure 2. Comparison of esterolysis rates for (●) PEI-D-NH$_2$-HCl and (■) PEI-D-Ip-HCl.

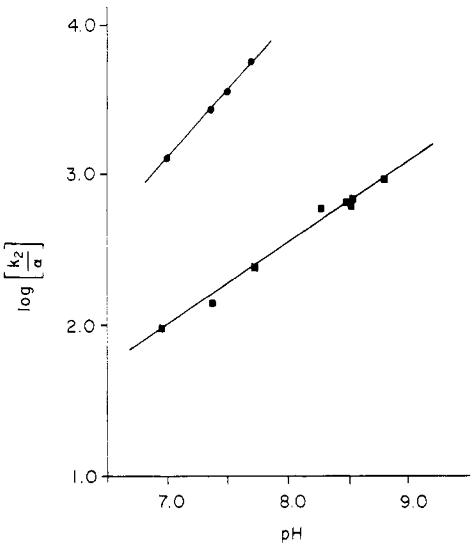

Figure 3. Plot of log (k_2/α) against pH for PEI-D-NH$_2$-HCl esterolysis of (●) PNPC and (■) PNPA.

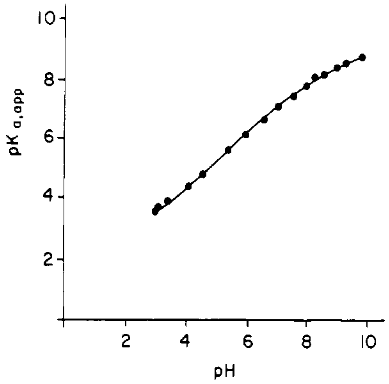

Figure 4. Plot of p$K_{a,app}$ vs. pH for PEI-D-NH$_2$-HCl.

small-molecule systems pH dependencies can often be explained on the basis of ionization. A protonated amine cannot act as a nucleophile, and thus the rate is dependent on the fraction of free amines.[31] In contrast to the small molecules, however, correction for ionization does not remove the pH dependency in the case of PEI-D-NH$_2$-HCl. We find that since the p$K_{a,app}$ of the polybase PEI-D is pH dependent (Figure 4) a well-defined Brønsted plot can be constructed from the reactions of PEI-D with PNPA and PNPC (Figure 5). Included on the same coordinate system is a reference plot for simple primary and secondary amines.[31] It can be seen from the values of β for aminolysis of PNPA by PEI-D (β = 0.81) and by reference amines (β = 0.83) that the difference in pK_a dependence is insignificant for the two systems. The pH dependence for the PEI-D-NH$_2$-HCl reaction with PNPA is thus completely accounted for by the dependence of nucleophilicity on base strength for the polymer. The value of β for the reaction of PEI-D with PNPC, 1.06, however, is significantly different from the reference value.

Interpretation of the polymeric reaction rate can be facilitated by assuming that k_2/α can be separated into two terms, k_a and E (eq 8). If the term E is taken to be

$$\log k_2/\alpha = \log (k_a E) = \log k_a + \log E = \mathrm{p}K_a + C \qquad (8)$$

the rate of enhancement due to the polymeric environment, then the term k_a can be estimated from the reference amines. That is, if the Brønsted equation for the reference amines (Figure 5) is subtracted from the Brønsted equation for the polymer systems, then E can be determined as a function of pK_a and thus α (eq 9). The value of E then can be plotted against pK_a or α (Figure 6).

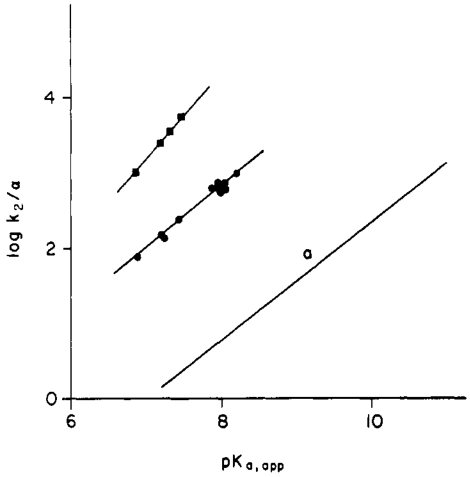

Figure 5. Brønsted plot for the esterolysis of (●) PNPA and (■) PNPC by PEI-D-NH$_2$-HCl. Line a is derived from values reported for simple primary and secondary amines.[31]

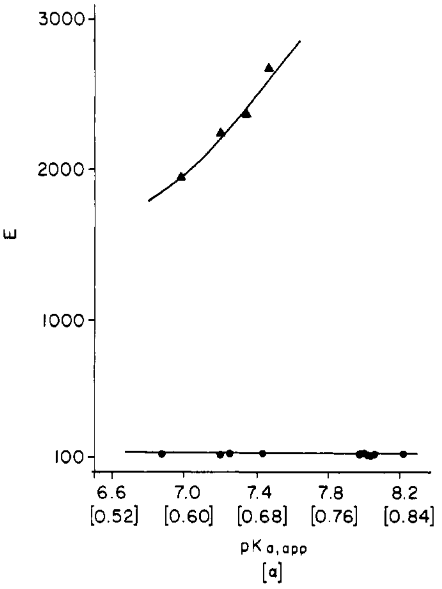

Figure 6. Plot of E vs. pK_a or [α] for the esterolysis of (▲) PNPC and (●) PNPA by PEI-D-NH$_2$-HCl.

$$\begin{array}{lll} \log (k_a\mathrm{E}) = \beta_\mathrm{p}\, \mathrm{p}K_a + C_\mathrm{p} & \mathrm{P} = \text{polymer system} & \\ \underline{-\log k_\mathrm{R} \quad = \beta_\mathrm{R}\, \mathrm{p}K_a + C_\mathrm{R}} & \mathrm{R} = \text{reference system} & (9) \\ \log E \quad = \beta_\mathrm{e}\, \mathrm{p}K_a + C_\mathrm{E} & \mathrm{E} = \text{polymeric enhancement} & \end{array}$$

The binding aspects of the polymer can be examined more closely via the PNPC reaction. The reactivity of the reference amines with PNPA is used to dissect the rates of the PEI-D reaction with PNPC. In the case of the PNPC aminolysis the dependence of rate on p$K_{a,app}$ is not entirely resolved by the subtraction of the reference equation as in the case of PNPA. The caproate ester and acetate ester aminolyses must proceed by the same mechanism since the only structural change is replacement of a methyl group by a n-pentyl group. Although this change would not be expected to affect the reaction mechanism, the hydrophobic binding properties are greatly affected. Increased hydrophobic binding with reduced charge density then must be the explanation for the additional pH dependence in the case of the PNPC reaction.

The above discussion adequately accounts for the pH dependencies of the reactions of both PNPA and PNPC with PEI-D-NH_2-HCl. However, a significant pH-independent enhancement in the polymer reactions remains unaccounted for. The rate constant for the PEI-D-NH_2-HCl reactions with PNPA at any given pK_a within the range studied is approximately 160-fold larger than that of a reference amine of the same pK_a. There are several possible explanations for this enhancement, for example, a solvent effect of pH-dependent binding. Alternatively, the apparent enhancement may be due to error in concentration of primary amine and/or in the value of C. Unfortunately, there are insufficient data to determine the cause of this enhancement. In spite of insufficient data, this ambiguity does not diminish the importance of the p$K_{a,app}$–rate correlation.

Summary

The reactions of PEI-D-NH_2-HCl with PNPA and PNPC have been shown to proceed via nucleophilic attack of polymeric amine on ester. The rate of reaction is a function of the state of protonation of the polymer which in turn is a function of pH. Correction of the rate constant for fraction of nucleophiles protonated does not lift the pH dependency. However, the pH dependency can be quantitatively dissected by use of the Brønsted relation. The dependence of the PNPA reaction was found to be due to increased nucleophilicity of the polymeric amine with increasing pH. The PNPC reaction exhibits increased binding as well as increased nucleophilicity with increasing pH. To the best of our knowledge, the Brønsted relation has not been used directly before to quantitate electrostatic effects in polyionic nucleophiles.[32] The utility and significance of this approach will be explored further in the following paper.

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