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Polymeric Catalysts Based on 4-(Diallylamino)pyridine

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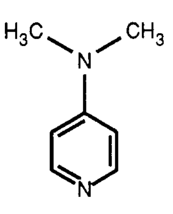
ABSTRACT: Copolymers of 4-(diallylamino)pyridine (DAAP) with neutral, anionic, and cationic monomers were investigated as catalysts for esterolysis and esterification reactions. The former were carried out with *p*-nitrophenyl caproate as substrate in water at 30 °C and pH values ranging from 7 to 9. The copolymers proved in many cases to be more effective than the homopolymer of DAAP, which in turn was more active than the very effective low molecular weight nucleophilic catalyst 4-pyrrolidinopyridine (PPY). The specific catalytic activity increased with growing isolation of the DAAP monomer units in agreement with reports for other polymeric esterolytic catalysts. Copolymers with dimethylacrylamide followed Michaelis–Menten-like kinetics. The homopolymer of DAAP and the copolymers also catalyzed the esterification of linalool with acetic anhydride in toluene at 80 °C. The moderate increases in the esterification rates for polymeric catalysts were comparable to or somewhat less than that obtained with DMAP.

Introduction

We have been involved over the last several years in the synthesis and characterization of a family of polymeric catalysts containing 4-aminopyridine supernucleophiles similar to 4-(dimethylamino)pyridine (DMAP, 1) and the more reactive 4-pyrrolidinopyridine (PPY, 2).[1,2] Polymeric catalysts mimic enzymes in many respects:[3]



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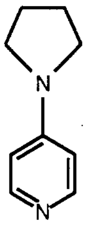

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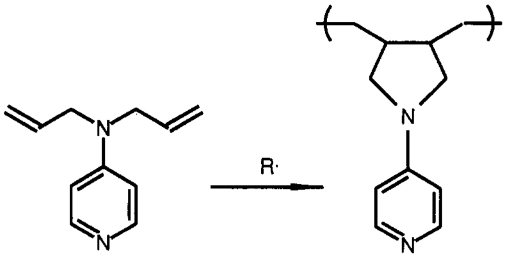
1. The reaction locus provides interactions of substrate and intermediate(s) with other reactive groups on the polymer that facilitate the reaction process by lowering the transition-state energy and/or raising the energy of the bound substrates.[4,5]
2. The local microenvironment controls substrate and product binding such that ionic[6] or hydrophobic[7] interactions may provide high local concentrations of both substrate and active groups (compared to their bulk concentrations), leading to an increase in the overall rate.

On the basis of initial results involving the relationship between backbone hydrophobicity and pH-induced changes of activity at the reactive sites,[8] we hoped to design polymeric catalysts capable of displaying high catalytic activity coupled with substrate selectivity. This goal involves controlling both the active site microenvironment and the pH range of maximum catlytic activity by introducing an additional functionality pendent to the backbone. This is readily accomplished through radical copolymerization of the monomer 4-(diallylamino)pyridine (3) with various comonomers.

Monomer 3 was designed to serve as a "nascent" catalyst monomer.[9] While 3 does not possess the desired pyrrolidino substituent in the 4-position, its cyclopolymerization generates polymer 4, which possesses predominantly 5-membered-ring repeat units analogous to the reactive supernucleophilic catalyst PPY (2). Thus, we *use* the polymerization mechanism to form the desired structural units with high catalytic activity.



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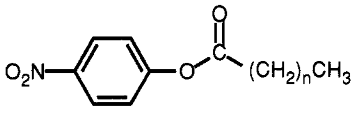

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In fact, homopolymer 4 has been found to display greater esterolytic activity than PPY for the series of esters 5 in water.[10] The polymer backbone was shown to provide hydrophobic binding, resulting in a higher substrate concentration in the catalytic microenvironment and giving higher rates of catalysis for longer alkyl esters. Good activity for the homopolymer as an *inverse* phase-transfer catalyst was also found by us[11] and others[12] in several types of interfacial reactions.

Copolymers of 3 were synthesized to evaluate the effect of neutral and ionic microenvironments on the catalytic activity of 3 repeat units.[8] Comonomers employed were *N,N*-dimethylacrylamide (DMAM), dimethyldiallylammonium chloride (DMDAACl), and acrylic acid (AA) to give copolymers 6–8, respectively. Reactivity ratios were determined as well as the dependence of the degree of protonation of the catalytic units on pH.[8] The latter is a critical variable in catalysis studies since only nonprotonated PPY units are nucleophilically active. The former allows control of the active site distribution in the polymers. The sluggish polymerizability of monomer 3 coupled with low feed ratios led to copolymers in which units of 3 were statistically separated from each other along the polymer backbone. The nature of the comonomer units and the

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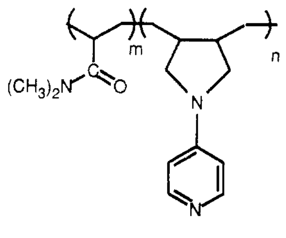

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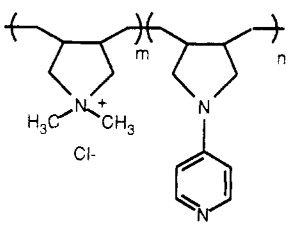

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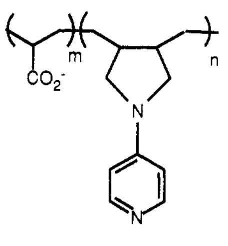

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relative concentration of 3 vs comonomer in the copolymer then determine the overall or average pK_a of the DAAP units and the pH of the microenvironment near the active catalytic sites.

In this paper, we report studies utilizing an active ester as substrate[13,14] to evaluate the esterolytic activity of these copolymers in aqueous solutions. We also describe a brief demonstration of the application of these catalysts in the formation of linalool acetate in toluene.[15,16]

Experimental Section

Analytical-grade absolute methanol and spectroscopic-grade acetonitrile were used for preparation of catalyst and substrate solutions, respectively. Analytical-grade potassium dihydrogen phosphate, tris(hydroxymethyl)aminomethane, and NaOH were used for buffer preparation. The substrate *p*-nitrophenyl caproate (PNPC, Sigma Chemical Co.) was used as purchased. 4-(Dimethylamino)pyridine (Reilly Chemicals), linalool (Aldrich), and decane (Aldrich) were used without further purification. Acetic anhydride, triethylamine, and toluene were distilled before use. Characterization of most of the catalytic polymers was described in the previous paper of this series, and all copolymer identification numbers in the figure footnotes refer to materials given there.[8] New copolymers described in Table II were synthesized at low conversions, and their compositions were calculated by using the reactivity ratios previously determined.[8] Buffered solutions were prepared according to standard procedures,[17] and the pH was checked with a Model 701-A pH meter with an Orion combination pH electrode 91-55, which was calibrated with standard buffer solutions (pH 7 and 10 from Curtis Matheson Scientific).

In the esterolysis reactions, the absorption of *p*-nitrophenolate anion at 400 nm (extinction coefficient of 15 600 L $\mathrm{mol^{-1}\ cm^{-1}}$ at pH 7.8)[18] was followed with a Bausch & Lomb Spectronic 710 instrument. Disposable polystyrene cuvettes (transparent at 400 nm) were used, and each experiment was repeated up to five times in order to ensure reproducibility. The use of quartz cuvettes did not markedly affect the precision of the kinetic measurements.

Kinetic analyses involved filling the cuvette with buffer (3 mL) and injecting the necessary volume (usually 5 μL) of catalyst dissolved in methanol or water. The final catalyst concentration (in moles of DAAP monomer units) was approximately 1×10^{-6} M. The exact catalyst concentrations are reported in the figures. The concentration values in Figure 1 are in grams per liter, selected to give the same approximate concentration of total DAAP units; concentrations used to obtain the data in all other figures were corrected to moles per liter of active, neutral DAAP groups (k_N values). The cuvette was then capped, shaken, and equilibrated in a water bath at 30 °C. The appropriate amount of substrate solution (0.5–10 μL) was then added, and the stopwatch started. The cuvette was recapped and shaken, and (after ensuring that no air bubbles were in the light path) the absorbance was measured. The initial substrate concentration was in the range (1–20) $\times 10^{-5}$ M. Absorbance measurements were repeated every 10 min.

The pseudo-first-order rate constants (k_{obs}) were obtained as the slope of the plot of ln ($[AB]_0/[AB]_t$) against time, where $[AB]_0$ and $[AB]_t$ are the substrate concentrations at the onset of the reaction and at time t. The instantaneous concentration ($[AB]_t$) of *p*-nitrophenyl caproate (PNPC) was obtained by subtracting the *p*-nitrophenolate (PNP) anion concentration (calculated by means of Beer's law) from $[AB]_0$. In all cases, straight lines were obtained with satisfactory correlation coefficients.

Differences between parallel experiment runs under identical conditions were on the order of 20% in the worst cases. We could not reduce the scatter even using the indirect injection method suggested by Menger and Venkataram,[19] although reproducibility of the amounts delivered by the microsyringe was checked with a precision balance. Adsorption onto the cuvette walls was also ruled out, since results were not significantly improved by replacing disposable cuvettes with quartz ones. A substrate concentration higher than the cmc (critical micellar concentration) might also give misleading results. According to Guthrie,[20] however, the possibility of micelle formation by this substrate can be disregarded at the concentrations used in this study.

The esterification reaction was followed by gas chromatography on a Hewlett-Packard 5880A instrument with flame ionization detector and a J & W Scientific fused-silica megabore column containing 5% poly(phenylmethylsiloxane). The temperature program consisted of a 3-min period at 60 °C, heating at 20 °C/min to 100 °C, followed by 4 min at 100 °C. Decane (GC standard) and linalool peak area ratios at different reaction times were compared with the initial ratio for determining percentage conversion. Duplicate runs generally showed a measurement error of less than 2%.

The esterification reactor consisted of a 100-mL three-neck flask fitted with a reflux condenser and magnetic stirrer. It was placed in an oil bath at 80 °C and charged with toluene (20 mL), triethylamine (0.03 mol), and decane (0.5 g). The appropriate amount of catalyst (varying from 10^{-2} to 10^{-5} mol of catalytic units) was dissolved in acetic anhydride and the resulting solution added to the reactor. The mixture was magnetically stirred for 30 min under an N_2 atmosphere, and linalool (0.02 mol) was added. After homogeneous mixing was ensured, a 0.1-mL aliquot was removed and dissolved in 0.9 mL of $CHCl_3$. This solution was analyzed by GC. Additional aliquots were taken over a 3-h period and analyzed in the same way.

Results and Discussion

Esterolysis of *p*-Nitrophenyl Caproate (PNPC). Preliminary evaluation of the copolymer catalysts showed that reaction rates depended on substrate concentration as given by eq 1, where AB is the substrate PNPC, and k_{obs} is the pseudo-first-order or observed rate constant.

$$\frac{d[AB]}{dt} = -k_{obs}[AB] \qquad (1)$$

In order to avoid nonlinear behavior at higher conversion, only initial rates were measured. The observed rate constant, k_{obs}, is given by eq 2, where k_N is the normalized

$$k_{obs} = k_N[C_N] + k_0 \qquad (2)$$

second-order rate constant, $[C_N]$ is the molar concentration of the free (unprotonated) DAAP monomer units in the copolymer, and k_0 is the reaction rate constant measured in the absence of added catalyst.[13]

The uncatalyzed rate constant, k_0, was determined for each pH and subtracted from the corresponding k_{obs}. $[C_N]$ was determined from the amount of injected polymer, the DAAP mole fraction in the polymer, and the ratio

$[C_N]/[CH^+]$ computed from the Henderson–Hasselbalch equation[21] (eq 3) where $[CH^+]$ is the concentration of protonated DAAP units.

$$\mathrm{pH} = \mathrm{p}K_a + n^* \log \frac{[C_N]}{[CH^+]} \qquad (3)$$

The catalytic activity of poly(DAAP) was determined under the same conditions as those for selected copolymers of DAAP with dimethylacrylamide (DMAM), dimethyldiallylammonium chloride (DMDAACl), and acrylic acid (AA). Figure 1 shows that, in general, the homopolymer had a higher activity than the copolymers when the values of k_{obs}/[polymer] are compared (based on grams per milliliter of polymeric catalyst). However, calculation of the normalized (second-order) rate constant yielded quite different results (Figure 2) since now the moles per liter of active (neutral) DAAP units are used. The copolymer with acrylic acid displayed a specific activity that is similar or superior to that of the homopolymer and the copolymers with neutral or cationic monomers. The high k_N of this copolymer catalyst is the result of the low concentration of free DAAP monomer units. That is, at the pH values of the study, most of the DAAP units were protonated and not available as catalytic centers.[8] Despite the anionic microenvironment and the low number of available nucleophilic sites, their individual activity was high.

Rate constants for the other copolymers were found to be comparable at lower pH values. At pH 8, however, the DMAM copolymer showed slightly greater activity than the homopolymer while the DMDAACl copolymer showed the highest activity of any of the polymeric catalysts. This suggested that the ionic copolymer units were increasing the rate of esterolysis through an additional effect. To evaluate the relationship between catalytic activity and the type and distribution of the comonomers, it was necessary to know if there was rate enhancement due to the microenvironment established by the comonomer groups.

Esterolysis rates for the homopolymers of DMAM, DMDAACl, and AA were determined under the same conditions as the experiments summarized in Figures 1 and 2. The k_{obs} values (in grams per milliliter) for these three homopolymers measured at the same approximate concentrations as the copolymers at pH values of 7.0, 7.5, and 8.0 were 2.90, 4.22, and 5.31; 6.24, 11.65, and 8.81; and 1.28, 4.17, and 5.29, respectively. All three homopolymers accelerated the esterolysis, with poly(DMDAACl) giving the fastest rates at each pH value. In fact, this polymer displayed rates comparable to poly(DAAP) at pH 7.0 and 7.5, although at pH 8.0 it was not as effective as the DAAP homopolymer. This indicates that catalysis involves a mechanism in addition to nucleophilic attack by the DAAP units. Poly(DMDAACl) is a cationic polymer and is expected to attract higher concentrations of OH^- and Cl^- near the polymer chain than in bulk solution. The difference in $[OH^-]$ reaches a maximum at pH 7.5, and this gave a higher overall esterolysis rate with OH^- as the catalyst.[23,24]

In such a cationic microenvironment, DAAP monomer units are less effective catalytic centers because the DAAP-catalyzed reaction involves formation of a pyridinium cation as an intermediate.[8,10] Coulombic repulsion from adjacent cationic comonomer units strongly hinders its formation. Moreover, as poly(DAAP) is less water soluble than the very hydrophilic poly(DMDAACl), the presence of DAAP units may actually lower catalyst solubility or lead to a more tightly coiled solution conformation for the copolymer, thus reducing its catalytic activity by reducing the availability of water and OH^-.

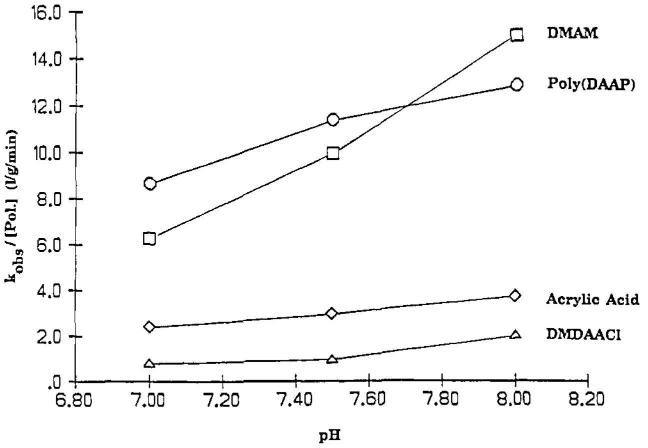

Figure 1. Dependence of the pseudo-first-order rate constant of hydrolysis of p-nitrophenyl caproate on the pH for poly(DAAP) and DAAP copolymers (labeled as the corresponding comonomers): poly(DAAP), sample A_0, [polym] = 1.65 × 10^{-4} g/L; poly(DAAP-co-DMAM), sample A_9, x_{DAAP} = 0.80, [polym] = 2.39 × 10^{-4} g/L; poly(DAAP-co-DMDAACl), sample B_3, x_{DAAP} = 0.10, [polym] = 2.02 × 10^{-3} g/L; poly(DAAP-co-AA), sample C_2, x_{DAAP} = 0.17, [polym] = 4.78 × 10^{-4} g/L.

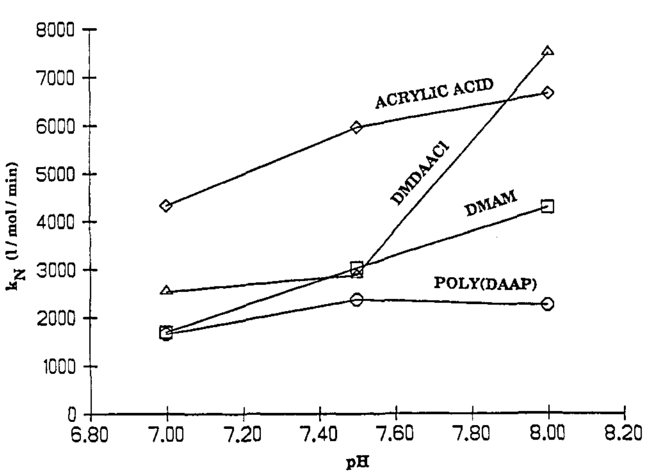

Figure 2. Dependence of the normalized rate constant of hydrolysis of p-nitrophenyl caproate on pH for poly(DAAP) and some DAAP copolymers; polymer compositions and concentrations as in Figure 1.

Comparison of the results for poly(AA) and the copolymer of DAAP with AA shows that the homopolymer is more reactive (as far as k_{obs} is concerned) at pH 7.5 and 8.0. We can only speculate that these results are due to the very low solubility of the copolymer compared with poly(AA). In fact, a special procedure was needed to obtain a homogeneous solution of the AA copolymers.[8] This raises questions about polymer coiling and the possibility of a fundamental change in mechanism of catalysis for AA copolymers. Work therefore concentrated on the other two copolymer systems.

Effect of Copolymer Composition on Esterolytic Activity. The results of the previous section indicate that copolymers of DAAP generally have a higher activity per nonprotonated DAAP unit than poly(DAAP). For a more detailed evaluation of the catalytic activity of DAAP units, it was desirable to determine which copolymer compositions maximize catalytic efficiency. While Figure 2 indicates that copolymers with acrylic acid should be the most promising for such a study, copolymers with DMAM and DMDAACl were studied further. The former were chosen as the most favorable from a solubility point of view.

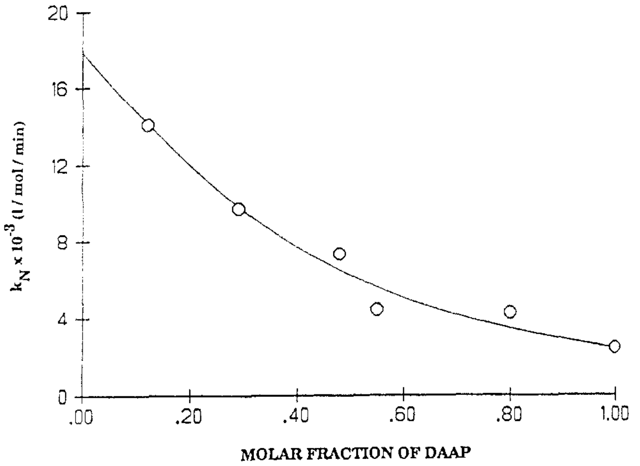

Figure 3. Esterolytic activity of poly(DAAP-*co*-DMAM) at pH 8 as a function of copolymer composition: polymer A_2, x_{DAAP} = 0.12, pK_a = 8.72, [polym] = 9.72 × 10^{-4} g/L; polymer A_3, x_{DAAP} = 0.29, pK_a = 8.55, [polym] = 3.96 × 10^{-4} g/L; polymer A_7, x_{DAAP} = 0.48, pK_a = 8.21, [polym] = 3.03 × 10^{-4} g/L; polymer A_8, x_{DAAP} = 0.55, pK_a = 8.01, [polym] = 2.93 × 10^{-4} g/L; polymer A_9, x_{DAAP} = 0.80, pK_a = 7.97, [polym] = 2.39 × 10^{-4} g/L.

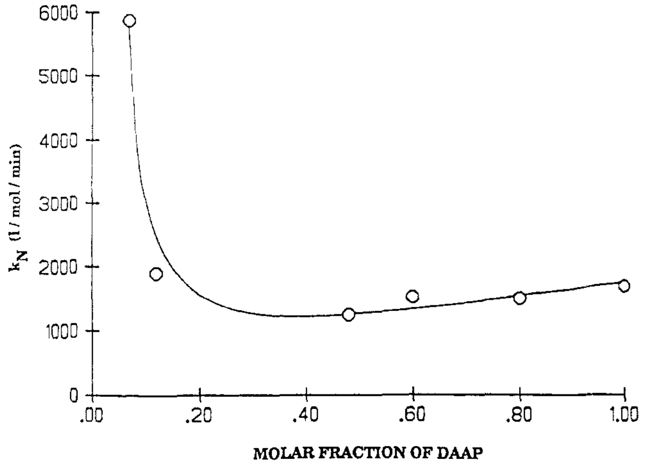

Figure 4. Esterolytic activity of poly(DAAP-*co*-DMDAACl) at pH 7 as a function of copolymer composition: polymer B_1, x_{DAAP} = 0.07, pK_a = 8.15, [polym] = 1.99 × 10^{-3} g/L; polymer B_2, x_{DAAP} = 0.12, pK_a = 8.13, [polym] = 1.49 × 10^{-3} g/L; polymer B_6, x_{DAAP} = 0.48, pK_a = 8.13, [polym] = 3.49 × 10^{-4} g/L; polymer B_7, x_{DAAP} = 0.60, pK_a = 8.14, [polym] = 2.79 × 10^{-4} g/L; polymer B_9, x_{DAAP} = 0.80, pK_a = 7.96, [polym] = 2.36 × 10^{-4} g/L.

Comparison of their behavior with that of copolymers of DMDAACl allows conclusions about the ionic comonomer type and distribution on the catalytic activity.

Poly(DAAP-*co*-DMAM). Copolymers of DAAP and DMAM of different composition were compared at pH 8 and 30 °C. The total concentration of DAAP monomer units (free plus protonated) was approximately the same in all experiments. Figure 3 summarizes the results. For comparison, k_{obs} for poly(DMAM) under these conditions was less than the values for all of the copolymers of Figure 3. There appears to be a measurable increase in catalytic activity per DAAP monomer unit with *decreasing* DAAP mole fraction in the copolymer. Similar behavior was observed by Klotz and co-workers[22] in polymeric catalysts based on derivatized poly(ethylene imine). In addition, polysiloxanes containing pendent pyridine 1-oxide groups as catalytic sites were also found to be more active than the derivative of the homopolymer of DAAP, poly[4-(diallylamino)pyridine 1-oxide] in the hydrolysis of diphenyl chlorophosphate.[25] Several possible reasons have been given[22] for this behavior:

(a) Too high a concentration of catalytic sites may reduce the availability of binding sites involving either the polymeric backbone or pendent groups.

(b) Association of catalytic sites may contribute to coil shrinkage, making it sterically difficult for the catalytic units to react. Poly(DAAP) is much less soluble in water than poly(DMAM),[8] and their copolymers display a solubility intermediate between the homopolymers. This certainly is related to overall hydrophobicity, the "tightness" of the polymer coil, and active-site availability.

(c) Cooperation between binding and catalytic sites may only be possible for a few catalytic sites along the chain. Backbone configuration and conformation may preclude many potentially interactive sites from functioning synergistically.

Poly(DAAP-*co*-DMDAACl). In these positively charged polymers, the dependence of catalytic activity on composition was studied at pH 7 because the greatest relative enhancement of activity with respect to poly(DAAP) was observed for some compositions at this value. Figure 4 summarizes the results. For comparison, k_{obs} for poly(DAAP) was 1.43 × 10^{-3} min^{-1} and k_N was 1.67 × 10^3 L mol^{-1} min^{-1} while k_{obs} for poly(DMDAACl) was 1.21 × 10^{-3} min^{-1} under the same conditions.

The dependence of catalyst activity on composition for these copolymers was different from that observed for the copolymers with DMAM. It seems reasonable that cationic comonomer units (DMDAACl) should destabilize the positively charged adducts resulting from nucleophilic attack by the DAAP units. This would explain the slight increase in catalytic activity with DAAP mole fraction up to a k_N value of 1.67 × 10^3 L mol^{-1} min^{-1} for poly(DAAP). This effect should lead to minimum activity when all DAAP monomer units have DMDAACl units on both sides. No further destabilization (at least on a molecular level) should then be possible, and additional DMDAACl units are too far away to interact electrostatically with the forming DAAP adduct.

Calculation of the approximate copolymer composition resulting in all DAAP units having DMDAACl monomer units on both sides is possible because this system was found to follow the first-order Markov copolymerization behavior.[8] The number-average sequence length of units of monomer 1 (n_1) was calculated from eq 4[26] where

$$n_1 = \frac{r_1[M_1] + [M_2]}{[M_2]} \quad (4)$$

$[M_1]$ and $[M_2]$ are concentrations of the monomers in the feed. Figure 5 gives the dependence of n_1 on feed composition for the system DAAP–DMDAACl (with r_1 = 0.27).[8] It was then possible to calculate the monomer fraction of DAAP units for which a copolymer is obtained with most of the DAAP monomer units adjacent to DMDAACl units. Using these values and the copolymerization diagram for this system,[8] it was found that, even at a DAAP mole fraction of 0.3, most DAAP units were located between DMDAACl groups. In the absence of additional effects, no further change in specific activity of the catalytic centers is expected with a further decrease in DAAP group concentration. A different mechanism must then be operational, one probably similar to that involved in the increase of catalytic activity with DMAM mole fractions in DAAP–DMAM copolymers. It must also be kept in mind that poly(DMDAACl) catalyzes the esterolysis itself, although pure poly(DMDAACl) has a pseudo-first-order rate constant, k_{obs}, of 1.21 × 10^{-3} min^{-1}. This value is lower than that of all DMDAACl copolymers except B_6 (see

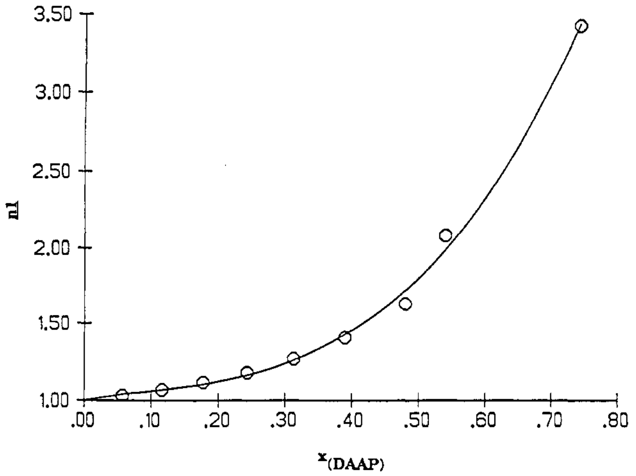

Figure 5. Number-average sequence length of DAAP units (n_1) in the copolymerization with DMDAACl, x_{DAAP} = molar fraction of DAAP monomer units.[8]

Figure 4), which displays a comparable value. It is suggested that both increased [OH$^-$] and availability of nucleophilic centers (so spaced that they do not interfere with each other) provide optimum conditions for catalysis with these copolymers.

Mechanism of the Catalyzed Esterolysis. The importance of binding site availability on the catalytic activity was further studied. Previous investigations with the homopolymer of DAAP as catalyst[10] suggested that the estrolysis of *p*-nitrophenyl esters involved a mechanism similar to that of enzyme-catalyzed reactions (Michaelis–Menten-like mechanism) where a complex between substrate and catalyst is formed prior to nucleophilic attack on the substrate.[27] In the case of poly(DAAP), the increased reactivity observed for esters of longer straight-chain aliphatic carboxylic acids suggested that strong association occurred through hydrophobic interaction between the nonpolar substrate and the polymer backbone. This effect was reported also for imidazole-containing polymeric catalysts.[6,28] In the Michaelis–Menten mechanism, a catalyst–substrate complex is initially formed, which reacts and then dissociates to products and regenerated catalyst. With enzymes, complex formation may involve very specific bond formation and electrostatic interaction along with other effects such as hydrophobic binding. The rate expression for this type of reaction is given by eq 5.[29]

$$V_0 = \frac{V_\infty}{\left|1 + \frac{K_{\mathrm{M}}}{[\mathrm{AB}]_0}\right|} \tag{5}$$

V_0 is the initial reaction rate, V_∞ is the reaction rate at infinite substrate concentration (when $[\mathrm{AB}]_0 \gg K_{\mathrm{M}}$), and K_{M} is the Michaelis–Menten constant. V_∞ and K_{M} are obtained by measuring V_0 for different substrate concentrations and plotting V_0^{-1} against $[\mathrm{AB}]_0^{-1}$ (Lineweaver–Burk plot). A linear plot strongly supports the presence of a Michaelis–Menten-like mechanism. Due to the fact that the experimental points are generally not evenly distributed, calculation of the most probable straight line by the least-squares procedure assigns too much weight to points far removed from the others. These points correspond to the lowest substrate concentration and are the least reliable. It has also been shown that the error envelope (the region of the plot inside which the experimental points should lie for a given error probability) is not confined by two lines parallel to the best fit line but is funnel-shaped with increasing uncertainty moving away from the origin. A corresponding increase in slope and intercept errors then exists.[30]

These problems may be overcome when eq 5 is rewritten in the form of eq 6.

$$\frac{[\mathrm{AB}]_0}{V_0} = \frac{[\mathrm{AB}]_0}{V_\infty} + \frac{K_{\mathrm{M}}}{V_\infty} \tag{6}$$

Plotting $[\mathrm{AB}]_0/V_0$ against $[\mathrm{AB}]_0$ gives the so-called half-reciprocal plot. V_∞ is obtained from the reciprocal slope and K_{M} from the product of V_∞ and the intercept of the least-squares straight line. Although the point distribution is not improved with respect to the Lineweaver–Burk procedure, the error envelope is now parallel to the least-squares straight line.[30] This method was chosen for parameter calculations below. When this procedure was applied to the reaction catalyzed by polymer A_7 (poly(DAAP-*co*-DMAM) with $x_{\mathrm{DAAP}} = 0.46$), a change was observed in the kinetic parameters over the range from pH 7 to pH 9. In all cases the catalyst concentration was 1.01×10^{-6} M in DAAP units and the substrate concentration was varied from 1 to 20×10^{-5} M (excess substrate conditions). Figure 6 shows the dependence of the corrected hydrolysis rate constants on substrate concentration. The most probable values of K_{M} and V_∞ were then calculated from the slopes and intercepts of straight lines of plots of $[\mathrm{AB}]_0/V_0$ against $[\mathrm{AB}]_0$ at different pH's (see Figure 7 for one example). Table I summarizes the results obtained at different pH values.

The plot in Figure 6 shows that saturation of the catalyst occurred in the pH range under investigation as shown by flattening of the curve at higher substrate concentrations. In addition, the linearity of the half-reciprocal plots (Figure 7) strongly supports the assumption that the catalyzed esterolysis proceeds by a Michaelis–Menten-like mechanism, with reversible substrate binding preceding the catalyzed cleavage step. While V_∞ is related to overall catalyst activity, K_{M} is proportional to the rate constant for hydrolysis and inversely proportional to the substrate binding ability of the catalyst as given by eq 7[31] where k_1

$$K_{\mathrm{M}} = (k_2 + k_{-1})/k_1 \tag{7}$$

is the rate constant of complex formation, k_{-1} the reverse rate constant, and k_2 the rate constant for product formation, which, in this case, is liberation of the *p*-nitrophenolate anion. Table I shows that the maxima of both V_∞ and K_{M} occur at pH 8, close to the pK_a of the catalytic units (pK_a = 8.20). We do not have enough data to separately evaluate the individual contributions of each of the rate constants for this system, nor can we determine whether the overall changes in K_{M} are due to changes in the actual values of individual constants or simply in the ratios of these constants. We can, however, draw some qualitative conclusions based on simple assumptions.

First, the maximum in V_∞ at the pK_a of the polymeric catalyst must reflect a balance among competing forces including (1) availability of nucleophilic DAAP groups, (2) a relatively high concentration of substrate through good binding via hydrophobic interactions, and (3) local availability of H_2O and OH$^-$ for cleavage of the acyl pyridinium intermediate. Increasing the pH from 7 to 8 liberates neutral DAAP sites, increasing factors (1) and (2) above at the expense of (3). A further increase in pH may enhance binding and nucleophile concentration more but should decrease the ionic nature of the microenvi-

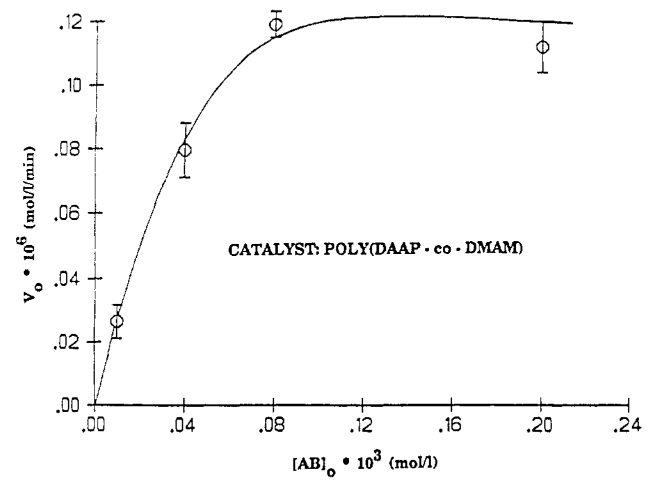

Figure 6. Dependence of the esterolysis rate on PNPC concentration at pH 7; catalyst = poly(DAAP-*co*-DMAM) with DAAP molar fraction = 0.46.

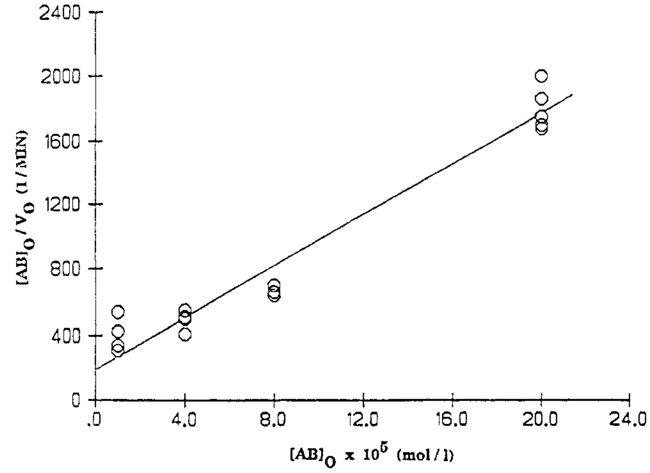

Figure 7. Calculation of the Michaelis–Menten parameters for poly(DAAP-*co*-DMAM) at pH 7.

Table I
Michaelis–Menten Constants for the Esterolysis of PNPC Catalyzed by Poly(DAAP-*co*-DMAM) at 30 °C

	pH 7	pH 8	pH 9
(a) From Half-Reciprocal Plots			
slope	7.61×10^6	1.21×10^6	3.45×10^6
intercept	222	181	59.8
V_∞, mol L^{-1} min^{-1}	1.3×10^{-7}	8.3×10^{-7}	2.9×10^{-7}
K_M, mol/L	2.9×10^{-5}	1.5×10^{-4}	1.7×10^{-5}
correlation coefficient	0.987	0.980	0.981
(b) From Lineweaver–Burk Plots			
slope	321	202	102
intercept	5.5×10^{-6}	6.6×10^{-5}	2.2×10^{-6}
V_∞, mol L^{-1} min^{-1}	1.8×10^{-7}	1.5×10^{-6}	4.58×10^{-7}
K_M, mol/L	5.8×10^{-5}	3.1×10^{-4}	4.6×10^{-5}
correlation coefficient	0.995	0.993	0.925

ronment. This not only will reduce the local concentrations of H_2O and HO^- but will make formation of the highly polar acyl pyridinium salt less favorable. Binding is increased but at the expense of conversion.

These trends should also be reflected in the values of K_M. The increase in K_M on changing the pH from 7 to 8 must reflect an increase in either or both k_2 and k_{-1} or a decrease in k_1. If, as we believe, hydrophobic interactions are the main binding force, increasing the concentration of the neutral DAAP units at the expense of the protonated species should increase the hydrophobicity of the polymer microenvironment and therefore the binding ability of the polymer. An increase in K_M must therefore result from a more than compensating increase in k_2; that is, as the number of DAAP units available for catalysis increases, the activity of individual units must also increase. This seems unlikely and may reflect a change in the rate-determining step and/or the contribution of a competing mechanism of hydrolysis involving OH^-. In fact, the activity of the ionic homopolymer, poly(DMDAACl), confirms the possibility of the latter, and the relative stability of acyl pyridinium salts of 4-(dialkylamino)pyridines supports the former.[1,2]

The possibility of Michaelis–Menten behavior is strongly supported by the experiments carried out with increasing substrate concentration, although more complicated mechanisms cannot be disproved by this data. For example, the mechanism proposed by Bender et al.[32] for chymotrypsin-catalyzed esterolyses and amidolyses involves formation of an acyl–enzyme complex after reaction of the substrate–enzyme complex. In addition, the observation of maximum values of the Michaelis–Menten parameters at pH = pK_a parallels the behavior of biological systems. Jencks[33] observed that enzymes, which react best at a pH close to 7, utilize groups such as imidazole (pK_a close to 7) that display the maximum ratio of nucleophilicity versus basicity of the catalytic group.

Finally, the results obtained with these linear polymers as esterolysis catalysts agree well with those using highly branched, substituted poly(ethylene imine),[22] both at different pH values and with different active group concentrations. We conclude that the most important variables for polymeric catalysts for hydrolysis of neutral substrates such as PNPC are active nucleophile concentration and availability (as determined by pK_a) and the balance of ionic and hydrophobic microenvironment properties generated by the polymer backbone, the catalytic group (again controlled by pK_a), and the concentration and distribution of neutral and/or charged comonomer groups. This study illustrates the complexity of polymeric catalysts and the inherent difficulties in attempting to separate the individual factors affecting overall binding and catalytic activity.

Esterification of Linalool. Catalysis of bond-forming reactions is important from a synthetic point of view. Following the initial work by Merrifield[34] on polymer-assisted peptide synthesis, many research groups have investigated the application of polymeric reagents to small molecule synthesis.[35-37] Cross-linked polystyrene has been preferred as the support, although other systems such as poly(4-vinylpyridine)[38,39] and acrylic polymers[40] have been investigated. Among the factors affecting catalyst activity are the concentration of active centers in the reactor and the microenvironment around individual active sites both of which depend on the composition and concentration of the copolymer under investigation and on its solubility and conformational behavior in the solvent chosen.[41,42] Polymeric catalysts based on polystyrene-bound DMAP (1) have been used previously for esterification reactions of tertiary alcohols like 1-methylcyclohexanol[15] and linalool[43] with acetic anhydride. We wished to evaluate DAAP homo- and copolymers for their synthetic utility in a model reaction. We therefore chose the reaction of linalool with acetic anhydride in toluene to compare the effectiveness of our polymeric catalysts with that of DMAP. While PPY would be more appropriate in our case, DMAP has been used as the small-molecule standard by most other groups evaluating polymer-bound 4-(dialkylamino)pyridine catalysts and its use here allows direct comparison with these earlier studies.

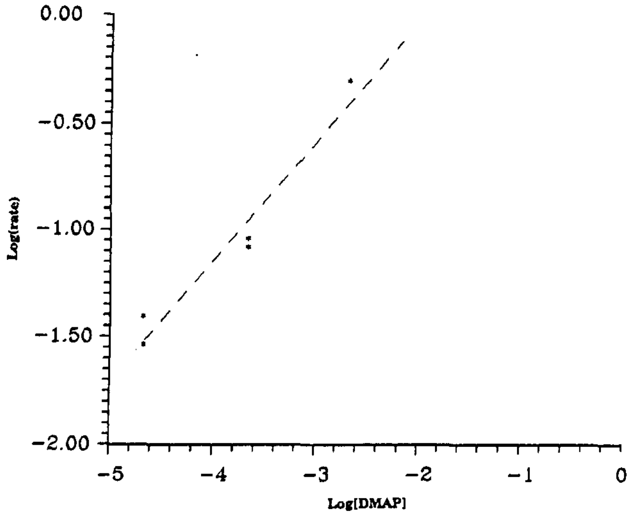

Figure 8. Dependence of the rate of esterification of linalool with acetic anhydride on [DMAP] in toluene at 80 °C.

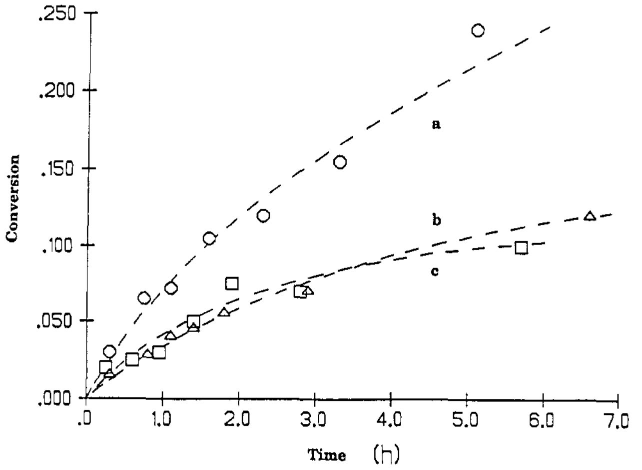

Figure 9. Kinetic curves for the esterification of linalool catalyzed by the homopolymer and copolymers of DAAP: (a) poly(DAAP-*co*-DMAM), $x_{\mathrm{DAAP}} = 0.24$; (b) poly(DAAP); (c) poly(DAAP-*co*-DMDAACl), $x_{\mathrm{DAAP}} = 0.07$.

Table II
Copolymers of DAAP with DMAM (A_{10}–A_{14}) and with DMDAACl (B_{10}–B_{14}) Used for Esterification Studies[a]

polymer	X_{DAAP}	x_{DAAP}	g_{DAAP}
A_{10}	0.10	0.03	0.05
A_{11}	0.20	0.06	0.10
A_{12}	0.30	0.10	0.16
A_{13}	0.40	0.14	0.22
A_{14}	0.50	0.18	0.28
B_{10}	0.10	0.06	0.06
B_{11}	0.16	0.09	0.09
B_{12}	0.30	0.18	0.19
B_{13}	0.40	0.24	0.26
B_{14}	0.50	0.31	0.33

[a] X_{DAAP} = molar fraction of DAAP in the feed. x_{DAAP} = molar fraction of DAAP in the copolymer. g_{DAAP} = weight fraction of DAAP in the copolymer.

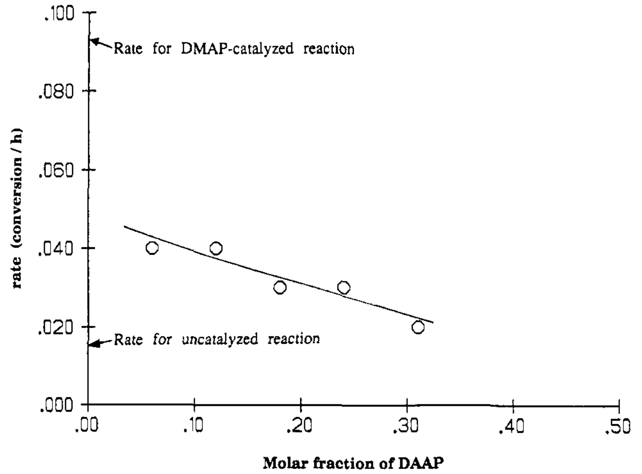

Figure 10. Dependence of the catalytic activity of copolymers of DAAP and DMAM on DAAP content in the esterification of linalool at 80 °C.

DMAP-Catalyzed Reaction. The initial rates of esterification at different concentrations of DMAP were determined and are summarized in Figure 8. The linear dependence between the logarithm of the esterification rate and DMAP concentration was used to calculate the esterification rates with DMAP as catalyst at active site concentrations available for the polymeric catalysts.

DAAP Copolymers as Catalysts. Preliminary experiments with the homopolymer and selected DAAP copolymers helped determine the range of rates to be expected in these systems. Figure 9 shows the conversion vs time plots from which the rates were calculated by using the initial slopes of the kinetic curves. All polymeric catalysts were less effective than DMAP in this reaction although the opposite was seen for esterolysis of *p*-nitrophenyl esters. Copolymers of DAAP with DMAM (dimethylacrylamide) showed a higher absolute and per unit efficiency than poly(DAAP), while copolymers with DMDAACl were more effective than poly(DAAP) only on a per DAAP unit basis. The activity of a given DAAP unit seems to be reduced by the reaction of neighboring units with substrate. That is, the acyl pyridinium intermediate formed in this reaction experiences electrostatic repulsion by nearby groups, which inhibit its buildup. Polymer-bound DMAP has also been found to display higher catalytic activity (per catalytic site) with decreasing concentration of units in this same reaction.[16] To further evaluate this effect, we synthesized a series of copolymers of DAAP with DMAM and with DMDAACl with low DAAP content as summarized in Table II.

Solutions of DAAP–DMAM copolymers in acetic anhydride were prepared to obtain a final concentration of approximately 2 × 10^{-4} mol of DAAP units in the reactor. DMAP-catalyzed esterifications were carried out simultaneously by using DMAP at the same molar concentration as DAAP units in the copolymer systems. The rates obtained were normalized to a catalyst concentration of exactly 2 × 10^{-4} mol of DAAP units. At this catalyst concentration (catalyst/linalool ratio = 10^{-2}), the activity of the catalyst at a DAAP mole fraction of approximately 0.4 was comparable to that displayed by the low molecular weight catalyst DMAP at the same molar concentration of catalytically active groups. Thus, no marked improvement in catalysis was observed on using the polymeric catalysts.

The same study was performed with DAAP–DMDAACl copolymers, and their reactivity proved to be much lower than that of DAAP–DMAM copolymers. Figure 10 shows that there is only a very slight dependence of catalytic efficiency on copolymer composition. We found also that catalyst activity was not very dependent on concentration even when the active unit concentration was reduced to 2 × 10^{-5} mol. Overall, none of the polymeric catalysts based on DAAP displayed activities higher than that of the low molecular weight species DMAP, although many proved to be as effective as polystyrene-bound DMAP.[15,43] We believe that the main reason for this is the low solubility of these copolymers in the reaction mixture and the inherently tight coiling that these polymers adopt in a poor solvent. Further study of these systems must await future effort.

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