Polymeric Supernucleophilic Pyridine Catalysts: Homogeneous Esterolysis of *p*-Nitrophenyl Esters

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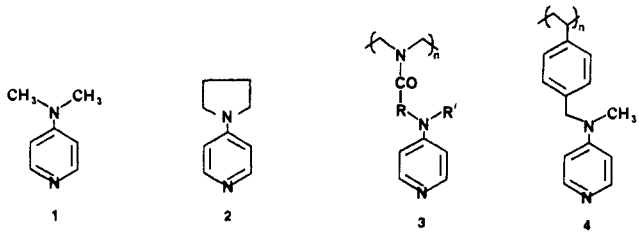
Abstract: The homopolymer of DAAP is a more effective catalyst for the esterolysis of *p*-nitrophenyl esters of straight-chain carboxylic acids than 4-(pyrrolidino)pyridine (PPY) under homogeneous aqueous conditions. Hydrophobic interactions between the polymer and the esters are shown to contribute to the polymer's effectiveness. Neighboring-group effects lowered the pK_a of the polymer to 7.8 compared to 10.5 for PPY. The lowered pK_a generally resulted in a greater number of available active catalyst units per total units employed for the polymer compared to PPY. Normalizing the catalytic effect of active units present in each case showed that supernucleophilic units in the polymer were inherently more active than unbound PPY. Both the uncatalyzed hydrolysis and the PPY-catalyzed reaction were shown to be pseudo-first-order in ester concentration. The polymer-catalyzed reaction was shown to follow Michaelis–Menten kinetics with formation of the acylpyridinium intermediate as the rate-determining step.

4-(Dialkylamino)pyridines have been employed as supernucleophilic catalysts in a large number of reactions. In many systems, these catalysts provide a level of reactivity combined with selectivity that is unique. Several reviews of the synthesis and applications of these catalysts have appeared.[1-3] Facile commercial synthesis has made 4-(dimethylamino)pyridine (**1**, DMAP) the most popular member of this class of supernucleophiles, although the pyrrolidine analogue (**2**, PPY) is the most active.[1]

Several types of polymer-bound (dialkylamino)pyridines have been reported. The first[4,5] dealt with reaction of several carboxylic acid containing (dialkylamino)pyridines with commercial poly(ethylenimine) (PEI) to give reagents of general structure **3**.



1 **2** **3** **4**

These compounds were examined for catalytic behavior in the hydrolysis of *p*-nitrophenyl esters and found to be highly active.

Other reports dealt with incorporation of the (dialkylamino)pyridine moiety into typical functionalized, cross-linked polystyrene (**4**) either by reaction on preformed polymer[6-9] or by synthesis of a monomer and subsequent copolymerization.[10,11] Application of these catalysts to esterification reactions under Michaelis–Menten conditions yielded results comparable to those obtained with the corresponding small molecule analogues.

More recently, polymers with structures similar to those obtained with our procedure have been obtained by reduction of 4-(*N*-maleimido)pyridine residues.[12] These polymers apparently react rapidly with benzyl halides, but have not been examined as catalysts. Moreover, insolubility greatly restricts characterization of the polymers and precludes their use as catalysts in homogeneous systems.

The polymeric catalysts synthesized in these reports have several limitations arising from the nature of the substrate polymer. First, many of these polymers have residual amine functionality that can provide general base catalysis, undergo competetive derivatization in most synthetically useful reactions, or generate a cationic environment that modifies the activity of the supernucleophile. All of these effects complicate kinetic studies and synthetic applications of these polymeric catalysts.

Catalysts based on polystyrene supports are inherently hydrophobic and suffer from several drawbacks.[13] They are generally synthesized by reactions on preformed polymer. Such reactions are cumbersome and rarely go to completion. Only catalysts made from preformed monomers result in formation of uniform and readily characterized polymers. Finally, while PPY has the highest activity of known (dialkylamino)pyridines, almost all of the previous polymeric catalysts have used analogues of DMAP, (benzylmethylamino)pyridine, or other pyridine derivatives which are 2 to 10 times less active than PPY.

We became interested in the synthesis of a new monomer that could lead to supernucleophilic polymers for several reasons. We wished to first of all overcome the limitations of hydrophobicity, incomplete derivation, side reactions, and use of less active 4-aminopyridine derivatives. Most importantly, we wanted to make a soluble homopolymer by applying a previously described concept of generating the desired repeat unit structure *during* the polymerization process. We have used this concept in the synthesis of polymers containing crown ether units through a macrocyclopolymerization procedure.[14,15] The cyclopolymerization reaction employed in the present report is based on the pioneering work of Professor George B. Butler and his colleagues on polymerization of quaternary diallylamines.[16,17] Synthesis and

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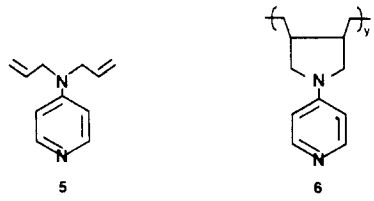
polymerization of the 4-diallylamino compound (**5**) have led to



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formation of the homopolymer (**6**) and a variety of copolymers that possess a range of solubilities and functional groups.[18]

The activities of all the supernucleophilic catalysts synthesized to date have been measured by ad hoc rate comparisons with model reactions. While proving activity of the polymeric catalyst, such studies shed little light on the mechanistic details of the processes by which the polymeric catalysts work. Without such a fundamental understanding, the design of superior catalysts becomes a matter of trial and error rather than rational synthesis. The necessary kinetic investigations of polymeric catalysts (including supernucleophilic polymers) are generally lacking because of complicated variables related to the very nature of the polymer. These include sample inhomogeneity, insolubility, nonproductive polymer–substrate interactions, diffusion-controlled processes, polyelectrolyte effects, cooperativity or inhibition of neighboring groups, tacticity and conformational effects, molecular mobility, and additional unexplained and unexpected behavior.

The homopolymer of 4-(*N*,*N*-diallylamino)pyridine (DAAP) is soluble and linear and consists of 4-(pyrrolidino)pyridine (PPY) units separated by flexible methylene groups along the backbone.[18] This provides a unique opportunity for detailed kinetic investigations without many of the complicating factors which interfere with the reactivity of individual catalytic groups along the polymer. In this paper we describe our initial results on homogenous catalysis using this polymer.

Results and Discussion

Choice of Reaction and Substrates. There are several factors governing the choice of reaction for studying the activity of a catalyst. A suitable reaction must proceed via known pathways to a set of unique products. No side reactions or reactive byproducts should form. A facile way of measuring the extent of reaction must exist. The substrates should be readily available and well characterized. Finally, data on the reaction catalyzed by other catalysts should exist in order to provide benchmarks for comparison. The hydrolysis of activated *p*-nitrophenyl esters was chosen because it meets these criteria.

The catalyzed reaction is shown in Scheme I. An aqueous tris(ammonium) buffer is used as the reaction medium. The reaction proceeds cleanly to yield only the phenoxide and carboxylate anions via attack on the acylpyridinium phenoxide. The nitrophenoxide anion is a very weak base and does not interfere in the reaction. This anion has a high extinction coefficient at 400 nm which allows monitoring of the reaction rates in dilute solutions.

p-Nitrophenyl esters of a series of straight-chain carboxylic acids with chain lengths varying from 1 to 18 carbons are commercially available.[19] Catalysis of this esterolysis reaction by polymer-bound imidazole has been studied.[20] This reaction was also used to evaluate the activity of supernucleophiles bound to poly(ethylenimine), although detailed kinetic investigations of this system have not been reported.[4,5] Mechanistic studies on the uncatalyzed reaction and the reaction aided by small-molecule nucleophilic catalysts have been published.[21,22] Finally, this reaction proceeds

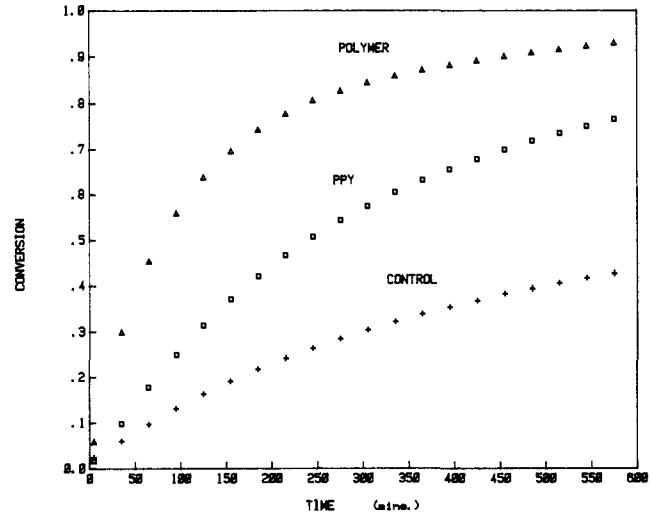
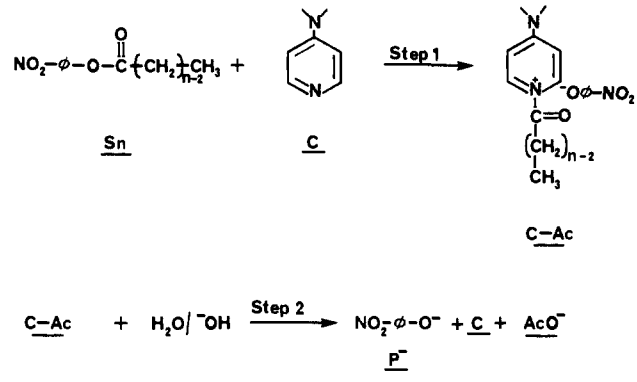


Figure 1. Hydrolysis of S6 at pH 7.8: (△) polymer catalyzed; (□) PPY catalyzed; (+) uncatalyzed reaction.

Scheme I



at a reasonable rate and can be studied by using normal spectroscopic techniques.

Data Acquisition. A Perkin-Elmer Model 320 ultraviolet–visible spectrometer was used for all kinetic studies. This spectrometer has been interfaced to the computer of a Nicolet 5-DX FTIR spectrometer for data collection and analysis. Two programs were written in FORTH to enable computer-controlled scanning and digital storage of the spectra and subsequent determination of the wavelength and absorbance at the product peak maximum. Full automation of the experiment required that the solution in the cuvette be continuously stirred using a magnetic stir-bar driven by a specially built air-driven stir motor recessed into the cuvette holder.[23]

Initial Comparisons between the Polymer and PPY. Initial experiments were performed using *p*-nitrophenyl caproate (the PNP ester of *n*-hexanoic acid, abbreviated "S6" to denote a six-carbon acid). The pK_a of the polymer was expected to be around 1 to 1.5 pK_a units lower than PPY, which has a pK_a of approximately 10. In order to ensure solubility of the polymer, a tris(ammonium) buffer at pH 7.8 was used as the basic aqueous medium. The substrate S6 was injected as a solution in acetonitrile and the supernucleophile injected as a solution in methanol. The final reaction mixture contained 3 mL of the buffer and approximately 5 μL each of acetonitrile and methanol. The concentration of the substrate was 5×10^{-5} M and that of the catalyst was 2.5×10^{-6} M, to give an initial ratio of 20:1. The absorbance at 400 nm was monitored as a function of time. A Beer's law plot of *p*-nitrophenol in the buffer gave a molar extinction coefficient of 15 600. This value was used to convert absorbance at 400 nm to the concentration of the phenoxide anion. Each

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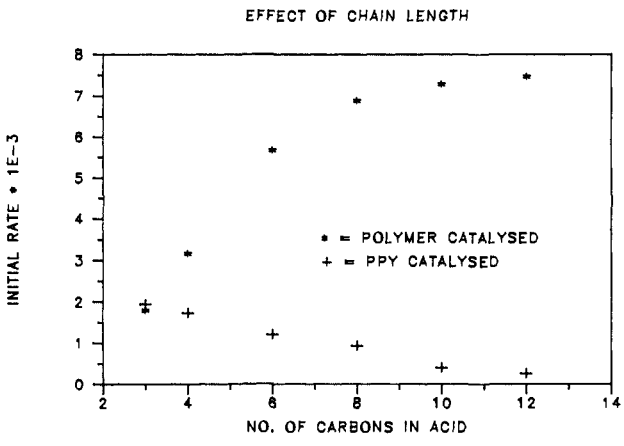

Figure 2. Effects of substrate hydrophobicity on the hydrolysis reaction.

reaction was repeated at least 3 times to ensure that the rate data represented real trends.

Figure 1 shows the initial results obtained for the reactions catalyzed by the polymer and PPY compared to the uncatalyzed reaction. The polymer-catalyzed reaction is significantly faster than that catalyzed by PPY, and both catalysts speed the reaction beyond its uncatalyzed rate. These data represent the first experimental evidence for a supernucleophilic polymer *more* active than its monomolecular model in the excess substrate regime.

There are several possible explanations for the enhanced activity of the polymer. First, due to neighboring-group effects, the polymer has a lower pK_a than PPY. At a given concentration of the supernucleophile, this lower pK_a implies that fewer catalytic sites are deactivated by protonation in the polymer than in PPY. The higher activity of the polymer could be a result of a greater concentration of active supernucleophilic centers. The second explanation arises from work on polymer-bound imidazoles. In this system it has been shown that increasing apolar character of the polymer backbone resulted in higher activity toward the hydrolysis of activated ester containing long carbon chains.[24] These two explanations would only be valid if the first step of the hydrolysis reaction (the generation of the acylpyridinium intermediate) is rate controlling. Both were examined in more detail.

Hydrophobic Effects. In 1967 Professor Overberger and coworkers discovered that under catalysis by poly(4(5)-vinylimidazole), the hydrolysis of long-chain activated esters proceeded at anomalously high rates.[24] This effect was attributed to interactions between the hydrophobic backbone of the polymeric imidazole and the hydrocarbon portions of the substrate. Further evidence for this interaction came from experiments in which terpolymers of 4(5)-vinylimidazole, acrylamide, and alkyl vinyl ketones showed increased activity toward hydrolysis of hydrophopic substrates when the alkyl portion of the vinyl ketone increased in size.[25] Similar effects were later demonstrated with imidazoles grafted into poly(vinylamine) with spacers of differing hydrophobicity.[20]

A series of *p*-nitrophenyl esters of straight-chain aliphatic acids ranging from the propionate (S3) to the dodecanoate (S12) were used to study hydrophobic effects in hydrolysis catalyzed by the homopolymer of DAAP. Reactions were carried out in a tris(ammonium) buffer at pH 7.8 using the same substrate and catalyst concentrations, and reaction conditions as before. The reaction was followed in its initial stages by collecting 12 data points within the first 30 min of the reaction. In this region the reaction profile is approximately linear. The slope of this line was taken as the initial rate of reaction in the units of absorbance per minute. Figure 2 shows a plot of the rates obtained for the polymer- and PPY-catalyzed reactions as a function of the chain length of the acid portion of the substrate.

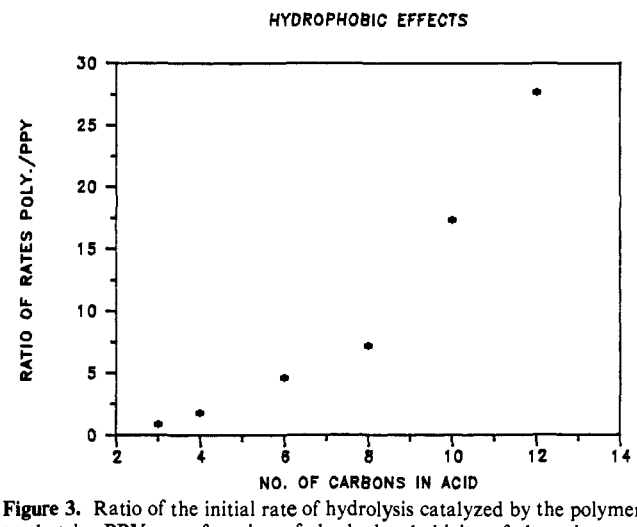

Figure 3. Ratio of the initial rate of hydrolysis catalyzed by the polymer to that by PPY as a function of the hydrophobicity of the substrate.

The reaction rates for the PPY-catalyzed reaction show a steady decrease in going from S3 to S12. This can be attributed to the fact that, while S3 is soluble in the aqueous medium, longer substrates exhibit decreasing solubility and increasing self-association or aggregation.[26] These effects are supported by the fact that S18 is insoluble even in acetonitrile at moderate concentrations. Limiting solubility of long substrates has forced previous researchers to use ethanol–water mixtures as reaction media and to limit chain length to about 7 to 10 carbons.[25]

The rates for the polymer-catalyzed reactions increase with increasing substrate size, although the effect seems to approach an asymptotic value at long-chain lengths. These observations suggest that the backbone of the homopolymer of DAAP is hydrophobic and that the substrate prefers to be in this hydrophobic environment at long chain lengths. The migration of hydrophobic substrates to hydrophobic domains in aqueous media has been proven recently.[27]

Figure 3 shows the ratio of the initial rate of the polymer-catalyzed reaction to that catalyzed by PPY for the various substrates. Increasing chain lengths enhance the relative activity of the polymer. Hydrophobic interaction between the substrate and the homopolymer of DAAP must therefore be an operative factor contributing to the enhanced activity of the polymer as compared to PPY.

Effect of pH of the Reaction Medium. Polyamines as a rule have lower pK_a's than their monomeric analogues. This effect stems from the fact that partial protonation of the polyamine generates a cationic environment in which further protonation is energetically less favorable. Previously synthesized poly(ethylenimine)-bound supernucleophiles were found to have pK_a's that were one to two units lower than those for their corresponding monomeric analogues.[4,5] The pK_a of the homopolymer was determined spectrophotometrically, using the fact that protonation of a free or bound PPY residue results in a bathochromic shift of approximately 20 nm in the ultraviolet spectrum. The pK_a of the polymer was determined to be 7.82 and that of PPY was calculated to be 10.5. The latter value is in agreement with reported values.[1,4]

As discussed earlier, the lower pK_a of the polymer as compared to PPY implies that at any given concentration of supernucleophile in solution, a smaller fraction is deactivated by protonation for the polymer than for PPY. This can be demonstrated easily by using the spectrophotometric data to compute the ratio of unprotonated supernucleophile in the polymer to that in PPY at any given pH. Figure 4 shows a plot of this ratio as a function of pH. The plot shows a maximum at a pH of 7.5 with a sharp decline at lower pHs and a slower decline at higher pHs. It should be pointed out that Figure 4 is based on experimentally determined

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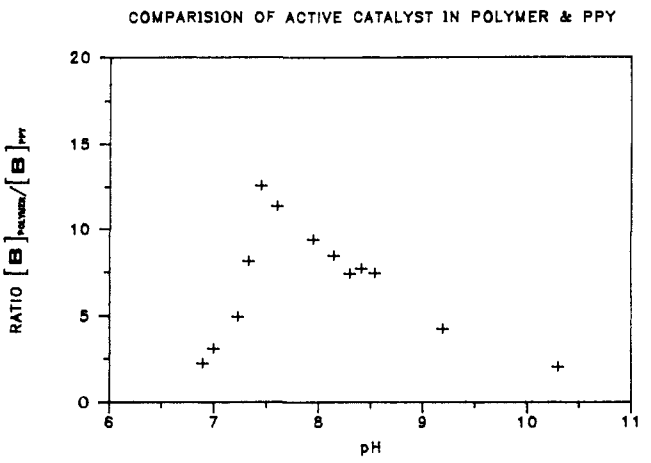


Figure 4. Comparison between active catalyst in the polymer and PPY.

Table I. Ratio of Initial Reaction Rates and Active Catalyst Concentrations for Polymer and PPY as a Function of pH

pH of buffer	ratio of corrected reaction rates polym/PPY	ratio of active catalyst concn. polym/PPY
7.2	8.08	4.99
7.8	21.2	12.6
8.3	12.9	7.42
9.2	11.5	4.70

concentrations of neutral and protonated PPY units. These numbers compensate for any nonideality that may exist in these systems. Use of calculated concentrations from the Henderson–Hasselbach equation, for example, might lead to greater errors and greater differences between the polymer and PPY.

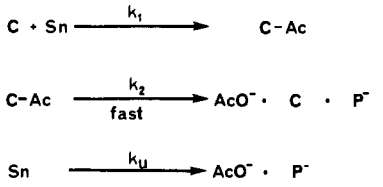
These data suggest that the polymer should demonstrate maximum rate enhancement in comparison to PPY at a pH of 7.5 if only the concentration of free nucleophile is important in determining the rate of hydrolysis. The initial rate of hydrolysis for S6 was measured in several buffers using the same concentrations of the substrate and catalyst and the same reaction procedure as before. The rates obtained for the uncatalyzed reactions were subtracted from the catalyzed reaction rates to obtain corrected rates for the two catalysts. Table I lists the ratio of the corrected initial rates for the polymer-catalyzed reaction to those for the PPY-catalyzed reaction at different pHs. The ratio of active catalyst from the data in Figure 4 is tabulated in the third column.

Two important results emerge from these data. First, the ratio of rates shows a maximum at pH 7.8, which coincides with the maximum for the ratio of active catalyst units. Thus, the lowered pK_a of the polymer contributes strongly to its enhanced activity over PPY. The second result is more important. If the activity per active supernucleophilic unit were the same for the polymer and PPY, then the ratio of active catalyst concentration would equal the ratio of reaction rates. However, the later ratio is always *higher* than the former one. The ratio of the value in the second column to that in the third column in Table I is a measure of the relative activity of polymer-bound vs. monomeric PPY units. This ratio is consistently and significantly above unity in all cases and implies that the PPY units in the polymer backbone are intrinsically more active than monomeric PPY.

Mechanistic Studies: Description of the Reaction. As shown in Scheme I, the esterolysis reaction takes place in two steps. These two steps need not be elementary processes in the mechanism. A complete description of the mechanism requires that (i) each of these steps be either identified as elementary or be split into a set of elementary processes; (ii) the rate-limiting process be identified; (iii) pertinent rate constants be estimated.

The Rate-Determining Step. Either the generation of the acylpyridinium species or its disappearance should be the slow step in the reaction. The latter has been identified to be rate limiting in imidazole-catalyzed esterolysis of active esters.[28] If

Scheme II



deacylation is rate determining, the acylpyridinium intermediate should build up in the reaction medium. The acylpyridinium species generated with PPY absorbs at approximately 312 nm in the ultraviolet spectrum. PPY itself and its protonated form absorb at 258 and 280 nm, respectively. Thus the detection of absorbance at 312 nm should distinguish between the two possible candidates for the slow step.

Previous research on supernucleophiles bound to poly(ethylenimine) employed the hydrolysis of S6 under excess catalyst conditions as the model reaction.[4] A bathochromic shift from 258 to 315 nm confirmed the presence of the acylpyridinium species as an intermediate in the hydrolysis of S6 under these conditions.

These reaction conditions were very similar to those in our experiments. The reaction medium was at pH 7.8 and the substrate S6 was in excess over the catalyst. This would suggest that deacylation should be rate controlling in our case. Experiments to observe the peak at 315 nm failed consistently. In an effort to improve detection, the concentrations of the catalyst and substrate were increased by a factor of 10 while their relative ratio was maintained. Again, no peak was observed at 315 nm. Since absorption due to S6 masks any absorption due to CAc at 312 nm, the concentration of S6 is always much greater than that of CAc in our systems. Even when S6 was replaced by hexanoyl chloride, the acylpyridinium absorption was still not detected. We conclude from these data that buildup of the acylpyridinium intermediate to a detectable level does not take place. The deacylation of the acylpyridinium species is therefore the faster of the two processes with the homopolymer of DAAP under the reaction conditions employed. Additional mechanistic studies (below) are consistant with this conclusion.

The Uncatalyzed Reaction. Detailed kinetic studies are complicated by the fact that at a pH of 7.8, the uncatalyzed reaction proceeds at a finite rate. Since the base is present in large excess, its concentration may be considered invariant during this process.

A series of reactions at pH 7.8 with different amounts of the substrate S6 were performed. The concentration of the phenoxide ion generated was monitored at 5-min intervals for the first hour of reaction. Plots of absorbance vs. time were linear in this region. The slope of the straight line divided by the molar extinction coefficient of the phenoxide ion is the initial rate of reaction expressed in moles per minute. Data for the initial concentration of the ester ($S6_0$) and the initial reaction rate (R_0) were collected for seven different reactions. If the reaction has an order n in S6 concentration, the reaction rate would be given by eq 1 where

$$(R_0) = k(B)^m(S6_0)^n \quad (1)$$

k = rate constant, (B) = base concentration, and m = order in base concentration. The base concentration is essentially invarient, and the product, kB^m, is the pseudo rate constant for the reaction (k_u). Equation 1 can thus be written in a logarithmic form as

$$\ln (R_0) = \ln k_u + n \ln (S6_0) \quad (2)$$

A plot of ln (R_0) vs. ln ($S6_0$) yields a straight line with slope n of 0.98. The reaction is therefore first order in substrate concentration. The pseudo-first-order rate constant k_u is estimated to be 1.56×10^{-3} min^{-1} from the intercept.

The Elementary Processes. In order to ensure that the simplest possible mechanism explaining the rate data was examined first, the steps in Scheme I were assumed to be elementary. This results in the mechanism outlined in Scheme II.

(28) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 67.

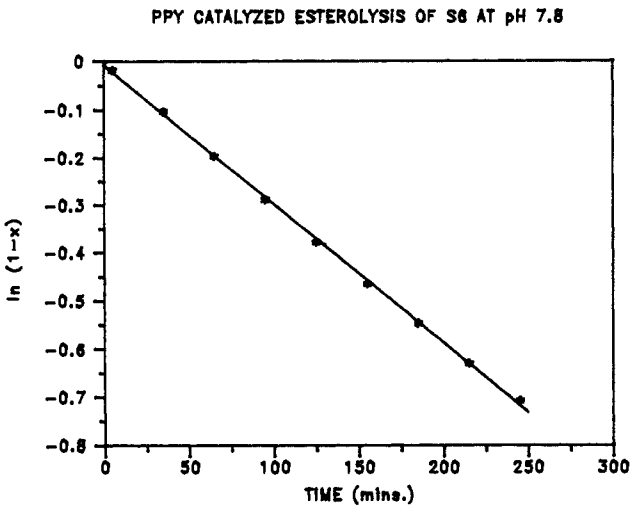


Figure 5. PPY-catalyzed esterolysis of S6 st pH 7.8 with substrate in 20-fold excess over catalyst.

Rigorous treatment of this mechanism along with mass balance equations for the substrate and catalyst yields two simultaneous, nonlinear, first-order differential equations with the concentration of the catalyst and phenoxide ion as the two time-variant quantities. There are no universal methods for solving such equations. All methods employed to solve this set failed to yield a closed-form analytical solution. Differential treatment of the kinetics data was impossible because the instantaneous concentration of the catalyst was unknown. Thus further simplification was necessary.

The commonly used steady-state approximation for the intermediate is not applicable in this case because the faster second step precludes buildup of the intermediate. However, under conditions where deacylation is fast, an approximation pertaining to the concentration of the catalyst in solution can be made. The mass balance for the catalyst is given by eq 3, where (C_0) = initial

$$(C_0) = (C) + (CH^+) + (CAc^+) \qquad (3)$$

catalyst concentration, (C) = instantaneous free catalyst concentration, (CH^+) = instantaneous concentration of protonated catalyst, and (CAc^+) = instantaneous concentration of acylated catalyst.

Since deacylation is fast, the amount of acylated catalyst is very small. As a first approximation the third term in eq 3 may be neglected. The relative amount of protonated catalyst is calculated knowing the pH of the reaction and the pK_a of the catalyst. The active catalyst concentration may then be considered to be time invariant and can be calculated from eq 3.

The rate of generation of the phenoxide ion is now a combination of two pseudo-first-order processes (i.e., the uncatalyzed reaction and step 1 of the catalyzed process). The differential equation corresponding to this process is

$$d(S6)/dt = -(k_u + k_1(C))(S6)$$

This can be solved to yield

$$(P) = (S6_0)(1 - \exp(-(k_u + k_1(C))t)) \qquad (4)$$

where (P) = concentration of phenoxide ion at any time t.

In the case of PPY, the simple pseudo-first-order process described by eq 4 adequately describes this reaction. Equation 4 can written in a linear form, and concentrations can be replaced by conversion. The modified equation predicts that a plot of the natural logarithm of $1 - x$ (x = conversion of ester to phenoxide) vs. time should be a straight line passing through the origin. Figure 5 shows the data for PPY-catalyzed esterolysis of S6 at a pH of 7.8 (catalyst and substrate concentrations of 2.5×10^{-6} M and 5×10^{-5} M, respectively) plotted in this fashion. The excellent fit confirms that the reaction is pseudo-first-order in substrate concentration. The value of the pseudo-first-order rate constant from this plot is 0.57 min^{-1}.

A series of reactions at pH 7.8 with a constant initial substrate concentration and varying amounts of the homopolymer was carried out. Figure 6 shows the data obtained from these runs. If the pseudo-first-order mechanism adequately describes the reaction, eq 4 should describe the family of curves shown. Nonlinear least-squares fitting techniques used in an attempt to fit the equation to the data failed. Thus the mechanism described in Scheme II inadequately describes the system.

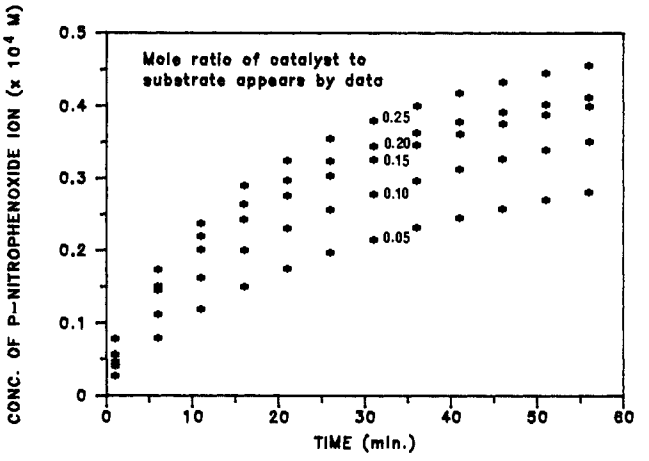
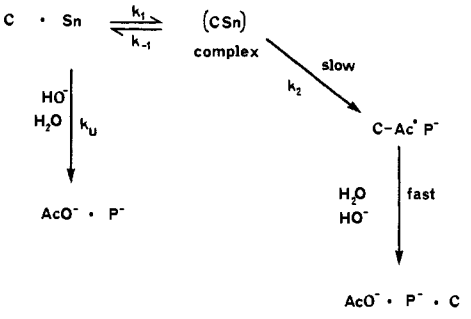


Figure 6. Kinetics of esterolysis of S6 at pH 7.8 with varying amounts of supernucleophilic homopolymer catalyst with substrate in excess.

Scheme III



The results obtained from these experiments imply that step 1 was in fact not an elementary step as assumed initially. If step 1 were the elementary process describing acylation, then the bulk solution concentration of the substrate would be the driving force behind the acylation rate. However, hydrophobic effects have already been shown to lead to association between the substrate and the polymeric catalyst. The concentration of the substrate around the catalyst is higher than the bulk solution concentration of the substrate, and the classic Michaelis–Menten kinetic scheme can be applied to this system which appears to involve substrate–catalyst complexation prior to reaction.

Michaelis–Menten Kinetics. Scheme III describes a Michaelis–Menten scenario for the esterolysis reaction. The generation of the acylpyridinium species is divided into two steps. The substrate reversibly complexes with the catalyst in the first step. This complex breaks down to form the acylpyridinium species in the slow second step of the reaction. The situation differs from the classic Michaelis–Menten scheme in that the uncatalyzed reaction occurs at a significant rate. If the differential equations for the process are written to incorporate this deviation, they become intractable. Thus, the uncatalyzed rate cannot be rigorously accounted for. Approximate corrections for this deviation are made by subtracting the uncatalyzed rate from the observed reaction rate to generate a corrected rate corresponding only to the catalyzed reaction.

Michaelis–Menten kinetics may be described by the linear Lineweaver–Burk relationship given in eq 5.[29] A plot of the

$$1/R_i = 1/(k_2(C_0)) + K_m/(k_2(C_0))(1/(S)) \qquad (5)$$

reciprocal of the reaction rate vs. the reciprocal of the substrate concentration should give a straight line. The constants k_2 and K_m can be obtained from the slope and intercept if the initial

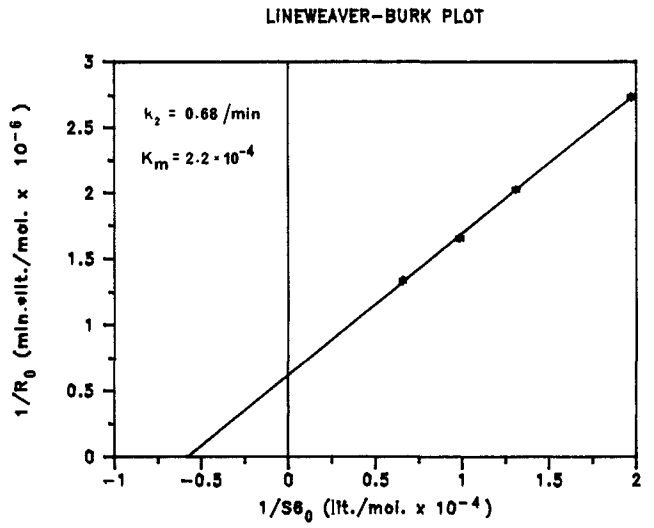


Figure 7. Uncorrected Lineweaver–Burk plot for the esterolysis of S6 at pH 7.8.

catalyst concentration is known. The values of k_1 and k_{-1}, or their ratio, cannot be calculated from this analysis.

Lineweaver–Burk plots are best made by use of initial reaction rates. In this regime the substrate concentration is in excess of that of the complex, and hence the steady-state assumption is valid. This also avoids complications due to product inhibition which have been observed in the esterolysis of 3-nitro-4-(acyloxy)benzoic acid substrates catalyzed by polymeric imidazoles.[25,30]

A series of reactions at a pH of 7.8 using a fixed catalyst concentration of 2.5×10^{-6} M and varying substrate concentrations was carried out. Initial rates were computed by fitting a straight line through data points in the initial linear region of the reaction profile. A Lineweaver–Burk plot for these data is presented in Figure 7. The values of k_2 and K_m were computed to be 0.68 min^{-1} and 2.2×10^{-4}, respectively.

The linearity of this plot attests to the fact that Michaelis–Menten kinetics adequately describe the polymer-catalyzed esterolysis reaction. Thus, the polymer mimics an enzyme in its catalysis of the esterolysis of S6 in that rapid complexation of the substrate with the catalyst (through hydrophobic interactions) is followed by slower formation of the acylated intermediate and rapid hydrolysis of this intermediate to the esterolysis products.

The data in Figure 7 are not corrected for uncatalyzed hydrolysis. Corrected reaction rates were computed by subtracting the uncatalyzed rate (computed using the value of k_3 and the initial substrate concentration) from the observed initial rate. The values of k_2 and K_m were 0.44 min^{-1} and 1.5×10^{-4}, respectively. However, it must be pointed out that this process overcorrects for uncatalyzed hydrolysis. The rates for the latter depend on the bulk concentration of uniformly distributed substrate while in the presence of catalyst the substrate is concentrated in the vicinity of the polymer backbone. The rate of uncatalyzed hydrolysis should therefore be greatly reduced. In fact, the linearity of the uncorrected plot suggests that the uncatalyzed rate is low enough to be neglected.

Conclusions

The homopolymer of DAAP proved to be an effective supernucleophilic catalyst under homogeneous aqueous conditions. The polymer was a more effective catalyst for the esterolysis of *p*-nitrophenyl esters of straight-chain carboxylic acids than 4-(pyrrolidino)pyridine (PPY). Hydrophobic interaction between the polymer and the esters was shown to contribute to the polymer's effectiveness. Neighboring-group effects lowered the pK_a of the polymer to 7.8, in contrast to 10.5 for PPY. The lowered pK_a resulted in a greater amount of available active catalyst per unit of catalyst employed for the polymer compared to PPY. Normalizing the catalytic effect of the polymer and PPY with the amount of active catalyst present in each case showed that supernucleophilic units in the polymer were more active than unbound PPY.

The uncatalyzed reaction was shown to be a pseudo-first-order process. In the catalyzed reactions, formation of the acylpyridinium intermediate was the rate-determining step. The PPY-catalyzed reaction was pseudo-first-order in ester concentration while the polymer-catalyzed reaction was shown to follow Michaelis–Menten kinetics.

Experimental Section

Materials. All reagents and chemicals were used as received from commercial sources. Reagent grade solvents and deionized water were utilized for all synthetic procedures. Spectrophotometric grade acetonitrile and absolute methanol were used for the kinetics experiments.

Distillation of Diallylamine. The pale yellow diallylamine obtained commercially was only 97% pure by GC. Distillation at a vacuum of 15 in. of mercury, with a pot temperature of 75 °C and a vapor temperature of 62 °C, gave a clear, colorless liquid.

4-Chloropyridine. 4-Chloropyridine hydrochloride (10 g) was dissolved in deionized water (20 mL), and excess 6 N NaOH was added to the solution to reach a pH of 12. The 4-chloropyridine formed an organic layer above the aqueous phase. The mixture was extracted with four 50-mL portions of ether. The combined ether extracts were filtered over two layers of phase separation paper (Whatman 1PS) to remove water. The ether was evaporated and the remaining dark brown liquid was kept at high vacuum for 20 min. The overall yields based on 4-chloropyridine hydrochloride were 70–80%.

Synthesis of 4-(Diallylamino)pyridine (DAAP). 4-Chloropyridine (13.24 g) was refluxed with excess diallylamine (28.04 g, 2.5-fold molar excess) under a nitrogen atmosphere of 3 days. The product mixture was neutralized with 1 N NaOH and extracted with four portions of ether (100 mL each). The combined ether extracts were filtered over two layers of phase separation paper. The ether was evaporated to leave a dark reddish brown viscous liquid. This liquid was fractionally distilled at a vacuum of 20 in. of mercury. Four fractions were isolated. The boiling ranges for these fractions were below 100 °C, 100 °C to 150 °C, 150 °C to 175 °C, and above 175 °C, respectively. The highest boiling fraction was the desired monomer. The distillation flask contained a dark brown solid at the end of the distillation. The fractions are capable of reacting with atmospheric oxygen when hot and nitrogen was used to purge the distillation apparatus before the disttlation and to release the vacuum after the flasks had been cooled.

Cyclopolymerization of DAAP. DAAP (10 g) was dissolved in concentrated aqueous HCl (2.308 mL, 10% molar excess) at 0 °C under a nitrogen atmosphere. Deionized water (8.3 mL) was added to form a 50% by weight solution of DAAP·HCl. The solution was degassed under high vacuum and the vial filled with nitrogen. 2,2′-Azobis(amidinopropane) hydrochloride (V-50) (0.156 g, 1 mol %) was added to the solution and the polymerization carried out at 65 °C under a nitrogen atmosphere for 12 h. Two further doses of initiator (0.156 g each) were added to the system at 12-h intervals. The resulting polymer solution was dialyzed against 5% aqueous NaCl, and then water, to remove unreacted monomer and oligomers. The final solution was made basic and the precipitated polymer was filtered over a polycarbonate membrane in a Buchner funnel. The polymer was dissolved in a water–methanol mixture and then freeze-dried to obtain a dry product.

The weight average molecular weight of this polymer was determined with low-angle laser light scattering using a Chromatix KMX-16 differential refractometer and a Chromatix KMX-6 spectrophotometer. The M_w value was calculated to be 8000 by using the obtained dn/dc value of 0.20.

Solutions of polymer catalyst were prepared by diluting stock solutions used for M_w measurements. Concentrations of the stock solutions were verified by evaporating known weights of solutions to constant weights of polymer present; 10 values were obtained for each concentration to ensure accuracy. The calculated concentrations were confirmed by UV spectroscopy using a Beer's law relationship established for PPY.

Composition of Aqueous Buffers. The aqueous buffer at pH 9.2 was a 0.1 M sodium borate solution bought premixed from a commercial source.[19] Buffers at pHs 13, 12, 11, 10, and 6 were made from preweighed dry powders. Each buffer was made by dissolving the powder in deionized water to make 500 mL of buffer solution.

Buffers at pHs between 7 and 9 were made by mixing varying amounts of 0.1 N aqueous HCl with 50 mL of 0.1 M tris(hydroxymethyl)aminomethane.[31] The pH of each buffer so made was measured

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by using a Corning combination pH electrode with a Orion Model 701 pH meter standardized with buffers at pH 7.0 and 10.00.

General Procedure for Homogeneous Esterolysis Reactions. Three milliliters of the aqueous buffer at the desired pH was pipetted into a cuvette. The substrates were dissolved in acetonitrile to make solutions at concentrations such that injection of 1 μL of the solution into the buffer in the cuvette would result in a substrate concentration of 1×10^{-5} M. The polymer and PPY were dissolved in methanol to obtain solutions such that each microliter when injected into 3 mL of buffer yielded a catalyst concentration of 5×10^{-7} M. For catalyzed reactions the desired amount of catalyst was injected into the cuvette and the contents were shaken to ensure mixing. The cuvette was introduced into the UV spectrometer and the stirrer started. The data acquisition programs were loaded into the computer along with a data disk in the appropriate drive. The desired amount of substrate was injected and a stopwatch started. After exactly 1 min, data acquisition was initiated. Spectra were collected at time intervals of 3, 5, or 60 min depending on the experiment. After the required number of spectra had been collected, the data analysis routine was initiated and the absorbance at 400 nm was determined as a function of time. Knowing the extinction coefficient for the *p*-nitrophenoxide ion and the initial substrate concentration, we calculated the conversion of substrate. Each kinetic run was repeated at least 3 times.

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Esterolytic Chemistry of a Vesicular Thiocholine Surfactant

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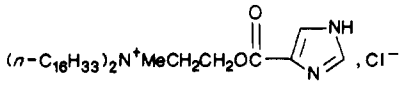
Abstract: The thiol-functionalized surfactant *N,N*-dihexadecyl-*N*-methyl-*N*-(2-mercaptoethyl)ammonium chloride (**2**) (16_2SH; 16 = n-$C_{16}H_{33}$) was synthesized. Vesicles prepared from 16_2SH were characterized by electron microscopy, gel filtration, dynamic light scattering, differential scanning calorimetry, and permeability toward 1-anilino-8-naphthalenesulfonate (fluorescence stopped-flow spectroscopy). Excess vesicular 16_2SH in aqueous solution at pH 7.7 cleaved various activated ester substrates; k_ψ^{max} values (s^{-1}) are as follows: *p*-nitrophenyl acetate, 4.9; *p*-nitrophenyl hexanoate, 13.4; 4-acetoxy-3-nitrobenzenensulfonate, 7.3; and *p*-nitrophenyl palmitate, 21.7. Second-order rate constants ranged up to ~9000 L/(mol·s) for the hexanoate and ~9800 L/(mol·s) for the sulfonate substrates. At short reaction times, with hydrophobic substrates, deprotonation (to 16_2S^-) and attendant structural changes of the 16_2SH vesicles are rate limiting under reaction conditions where the pH is "jumped" from 2.0 to 7.7. After ~200 ms at pH 7.7, 16_2S^- thiolate cleavage of the substrates becomes rate limiting. Artifactual processes that mimic the reaction are identified at "long" reaction times (~10-100 s).

The introduction of functional surfactants was crucial to the development of micellar reagents as reaction catalysts and enzyme models.[1] A similar period in vesicular chemistry began about 1980 and has steadily gained momentum.[2] Exclusive of surfactants with unsaturated hydrocarbon moieties, intended for the preparation of polymerized vesicles,[3] many other functional vesicle-forming surfactants have been synthesized.[2,4] Frequently, these have been derived from amino acids,[5] but "unnatural" functionalities have also been incorporated. These include aryldiazonium,[6] azo,[7] carbazole,[8] isonitrile,[9] pyridinioamidate,[10] pyridoxal,[11] and viologen.[12]

Due to their importance in the chemistry of hydrolytic enzymes and the desire to develop vesicular chemistry along biomimetic lines,[2] special attention has been devoted to the imidazole and thiol functional groups. This has led to esterolytic reagents that feature imidazole derivatives noncovalently bound to dialkyldimethylammonium ion vesicles,[13] hydrophobic histidine derivatives that mediate stereoselective vesicular esterolyses,[14] and functional vesicle-forming surfactants synthesized from histidine.[5b,15] Recently, we introduced the simple imidazole ester surfactant **1** (16_2Im) and characterized its kinetic properties in the vesicular cleavage of several substrates.[16]



1 (16_2Im)

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