(14) The reduction of acetophenone in liquid ammonia gives rise to a one-electron irreversible peak at $E_p = -1.43$ V at low sweep rates and to two reversible monoelectronic peaks $E_{p1} = -1.51$ V and $E_{p2} = -2.07$ V at $v = 500$ V s^{-1}.
(15) Amatore, C.; Saveant, J. M., unpublished results.
(16) Amatore, C.; Saveant, J. M. *J. Electroanal. Chem.* **1978**, *86*, 227.
(17) That is also the reason why a smaller range of sweep-rate values was used in the case of ClPhS$^-$ (0.04–1 V s^{-1}) than in the case of PhS$^-$ (0.1–5 V s^{-1}). Indeed, upon raising the sweep rate wave (H) shifts negatively while wave (S) remains steady. The two waves thus overlap more readily with ClPhS$^-$ than with PhS$^-$.
(18) Herlem, M. *Bull. Soc. Chim. Fr.* **1967**, 1687,
(19) Herlem, M.; Minet, J. J.; Thiebault, A. *J. Electroanal. Chem.* **1971**, *30*, 203.
(20) Garreau, D.; Saveant, J. M. *J. Electroanal. Chem.* **1972**, *35*, 309.
(21) Butler, J. L.; Gordon, M. *J. Heterocycl. Chem.* **1975**, *12*, 1015.
(22) Barlin, G. B.; Benbow, J. A. *J. Chem. Soc. Perkin Trans. 2*, **1975**, 298.
(23) Illuminati, G.; Gilman, H. *J. Am. Chem. Soc.* **1949**, *71*, 3349.

Nucleophilic Catalysis by Polyethylenimines with Covalently Attached 4-Dialkylaminopyridine

Michael A. Hierl, Edward P. Gamson, and Irving M. Klotz*

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received April 19, 1979*

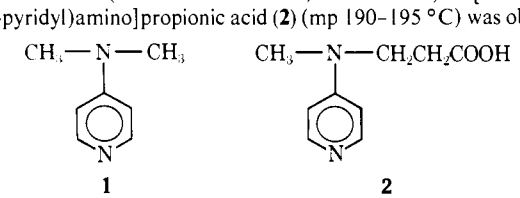
Abstract: A dialkylated pyridine, 3-[(*N*-methyl-*N*-4-pyridyl)amino]propionic acid, was attached covalently to laurylated poly(ethylenimine)s. It showed marked catalytic effects in the hydrolysis of nitrophenyl acylates. Spectrophotometric observations in the near-ultraviolet established that the hydrolysis proceeds through a nucleophilic pathway.

Polyethylenimine provides a versatile macromolecular matrix for the assembly of molecular environments that can accelerate a variety of chemical reactions.[1] Since the original discovery of the catalytic effects of imidazole per se,[2,3] this residue has been widely used in the polymeric state[4-8] to accelerate hydrolytic reactions. Alternatively, the hydroxamate group attached to polymers has been tried as a nucleophilic polymer catalyst.[8,9] There is still much scope, however, for development of more effective nucleophilic polymers.

In bulk solution pyridine has also been shown to catalyze the hydrolysis of esters[10] and acylpyridinium ion has been identified as a reaction intermediate.[11] Nevertheless, we have found no catalysis of cleavage of activated esters by pyridine attached to polyethylenimines (through a reduced Schiff base linkage). Evidently, in the polymer environment, the pK_a and nucleophilicity of the pyridine nitrogen are reduced substantially. On the other hand, Steglich and Höfle[12,13] have reported that 4-*N*,*N*-dialkylaminopyridines are acylation catalysts far superior to pyridine. Furthermore, acylation reactions with these dialkylaminopyridines are faster in apolar than in polar solvents.[15] Thus a 4-dialkylaminopyridine seemed to be a promising candidate for attachment to a modified polyethylenimine with apolar substituents to create a superior macromolecular nucleophilic catalyst.

Experimental Section

4-Dimethylaminopyridine (**1**) was purchased from Aldrich Chemical Co. and recrystallized from chloroform/ethyl acetate (9:1), mp 109–110 °C (lit.[13,14] 112–113 °C, 109–111 °C). 3-[*N*-Methyl-*N*-(4-pyridyl)amino]propionic acid (**2**) (mp 190–195 °C) was obtained



1 **2**

from Dr. H. Vorbrüggen. *p*-Nitrophenyl caproate was purchased from Sigma Chemical Co. and acetic anhydride was a spectrophotometrically pure, analytical grade sample.

Laurylated polyethylenimines, containing $C_{12}H_{25}$ adducts, were prepared by procedures described previously.[8,16,17] Compound **2** was coupled to a laurylated polyethylenimine from polyethylenimine 600 (Dow Chemical Co.), molecular weight 60 000, by the following method. An equimolar amount of **2** and a water-soluble carbodiimide [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride] (obtained from Sigma) was added to a four-fold residue-molar excess of laurylated polyethylenimine in H_2O. The pH was adjusted to 5.7 with 1.0 N HCl, and the reaction mixture was stirred at room temperature for 10 days. The solution was then placed in an Amicon ultrafiltration vessel with a PM-10 membrane, diluted to about 200 mL total volume and ultrafiltered with 30 L of distilled H_2O. Thin-layer chromatography on silica gel plates (Eastman no. 6060) with methanol as eluent showed no free pyridine compound. Finally, the solution was concentrated, and the polymer was isolated by lyophilization.

Both proton magnetic resonance spectra and elemental analyses are consistent with the following stoichiometric formulas for the two samples prepared with covalently attached dialkylaminopyridine **2**:

$$(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}$$

$$(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.17m}$$

The average molecular weight per monomer residue is 79 and 105, respectively.

Proton magnetic resonance measurements were made with a Hitachi Perkin-Elmer R-20B spectrometer operating at 60 MHz with a probe temperature of 35 °C. Samples were examined in D_2O (99.8%, Bio-Rad Co.) at a solute concentration of 5–10% by weight.

The hydrolysis of *p*-nitrophenyl caproate was followed by measurements, in a Cary 14 spectrophotometer, of the increase in absorbance at 400 nm due to released nitrophenolate ion. Below pH 9.0, 0.01 M tris(hydroxymethyl)aminomethane or 0.05 M bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane was used as a buffer, above pH 9.0, borate. Since *p*-nitrophenyl caproate was first dissolved in pure acetonitrile, the final aqueous solution contained 0.1% CH_3CN. Measurements of pH were made with an Orion Model 701A pH meter, at 25 °C. Pseudo-first-order rate constants were computed from semilogarithmic graphs of absorbance vs. time. Background rates were measured to assess the contribution from cleavage of activated ester in the presence of buffer and of each pyridine-free polymer in buffer and were subtracted to obtain corrected first-order constants, k_{obsd}, due to catalysis by the dialkylaminopyridine moiety. Below pH 9.7, background rates were less than 5% of k_{obsd}. Values of k_{obsd} were measured for a series of concentrations of dimethylaminopyridine (**1**) and for polymers with covalently attached 3-[*N*-methyl-*N*-(4-pyridyl)amino]propionic acid (**2**). From the linear dependence observed for k_{obsd} vs. concentration of pyridine moiety, second-order rate constants were calculated.

To reveal any acyldialkylaminopyridinium intermediate, the course of the acylation-deacylation reaction was followed spectrophotometrically with acetic anhydride as substrate, rather than *p*-nitro-

0002-7863/79/1501-6020$01.00/0

Table I. Second-Order Rate Constants for Hydrolysis of *p*-Nitrophenyl Caproate[a] at pH 7.3

catalyst	rate constant, M^{-1} min^{-1} obsd[b]	normalized[c]
imidazole	10[d]	17
dimethylaminopyridine (**1**)	18	4400
$(C_2H_4N)_m$-$(C_{12}H_{25})_{0.12m}$-$(C_9H_{11}N_2O)_{0.10m}$	5100	34000
$(C_2H_4N)_m$-$(C_{12}H_{25})_{0.21m}$-$(C_9H_{11}N_2O)_{0.17m}$	9300	63000

[a] Buffer was 0.05 M bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane, pH 7.30, temperature 25 °C. Concentration of *p*-nitrophenyl caproate was 1.0×10^{-5} M. [b] Calculated in terms of *total* concentration of imidazole or pyridine moiety, neutral plus cationic species. [c] Calculated in terms of concentration of neutral, nonprotonated species of imidazole or pyridine moiety. [d] See references 2 and 3.

phenyl caproate. The latter and its nitrophenolate reaction product absorb ultraviolet and visible light strongly and obscure any reaction intermediate, whereas the former absorbs weakly. The formation and subsequent deacylation of small molecule acetyldimethylaminopyridinium ion was monitored by its absorbance at 310 nm. The polymer bound acetyldialkylaminopyridinium moiety showed an absorbance maximum at 315 nm. The rate of deacylation was sufficiently slow at pH 7.3 that the spectrum of the intermediate could be recorded.

Results

A comparison of second-order rate constants for small molecule nucleophiles and for polymer-bound nucleophiles at pH 7.3 is given in Table I. It is apparent that dimethylaminopyridine in bulk solution is superior to imidazole at pH 7.3, for the former's second-order rate constant is almost twice as large as the latter's despite the fact that the pK_a of the dialkylpyridine is 9.7,[18] whereas that of imidazole is near 7. Furthermore, catalytic effectiveness is markedly increased when the dialkylaminopyridine is covalently attached to laurylated polyethylenimine.

That the acceleration in rate of cleavage of nitrophenyl caproate by the dialkylpyridine polymer is a manifestation of true catalysis was demonstrated by complete hydrolysis of a 50-fold excess of substrate over residue molar concentrations of pyridine moiety attached to polymer.

Since the pK_a of dimethylaminopyridine is 9.7,[18] only a small fraction (about 1/200th) of the substance is in the nucleophilic form. One would expect, therefore, substantial increases in catalyzed rates with increasing pH. Such increases indeed are observed (Figure 1). From the rate-pH profile, one can calculate a pK_a value of 9.69 for this small molecule pyridine in aqueous solution.

A rate-pH profile was also obtained for covalently bound dialkylaminopyridine in the polymer $(C_2H_4N)_m$-$(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}$. These results, illustrated in

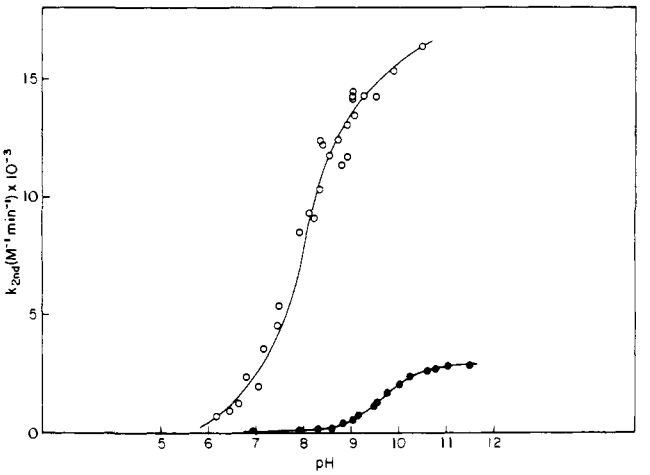


Figure 1. Rate-pH profiles for (●) dimethylaminopyridine in aqueous solutions, and (○) for $(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}$, a 60 000 molecular weight polyethylenimine with 10% of the nitrogens covalently attached (by an amide bond) to 3-[*N*-methyl-*N*-(4-pyridyl)-amino]propionic acid and 12% linked to lauryl groups.

Figure 1, reveal an inflection point at pH 8.0, which can be ascribed to an average pK_a of the polymer-bound pyridine. In contrast to the small molecule in bulk solution, the titration curve for the polymer-bound dialkylpyridine is spread over a wide range of pH. Despite the substantial amount of nucleophilic form evident as early as pH 6, a plateau in rate has still not been attained at pH 11. This type of titration behavior reflects the progressively decreasing electrostatic effect on the pyridine moiety of the cationic amine nitrogens of the polymer backbone as they progressively dissociate H^+ ions over the entire range of pH.

An acylated pyridinium species can be detected in aqueous solutions of polymer-bound dialkylaminopyridine. A characteristic bathochromic shift (from λ_{max} of 259 nm to 280 nm) has been reported[19] for dimethylaminopyridine, **1**, when the ring nitrogen of this small molecule is protonated. The absorption spectra of 3-[*N*-methyl-*N*-(4-pyridyl)amino]propionic acid covalently linked to laurylpolyethylenimines show similar displacements (Table II). Thus at pH 7.3, where the pyridine is largely protonated, the polymer-bound nucleophile has a peak at 280 nm (Figure 2). Upon addition of excess acetic anhydride, an entirely new peak at 315 nm is generated (Figure 2), which disappears very rapidly. Clearly the peak at 315 nm reflects the accumulation and disappearance of an acylpyridinium intermediate (Scheme I). Thus a nucleophilic pathway for the catalytic hydrolysis is established.

Discussion

The electron-donating capacity of a 4-amino substituent has been known to augment the basicity of the pyridine ring.[18] This is clearly evident from the shift in pK_a from 5.2[20] to 9.7[18] that

Table II. Absorption Maxima in Ultraviolet Spectra of Pyridine Moiety

catalyst	solvent	nonprotonated species	protonated species	acetylated intermediate
4-dimethylaminopyridine	hexane	250	270–275	
	water: pH 7.30		280	310
	pH 9.70	260	280	310
$(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}$	water: pH 7.30	260	280	315
	pH 9.70	260	280	
$C_2H_4N)_m(C_{12}H_{25})_{0.21m}(C_9H_{11}N_2O)_{0.17m}$	water: pH 7.30	260	280	318
	pH 9.70	260	280	

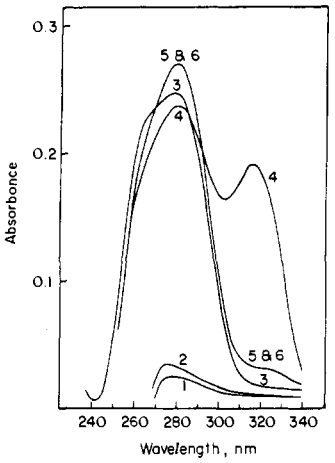
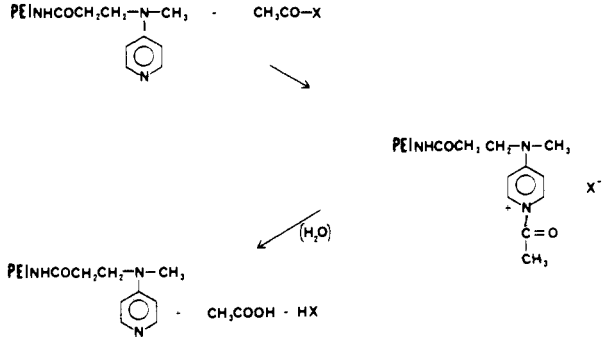
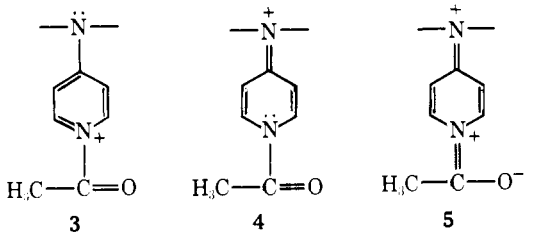


Figure 2. Ultraviolet spectra of modified polyethylenimine, $[(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}]$, upon reaction with anhydride in 0.05 M Bistris buffer, pH 7.30: 1, buffer only; 2, buffer and acetic anhydride only; 3, buffer and polymer; 4, buffer, polymer, and acetic anhydride at time $t = 0$; 5, buffer, polymer, and acetic anhydride at $t = 3.5$ min after mixing; 6, buffer, polymer, and acetic anhydride at $t = 7$ min after mixing. Concentration of $C_9H_{11}N_2O$ pyridine moiety, 4.0×10^{-5} residue molar, of acetic anhydride 7.5×10^{-4} M.

Scheme I



is observed when pyridine is converted to 4-dimethylaminopyridine. The catalytic activity of dimethylaminopyridine is a manifestation of both the increased electron-donating ability of the ring nitrogen and of the augmented stability of the acylpyridinium species due to charge delocalization:



3 4 5

Höfle et al.[13] demonstrated by NMR studies that mesomeric form **5** makes a considerable contribution to the stabilization of the *N*-acylpyridinium ion. Although the acylation rate is accentuated by these factors, the deacylation step is retarded by the delocalization of the positive charge facilitated by the 4-amino substituent. Thus it has been reported[10] that *N*-acetyl-4-dimethylaminopyridinium chloride is hydrolyzed at a rate 1/2000 that of the unsubstituted *N*-acetylpyridinium chloride.

Since the nonprotonated form of these nitrogen compounds is the active nucleophilic species, comparisons of catalytic activity should be normalized in terms of these species. On this basis, the superiority of dialkylaminopyridine to imidazole is more conspicuous. For the small compounds in bulk solution, where the pK_a of the former is 9.7 and that of the latter 7.0, the pyridine derivative is 250 times more effective as a nucleophile (Table I). Comparisons of corresponding polymer-bound adducts are more difficult. Imidazole propionic acid coupled to laurylpolyethylenimine by a bridge similar to that of the aminopyridine derivative shows an observed second-order rate constant of 1280 M^{-1} min^{-1}, and, since its pK_a on the polymer is near 5.5 (D. Mirejovsky, unpublished experiments), the normalized rate constant is the same. Alternatively an imidazole linked to laurylated polyethylenimine by an alkylation reaction with chloromethylimidazole, which creates a single $-CH_2-$ bridge, shows a rate constant of 3300 (D. Mirejovsky, unpublished experiments). This value also is unchanged if computed in terms of concentration of neutral nucleophilic species. The two dialkylaminopyridine polymers give normalized second-order rates 8–15 times higher (Table I). The superiority of the second aminopyridine polymer is likely a reflection of the more apolar local environment due to the higher content of lauryl and aromatic groups in the macromolecule. Apolar environments have been observed to be beneficial to reactivity with the small molecule dialkylaminopyridine.[15] With neither polymer is the 250-fold advantage of the small molecule pyridine over imidazole maintained. This loss of catalytic effectiveness probably is a reflection of the electrostatic influence of the cationic framework of the polymer, which is also evident in the drop in pK_a of the dialkylaminopyridine from 9.7 to 8.0.

It will be of interest to ascertain the catalytic effectiveness of covalently attached dialkylaminopyridines for different chemical reactions and in a variety of polymer environments.

Acknowledgment. This investigation was supported in part by a grant (No. DMR77-24152) from the Polymers Program, Division of Materials Research, National Science Foundation. We are also grateful to Professor H. Vorbrüggen (Schering AG, Berlin) for a gift of a sample of compound **2**, and to Dr. D. Mirejovsky for helpful discussions.

References and Notes

(1) I. M. Klotz, *Adv. Chem. Phys.*, **39**, 109 (1978).
(2) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).
(3) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1957).
(4) E. Katchalski, G. D. Fasman, E. Simons, E. R. Blout, F. R. N. Gurd, and W. L. Koltun, *Arch. Biochem. Biophys.*, **88**, 361 (1960).
(5) R. L. Letsinger and I. S. Klaus, *J. Am. Chem. Soc.*, **85**, 951 (1965).
(6) C. G. Overberger and N. Vorchheimer, *J. Am. Chem. Soc.*, **85**, 951 (1963).
(7) C. G. Overberger and J. C. Salamone, *Acc. Chem. Res.*, **2**, 217 (1969).
(8) I. M. Klotz, G. P. Royer, and I. S. Scarpa, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 263 (1971).
(9) T. Kunitake and Y. Okahata, *Macromolecules*, **9**, 15 (1976).
(10) For a review, see A. K. Sheinkman, S. I. Suminov, and A. N. Kost, *Russ. Chem. Rev.*, **2**, 642 (1973).
(11) A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432 (1970).
(12) W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, **8**, 981 (1969).
(13) G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **17**, 569 (1978).
(14) D. Jerchel, H. Fischer, and K. Thomas, *Chem. Ber.*, **89**, 2921 (1956).
(15) A. Hassner, L. R. Krepski, and V. Alexanian, *Tetrahedron*, **34**, 2069 (1978).
(16) T. W. Johnson and I. M. Klotz, *Macromolecules*, **7**, 149 (1974).
(17) J. Suh, I. S. Scarpa, and I. M. Klotz, *J. Am. Chem. Soc.*, **98**, 8060 (1976).
(18) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961).
(19) L. Pentimalli, *Gazz. Chim. Ital.*, **94**, 458 (1964).
(20) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965, p 156.