Poly(ethylenimines) with Alternative (Alkylamino)pyridines as Nucleophilic Catalysts

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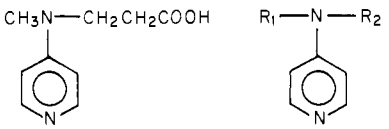
Abstract: A series of substituted aminopyridines have been synthesized and attached to poly(ethylenimines). These modified polymers are markedly effective catalysts of the hydrolysis of nitrophenyl esters. At pH 7.3, the observed rates of hydrolysis of *p*-nitrophenyl caproate are 50–2000-fold greater than for the isolated aminopyridine. Variations in effectiveness with differences in structure of the nucleophile and with its content on the polymer have also been examined, and these have been interpreted in terms of the conformation and properties of the macromolecule.

Since poly(ethylenimine) derivatives with apolar groups attached covalently show strong affinities for binding of small molecules in aqueous solution, we have been examining several covalently linked nucleophiles for their potential as catalysts in reactions of these molecules.[1] Following the reports by Steglich, Höfle, and Vorbrüggen[2,3] that (dialkylamino)pyridines are excellent acylation catalysts, we prepared poly(ethylenimine) derivatives with 3-[methyl(4-pyridyl)amino]propionic acid (**1**) linked to the polymer.[4] These were found to be superior to previous polymer catalysts of hydrolysis of nitrophenyl esters in aqueous solution.



1 2

Compound **1** is only one of a large class of (dialkylamino)-pyridines (**2**) that could provide interesting adducts of poly-(ethylenimines). Höfle et al.[3] have already pointed out that catalytic effectiveness in acylation reactions is sensitive to the nature of the R substituents in **2**. Furthermore, since R_1 and R_2 can be different structures, it is possible to place special functionalities such as binding groups in the immediate neighborhood of the nucleophile before coupling to the polymeric matrix. A variety of substituted aminopyridines of the type of **2** have been explored, therefore, as adducts that might further increase the catalytic effectiveness of poly(ethylenimines).

Experimental Section

Dimethyl 3,3′-[*N*-(4-Pyridyl)imino]diproprionate (3). A mixture of 4-aminopyridine (5.00 g, 0.053 mol) and methyl acrylate (30 mL) was heated under reflux for 24 h. The excess methyl acrylate was evaporated, in vacuo, and the residue taken up in toluene (~25 mL). The product was crystallized by carefully layering petroleum ether (~50 mL) on to the toluene solution and allowing the liquids to stand for 24 h at −20 °C. A similar recrystallization from toluene/petroleum ether yielded the pure product (6.75 g, 48%): mp 59–60.5 °C; NMR ($CDCl_3$) δ 2.62 (t, 4 H), 3.62 (t, 4 H), 3.62 (s, 6 H), 6.37 (apparent d, 2 H), 8.06 (apparent d, 2 H). Anal. ($C_{13}H_{18}N_2O_4$): C, H, N.

3,3′-[*N*-(4-Pyridyl)imino]dipropionic Acid (4). A standard procedure was established for obtaining acids such as **4**, from the corresponding esters, in this case **3**. The 4-(dialkylamino)pyridine ester was dissolved in water or water/methanol and heated with several equivalents NaOH on a steam bath for 0.5 h. After concentration, in vacuo, to a small volume, the mixture was applied to a column of Dowex MSC-1 (250 g, NH_4^+ form) and the compound eluted with 1% NH_4OH. Fractions containing ultraviolet-absorbing material were combined and evaporated, in vacuo, to give the product.

Dimethyl 3,3′-[*N*-(4-pyridyl)imino]dipropionate, **3** (1.02 g, 0.0038 mol), was hydrolyzed, and the product was recrystallized from distilled water to provide the diacid, **4** (0.85 g, 92%): mp 198–200 °C; NMR (D_2O) δ 2.65, (t, 4 H), 3.87 (t, 4 H), 6.97 (apparent d, 2 H), 8.08 (apparent d, 2 H). Anal. ($C_{11}H_{14}N_2O_4$): C, H, N.

***N*-(4-Pyridyl)decanamide (5).** To a solution of 4-aminopyridine (5 g, 0.053 mol) in anhydrous ether (800 mL) was added decanoyl chloride (10.10 g, 0.053 mol), and the mixture was stirred for 24 h at room temperature. The solid formed was separated by filtration and taken up in water (75 mL) and the mixture brought to pH 8 with $NaHCO_3$. The aqueous layer was extracted three times with ether (75 mL), and the combined ether layers were washed three times with dilute aqueous $NaHCO_3$ (50 mL). The ether solution was then dried with $MgSO_4$ and evaporated, in vacuo, to give the amide (**5**), which was recrystallized from water/absolute ethanol (11.06 g, 84%): mp 61–62.5 °C; NMR ($CDCl_3$) δ 0.63–2.57 (m, 19 H), 7.52 (apparent d, 2 H), 8.35 (apparent d, 2 H), 9.48 (br s, 1 H). Anal. ($C_{15}H_{24}N_2O$): C, H, N.

1-[(4-Pyridyl)amino]decane (6). Over a period of 15 min at 0 °C a solution of (4-pyridyl)decanamide, **5** (5.00 g, 0.020 mol), in anhydrous ether (125 mL) was added to a suspension of $LiAlH_4$ (1.02 g, 0.027 mol) in anhydrous ether (100 mL). This mixture was then refluxed for 3 h. The container was cooled to 0 °C and excess $LiAlH_4$ decomposed by the careful addition of ethyl acetate. The mixture was filtered and the filtrate evaporated, in vacuo, to yield the crude product, which was recrystallized from toluene (3.14 g, 67%): mp 71–72 °C; NMR ($CDCl_3$) δ 0.74–1.65 (m, 19 H), 3.05 (br q, 2 H), 4.25 (br s, 1 H), 6.32 (apparent d, 2 H), 8.07 (apparent d, 2 H). Anal. ($C_{15}H_{26}N_2$): C, H, N.

Methyl 3-[Decanyl(4-pyridyl)amino]propionate (7). A mixture of 4-(decanylamino)pyridine (3.0 g, 0.0128 mol) and methyl acrylate (30 mL) was heated under reflux for 24 h. The excess methyl acrylate was evaporated, in vacuo, and the residue chromatographed on silica gel (200 g) by washing the column with 95% ethanol/acetone (17/3) and eluting with 95% ethanol/concentrated aqueous NH_4OH (97/3). The fractions containing the desired material were evaporated, in vacuo, and the product was taken up in a small volume of anhydrous ether and filtered through celite to remove traces of silica gel. The ether was then evaporated, in vacuo. The product crystallized on standing at 0 °C overnight (2.32 g, 81%): mp 35–36.5 °C; NMR ($CDCl_3$) δ 0.8–2.0 (complex m, 19 H), 2.2–2.6 (t, 2 H), 3.0–3.4 (m, 2 H), 3.57 (s, 3 H), 3.4–3.7 (t, 2 H), 6.27 (apparent d, 2 H), 7.94 (apparent d, 2 H). Anal. ($C_{19}H_{32}N_2O_2$): C, H, N.

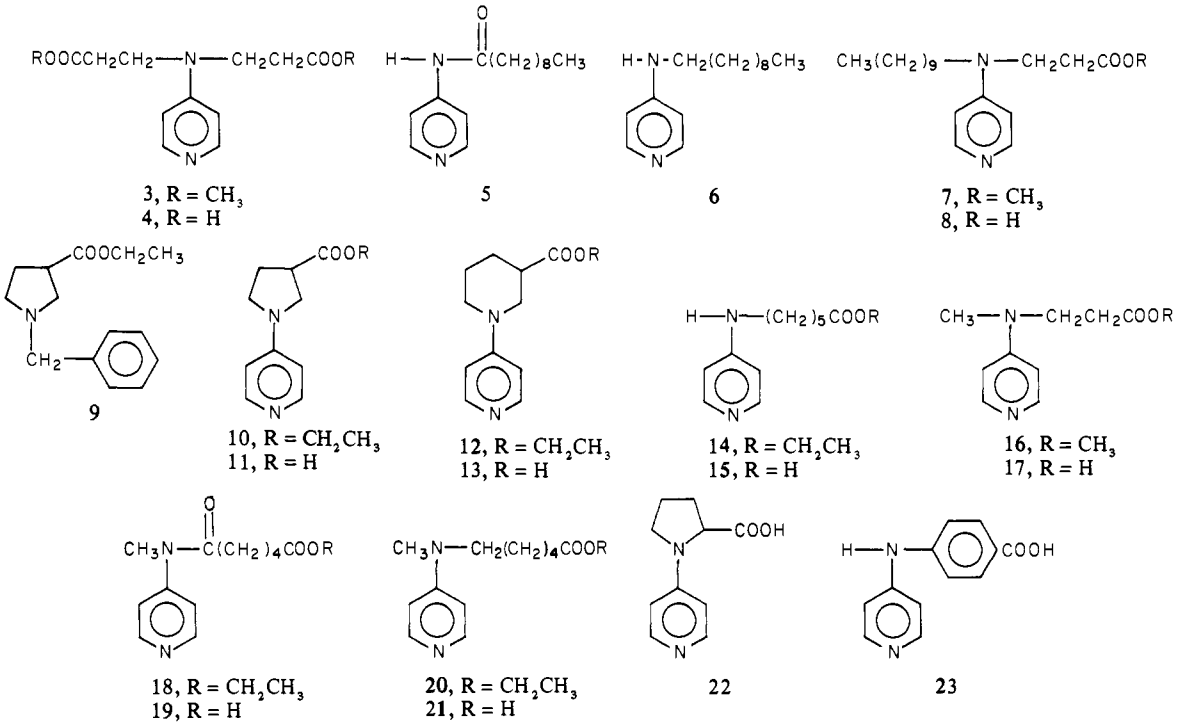
3-[Decanyl(4-pyridyl)amino]propionic Acid (8). Methyl 3-[decanyl-(4-pyridyl)amino]propionate (1.42 g, 0.0044 mol) was hydrolyzed and isolated as described above to give the acid **8** (1.29 g, 95%). Two recrystallizations from ethanol/ether provided an analytical sample: mp 96–96.5 °C; NMR (C_5D_5N) δ 0.7–1.8 (m, 19 H), 2.75 (t, 2 H), 3.33 (t, 2 H), 3.63 (t, 2 H), 6.12 (s, exchangeable, 1 H), 6.57 (apparent d, 2 H), 8.32 (apparent d, 2 H). Anal. ($C_{18}H_{30}N_2O_2$): C, H, N.

Ethyl 1-Benzyl-3-pyrrolidinecarboxylate (9). The procedure of Kornet et al.[5] was employed with the following modifications. Borane was generated, in situ, by the dropwise addition of $BF_3(C_2H_5)_2O$ (19.5 g, 0.137 mol) in 100 mL of tetrahydrofuran to a stirred suspension of $NaBH_4$ (5.5 g, 0.145 mol) in 100 mL of tetrahydrofuran at 0 °C under a nitrogen atmosphere. A solution of 1-benzyl-3-(ethoxycarbonyl)-5-pyrrolidinone[6] (22.6 g, 0.091 mol) in 100 mL of tetrahydrofuran was added over 5 min and the mixture stirred for an additional 15 min. After decomposition of excess borane and boron complexes with ethanolic HCl,

(1) Klotz, I. M. *Adv. Chem. Phys.* **1978**, *39*, 109.
(2) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(3) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(4) Hierl, M. A.; Gamson, E. P.; Klotz, I. M. *J. Am. Chem. Soc.* **1979**, *101*, 6020.
(5) Kornet, M. J.; Thio, P. A.; Tan, S. I. *J. Org. Chem.* **1968**, *33*, 3637.
(6) Jerchel, D.; Jakob, L. *Chem. Ber.* **1958**, *91*, 1266.

0002-7863/82/1504-0799$01.25/0

Chart I



the mixture was filtered, concentrated, in vacuo, and partitioned between water (200 mL) and toluene (200 mL). After a second extraction of the toluene phase with 5% aqueous HCl, the combined aqueous layers were made basic and extracted three times with ethyl ether (100 mL). The combined ether solutions were dried over $MgSO_4$, filtered, and concentrated, in vacuo. The resulting clear oil was then chromatographed on 200 g of silica gel. Elution with 1% ethanol in $CHCl_3$ yielded the amine ester 9 (10.3 g, 48%): bp 125–27 °C (1 mm) (lit.[6] bp of Me ester 122 °C (0.8 mm); NMR ($CDCl_3$) δ 1.20 (t, 3 H), 1.9–3.1 (complex m, 7 H), 3.54 (s, 2 H), 4.04 (q, 2 H), 7.14 (s, 5 H).

Ethyl *N*-(4-Pyridyl)pyrrolidine-3-carboxylate (10). This compound was obtained by the reaction[6] between ethyl pyrrolidine-3-carboxylate hydrochloride and 4-phenoxypyridine. These reactants were obtained as follows.

Ethyl 1-benzyl-3-pyrrolidinecarboxylate (9) (3.00 g, 0.0129 mol) was mixed with 5% palladium on carbon (2.00 g) in absolute ethanol (200 mL) and hydrogenated for 48 h at 40 psi. The mixture was filtered, the residual liquid was evaporated, in vacuo, and the residue therefrom was chromatographed over alumina (200 g, Alcoa Chemicals, Alumina F-20, prepared with $CHCl_3/CH_3OH$, 9/1). The amine product[7] (1.71 g, 92%) was eluted with the same solvent. The fractions containing the amine were evaporated, in vacuo, the residue was dissolved in absolute ethanol and treated with 1 equiv of HCl in absolute ethanol, and the solution was evaporated to yield the desired hydrochloride quantitatively; mp 161–163 °C.

The 4-phenoxypyridine was obtained by the method of Koenigs and Greiner.[8]

A mixture of ethyl pyrrolidine-3-carboxylate hydrochloride (1.170 g, 0.0065 mol) and 4-phenoxypyridine (1.115 g, 0.0065 mol) was heated at 150 °C for 3 h and then partitioned between toluene (50 mL) and 2 N aqueous phosphoric acid (50 mL). After a second extraction with 50 mL of toluene, the aqueous layer was adjusted to pH 7 with concentrated NH_4OH and again extracted twice with toluene (50 mL). The aqueous layer was then adjusted to pH 9 with concentrated NH_4OH and extracted three times with toluene (50 mL). These toluene extracts were combined, dried over $MgSO_4$, filtered, and concentrated, in vacuo. Crude product, an oil, was chromatographed on silica gel (100 g) with 5% ethanol in chloroform plus 0.1% concentrated NH_4OH. Eluted fractions containing product were combined and evaporated, in vacuo, dissolved in anhydrous ether, filtered, and reevaporated to give purified **10** as an oil (0.45 g, 31%): NMR ($CDCl_3$) δ 1.3 (t, 3 H), 2.0–2.4 (m, 2 H), 2.7–3.6 (m, 5 H), 4.07 (q, 2 H), 6.17 (apparent d, 2 H), 8.02 (apparent d, 2 H). An analytical sample as the hydrochloride was prepared by treatment with 1 equiv of HCl in absolute ethanol, layering with ether, and crystallization overnight at −20 °C; mp 161–163 °C. Anal. ($C_{12}H_{17}N_2O_2Cl$): C, H, N.

1-(4-Pyridyl)-3-pyrrolidinecarboxylic Acid (11). Ethyl 1-(4-pyridyl)-3-pyrrolidinecarboxylate (**10**) (230 mg, 1.05 mol) was hydrolyzed and the acid isolated as described above (195 mg, 97%). Three recrystallizations from H_2O/EtOH (2/1) provided a pure sample: mp >300 °C; NMR (D_2O) δ 1.5–1.9 (m, 2 H), 2.1–2.7 (m, 1 H), 2.8–3.2 (m, 4 H), 6.12 (apparent d, 2 H), 7.37 (apparent d, 2 H). Anal. ($C_{10}H_{12}N_2O_2$): C, H, N.

Ethyl *N*-(4-Pyridyl)piperidine-3-carboxylate (12). A mixture of ethyl nipecotate hydrochloride (2.32 g, 0.012 mol) and 4-phenoxypyridine (2.05 g, 0.012 mmol) was heated at 180 °C for 1.5 h and then partitioned between ethyl ether (100 mL) and 1 N NaOH (100 mL). After two extractions of the ether layer with 1 N phosphate buffer (pH 7.4, 100 mL), the combined aqueous layers were made strongly basic and extracted twice with ethyl ether (100 mL). The ether phase was then dried over $MgSO_4$ and filtered, and the solvent was removed, in vacuo, to give ethyl *N*-(4-pyridyl)nipecotate (2.03 g, 72%) as a viscous oil: NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.4–3.8 (complex m, 9 H), 4.05 (q, 2 H), 6.48 (apparent d, 2 H), 8.04 (apparent d, 2 H). An analytical sample of the hydrochloride was prepared by treatment with **12** with 1 equiv of HCl in ethanol, layering with ether and crystallizing at −20 °C overnight; mp 105–107 °C. Anal. ($C_{13}H_{20}ClN_2O_2$): C, H, N.

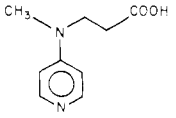
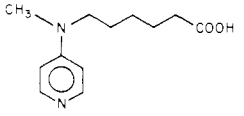
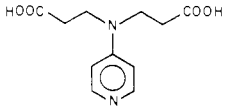
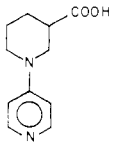
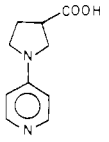
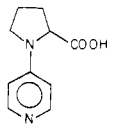
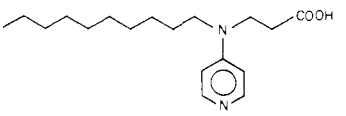
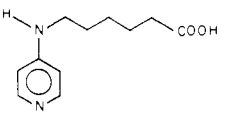
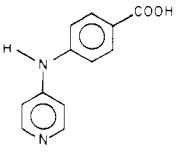
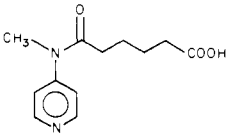
***N*-(4-Pyridyl)piperidine-3-carboxylic Acid (13).** Ethyl *N*-(4-pyridyl)piperidine-3-carboxylate, **12** (220 mg, 0.94 mmol), was hydrolyzed as described above and the product recrystallized three times from absolute ethanol to give the pure acid, **13** (143 mg, 74%): mp 224–226 °C; NMR (D_2O) δ 1.2–2.2 (m, 5 H), 2.6–3.9 (m, 4 H), 6.62 (apparent d, 2 H), 7.65 (apparent d, 2 H). Anal. ($C_{11}H_{14}N_2O_2$): C, H, N.

Ethyl 6-[(4-Pyridyl)amino]hexanoate (14). Ethyl 6-aminohexanoate (2.16 g, 0.011 mol) and 4-phenoxypyridine (1.71 g, 0.010 mol) were heated at 180 °C for 2 h. The residue was partitioned between toluene (100 mL) and 5% aqueous NaOH (100 mL). The toluene layer was extracted three times with 1 N sodium phosphate buffer (pH 6.5, 50 mL). The combined aqueous extracts were adjusted to pH 9 with dilute NaOH and extracted three times with ethyl ether (50 mL). The combined toluene and ether extracts were dried over $MgSO_4$, filtered, and evaporated, in vacuo, to give **14** as a viscous oil (1.29 g, 55%): NMR ($CDCl_3$) δ 1.20 (t, 3 H), 1.2–1.9 (m, 6 H), 2.23 (t, 2 H), 3.02 (m, 2 H), 4.00 (q, 2 H), 5.40 (apparent t, exchangeable, 1 H), 6.27 (apparent d, 2 H), 7.93 (apparent d, 2 H). An analytical sample was prepared as the hydrochloride by treatment of **14** with 1 equiv of HCl in absolute ethanol, layering with ether and allowing the solution to stand overnight at −20 °C. A second similar recrystallization was also carried out; mp 94–96 °C. Anal. ($C_{13}H_{21}N_2O_2Cl$): C, H, N.

6-[(4-Pyridyl)amino]hexanoic Acid (15). Ethyl 6-[(4-pyridyl)-amino]hexanoate (**14**) (1.06 g, 0.045 mol) was hydrolyzed to give the

(7) Cavalla, J. F. *J. Chem. Soc.* **1959**, 851.
(8) Koenigs, E.; Greiner, H. *Ber.* **1931**, *64*, 1049.

Table I. Properties of Substituted Aminopyridines

aminopyridine	pK_a	k_2 (pH 9.2)	k_2^N (normalized)	ϵ_{max}[a] of protonated form, M^{-1} cm^{-1}
 **17**	9.78	544	2300	19 100
 **21**	9.96	617	4380	19 300
 **4**	9.76	450	2170	21 300
 **13**	9.59	616	2770	19 300
 **11**	9.94	662	5090	22 300
 **22**	9.81	538	3090	19 300
 **8**	9.90	748	4680	19 800
 **15**	9.95	509	3030	19 300
 **23**	8.6	111	160	
 **19**	<6	0	0	

[a] Absorbance peak always near 280 nm.

acid **15** (805 mg, 86%). An analytical sample was obtained after three recrystallizations from distilled water: mp 228–230 °C; NMR (D_2O) δ 1.3–1.9 (complex m, 6 H), 2.0–2.3 (m, 2 H), 3.1–3.4 (m, 2 H), 6.67 (apparent d, 2 H), 7.83 (apparent d, 2 H). Anal. ($C_{11}H_{16}N_2O_2$): C, H, N.

Methyl 3-[Methyl(4-pyridyl)amino]propionate (16). A solution of 4-(methylamino)pyridine (1.16 g, 0.0107 mol) in 20 mL of methyl acrylate was refluxed for 16 h. Thereafter it was concentrated, in vacuo, and then chromatographed on silica gel (100 g) with 5% methanol in chloroform plus 0.5% triethylamine. Fractions containing product were combined and concentrated, in vacuo, to give the ester **16** (1.04 g, 50%) as an oil: NMR ($CDCl_3$) δ 2.52 (t, 2 H), 2.93 (s, 3 H), 3.60 (s, 3 H), 3.63 (t, 2 H), 6.37 (apparent d, 2 H), 8.07 (apparent d, 2 H). An analytical sample was prepared by treatment with 1 equiv of HCl in

Table II. Properties of Poly(ethylenimines) with Covalently-Linked Aminopyridines

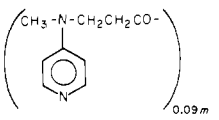
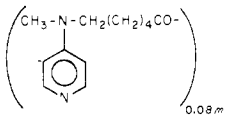
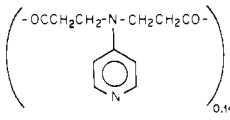
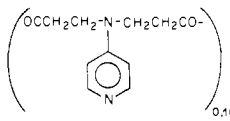
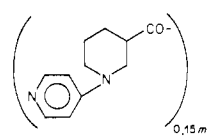
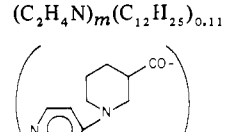
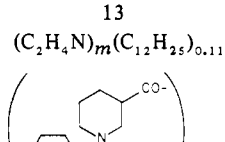
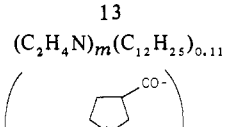
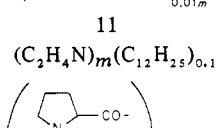
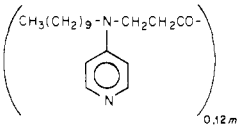
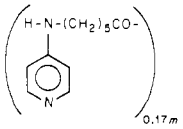
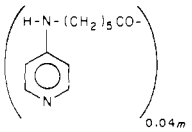
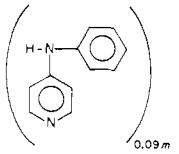
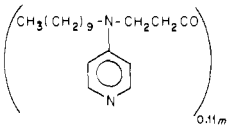
	polymer derivative[a]	content of amino pyridine, (μmol/mg of polymer)	pK_a	molecular extinction coeff, ϵ_{max},[b] of protonated form of nucleophile	second-order rate constants, pH 7.3 k_2	pH 7.3 k_2^N	pH 9.2 k_2	pH 9.2 k_2^N
A	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  17	0.950	7.31	20 300	10 400	20 800	34 300	36 400
B	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  21	0.735	7.54	20 000	14 900	34 700	34 400	35 800
C	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  4	1.407	7.06	20 500	7360	12 100	16 400	17 100
D	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  4	1.019	7.23	18 800	10 900	20 800		
E	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  13	1.222	7.13	19 400	9030	16 100		
F	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  13	0.304	6.64	20 900	14 700	25 000	53 300	55 500
G	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  13	0.131	6.68	23 400	25 300	35 200	164 000	168 000
H	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  11	0.151	7.51	23 100	28 200	65 500	163 000	180 000
I	$(C_2H_4N)_m(C_{12}H_{25})_{0.11\,7m}$  22	1.367	6.93	17 100	6010	9400	20 800	21 400

Table II (*Continued*)

	polymer derivative[a]	content of amino pyridine, (μmol/mg of polymer)	pK_a	molecular extinction coeff, ϵ_{max},[b] of protonated form of nucleophile	second-order rate constants, pH 7.3 k_2	pH 7.3 k_2^N	pH 9.2 k_2	pH 9.2 k_2^N
J	$(C_2H_4N)_m(C_{12}H_{25})_{0.117m}$  8	0.961	5.82	20 400	17 800	19 300	35 200	35 300
K	$(C_2H_4N)_m(C_{12}H_{25})_{0.117m}$  15	1.431	7.58	17 500	15 300	42 400	55 700	58 500
L	$(C_2H_4N)_m(C_{12}H_{25})_{0.117m}$  15	0.413	6.90	19 400	29 200	47 300	108 000	115 000
M	$(C_2H_4N)_m(C_{12}H_{25})_{0.117m}$  23	0.989			1190		1900	
N	$(C_2H_4N)_m$  8	1.053	5.83	18 100	16 400	17 800	34 000	34 100

[a] Stoichiometric composition given: C_2H_4N represents ethylenimine residue and $(C_{12}H_{25})$ lauryl group. For poly(ethylenimine) 600, m is approximately 1400. [b] Absorbance peak is near 280 nm.

absolute ethanol, layering with anhydrous ether, and crystal formation at −20 °C overnight; mp 115–117 °C. Anal. ($C_{10}H_{15}N_2O_2Cl$): C, H, N.

3-[Methyl(4-pyridyl)amino]propionic Acid (17). Methyl 3-[methyl-(4-pyridyl)amino]propionate **16** (0.94 g, 0.0048 mol) was hydrolyzed and isolated as described above to give the acid, **17**. This was recrystallized twice from water/ethanol (0.45 g, 52%): mp 195–197 °C; NMR (D_2O) δ 2.54 (t, 2 H), 3.19 (s, 3 H), 3.83 (t, 2 H), 6.90 (apparent d, 2 H), 8.02 (apparent d, 2 H). Anal. ($C_9H_{12}N_2O_2$): C, H, N.

Ethyl *N*-Methyl-*N*-(4-pyridyl)adipamate (18). A solution of 4-(methylamino)pyridine (2.94 g, 0.027 mol) and adipoyl chloride monoethyl ester (5.39 g, 0.028 mol) in 200 mL of dry acetonitrile containing triethylamine (10 mL) and catalytic amounts of 4-(dimethylamino)pyridine was stirred for 2 h at room temperature. After removal of solvent, the residue was dissolved in water and extracted three times with toluene (50 mL). The combined toluene layers were extracted three times with 1% aqueous phosphoric acid (75 mL). The combined aqueous layers were adjusted to pH 7.4 with dilute aqueous NaOH and then extracted twice with chloroform (100 mL). The combined chloroform extracts were dried over $MgSO_4$, filtered, and evaporated, in vacuo, to yield the compound **18** as a viscous oil (6.85 g, 95%): NMR ($CDCl_3$) δ 1.20 (t, 3 H), 1.4–1.8 (m, 8 H), 3.25 (s, 3 H), 4.02 (q, 2 H), 7.03 (apparent d, 2 H), 8.45 (apparent d, 2 H). An analytical sample as the hydrochloride was obtained by treatment of **18** with 1 equiv of HCl in absolute ethanol, layering with anhydrous ether, and crystallization overnight at −20 °C, followed by a second similar recrystallization; mp 134–136 °C. Anal. ($C_{14}H_{21}N_2O_3Cl$): C, H, N.

***N*-Methyl-*N*-(4-pyridyl)adipamic Acid (19).** Ethyl *N*-methyl-*N*-(4-pyridyl)adipamate (500 mg, 1.89 mmol) was dissolved in 100 mL of H_2O/MeOH (2/1) containing Na_2CO_3 (800 mg, 7.55 mmol) and the solution was stirred for 3 days at ambient temperature. The mixture was extracted twice with ethyl acetate (100 mL) to remove any remaining starting material and the aqueous layer concentrated, filtered, and applied to a column of Amberlite CG-50 (200 g, NH_4^+ form). After elution from the column with water, fractions containing product were combined and evaporated, in vacuo, to give compound **19** (360 mg, 81%); mp 150–154 °C. Three recrystallizations from 95% ethanol gave 163 mg of pure product: mp 160–161 °C; NMR (D_2O/NaOD) δ 1.3–1.7 (m, 4 H), 1.9–2.5 (m, 4 H), 3.28 (s, 3 H), 7.32 (apparent d, 2 H), 8.55 (apparent d, 2 H). Anal. ($C_{12}H_{16}N_2O_3$): C, H, N.

Ethyl 6-[Methyl(4-pyridyl)amino]hexanoate (20). Boron trifluoride etherate (1.25 g, 0.0088 mol) in 20 mL of dry dimethoxyethane was added dropwise to a suspension of $NaBH_4$ (0.250 g, 0.0066 mol) in 30 mL of dry dimethoxyethane under nitrogen atmosphere at 0 °C. The amide ester, **18**, (1.32 g, 0.005 mol) in 20 mL of dimethoxyethane was added over a period of 5 min and the mixture stirred an additional 15–20 min. Excess borane was then decomposed by the slow addition of 5% HCl in ethanol. The mixture was stirred at room temperature for several hours and stripped of solvent. The residue was dissolved in water, and the solution was made basic with dilute NaOH then extracted twice with

toluene (50 mL). The combined toluene phases were extracted twice with 1% phosphoric acid (50 mL), the aqueous extracts were brought to pH 7.0 with concentrated NH_4OH, and all residual amide ester was removed by four extractions with fresh toluene (25 mL). The remaining aqueous layer was then made basic with 5% NaOH and extracted three times with ethyl ether (50 mL). The ether phase was dried over $MgSO_4$ and filtered and the solvent stripped to yield pure ethyl 6-[methyl(4-pyridyl)-amino]hexanoate, **20** (0.54 g, 43%): NMR ($CDCl_3$) δ 1.18 (t, 3 H), 1.2–1.8 (m, 6 H), 2.0–2.4 (apparent t, 2 H), 2.82 (s, 3 H), 3.0–3.4 (m, 2 H), 3.93 (q, 2 H), 6.20 (apparent d, 2 H), 7.92 (apparent d, 2 H). An analytical sample was obtained as the hydrochloride by treatment of **20** with 1 equiv of HCl in absolute ethanol, layering with anhydrous ether, and crystallization overnight at −20 °C; mp 223–225 °C. Anal. ($C_{14}H_{23}N_2O_2Cl$): C, H, N.

6-[Methyl(4-pyridyl)amino]hexanoic Acid (21). Ethyl 6-[methyl(4-pyridyl)amino]hexanoate, **20**, (500 mg, 2.0 mmol) was hydrolyzed and isolated as described above to give the acid **21** (445 mg, 100%). An analytical sample was obtained by recrystallization from absolute ethanol/ether at −20 °C: mp 176–178 °C; NMR (D_2O) δ 1.3–1.9 (m, 6 H), 2.1–2.4 (m, 2 H), 3.12 (s, 3 H), 3.3–3.7 (m, 2 H), 6.69 (apparent d, 2 H), 7.82 (apparent d, 2 H). Anal. ($C_{12}H_{18}N_2O_2$): C, H, N.

***N*-(4-Pyridyl)proline (22).** An intimate mixture of DL-proline (0.67 g, 0.0059 mol) and 4-phenoxypyridine (1.00 g, 0.0059 mol) was heated at 180 °C for 3 h. The product was dissolved in saturated aqueous $NaHCO_3$ (25 mL) and extracted three times with ethyl acetate (25 mL). The aqueous layer was made acidic by the addition of concentrated HCl and placed on a column of Dowex MSC-1 (200 g, prepared as described above), the column was washed with 4 L of distilled water, and then compound **22** was eluted with dilute aqueous NH_4OH. The fractions containing the desired product were evaporated, in vacuo, and the residue was recrystallized from 90% ethanol/ether (0.68 g, 60%): mp >260 °C; NMR (D_2O) δ 2.0–2.5 (m, 4 H), 3.5–3.8 (m, 2 H), 4.1–4.6 (m, 1 H), 6.4–7.1 (m, 2 H), 8.02 (apparent d, 2 H). Anal. ($C_{10}H_{12}N_2O_2$): C, H, N.

4-(*p*-(Carboxyphenyl)amino)pyridine (23). This compound was prepared by the method of Vereshchagina and Postovshii:[9] mp >250 °C (lit.[9] >250 °C); NMR δ 7.37 and 7.47 (overlapping apparent d's, 4 H), 8.07 (apparent d, 2 H), 8.33 (apparent d, 2 H), 11.37 (s, 1 H).

Comparison of Michael Reaction of Acrylic Acid and Acrylate Ester. In the preparation of several derivatives, addition of the aminopyridine to acrylic acid led to alkylation of the ring nitrogen whereas with the acrylate ester the exocyclic amine was alkylated. It was observed further[10] that the alkylated ring nitrogen products readily underwent reverse Michael reactions. This behavior has prompted us to make a study of the feasibility of using ring-alkylated adducts as intermediates in the production of exocyclic-substituted aminopyridines by reactions with alkyl halides and similar compounds. When such reactions are attempted with aminopyridines having a free ring nitrogen, alkylation occurs on the ring nitrogen, unless strong base is used to generate the anion of the exocyclic amine.[11]

Polymers. Poly(ethylenimine) 600 (Dow Chemical Co.) having an average molecular weight of 60 000 was alkylated with lauryl bromide, to the extent of 12 residue per cent, according to procedures described previously.[12,13] Covalent attachment of the pyridine catalysts to laurylated poly(ethylenimine) was achieved by the following general method. An amount of catalyst in slight excess to the number of groups to be introduced was dissolved with laurylated poly(ethylenimine) (100 mg) in distilled water (200 mL) and the solution adjusted to pH 6.0. Several equivalents of 1-ethyl-3-(3-dimethylamino)propyl)carbodiimide hydrochloride (Sigma Chemical Co.) were added in successive portions over 3–4 h to the solution at room temperature with stirring and maintenance of pH 6.0. After overnight stirring, the solution was acidified with dilute HCl, filtered, and placed in an Amicon ultrafiltration vessel with a PM-30 membrane. Following ultrafiltration with 20 L of distilled water, the polymer was isolated by lyophilization.

In some cases, it proved difficult to achieve incorporation of more than a few percent of the aminopyridine into polymer. Some of these pyridines (especially the alicyclic ones **11**, **13**, and **22**) tended to form considerable amounts of unwanted side products (presumably *N*-acylureas) in the reaction with the carbodiimide.

With *N*-(4-pyridyl)proline, **22**, an alternate coupling method was employed. After treatment of this pyridine with an excess of $SOCl_2$ at room temperature for 5 min, anhydrous ether was added slowly so that a suspended solid appeared. This was filtered and washed with anhydrous ether. The solid was then dissolved in dry acetonitrile and this solution added dropwise to a stirred solution of laurylated poly(ethylenimine) in acetonitrile. The combination was stirred for 1 h, concentrated in vacuo to a gum, and then ultrafiltered as described above and lyophilized.

Polymers were analyzed for content of catalyst group by placing weighed samples in sealed tubes with 6 N HCl and heating for 48 h at 110 °C. As experimental controls, samples of catalyst mixed with poly(ethylenimine) were subjected to identical conditions. Comparison of ultraviolet spectra of these control mixtures with those of the unheated small molecule pyridines indicates that the pyridine moieties are stable to the hydrolysis conditions employed. The content of covalently attached pyridine on the polymer (expressed as μmol of catalytic group per mg of polymer) was calculated from the ultraviolet absorbance of the solution containing the polymer and hydrolytically cleaved pyridine.

Analytical Methods. Uncorrected melting points were determined with a Büchi capillary melting point apparatus. Elemental analyses were performed by Micro-Tech Laboratories of Skokie, Illinois. Proton magnetic resonance spectra were obtained with a Varian T-60A (60 MHz) spectrometer; chemical shifts are reported in parts per million downfield from internal tetramethylsilane or sodium 4,4-dimethyl-4-silapentanesulfonate, in deuteriochloroform and deuterium oxide, respectively. Measurements of pH were made with an Orion 701A meter at ambient temperature. Ultraviolet spectra were recorded with a Cary 14 recording spectrophotometer.

Most of the pyridine moieties showed a 20-nm shift in λ_{max} when basic (B) and conjugate acid forms (BH^+) were compared, peaks appearing typically at 260 and 280 nm, respectively. For each such compound, the pK_a was determined spectrophotometrically. The absorbance of B was fixed by measurement in 0.01 M NaOH and that of BH^+ by measurement in 0.01 M bis tris buffer (pH 6.5) for small molecule and in 0.01 M HCl for polymer-linked pyridine derivative. Measurements of absorbance were then made at a series of pH values and the pK_a calculated from the equation

$$pH = pK_a + n \log (B)/(BH^+)$$

where n is a measure of deviation from ideal titration behavior in the polymer matrix. The pK_a's obtained served also to permit calculation of normalized rate constants (k_2^N) adjusted to concentrations of free B in solution.

Kinetics of hydrolysis of *p*-nitrophenyl caproate were followed by the increase in absorbance at 400 nm due to *p*-nitrophenoxide formation. Rates were measured in 0.05 M tris(hydroxymethyl)aminomethane buffer at pH 7.30 or in 0.01 M sodium borate at pH 9.20. Final aqueous solutions contained also 0.1% acetonitrile as a result of introduction of substrate in this solvent. Pseudo-first-order rate constants (k_{obsd}) were calculated from the variation of $-\ln (A_\infty - A_t)$ with time (where A_∞ and A_t represent final absorbance and absorbance at time t, respectively). Values of k_{obsd} were measured for a series of concentrations for each catalyst and catalyst-containing polymer. The concentration of substrate was 6×10^{-6} M and that of the pyridine moiety 6×10^{-5}–6×10^{-4} M. Second-order rate constants (k_2) were calculated from the slope of the linear relationship between k_{obsd} and catalyst concentration. Background rates were subtracted from values of k_{obsd} when they exceeded 2% of the rate in presence of catalyst.

Results

Some characteristics of each of the small molecule aminopyridines have been assembled in Table I.

The pK_a values of the pyridine nucleus are, with two exceptions, all in the range of 9.7, in good agreement with acidities reported[14] for related structures. Compound **23** with an aromatic substituent on the amino nitrogen shows a lower pK_a, 8.6, and compound **19**, in which the amino group has been converted into an amide has a pK_a, <6, that reflects the electron-withdrawing power of the carbonyl group.

Second-order rate constants were measured quantitatively at pH 9.2 since previous investigations[4] have shown that these small nucleophiles have little of the catalytically effective nonprotonated form present at pH 7. The observed rate constants for pH 9.2 are listed in Table I, as are the calculated rate constants normalized to 100% of the molecule in the nonprotonated form. All rates were measured at 25 °C.

Listed in Table II are analytical data for the nucleophile–polymer adducts as well as acidity constants and rate constants

(9) Vereshchagina, H. N.; Postovski, I. Y. *Tr. Ural. Politekh. Inst. im. S.M. Kirova* **1960**, *94*, 24; *Chem. Abstr.* **1960**, *56*, 8681d.
(10) Wood, L. E., unpublished experiments.
(11) Palmer, M. H. "The Structure and Reactions of Heterocyclic Compounds"; William Clowes and Sons, Ltd.: London, 1967; pp 51–52.
(12) Johnson, T. W.; Klotz, I. M. *Macromolecules* **1974**, *7*, 149.
(13) Suh, J.; Scarpa, I. S.; Klotz, I. M. *J. Am. Chem. Soc.* **1976**, *98*, 8060.
(14) Essery, J. M.; Schofield, K. *J. Chem. Soc.* **1961**, 3939.

at 25 °C for the hydrolysis of *p*-nitrophenyl caproate at each of two pH values, 7.3 and 9.2. The second-order rate constants for the polymer correspond to $k_{cat.}/K_M$ of enzyme kinetics, but rates were not followed at excess substrate concentrations so K_M or $k_{cat.}$ could not be evaluated separately.

The absorption spectra of the aminopyridine–polymer adducts were not markedly different from those of the small molecules in solution individually. Extinction coefficients of the covalently linked pyridine, in the protonated state (Table II), were close to those of the corresponding protonated small molecule (Table I).

Discussion

With two exceptions, compounds **23** and **19**, the small molecule nucleophiles show second-order rate constants that are within a factor of 2 of each other. At pH 9.2 these constants are some 50 times larger than that for imidazole at pH 7, and normalized values for the (dimethylamino)pyridine derivatives are 200–500 times larger than that for imidazole. Thus the aminopyridines are intrinsically more promising as adducts for modification of polymers into catalytic macromolecules.

Compound **23** with an aromatic substituent containing an electron-withdrawing carboxyl group is markedly weaker as a nucleophile than are the preceding aminopyridines in Table I, although it is still 1 order of magnitude superior to imidazole. The electron-withdrawing effect lowers the pK_a of **23** by about 1.3 units and simultaneously decreases the nucleophilicity of the pyridine nucleus. This effect is even more striking in compound **19** where the amide C=O weakens the acidity by at least 4 pK units and for all practical purposes abolishes the catalytic activity.

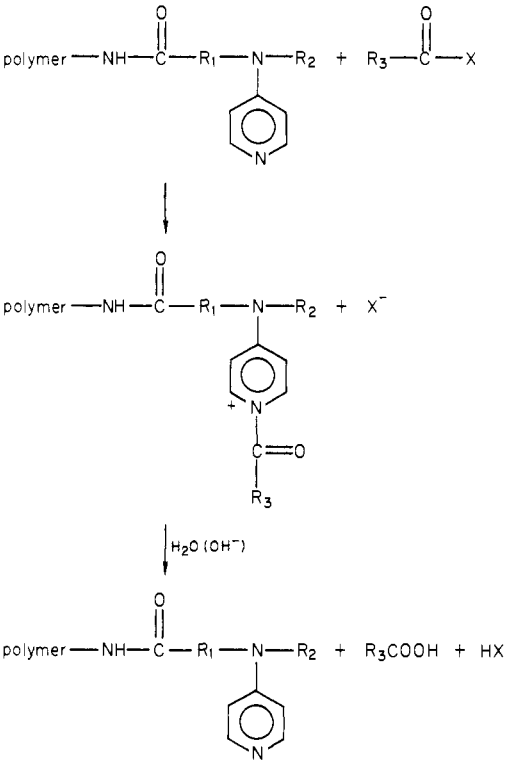
The pK_a values of the aminopyridines attached to the polymer (Table II) are invariable lower than those of the corresponding isolated small molecules (Table I). The cationic character of poly(ethylenimine) produces an electrostatic field that weakens the acidity of the nucleophile by 2–3 pK units. A lowering of an additional unit is observed in the adduct *J* that has a long apolar group attached to the aminopyridine moiety. Evidently in this molecule the apolar environment favors further the unchanged, nonprotonated form of the pyridine.

For all of the adducts, the polymer environment increases markedly the concentration of the nucleophilic state of the pyridine nitrogen. It is not surprising, therefore, that in every case (Table II) the observed rates of hydrolysis of *p*-nitrophenyl caproate at pH 7.3 are 50–2000-fold greater than for the isolated aminopyridine. The nucleophilic forms of the small molecule aminopyridines are about 200 times more effective than imidazole; the observed rates[4] in the pH region 7–11 are 2–250 times greater, depending on the pH.

The catalytic effectiveness of the small molecule or the polymer adduct is increased when the pH of the solution is raised from 7.3 to 9.2. For most of these derivatives, the increase reflects the rise in concentration of nonprotonated nucleophile, but in some cases (e.g., G and H in Table II), the polymer must be affecting the nucleophile directly.

An assessment of the effect of the polymer on the *intrinsic* effectiveness of the nonprotonated pyridine moiety can be made by comparison of the normalized rates k_2^N (Tables I and II), that is, those expressed in terms of the concentration of >N̈— species in the solution. The intrinsic activity of the most effective nucleophiles, derivatives G and H, are enhanced by a factor of 35 and 60, respectively, when they are attached to poly(ethylenimine). For the others the increase varies from 6 to 35-fold, but for every one there is an accentuation in intrinsic activity in the polymer adduct. This increase is in addition to that due to the ability of the polymer at any pH to increase the fraction of aminopyridine in the uncharged >N̈— form.

For a specific nucleophile in which polymer adducts have been prepared with different contents of aminopyridine, the catalytic effect, per pyridine, increases with decreased residue concentration of nucleophile (compare derivatives E, F, and G and also K and L). There are several possible rationalizations for this behavior. The smaller the extent of insertion of aminopyridine residues, with a –CO–NH bond, the higher the number of remaining ethylenimine nitrogens and hence the larger the positive charge on the polymer. Furthermore, the more –CO–NH linkages introduced, the more electron-withdrawing centers inserted, and these will weaken the basicity of neighboring amines at all pHs. Consequently the local concentration of OH^- in the environment is greater for the preparations with lower aminopyridine content (for these carry a higher positive charge), and OH^- ion may play a vital role in the deacylation of the acylpyridinium intermediate[4] in the hydrolytic pathway (eq 1). Alternatively, the increased



(1)

effectiveness of the polymers with fewer pyridine residues may reflect the larger number of remaining >N- or >NH⁺— nitrogens in the poly(ethylenimine) framework. These could participate as general-base or general-acid functionalities in the hydrolysis of the acyl pyridinium intermediate. Still another interpretation is one that assumes that the aminopyridine side chains on the polymer can form clusters in themselves and that the individual residues are less effective in such a cluster. The very process of clustering may also shrink the polymer into a more compact, tight conformation. Such an explanation has been suggested[15] to account for the decreased effectiveness of imidazole adducts on poly(ethylenimine) as their concentration is increased (but other interpretations have not been examined). It must also be recognized that with these aminopyridines (as with imidazoles) the first attachment of nucleophile will take place at the most accessible locations on the poly(ethylenimine), presumably positions near the surface, and the successive further increments of adduct will form bonds at other loci, depending on how many and what kinds of moieties have already been attached to the polymer. Thus the environments of the progressively introduced groups may vary substantially and are likely to be sterically more hindered. Furthermore, these groups attached later will be near internal secondary and tertiary amines whose pK_a's will be different from those of the primary and secondary ones at the external periphery of the macromolecule, and these differences may manifest themselves through charge and chemical effects.

Of the several explanations of decreasing effectiveness of increasing contents of aminopyridine, the assumption of clustering of these nucleophiles seems least tenable since it does not fit the pK_a observations (Table II, derivatives E, F, and G). One would expect increased clustering with increased content of pyridine

(15) Mirejovsky, D. *J. Org. Chem.* **1979**, *44*, 4881.

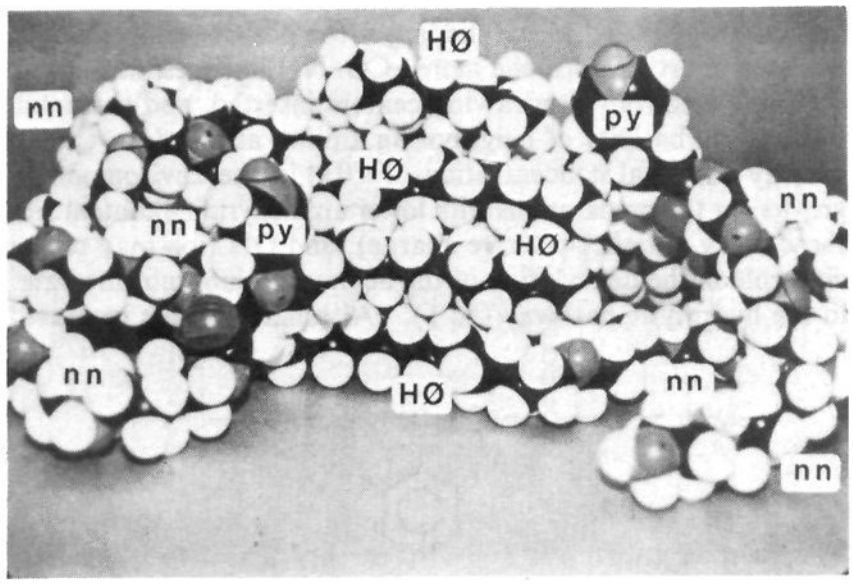


Figure 1. Photograph of space-filling molecular model of a segment of modified poly(ethylenimine) constituted of 100 ethylenimine residues, 10 lauryl groups, and 2 aminopyridines. In the central area, marked with Hϕ symbols, is the hydrophobic cluster of apolar lauryl residues. Flanking this domain, on the right and on the left and marked with nn symbols, are the ethylenimine residues of the polymer framework. The two nucleophilic pyridines, marked py, are at the periphery of the hydrophobic domain.

moiety to be paralleled by a drop in pK_a, due to local electrostatic and apolar interactions. The observed pK_a with 1% pyridine adduct G is not significantly different from that with 3% F despite the threefold drop in k_2^N at pH 9.2. Furthermore, the adduct with 15% pyridine E shows a raised pK_a, 7.1 compared to 6.7, whereas electrostatic or apolar effects should lower the value to somewhere near 6 or below.

All of the factors other than clustering of nucleophiles could be contributing to the behavior of the poly(ethylenimine) derivatives, since the virtue of this macromolecule in making a variety of environments possible is simultaneously a potential source of infirmities. It is difficult to assess the relative importance of individual factors. Nevertheless, examination of a space-filling molecular model of a portion of the macromolecule (Figure 1) illustrates very clearly the variation of environments in different regions. Figure 1 shows a segment of polymer constituted of 100 monomer residues, 10 lauryl groups (10% substituted residues), and 2 aminopyridines (2% substituted residues). From NMR[16,17] and excimer[18] studies, it has become evident that the lauryl residues assemble into an aggregate which creates an apolar domain (shown in center of Figure 1). This assembly, particularly of groups attached to primary amines, at the periphery of the macromolecule, of necessity forces many of the secondary and tertiary amines of the polymer out and away from the hydrophobic domain. Consequently when the nucleophile is coupled to the polymer backbone, only a few groups can be linked to ethylenimine nitrogens that are near the hydrophobic domain. These are likely to be the first ones introduced because the small-molecule aminopyridine reactants, being substantially hydrophobic, are likely to be bound in the apolar lauryl core prior to reaction with the carbodiimide. Since the hydrophobic substrate is bound in the apolar domain, the pyridine nucleophile must be at the periphery of this aggregate if it is to interact with the substrate. Thus it becomes apparent that increasing quantities of covalently linked aminopyridine, being attached to imine nitrogens progressively more distant from the lauryl core, will be less and less likely to have access to bound substrate. Consequently even if the first few attached aminopyridines maintain their high activity, the much weaker effectiveness of those added later will reduce the average rate constant observed experimentally.

If this interpretation is valid, the decrease in catalytic effectiveness with concentration should not be limited to a specific nucleophile. In practice the same concentration trend has been observed with two aminopyridines, adducts E, F, and G and K and L (Table II) of this investigation, as well as in a series of imidazole adducts of a previous study from this laboratory.[15]

This picture also allows one to rationalize other features of the behavior of these catalytic polymers. With most of the adducts, there is an increase in k_2^N, that is, in normalized or intrinsic effectiveness, with increase in pH from 7 to 9. Concurrent with this pH increase there will be a decrease in charge and electrostatic repulsions within the polymer framework, and hence the macromolecule will contract into a more compact conformation. In such a conformation there is a greater likelihood of distant nucleophiles being pulled toward the periphery of the hydrophobic lauryl domain, as well as an increased affinity for an apolar substrate.

One can also rationalize now the increase in catalytic effectiveness produced by increased content of lauryl groups in the polymer. This was observed in previous studies of the aminopyridine adducts[4] as well as in work with imidazole derivatives.[15] In general, one would expect that an increase in content of lauryl groups will place these hydrophobic moieties on more and more of the distant imine nitrogens and create apolar domains in previously empty areas. The more such domains are created the greater the likelihood that a less favorable ethylenimine nitrogen will find itself in a region near the surface of an apolar binding aggregate.

The different adducts prepared are designed to examine specific structural contributions to catalytic effectiveness. Derivatives A and B allow one to place the pyridine moiety at different distances from the –C(=O)NH– linkage to the polymer. The first is two carbons away and the second is five. No substantial difference in activity is observed. In either case, evidently the flexibility of the side chain is such that the nucleophile can experience the same environments. Derivatives C and D were prepared to link the nucleophile to polymer with two arms and thereby to constrain its mobility. However, this feature did not improve activity. Derivatives E–I were synthesized to introduce aminopyridines with alicyclic amines since published work with the small molecules[2,3] shows these to be more effective than linear dialkyl derivatives. These derivatives are indeed the most active pyridine polymers that we have encountered. With 1% content of nucleophile, polymers G and H show intrinsic k_2^N values at pH 9 of 170 000–180 000. However, it should be kept in mind that some of the linear dialkyl derivatives might also have shown considerably greater activities if they had been tested at lower contents in the polymer.

Derivatives J and N were constructed to place a long apolar side chain immediately adjacent to the aminopyridine moiety so that when the hydrophobic long chains assemble into clusters, they would automatically carry the nucleophiles into the vicinity. That indeed appears to occur, for the pK_a values of these polymer adducts, 5.82 and 5.83, are the lowest observed in the series in Table II. On the other hand it is noteworthy that whether or not the polymer has added lauryl groups (compare J and N), the pK_a of the pyridine is the same. It is, of course, possible in both cases that the molecular local environment is similar, a long chain aliphatic hydrophobic cluster being present with aminopyridine moieties placed around the periphery of the apolar domain. In polymer J these hydrophobic clusters may be comprised of the lauryl groups first introduced separately together with the hydrocarbon chain of the aminopyridine moiety **8** linked subsequently, whereas in the nonlaurylated polymer N, the hydrophobic clusters can be constituted only from the hydrocarbon chains attached to the aminopyridine **8**. In either system the pyridine nucleophile resides at the periphery of the binding site. Consequently the catalytic effectiveness of each of these two polymer derivatives J and N is comparable to the other.

Derivatives K and L illustrate that one of the substituents on the amine nitrogen of the aminopyridine can remain an H atom. Catalytic effectiveness still is manifested in the hydrolysis of nitrophenyl esters. That the acceleration in observed rates were not just increased aminolysis was shown by using a 22-fold excess of substrate and obtaining complete reaction. Furthermore, after the hydrolysis of this excess of substrate, the activity of the polymer was unchanged. Thus free amine nitrogens on the polymer do

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not seem to play any role in the catalysis.

In all of our experiments a branched form of a poly(ethylenimine) was used. It is likely that this is essential. Past work[19] with a linear polyvinylpyridine and a neutral nitrophenyl ester substrate revealed no catalysis at all. However, this may not be relevant since the pK_a of the pyridine moiety in the latter polymer was very low and hence its nucleophilicity was poor.

The successful preparation of D,L-*N*-(4-pyridyl)proline, **22**, and of D,L-*N*-(4-pyridyl)phenylalanine[10] indicates that it should be feasible to synthesize a broad series of *N*-(4-pyridyl)amino acids through the reaction of specific amino acids with 4-phenoxypyridine. These can then be coupled to poly(ethylenimines) by the same procedure used to prepare the proline adduct I (Table II). Furthermore, the amino acid need not be converted to an *N*-alkyl derivative, for the catalytic effectiveness of the aminopyridine adduct to poly(ethylenimine) is not decreased if the exocyclic nitrogen is a secondary amine instead of a tertiary one (see derivatives K and L of Table II). Thus a general approach has been opened up for introducing chirality into these polymers.

It has been shown previously[20] that stereoselectivity in hydrolysis of amino acid nitrophenyl esters is manifested by poly(ethylenimines) containing covalently linked L-histidine. Other optically active amino acids could also be attached to poly(ethylenimine), but in general, they provide no effective nucleophile. With the aminopyridines, in contrast, essentially any amino acid could be coupled to the amine nitrogen to give a chiral entity with the desired side chain automatically linked to a pyridine nucleophile. Furthermore, the same procedure should work with peptides. Thus a wide range of specificities and stereoselectivity may be attainable. Thus these investigations demonstrate additional aspects of the versatility of poly(ethylenimines) as a macromolecular framework for the construction of synzymes.[1]

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Registry No. **3**, 80028-19-9; **4**, 80028-20-2; **5**, 80028-21-3; **6**, 64690-61-5; **7**, 80028-22-4; **8**, 80028-23-5; 9, 5747-92-2; **10**, 80028-24-6; **10**·HCl, 80028-25-7; **11**, 80028-26-8; **12**, 80028-27-9; **12**·HCl, 80028-28-0; **13**, 80028-29-1; **14**, 80028-30-4; **14**·HCl, 80028-31-5; **15**, 80028-32-6; **16**, 80028-33-7; **16**·HCl, 80028-34-8; **17**, 80028-35-9; **18**, 80028-36-0; **18**·HCl, 80028-37-1; 19, 80028-38-2; **20**, 80028-39-3; **20**·HCl, 80028-40-6; **21**, 80028-41-7; DL-**22**, 80028-42-8; **23**, 80028-43-9; 4-aminopyridine, 504-24-5; methyl acrylate, 96-33-3; decanoyl chloride, 112-13-0; 1-benzyl-3-(ethoxycarbonyl)-5-pyrrolidinone, 5733-87-9; ethyl pyrrolidine-3-carboxylate HCl, 80028-44-0; 4-phenoxypyridine, 4783-86-2; ethyl nipecotate HCl, 65550-28-9; ethyl 6-aminohexanoate, 371-34-6; 4-(methylamino)pyridine, 1121-58-0; adipoyl chloride monoethyl ester, 1071-71-2; DL-proline, 609-36-9; poly(ethylenimine), 9002-98-6.

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The Pyridinium–Dihydropyridine System. Reduction Potentials and the Mechanism of Oxidation of 1,4-Dihydropyridines by a Schiff Base

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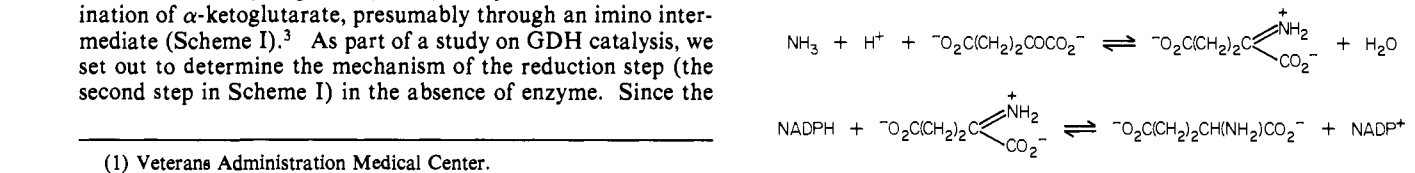
Abstract: As a model system for the glutamate dehydrogenase catalyzed reductive amination of α-ketoglutarate we have studied the reduction of a Schiff base, Δ¹-pyrroline-2-carboxylic acid, by a series of 14 N-1 and C-3 substituted 1,4-dihydropyridines, including NMNH, NADH, and NADPH. The reversible electrode potentials of eight of the dihydropyridines, all dihydronicotinamides, have also been determined. The reduction reaction has the following characteristics: (a) it is first order in protonated Schiff base (zwitterionic form) and first order in the dihydropyridine, (b) there is a small deuterium isotope effect when the C-4 position of the dihydropyridine is deuterated (1.20–1.57 at 25 °C), (c) there is a direct transfer of hydrogen from C-4 of the dihydropyridine to C-2 of the pyrroline, (d) the rates for seven N-1 substituted dihydronicotinamides are correlated satisfactorily with σ^* giving $\rho^* = -1.98$ (H_2O) and −1.78 (aqueous methanol), there being only a modest difference in rates in these two solvents, (e) there is a good correlation between the rates of reduction by the dihydronicotinamides and the E^0 values of the reversible two-electron dihydropyridine–pyridinium couple, the effect being 31.0 mV per logarithmic unit of rate, (f) there is a close correlation between the rates of reduction of pyrroline and of flavin by the dihydropyridines, and (g) the enthalpy and entropy of activation for the rate-controlling step in the reduction by 1-benzyl-1,4-dihydronicotinamide are 15.7 kcal mol^{-1} and −7.6 eu. We believe that direct hydride transfer has taken place to produce proline in a single step and it can be inferred that the transition state closely resembles products in structure. The similarity between pyrroline and flavin reduction suggests that the latter reaction may also be a direct hydride transfer.

Glutamate dehydrogenase (GDH) catalyzes the reductive amination of α-ketoglutarate, presumably through an imino intermediate (Scheme I).[3] As part of a study on GDH catalysis, we set out to determine the mechanism of the reduction step (the second step in Scheme I) in the absence of enzyme. Since the imino intermediate is very unstable in water, we used as a model the Schiff base, Δ¹-pyrroline-2-carboxylic acid, **1**, which is known to be reduced by NADH to proline.[4] We have studied the kinetics

Scheme I



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