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N-Hydroxy Amides. I. Synthesis of *N*-Benzyloxy and *N*-Hydroxy Peptides *via* Polymerization of *N*-Benzyloxy DL-α-Amino Acid *N*-Carboxy Anhydrides

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Polymerization of *N*-benzyloxy DL-α-amino acid *N*-carboxy anhydrides (*N*-benzyloxy-NCAs) has been carried out in benzene for 30 d with cyclohexylamine as initiator. The N-benzyloxy-NCAs of glycine, alanine, 2-aminobutyric acid, and leucine give the corresponding polymers in good yields, while the starting material is recovered from those of valine and phenylalanine. The different behavior in the polymerization is discussed in terms of steric crowding. Catalytic hydrogenation of the *N*-benzyloxy polymers produces poly(*N*-hydroxy peptide)s. Complex formation of these polymers with iron(III) has been examined. Among the polymers, poly(*N*-hydroxyalanine) is further converted into poly(*N*-acetoxyalanine), which acts as an acyl active polymer. Treatment of poly(*N*-benzyloxyalanine) with $B(CF_3CO_2)_3$ gives 1,4-dihydroxy-3,6-dimethyl-2,5-piperazinedione.

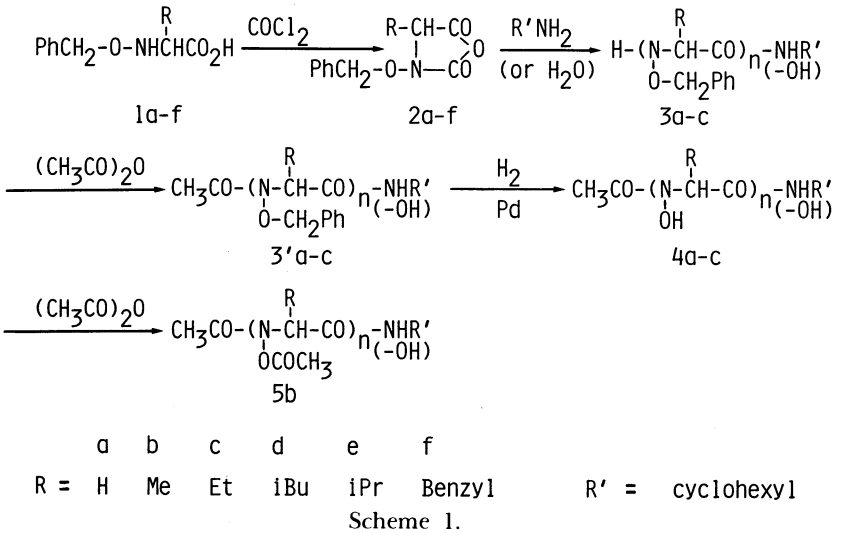
A number of hydroxamic acid derivatives have been found in nature. These natural hydroxamic acids show unique biological activities, including microbial iron transport (siderophore).[1-3] It is worthwhile to synthesize *N*-hydroxy peptides which have hydroxamic acid functions in their peptide backbone. Several simple *N*-hydroxy peptides have already been prepared by a few procedures,[4-7] and studies in this field have become increasingly active.[8-11] In a preliminary letter, we have shown a stepwise synthesis of an alternating *N*-hydroxy peptide by use of *N*-benzyloxy DL-α-amino acid *N*-carboxy anhydrides (*N*-benzyloxy-NCAs).[8] The synthesis was successful because of the slowness of the NCA polymerization. In an attempt to obtain homodetic poly(*N*-hydroxy peptide)s, a prototype of *N*-hydroxy peptides, we felt it necessary to examine polymerization of these new NCAs. This paper describes polymerization of these NCAs and subsequent removal of the benzyl group in the polymers, which will lead to hitherto unknown poly(*N*-hydroxy peptide)s.

Results and Discussion

Scheme 1 depicts the outline of the reactions. *N*-Benzyloxy DL-α-amino acids (**1a—f**) were obtained by reaction of α-bromoalkanoic acids with *O*-benzylhydroxylamine.[12] Their amino group has a low pK_a due to the inductive effect of the oxygen. Phosgenation of **1a—f** in benzene–THF gave *N*-benzyloxy-NCAs (**2a—f**) in good yields.

It is known that NCAs having bulky substituents seldom polymerize, and successful examples are limited to certain polymers, polyproline, poly(*N*-methylalanine), and a few poly(*N*-substituted glycines).[13-16] Preliminary experiments did show, however, that some of the present NCAs can be polymerized into peptide derivatives under well-chosen conditions. The first-order plots of the reactions show a small upward break, familiar in the usual NCA (Fig. 1). They indicate a slow reaction.

Accordingly, polymerization of **2a—f** was performed in benzene at 40 °C for 30 d using cyclohexylamine as an initiator. Water also proved to be an efficient initiator. Typical polymerization results are summarized in Table 1. **2a—d** afforded polymerization products (**3a—d**), although **3d** was a glassy solid and showed a slight deviation in elemental analysis. The starting material was recovered from **2e** and **2f**, and even more forcing conditions failed to give a polymer from **2e**. The degree of polymerization (DP) for polymers obtained is smaller than the value expected from the ratio of NCA



Scheme 1.

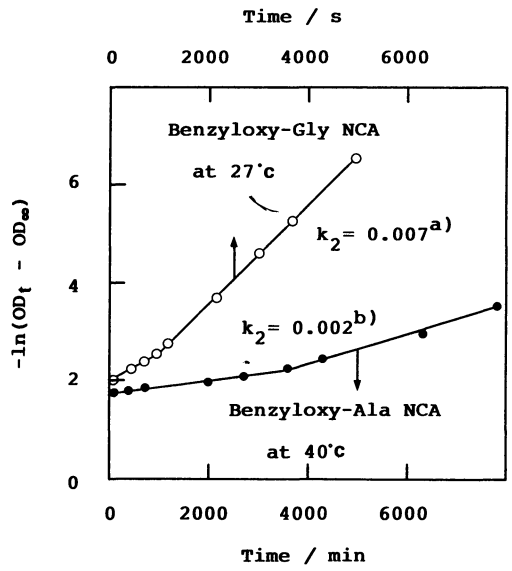


Fig. 1. Pseudo-first-order plots for cyclohexylamine initiated polymerization of *N*-benzyloxy-NCAs of glycine and alanine, as followed by the optical density difference, (OD_t—OD_∞), of the anhydride carbonyl group at 1860 cm^{-1}. [NCA]/[amine]=10. The corresponding second-order rate constants (k_2) appear along with linear portions of the plots: a) 1 $mol^{-1}s^{-1}$: b) 1 $mol^{-1}min^{-1}$.

TABLE 1. POLYMERIZATION OF *N*-BENZYLOXY-NCAs[a]

NCA	R	Yield %	Product	Mol wt (DP)[b]
2a	H	99	**3a**	2350 (14)
2b	Me	99	**3b**	2300 (13)
		95	**3b**	5500 (30)[c]
2c	Et	83	**3c**	1290 (7)
2d	*i*-Bu	96	**3d**	1280 (6)
2e	*i*-Pr		No polymer[d]	
2f	Benzyl		No polymer[d]	

a) Carried out in benzene at 40 °C for 30 d in the presence of cyclohexylamine with a ratio of [NCA]/[amine]=25. b) Degree of polymerization. c) [NCA]/[cyclohexylamine]=50. d) Most of the NCA was recovered unchanged.

to initiator, and a decrease in DP with increasing bulkiness of α-substituents, is also noted. These results indicate that there is a boundary line between α-substituents, *i*-Bu and *i*-Pr, as to polymerizability of these NCAs. The fact that DP is low while the yield is high suggests a concurrent initiation other than that caused by the initiator amine.[17] Initiation by water is most plausible for the present system.

A key factor for the polymerization seems to be steric bulk rather than basicity, since the *N*-benzyloxyamino group has much weaker basicity than the *N*-alkylamino group. Compare, for example, *N*-benzyloxyalanine with *N*-benzylalanine. The NCA of the latter does not polymerize.[15] The former has a less hindered environment around the nitrogen than the latter; there are only two unshared electron pairs and one methylene group on the oxygen adjacent to the nitrogen in the former, while two hydrogens and one phenyl group exist on the adjacent carbon atom in the latter. The failure of **2e** and **2f** in the polymerization is ascribed to a combined steric hindrance of *N*- and C^α-substituents.[18]

In the IR spectra poly(*N*-benzyloxy peptide)s show an amide I band at slightly higher wave number (1670 cm^{-1}) than those of *N*-alkyl substituted polypeptides[15] (1635—1639 cm^{-1}). ^{1}HNMR peaks correspond to protons of the expected structures for the polymers; common peaks observed are around δ=5.0 for $PhCH_2O$–, 5.4 for α-CH, and 7—7.5 for C_6H_5. A molecular formula for each polymer is provided by adequately adding fractions of a water molecule on the basis of observed DP and the initiator used. The detailed data for polymer characterization are presented in the experimental section.

For conversion of poly(*N*-benzyloxy peptide)s into poly(*N*-hydroxy peptide)s several debenzylation procedures were attempted. Treatment of poly(*N*-benzyloxyalanine) (**3b**) with $B(CF_3CO_2)_3$[7] in CF_3CO_2H gave the cyclic dimer of *N*-hydroxy-DL-alanine in 68% yield. The product was identified on the basis of IR, NMR and mass spectral data. The preferential cyclodimerization seemed to occur through fragmentation from a formed *N*-hydroxy peptide *N*-terminus, since no decrease in DP was observed when **3b** was dissolved in CF_3CO_2H for the same period. Hydrogenolysis with Pd catalysts gave partially debenzylated products, or extensively hydrolyzed products when subjected to a prolonged reaction. Hydrolysis in this case is considered to take place on the catalyst surface by the action of water which is generated from occluded oxygen.[19]

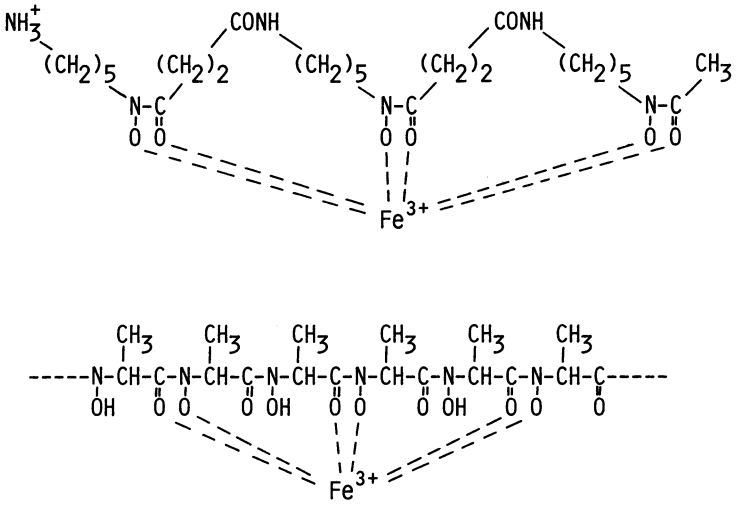
Hydrogenolysis was accomplished by reducing *N*-terminal-acetylated polymers (**3′**) with $Pd(AcO)_2$, giving the desired poly(*N*-hydroxy peptide)s (**4**). The catalyst was effective because $Pd(AcO)_2$ is soluble and can penetrate into the polymer entanglement at the outset of the reaction. Typical results are summarized in Table 2. Times required for the reaction apparently depend on the size of the α-substituents. Decrease in DP during the hydrogenolysis was inevitable with **4a**. Polymers (**4a—c**) show ^{1}HNMR signals which correspond to the expected structure; common signals are at δ=2.0 for CH_3CO, 5.3 for α-CH, and 9.2 for HO-N. IR spectra show a broad and strong band in the carbonyl region (1650 cm^{-1}) and new peaks at 3200 and 1180 cm^{-1} due to the *N*-OH moiety.

Hydroxamic acid polymers **4a—c** when mixed with $FeCl_3$ gave an intense violet color characteristic of the complex with $FeCl_3$. The absorbancy of the complex with increasing amounts of iron (III) is shown for poly(*N*-hydroxyalanine) as a representative example (Fig. 2). For comparison, the complex formation

TABLE 2. DEBENZYLATION OF POLYMERS (**3**) BY HYDROGENOLYSIS[a]

Polymer used	(mg)	(DP)	Solvent	Temp °C	Time h		Yield mg	(DP)
3a′	350	(14)	TFA	35	1	**4a**	175	(8)
3b′	350	(30)	DMF	30	4	**4b**	189	(30)
3c′	350	(7)	DMF	40	40	**4c**	167	(7)

a) Under atmospheric pressure with 500 mg of $Pd(CH_3COO)_2$.



Scheme 2.

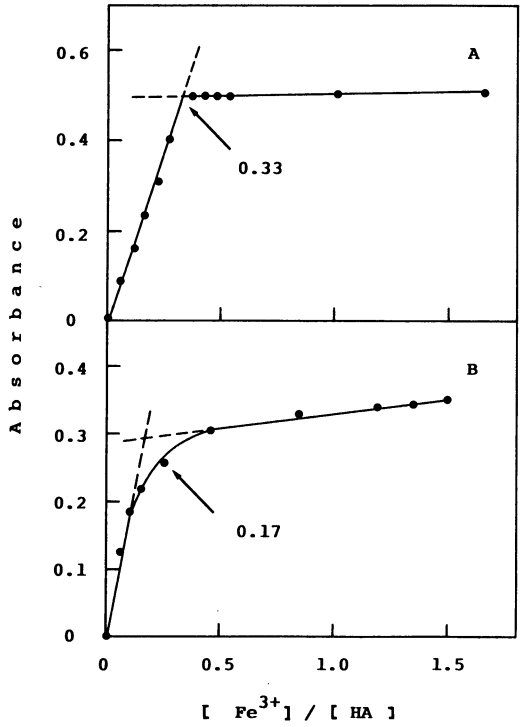


Fig. 2. Plot of absorbance *vs.* the ratio of iron(III) to the hydroxamic acid units; A: DFO and B: poly(*N*-hydroxyalanine) as a representative of these poly(*N*-hydroxy peptide)s. Absorbance at 430—450 nm in A and 450—470 nm in B, in 50% aqueous DMF, pH=3, ionic strength=0.1 (KNO_3).

of a typical trihydroxamic acid, desferrioxamine B (DFO),[20] was measured under similar conditions. An intersection of the dashed lines corresponds to an average molar ratio between Fe^{3+} and the hydroxamic acid groups. DFO gives a sharp inflection, while the polymer reveals considerable curvature. Compared with the ratio of DFO (0.33), values of the ratio for polymers decreased gradually from **4a** to **4c**; 0.26 for **4a**, 0.17 for **4b**, and 0.15 for **4c**. The absorbance of the complex is larger for DFO than that for the polymers under these conditions. These differences clearly indicate that for effective iron binding, considerable chain spacing is necessary between hydroxamic acid groups, while bulky α-substituents in the polymers are unfavorable for formation of stable iron complexes.

By acylation with acetic anhydride, polymer **4b** gave poly(*N*-acetoxyalanine) (**5b**). Strong carbonyl absorptions are observed for **5b** at 1800 (N–O–$COCH_3$) and 1670 (N–CO–) cm^{-1}, the latter amide band being shifted again close to that of the poly(*N*-benzyloxy peptide)s. As expected from the structure, **5b** was able to acetylate cyclohexylamine readily at room temperature.

Experimental

All melting points are uncorrected. IR spectra were taken with a JASCO model DS 403G infrared spectrophotometer. ^1HNMR spectra were recorded on a JEOL FX 200 spectrometer with Me_4Si as internal standard. Visible spectra were obtained on a Hitachi 320 spectrophotometer. Elemental analyses was performed by the analytical section, Institute of Physical and Chemical Research, Saitama. *N*-Benzyloxy α-amino-acids were prepared by the reported procedure with slight modifications.[12] Methanesulfonate salt of desferrioxamine B (Desferal) was obtained through Ciba-Geigy, Japan.

N-Benzyloxy α-Amino Acid N-Carboxy Anhydrides (2). *N*-Benzyloxy α-amino acid (0.10 mol) was suspended in a benzene–THF mixture (70 ml, 1:1 v/v). Phosgene from trichloromethyl chloroformate (24 ml, 0.20 mol) was bubbled to the suspension at 40 °C for 1 h, the clear solution which resulted was concentrated before the addition of THF (30 ml). The THF solution was treated with triethylamine (5 g, 0.05 mol) with stirring at −5—−10 °C for 1 h. After filtration of triethylammonium chloride and evaporation of the solvent, the residue was dissolved in diethyl ether and hexane was added. The mixture was kept at −20 °C until crystallization was completed. The crystals were collected and dried in a desiccator over P_2O_5. *N-Benzyloxyglycine NCA (2a)*: Mp 70—71 °C (lit,[8] 63—64 °C) (Found: C, 58.28; H, 4.39; N, 6.86%. Calcd for $C_{10}H_9NO_4$: C, 57.96; H, 4.39, N, 6.76%). *N-Benzyloxy-DL-alanine NCA (2b)*: Mp 71—72 °C (lit,[8] 71—72 °C). (Found: C, 59.67; H, 4.97; N, 6.30%. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33%). *N-Benzyloxy-DL-α-aminobutyric Acid NCA (2c)*: Mp 67—68 °C (lit,[8] 65—66 °C) (Found: C, 61.58; H, 5.73; N, 6.96%. Calcd for $C_{12}H_{13}NO_4$: C, 61.28; H, 5.53; N, 6.96%). *N-Benzyloxy-DL-leucine NCA (2d)*: Oil, (Found: C 3.92; H, 6.56; N, 5.40%.

Calcd for $C_{13}H_{17}NO_2$: C, 63.86; H, 6.51; N, 5.32%). *N-Benzyloxy-DL-valine NCA (2e)*: Mp 51—52 °C (lit,[8] 50—51 °C) (Found: C, 62.71; H. 6.03; H, 5.38%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%). *N-Benzyloxy-DL-phenylalanine NCA (2f)*: Mp 147—148 °C (lit,[8] 147—148 °C) (Found: C, 68.45; H, 5.12; N, 4.68%. Calcd for $C_{17}H_{15}NO_4$ C, 68.67; H, 5.08; N, 4.71%). These NCAs were stable for several months in the refrigerator. For polymerization they were recrystallized (or reprecipitated) twice from diethyl ether–hexane.

Kinetics by IR. Polymerization of NCAs (**2a** and **2b**) in benzene was initiated with [NCA]/[cyclohexylamine]=10. For **2a**, a portion of the mixture was transferred to the IR cell and spectra of the mixture were taken at appropriate time intervals through a range of 1900—1600 cm^{-1}. The temperature of the cell was 27±1 °C. For **2b**, aliquots were transferred at intervals from a polymerization solution maintained at 40± 0.1 °C to the IR cell, and the spectra were taken as above.

Polymerizaion. To a solution of the NCA (**2**) (2—3 g, 9.45 mmol) in benzene (19 ml) was added 3.0 ml solution of cyclohexylamine (0.312 g, 3.15 mmol) in benzene (25 ml). The mixture was cooled, degassed, and sealed off under vacuum; it was kept at 40 °C for one month. After the tube was opened and the solvent was evaporated, the residue was washed with diethyl ether on a glass filter. The product was dissolved in benzene (**3a** in dioxane) and precipitated into hexane.

Poly(N-benzyloxyglycine) (3a): Mp 164—167 °C; IR 1665 cm^{-1} (C=O); ^{1}H NMR ($C_4D_8O_2$) δ=0.8—1.3 (weak m, cyclohexyl), 4.4—4.7 (2H, m, NCH_2), 4.83 (2H, br s, OCH_2), and 7.1—7.6 (5H, m, phenyl). Found: C, 66.23; H, 5.95; N, 8.51%. Calcd for $(C_9H_9NO_2)_{14}\cdot C_6H_{13}N\cdot(11/14)H_2O$: C, 66.18; H, 5.76; N, 8.68%.

Poly(N-benzyloxy-DL-alanine) (3b): Mp 119—121 °C; IR 1665 cm^{-1} (C=O); ^{1}H NMR ($C_4D_8O_2$) δ=1.2—1.5 (3H, m, Me), 4.9—5.1 (2H, m, OCH_2), 5.4 (1H, br s, α-H), and 7.1—7.5 (5H, br s, phenyl). Found: C, 67.77; H, 6.57; N, 8.11%. Calcd for $(C_{10}H_{11}NO_2)_{13}\cdot C_6H_{13}N\cdot(12/13)H_2O$: C, 67.62; H, 6.42; N, 8.01%.

Poly(N-benzyloxy-DL-α-aminobutyric acid) (3c): Mp 106—109 °C; IR 1655 cm^{-1} (C=O); ^{1}H NMR ($C_4D_8O_2$) δ=0.5—0.9 (3H, m, Me), 1.8—2.2 (2H, br d, C-CH_2), 4.9—5.5 (3H, m, OCH_2 and α-H), and 7.1—7.5 (5H, m, phenyl). Found: C, 68.70; H, 7.10; N, 7.70%. Calcd for $(C_{11}H_{13}NO_2)_7\cdot C_6H_{13}N\cdot(18/7)H_2O$: C, 68.59; H, 7.05; 7.44%.

Poly(N-benzyloxy-DL-leucine) (3d): A glassy solid, IR 1655 cm^{-1} (C=O); ^{1}H NMR ($C_4D_8O_2$) δ=0.4—1.1 (6H, m, 2Me), 1.1—2.2 (3H, m, CH-CH_2), 4.7—5.8 (3H, m, OCH_2 and α-H), and 7.1—7.6 (5H, m, phenyl). Found: C, 70.19; H, 7.94; N, 7.03%. Calcd for $(C_{13}H_{17}NO_2)_6\cdot C_6H_{13}N\cdot H_2O$: C, 70.46; H, 8.23; N, 6.89%.

None of the following solvents gave better polymerization results than benzene; acetonitrile, dichloromethane, dioxane, THF, and toluene.

Debenzylation. *(a) With $B(CF_3CO_2)_3$*: To a solution of the *N*-benzyloxyalanine polymer (**3b**) (400 mg, 2.2 mmol) in trifluoroacetic acid (5 ml) was added $B(CF_3CO_2)_3$ (7.9 g, 22.5 mmol) and stirred for 48 h at room temperauture. The acid was evaporated and methanol was added to the residue. Evaporation and addition of methanol were repeated three times. After filtration of the orthoboric acid derivative and concentration to 3 ml, the solution was introduced into an LH-20 Sephadex column and eluted with methanol. Evaporation of the main fraction gave a crystalline compound (132 mg): yield 68%; mp 212 °C (decomp); R_f 0.66 (*n*-BuOH:AcOH:H_2O 4:1:1); IR 1670 cm^{-1} (C=O); ^{1}H NMR (D_2O) δ=1.46 (6H, d, Me), 4.30 (2H, q, α-H). Found: C, 41.33; H, 5.82; N, 15.70%; M^+, 174. Calcd for $C_6H_{10}N_2O_4$: C, 41.60; H, 5.85; N, 15.66%; M^+, 174.

(b) Hydrogenolysis: Before hydrogenolysis, *N*-terminal acetylation was performed by heating the polymers (**3a—c**) (800 mg) with Ac_2O (10 ml) in dioxane (10 ml) at 80 °C for 1 h, to give acetylated polymers (**3a′—c′**) (778 mg). A solution of **3a′** (350 mg) and $Pd(AcO)_2$ (500 mg) in trifluoroacetic acid (20 ml), or **3b′** or **3c′** (350 mg) in DMF (20 ml), was reduced with H_2 under atmospheric pressure until Pd metal separated from the solution. After removal of the Pd catalyst and evaporation of the solvent, the residues were washed with Et_2O and dried under vacuum to give white powders (**4a—c**) (Table 2).

Poly(N-hydroxyglycine) (4a): Mp 169—173 °C (decomp); ^{1}H NMR (Me_2SO-d_6 at 80 °C) δ=1.5 (br, C_6H_{11}–), 2.0 (s, CH_3CO–), 4.5 (2H, CH_2), and 9.5 (1H, HO-N). Found: C, 34.37; H, 4.64; N, 16.98%. Calcd for (8/14)CH_3CO(6/14)H-$(C_2H_3NO_2)_8\cdot(8/25)C_6H_{12}N\cdot(17/25)OH+H_2O$: C, 34.15; H, 4.87; N, 17.39%.

Poly(N-hydroxy-DL-alanine) (4b): Mp 139—142 °C; ^{1}H NMR (Me_2SO-d_6 at 80 °C) δ=1.35 (3H, CH_3), 1.7 (br, C_6H_{13}), 2.0 (CH_3CO), 5.3(1H, α-H), and 9.2 (1H, HO-N). Found: C, 42.48; H, 6.33; N, 15.33%. Calcd for $CH_3CO(C_3H_5NO_2)_{30}\cdot(30/50)C_6H_{12}N\cdot(20/50)OH$: C, 42.18; H, 5.98; N, 15.75% .

Poly(N-hydroxy-DL-α-aminobutyric acid) (4c): Mp 161—163 °C; ^{1}H NMR (Me_2SO-d_6 at 80 °C) δ=0.85 (3H, CH_3), 1.85 (2H, -CH_2), 2.1 (CH_3CO), 5.3 (1H, α-H), and 9.1 (1H, HO-N). Found: C, 46.81; H, 7.09; N, 13.25%. Calcd for $CH_3CO(C_4H_7NO_2)_7\cdot(7/25)C_6H_{12}N\cdot(18/25)OH+H_2O$: C, 47.07; H, 7.19; N, 12.62%.

Poly(N-acetoxy-DL-alanine) (5b) and Its Use as an Acyl Active Polymer. *(a) Acetylation*: To a suspension of **4b** (135 mg) in THF (10 ml) was added acetic anhydride (5 ml) in THF (10 ml); the mixture was heated at 50 °C for 1 h. The resulting solution was concentrated under vacuum and the residue was washed with Et_2O to give a white product. The product was precipitated from THF into Et_2O and dried under vacuum to give **5b** (161 mg, 80%). Mp 154—157 °C, IR 1800 (N-O-$COCH_3$) and 1670 (N-CO-) cm^{-1}. Found: C, 46.22; H, 5.59; N, 10.64%. Calcd for $CH_3CO(C_5H_7NO_3)_{30}\cdot(30/50)C_6H_{12}N\cdot(20/50)OH$: C, 46.93; H, 5.54; N, 10.79%.

(b) Acylation with 5b: To a solution of **5b** (95 mg, 0.74 mmol) in THF (10 ml) was added cyclohexylamine (65.6 mg, 0.66 mmol) in THF (10 ml). After the mixture was kept at 25 °C for 30 h, the solution was concentrated to dryness and the residue was extracted with Et_2O. Evaporation of the combined ethereal solution gave a crude product (86 mg, 92%) of mp 99—101 °C (*N*-cyclohexylacetamide, mp 104 °C).

Molecular Weight Determination. The degree of polymerization (DP) was determined by measuring the number average molecular weight of the products (**3a—c** and **4a—c**) with a Hitachi vapour pressure osmometer, model 117. A calibration line was made with benzil as a reference compound. Measurement was performed using dioxane for **3a** at 35 °C, benzene for **3b—c** at 40 °C, and DMF for **4a—c** at 55 °C, respectively. The values are accurate within±5% errors.

Molar Ratio Determination for Iron(III) Complexes. DMF stock solutions of samples were prepared at concentrations of 0.002 hydroxamic acid equiv/l. Aqueous ferric nitrate solutions of approximately 0.003 mol/l were prepared and standardized with EDTA (bismuth method). Aliquots (1 ml) of the sample solution were placed in each of a series of 10 ml volumetric flasks, and varying amounts of iron solution were added. The resulting solutions were diluted to 10 ml, so as to become aqueous 50% DMF solution of ionic strength of 0.1 (KNO_3). The pH of the solutions was made 3.0 with diluted nitric acid. The absorbance of each solution was measured at λ_{max} (450—470 nm).

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