Aliphatic Polyamides Prepared by Ester-Amine Polycondensation as Potential Drug Carrier Polymers

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ABSTRACT: Aliphatic polyamides of interest as macromolecular drug carriers are synthesized by base-catalyzed polycondensation of aliphatic diesters with diamines. The reactions are conducted in the presence of anhydrous sodium carbonate at temperatures ranging from ambient to 65°C, initially in the undilute state. The addition of aprotic solvent at a later stage serves to maintain sufficiently low viscosity for proper homogenization. The comonomers, diethyl 3,6,9-trioxaundecanedioate and 4,7,10-trioxa-1,13-tridecanediamine, copolymerize to form polymer 1, a straight-chain polyamide devoid of specific functionality. Use of diethyl tartrate in lieu of the aforementioned diester leads to polyamide 2 possessing hydroxyl side groups. Other experiments in which diamines incorporating additional (secondary) amino groups are employed afford polyamides 3–8 containing such secondary amine functions as main-chain constituents. The water-soluble target polymers are crudely fractionated by aqueous dialysis (12000–14000 molecular mass cut-off) and collected by freeze-drying in yields of 20 to 40%. The low-yield range has been accepted in this investigation as the price to be paid for the realization of linear polyamide structures in accordance with compositional expectations, a requirement vital for the proper functioning of the polymers as drug carriers. The practicability of drug binding (conjugating) is exemplified by the coupling of ferrocene as a drug model to polyamide 5 via amide linkage. The water-soluble conjugate 5-Fc features an iron content corresponding to one ferrocene group in the repeat unit. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 2143–2150, 1999

Key words: diesters; diamines; polyamides; drug carriers; polymer-ferrocene conjugate

INTRODUCTION

As part of an ongoing program in this laboratory to develop water-soluble macromolecules as carriers of medicinal agents[1,2] we reinvestigated the classical ester-amine condensation reaction with a view to elaborate a nonaggressive polymerization process suitable for the synthesis of functionally sensitive macromolecular compounds without having to take recourse to group protection strategies. We were encouraged in this endeavor by the recent report[3] of amide formation through nonpolymeric, base-catalyzed ester-amine condensation in dimethyl sulfoxide (DMSO) solvent, found to proceed over a 20-h period at ambient temperature. Appropriately modified, this procedure indeed proved suitable for the copolymerization of diesters with primary diamines under conditions mild enough to permit the unperturbed incorporation into the main chain of additional unprotected functionality, such as hydroxyl or secondary amino groups, these groups to serve subsequently as drug binding sites. In the following, we report on the results of this ester-amine polycondensation study.

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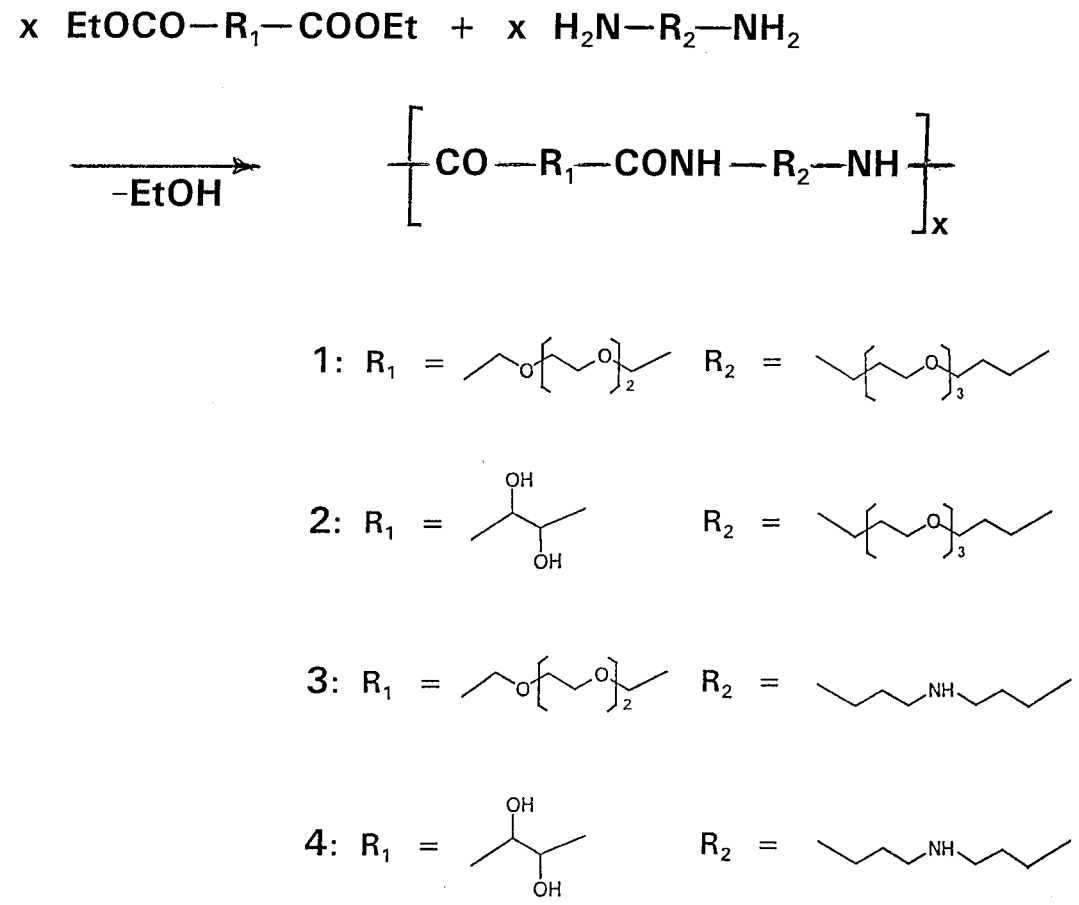


Scheme 1

RESULTS AND DISCUSSION

In this project, involving the polycondensation of diesters and diamines to produce linear polyamides, two diester monomers were used, *viz* diethyl 3,6,9-trioxaundecanedioate (TRIDEC) and diethyl L-tartrate (TART). These were paired up with five different diamine monomers used either singly or in certain combinations. Preliminary experiments employing a diamine devoid of additional functionality, namely, 4,7,10-trioxa-1,13-tridecanediamine (TRA), served to establish basic reaction conditions. Equimolar quantities of TRIDEC and TRA in the presence of anhydrous sodium carbonate (20% by mass of reactants) were allowed to undergo condensation with elimination of ethanol (Scheme 1). First, in a number of trial runs, suitable conditions of time, temperature, and solvent use were established. These included stirring the neat reactant mixture for 1 to 2 days at ambient temperature and, upon minor dilution with an aprotic solvent, such as tetramethylurea (TMU) or dimethyl sulfoxide (DMSO), for another 10 to 15 days at 55 to 65°C. The crude polymerization products, precipitated with suitable nonsolvents, were freed from low-molecular constituents by aqueous dialysis (molecular mass cut-off 12,000) and collected in the solid state by freeze-drying of the retentate in yields of 30 to 40%. The water-soluble products possessed inherent viscosities in the range of 5–8 mL g^{-1} and, as shown by ^1H nuclear magnetic resonance (NMR) spectroscopy, conformed in composition to the polyamide structure 1. This spectroscopic assignment was facilitated by the emergence of the α-CH_2 proton signal of the diacid component in the vicinity of 4.1 ppm, a region devoid of other bands (see Experimental). The emergence of a weak additional resonance at 3.95 ppm in the product spectra of these and other experiments employing the TRIDEC monomer attests to the presence of a CH_2—COOH end group; free TRIDEC gives a band at this position.

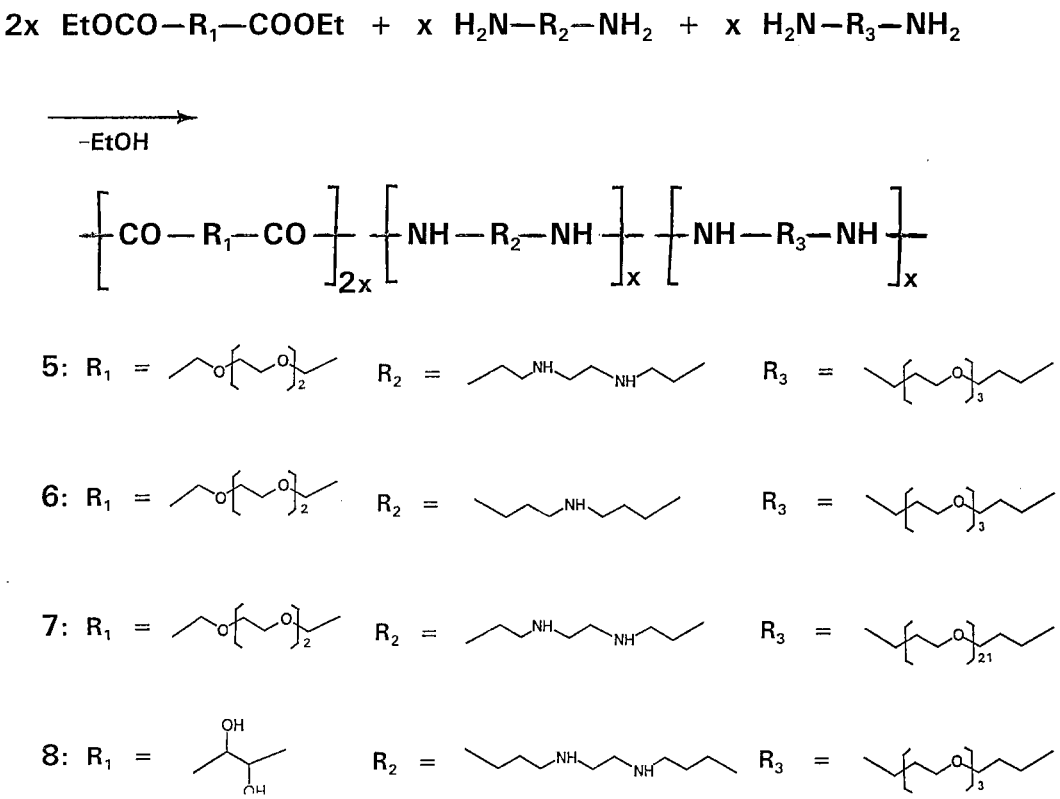
Analogous experiments performed with TART in place of TRIDEC as the diester gave polyamide 2 (Scheme 1) in yields of typically 45%. Although equivalent or better yields resulted from running the reactions neat (i.e., in the melt, with no solvent added) for the entire duration of the experiments, the dilution step was included routinely in order to facilitate regioselective *N*-substitution and, thus, simulate the conditions required for polycondensations involving monomers bearing additional functional groups. Structural characterization of 2 by ^{1}H NMR utilized the CH proton resonance of the tartrate segment near 4.4 ppm.

Extended heating periods or temperatures drastically elevated beyond the 60 to 65°C range in these polycondensations caused further increases in conversion and overall molecular size. However, again, such conditions were not routinely applied in view of the requirement to maintain conditions mild enough to preserve the integrity of additional drug-binding functionality, notably secondary amino groups, as introduced in the subsequent series of polycondensation runs. In those experiments, *N,N*-bis(3-aminopropyl)-amine (BPA) was chosen as the diamine monomer. Initial runs conducted at ambient temperature throughout (10–12 days), with just enough DMSO added to maintain sufficient fluidity, gave resinous polyamides 3 and 4 (Scheme 1) in yields as low as 5 to 20%. Under these mild conditions, the compositions were strictly in accord with the expected structures. Specifically, there was no attenuation of intensity at 2.8 ppm and no concomitant increase in intensity of the signal at 3.2 to 3.4 ppm in the NMR spectra at pH 10; such intensity reversals would be expected in the case of partial acylation of secondary amine functions with resultant branching. Subsequent experiments in which an ambient-temperature period (1 to 2 days) was now followed by a heating period at 55 to 60°C (15 days), gave 3 and 4 in yields of typically 25 and 29%, respectively, with no changes noticeable in the NMR spectra. On the other hand, changing the heating cycle to 24 h at 100°C, while resulting in further yield increase (35–55%), gave product polymers whose NMR spectra indeed showed a further increased proton count at 3.3 ppm and a decreased count at 2.8 ppm, strongly suggesting that some acylation at secondary amino groups did occur now at these further elevated temperatures. These findings suggested that ultimate condensation temperatures of up to 60°C would be tolerated without detriment to the intrachain-type secondary amino groups, yet is also became clear from these results that, in order to achieve correct polymer compositions, forcing experimental conditions that might lead to enhanced conversion should be avoided.

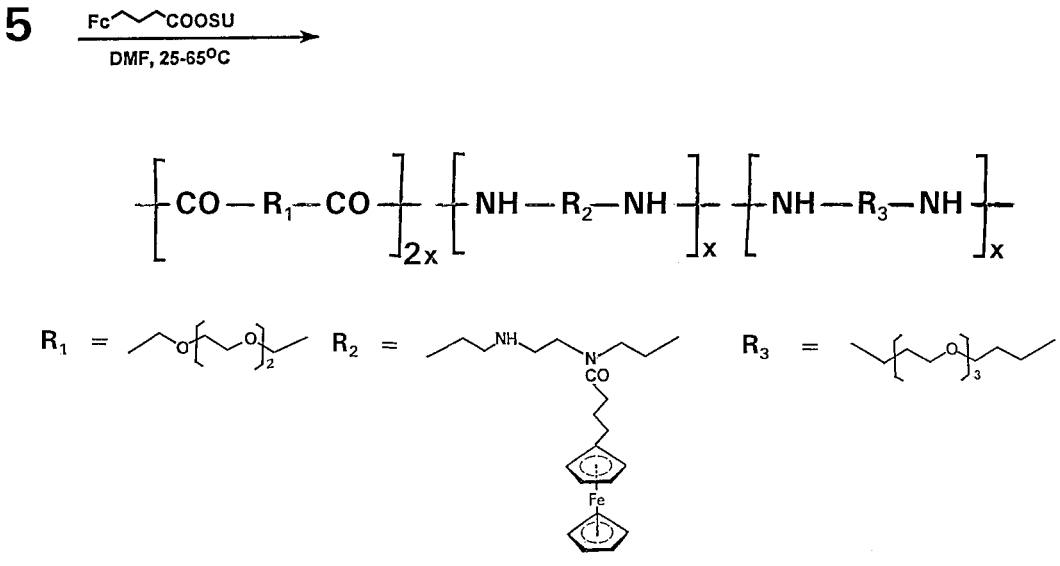
The main thrust of the project was focused on the preparation of copolyamides through use of two different diamines in the polycondensation process, one of these providing an oligo(ethylene oxide) segment serving as a solubilizing constituent, and the other acting as a vehicle for the introduction of secondary amino groups as drug binding sites. The combination of TRIDEC with the diamine pair, triethylenetetramine (TET) plus TRA, is representative of this approach. The diester was treated, again in the presence of sodium carbonate, with 0.5 equiv. each of the two diamines for 2 days at ambient temperature. Upon moderate dilution with DMSO, the mixture was heated for 15 days at 55°C. Work-up as elaborated for the homopolymers afforded copolyamide 5 (Scheme 2) as a water-soluble resin in yields of about 30%. NMR data confirmed the 1 : 1 stoichiometry of the incorporated diamine segments.

In a similar fashion the copolyamides 6, 7, and 8 (Scheme 2) were obtained, again in comparatively low yields, and the NMR spectra were well in accord with the assigned structures. As before, we did not generally use the expediency of applying higher condensation temperatures for enhancement of conversion in order to avoid involvement of the secondary amino groups as discussed in the foregoing. However, for comparison, in one experiment leading to 7 the temperature was raised to 70°C. While the yield increased to 50%, the NMR spectrum of 7, not unexpectedly, revealed a 12% intensity loss at 2.7 ppm and a corresponding intensity gain at 3.3 ppm, suggesting an ever so minor degree of acylation of the intrachain-type secondary amino groups despite the aforementioned temperature restrictions. The extent of such attack on —NH— was too insignificant, however, to cause ultimate crosslinking, and even on prolonged storage in the solid state no loss of water solubility was observed, nor was there an unexpected viscosity increase, the inherent viscosity being well within the range shown by other polyamides comprising poly(ethylene oxide) segments of comparable length.

A summary of the polymerization variables utilized in the preparation of 1–8 is provided in Table I. Spectroscopic data for the polymeriza-



Scheme 2



Scheme 3

Table I Synthesis of Polyamides 1–8

Reactants in Feed[a] (Mol-%)							DMSO	Reaction Conditions	Polyamide	
TRIDEC	TART	TRA	BPA	TET	BAP	DEP	(mL)[b]	(Time, temp.)	Yield[c]/%	Designation
50		50					5	1 d RT, 13 d 55°C	33[d,e,f]	1
	50	50					6	6 h RT, 9 d 60°C	47[e,f]	2
50			50				5	2 d RT, 15 d 55°C	25	3
	50		50				10	1 d RT, 15 d 60°C	29	4
50		25		25			5	2 d RT, 15 d 55°C	30[d,e]	5
50		25	25				5	2 d RT, 15 d 60°C	22[d,e,f]	6
50				25		25	10	3 d RT, 14 d 65°C	31[d,e,g]	7
	50	25			25		7.5	2 d RT, 14 d 60°C	26	8

[a] TRIDEC = diethyl 3,6,9-trioxaundecanedioate; TART = diethyl L-tartrate; TRA = 4,7,10-trioxa-1,13-tridecanediamine; BPA = *N,N*-bis(3-aminopropyl)amine; TET = triethylenetetramine hydrate; BAP = 1,2-bis(3-aminopropylamino)ethane; DEP = α-(3-aminopropoxy)-ω-(3-aminopropyl)-poly(ethylene oxide).

[b] For every 10 mmoles of diester.

[c] Main fraction, after dialysis in 12,000–14,000 molecular mass cut-off tubing. Additional material recovered from outer dialysis phase (redialyzed in 3500 cut-off tubing), 20–30%, not tabulated.

[d] Redialysis in 25000 cut-off tubing gave products of unchanged composition; recovery yields varied from 30 to 70%.

[e] Experiments conducted neat (i.e., no solvent), 2 days at 25°C, 2 days at 55°C, gave similar or higher yields, but unsatisfactory NMR spectra for 5, 6, and 7 (see text).

[f] Similar results in tetramethylurea solvent in place of DMSO.

[g] Changing the heating period to 10 days at 65°C gave a yield of 51%, yet caused minor branching (NMR).

tion products isolated after dialysis with a 12,000 to 14,000 molecular mass cut-off are listed in Table II. Selected polyamides were additionally subjected to dialysis with 25,000 molecular mass cut-off, and results are given as footnotes in Table I.

In order to demonstrate the suitability of incorporated drug anchoring functions for actual conjugation reactions, ferrocene (di-η^5-cyclopentadienyliron(II)) as an anticancer drug model[4,7] was bound via amide groups to polyamide 5 to give the conjugate 5-Fc as a water-soluble resin. Conjugation was brought about by treatment of 5 in DMF solution with 2.3 equiv. of the *N*-hydroxysuccinimide ester of 4-ferrocenylbutanoic acid[8] at 25 to 65°C in the presence of triethylamine, followed by aqueous dialysis and freeze-drying. The incorporation of one ferrocene unit per polymer repeat unit was established by microanalytical iron determination and ^{1}H NMR data.

Table II ^{1}H NMR Data[a] for Polyamides 1–8

Polymer Designation	Number of Protons Counted[b] (expected)[c]					
	δ 4.5–4.4[d]	δ 4.1–3.9	δ 3.7–3.6	δ 3.4–3.3	δ 2.7–2.2	δ 1.8–1.7
1	—	4 (4)	22 (20)	4 (4)	—	4 (4)
2	1.9 (2)	—	12.9 (12)	3.7 (4)	—	4 (4)
3	—	4 (4)	7.6 (8)	3.8 (4)	4.2 (4)	4 (4)
4	2 (2)	—	—	4.2 (4)	4.4 (4)	4.7 (4)
5	—	8.3 (8)	27 (28)	8.2 (8)	8.2 (8)	4 (4)
6	—	8.2 (8)	27 (28)	7.8 (8)	4 (4)	8 (8)
7	—	8 (8)	107 (100)	7.1 (8)	7 (8)	3.5 (4)
8	4.2 (4)	—	12.3 (12)	8.5 (8)	7.9 (8)	8 (8)

[a] In D_2O, pD 10. Chemical shifts, δ/ppm, referenced against internal sodium 3-trimethylsilyl-2,2,3,3-d_4-propionate.

[b] Integration error limits ± 12%.

[c] Expected for compositions in accordance with structures 1–8 normalized to $x = 1$.

[d] Proton assignments, 4.4_5–4.3 ppm : C<u>H</u>—OH. 4.1–3.9_5 ppm : O—CH_2—CO; 3.8–3.5_5 ppm : O—CH_2—CH_2—O, CH_2—CH_2—CH_2—O; $3.4–3.2_5$ ppm : CONH—C<u>H</u>$_2$; 2.8–2.5 ppm : C<u>H</u>$_2$—NH—C<u>H</u>$_2$; 1.9–1.6 ppm : CH_2—C<u>H</u>$_2$—CH_2.

EXPERIMENTAL

General Procedures

Inherent viscosities, η_{inh}, were determined in Cannon-Fenske tubes at 30.00 ± 0.05°C; deionized H_2O was the solvent (c = 0.2 g/100 mL), and the results, averages of two determinations, are given in units of mL g^{-1}. Dialysis operations were performed in cellulose tubing, types Spectra/Por 3 and Spectra/Por 4 dry tubing, as well as Spectra/Por 6 wet tubing (Spectrum Industries, Los Angeles, CA), with mass-average molecular mass cut-off limits of 3,500, 12,000 to 14,000, and 25,000, respectively, against several batches of deionized H_2O. Aqueous polymer solutions were freeze-dried in a VIRTIS Bench Top 3 freeze-drier operating at −30°C, 10 to 15 Pa. The freeze-dried polymers were routinely post-dried in a SARTORIUS Thermo Control infrared drying system (heating program: 10 min at 65°C). Analytical samples were additionally dried for 2 days at 70°C in an Abderhalden tube. Microanalyses were performed by W. Dindorf, Mikroanalytisches Laboratorium, Mainz, Germany. Iron determinations were made in the Analytical Laboratory, Polifin Ltd. Determinations were made in duplicate and the results averaged. Solid-state infrared spectra (KBr pellets) were recorded over the region of 400 to 200 cm^{-1}. ^1H NMR spectra (400 MHz) were recorded on D_2O solutions, with chemical shifts, δ in ppm, referenced against sodium 3-(trimethylsilyl)-2,2,3,3-d_4-propionate (integration error limits ± 12%). Spectral solutions were adjusted to pD 10 with Na_2CO_3 in order to eliminate protonation effects.

Solvents and Reactants

The aprotic solvents DMSO and TMU, purum, were dried over molecular sieves 4A. *N,N*-Dimethylformamide (DMF), dried over Molecular sieves, was distilled under reduced pressure. Deionized H_2O was used for dialysis and viscometric operations. The diamine monomers, commercial grades (Fluka Chemie), were used as received. These include: BPA, TET (see below; water content 15% b.wt.), BAP, and TRA. The long-chain di-amine, α-(3-aminopropoxy)-ω-(3-aminopropyl)-poly(ethylene oxide) (DEP), a gift from NOL Corporation, Tokyo, was used as received; ^1H NMR data showed the compound to have the composition: $H_2N—(CH_2)_3O—(CH_2CH_2O)_{20}—(CH_2)_3—NH_2$.

TART was a commercial product (Fluka Chemie). The commercial diacid, 3,6,9-trioxaundecanedioic acid (Fluka Chemie) was converted to its diethyl ester (TRIDEC) by treatment (48 h reflux) with triethyl orthoformate (3 eq.). Removal of volatiles under reduced pressure, washing of the residue with several portions (20 mL) of pentane, reprecipitation of the crude oily product from ethereal solution by pentane, and rewashing of the precipitated oil with pentane was followed by column chromatography on silica gel with hexane-EtOH (9 : 1, then 4 : 1) as the eluent. The diester, eluting as the first band (TLC on SiO_2 (hexane/EtOH = 3 : 2) : R_f = 0.8), was freed from solvent and dried for 3 days in an Abberhalden tube at 60°C under reduced pressure. Yield, 48%. Purity of the oily product was checked by ^1H NMR ($CDCl_3$, δ/ppm): 4.22(q), 4H ($CH_3C\underline{H}_2$); 4.17(s), 4H ($CO—CH_2—O$); 3.72(m), 8H ($O—CH_2CH_2—O$); 1.29(t), 6H ($C\underline{H}_3CH_2$).

N-Succinimidyl 4-ferrocenylbutanoate, the active *N*-hydroxysuccinimide ester of 4-ferrocenylbutanoic acid, was prepared as described[8]; mp. 89–91°C.

Polyamides 1–8

Amounts of polymeric compounds are given as base moles and, hence, refer to the simplest recurring units defined as structures 1–8 (and 5-Fc), each normalized to $x = 1$.

Polyamide 1. The mixture of TRIDEC, 2.784 g (10 mmol), TRA, 2.240 g (10 mmol), and anhydrous Na_2CO_3 (1 g ≈ 20% of total mass of reactants) was saturated with N_2 and stirred for 24 h at ambient temperature in a stoppered flask. Upon dilution with 5 mL of DMSO and resaturation with N_2, stirring was continued for 13 days at 55°C in an incubator. Intermittently, reduced pressure was applied in a rotating evaporator for 30 min at 60°C bath temperature for removal of eliminated EtOH, and the contents were resaturated with N_2. Suspended carbonate was removed from the mixture by centrifugation, and the supernatant, diluted with 10 mL of H_2O, was dialyzed in Spectra/Por 4 tubing for 45 h against H_2O at pH 7. The tube contents were freeze-dried, giving 1.34 g (33.0%) of a light tan-colored, hygroscopic, and water-soluble resin; η_{inh}, 13 mL g^{-1}. Anal. Found: C, 51.30; H, 8.61; N, 6.33%; C/N, 9.4. Calcd. for $(C_{18}H_{34}N_2O_8)_x$ $(406.5)_x$ (1): C, 53.18; H, 8.43; N, 6.89%; C/N, 9.

A sample of the polymer was redialyzed for 40 h in Spectra/Por 6 tubing; upon freeze-drying of the retentate, the material was recovered in 70% yield; η_{inh}, 13 mL g^{-1}.

Polyamide 2. An experiment performed as in the foregoing, except that TRIDEC was replaced by TART, 2.062 g (10 mmol), the solvent (6 mL) added in 2-mL aliquots during the reaction period, and the heat treatment performed for 9 days at 60°C, afforded 2 as a water-soluble solid in a yield of 1.56 g (46.7%); η_{inh}, 13 mL g^{-1}. Anal. Found: C, 49.31; H, 7.91; N, 8.19%; C/N, 7.0. Calcd. for $(C_{14}H_{26}N_2O_7)_x$ $(334.4)_x$ (2): C, 50.29; H, 7.84; N, 8.38%; C/N, 7.

Polyamide 3. In an experiment conducted as described for 1, yet with reaction periods of 2 days at room temperature and 15 days at 55°C, the polycondensation of TRIDEC with BPA (10 mmol each) gave rise to the formation of 3 in 25% yield as a tan-colored, water-soluble sticky resin, η_{inh}, 10 mL g^{-1}. Anal. Found: C, 50.70; H, 8.67; N, 12.67%; C/N, 4.7. Calcd. for $(C_{14}H_{27}N_3O_5)_x$ (317.4) (3): C, 52.98; H, 8.57; N, 13.24%; C/N, 4.7.

Polyamide 4. Performed by the procedure for the preparation of Polyamide 2, except that a total of 10 mL of solvent was used and the heating period maintained for 15 days at 60°C, the polycondensation of TART and BPA (10 mmol each) gave 4 as a yellowish, water-soluble solid in 29% yield; η_{inh}, 11 mL g^{-1}. Anal. Found: C, 47.82; H, 7.89; N, 16.21%; C/N, 3.4. Calcd. for $(C_{10}H_{19}N_3O_4)_x$ $(245.3)_x$ (4): C, 48.97; H, 7.81; N, 17.13%; C/N, 3.3.

Polyamide 5. Anhydrous Na_2CO_3, 2.36 g, was added to the stirred and homogenized mixture of TRIDEC, 5.567 g (20 mmol), TRA, 2.203 g (10 mmol), and TET, 1.681 g (10 mmol TET anhydrous + 15%). The resulting suspension, saturated with N_2, was stirred in a stoppered flask for 2 days at ambient temperature and, upon the addition of 10 mL of DMSO, for another 15 days at 55°C with intermittent evacuation and admission of N_2. A mixture of Et_2O-hexane (2 : 1) was added, yielding two phases, with the polymeric product settling out as the oily-resinous bottom phase. Upon dissolution in H_2O (15 mL), this was dialyzed in Spectra/Por 4 for 40 h against H_2O and collected from the retentate by freeze-drying as a water-soluble, sticky resin. The yield was 2.18 g (30.1%); η_{inh}, 8 mL g^{-1}. Anal. Found: C, 50.67; H, 8.53; N, 11.01%; C/N, 5.4. Calcd. for $(C_{32}H_{62}N_6O_{13})_x$ $(738.9)_x$ (5): C, 52.01; H, 8.46; N, 11.37%; C/N, 5.3.

A sample, washed with boiling Et_2O—Me_2CO (1 : 1) for removal of any possible traces of TRA, was redialyzed in Spectra/Por 6 tubing for 44 h and the retentate freeze-dried. The resinous 5 (recovery yield, 66%) gave practically the same NMR data as recorded for the precursor material; η_{inh}, 17 mL g^{-1}.

Polyamide 6. This polymer was prepared from TRIDEC, 5.567 g (20 mmol), BPA, 1.312 g (10 mmol), TRA, 2.203 g (10 mmol), Na_2CO_3, 1.82 g (25% of total reactant mass), and 10 mL of DMSO. The procedure of the preceding experiment was used, except that the heating period was conducted for 15 days at 60°C in an attempt to obtain an acceptable yield. The polymeric material isolated after dialysis in Spectra/Por 4 tubing was a yellowish, sticky resin possessing complete solubility in H_2O. Yield, 1.57 g (21.7%); η_{inh}, 12 mL g^{-1}. Anal. Found: C, 52.22; H, 8.53; N, 9.35%; C/N, 6.5. Calcd. for $(C_{32}H_{61}N_5O_{13})_x$ $(723.8)_x$ (6): C, 53.09; H, 8.49; N, 9.68%; C/N, 6.4.

A sample was redialyzed in Spectra/Por 6 tubing as described for 5. The recovery yield was 35%. The NMR spectrum of the product fraction so obtained was substantially identical to that of the precursor material.

Polyamide 7. To the stirred solution of DEP, 5.065 g (5 mmol), in 10 mL of DMSO was added TET, 841 mg (5 mmol TET anhydrous + 15%), and TRIDEC, 2.783 g (10 mmol). After brief continued stirring, Na_2CO_3, 2.17 g (25% of total reactant mass) was added. The suspension was treated as described for 1 except that the reaction period was changed to 3 days at ambient temperature and 14 days at 65°C. After dialysis in Spectra/Por 4 tubing and freeze-drying, the polymeric product was collected in a yield of 2.35 g (30.7%) as a nearly colorless, somewhat waxy solid completely soluble in H_2O; η_{inh}, 10 mL g^{-1}. Anal. Found: C, 52.66; H, 8.87; N, 5.27%; C/N, 11.6. Calcd. for $(C_{68}H_{134}N_6O_{31})_x$ $(1531.8)_x$ (7): C, 53.32; H, 8.82; N, 5.49%; C/N, 11.3.

Polyamide 8. The monomers were TART, 1.237 g (6 mmol), TRA, 661 mg (3 mmol), and BAP, 523 mg (3 mmol), with 5 mL of DMSO used as the solvent. The method of polymerization was similar to that described for 1, but the reaction period was changed to 3 days at room temperature and 14 days at 60°C, and the quantity of Na_2CO_3 was 484 mg (20% of total reactant mass). The water-soluble 8 was collected as a light-yellow solid in a yield of 480 mg (25.7%). Anal. Found: C, 49.51; H, 8.22; N, 13.07%;

C/N, 4.4. Calcd. for $(C_{26}H_{50}N_6O_{11})_x$ $(622.7)_x$ (8): C, 50.15; H, 8.09; N, 13.50%; C/N, 4.3.

Ferrocene conjugate 5-Fc. A solution was prepared of polyamide 5, 221 mg (0.3 mmol), and triethylamine, 61 mg (0.6 mmol), in 2.5 mL of DMF. Upon the addition of *N*-succinimidyl 4-ferrocenylbutanoate, 223 mg (0.6 mmol), the mixture, saturated with N_2, was stirred for 3 days at room temperature in the dark. During this period, the pH of the brown solution slowly decreased from 9 to 7.5. The addition of 10 mL of Et_2O : hexane (2 : 1) to the stirred reaction solution caused precipitation of the conjugate as a brown, sticky resin, which was dissolved in 10 mL H_2O and dialyzed in Spectra/Por 4 tubing for 0.5 h against H_2O at pH 9 (Na_2CO_3) and another 24 h against plain H_2O. Freeze-drying of the retentate and postdrying of the residue afforded dark-brown, resinous 5-Fc, 121 mg (40.6%). The conjugate was completely soluble in H_2O; η_{inh}, 9 mL g^{-1}. ^1H NMR (D_2O), δ/ppm: 4.15-3.85, 16.4H (17H, cyclopentadienyl rings, O—CH_2—CO); 1.8-1.6, 6H (6H, CH_2—$C\underline{H}_2$—CH_2).

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