Articles

Block Copolymers Containing Poly(ethylene glycol) and Poly(amido–amine) or Poly(amido–thioether–amine) Segments

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ABSTRACT: New hydrolyzable block copolymers containing poly(ethylene glycol) (PEG) and poly(amido–amine) (PAA) or poly(amido–thioether–amine) (PATA) segments have been prepared from synthesized secondary amino end-functionalized PGE's of different molecular weight. The latter have been also utilized as macromonomers for preparing poly(PEG–amido–amine–urethanes). The products were characterized by ^{1}H NMR, GPC, elemental analysis, and viscometric measurements.

Introduction

Poly(amido–amines) (PAA's) are a family of tertiary amino polymers of regular structure, which in a linear form are obtained by Michael-type polyaddition of primary monoamines or secondary bisamines to bisacrylamides (Scheme I). The polymerization reaction in Scheme I takes place readily in water or alcohols, at room temperature, and without added catalysts. Almost all aliphatic amines can be used as monomers, and the presence of many additional functions does not interfere with the polymerization process.[1-3]

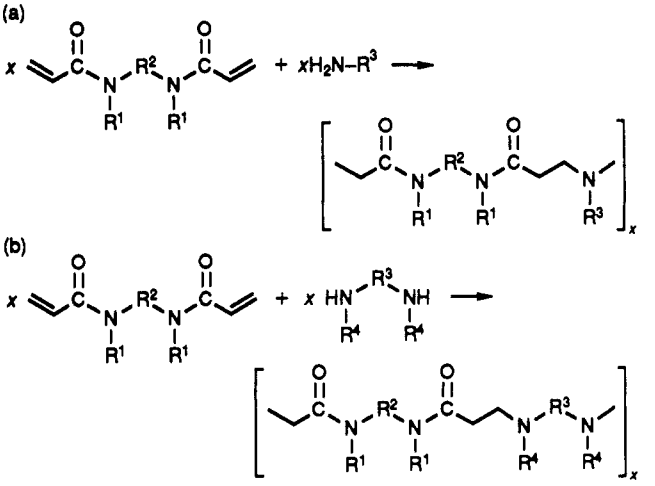
Many PPA's are water soluble. In aqueous solution they behave as bases of medium strength. The protonation and heavy-metal ion complexing behavior of a large number of PAA's have been thoroughly studied.[4-6] Some PAA complexes exhibit interesting properties as oxidation catalysts.[7,8]

It is apparent from the polymerization mechanism that, by suitable adjustment of the initial monomer ratio, PAA's prevailing or totally end-capped with either acrylamido, or secondary amino groups can be obtained. These PAA macromonomers have been used to prepare new PAA-containing materials.[9-15] In particular, they proved to be easily grafted on the surface of various polymeric and inorganic materials, thus modifying dramatically their surface properties.[13-15]

The possibilities of biomedical applications of PAA's lie in their ability to form stable complexes with heparin. Thus, PAA-grafted materials can be stably heparinized, acquiring nonthrombogenic properties,[9-15] while PAA-based cross-linked hydrogels act as selective heparin adsorbers from plasma or blood.[16-18] Some PAA's are also being studied as promoieties for polymeric prodrugs, showing, as polycations, a unique combination of water solubility, reduced toxicity, and degradability in biological media.[19]

Recently, tertiary amino polymers structurally related to PAA's, namely, poly(amido–thioether–amines) (PATA's), have been prepared by polyaddition of bis(β-mercaptoethylamines) to bisacrylamides.[20] These polymers, though on the whole similar to PAA's, are much less hydrophilic: they are insoluble in water but soluble in aqueous acids.

Scheme I



On the other hand, poly(ethylene glycols) (PEG's) and their derivatives have received a great deal of interest,[21] for instance as promoieties for preparing oligomeric prodrugs,[22,23] for protein modification,[24-27] and as phase-transfer catalysts.[28-30] They are the chief components of most polyurethanes commonly used as biomaterials.[31-33] Increasing attention is devoted to surface grafting of PEG's on polymeric materials to improve their biocompatibility, either per se or by providing hydrophilic spacers for attaching heparin or other substances inhibiting thrombus formation.[34,35]

The aim of this paper is to relate on a synthetic method for PEG–PAA and PEG–PATA block copolymers, starting from commercial PEG samples. A single PAA and a single PATA have been chosen as models for this study. However, the synthetic method devised can be resonably applied to any PAA and PATA. Furthermore, we have prepared novel polymeric substances which, though formally belonging to the domain of PAA's, are in fact high molecular weight, potentially hydrolyzable PEG's containing a few cationc groups along their macromolecular chain.

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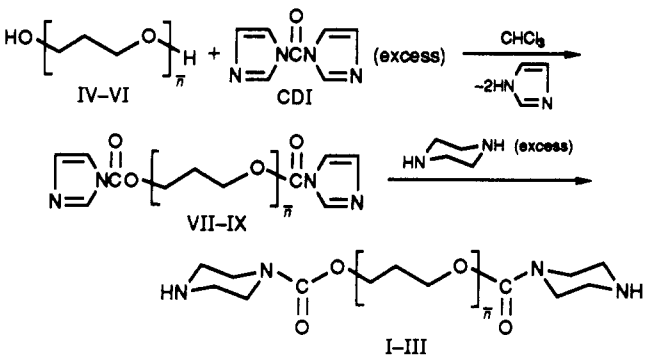
Scheme II



I, IV, VII: $\bar{n}$ = 181, PEG 8000
II, V, VIII: $\bar{n}$ = 45, PEG 2000
III, VI, IX: $\bar{n}$ = 22, PEG 1000

Results and Discussion

Synthesis. PEG–Piperazinylformates. The preparation of PEG–piperazinylformates I–III from commercial PEG's IV–VI is the starting point of the synthetic method described in this paper. It was performed via PEG–imidazolylformates VII–IX according to Scheme II.

The reaction of PEG's with excess *N,N'*-carbonyldiimidazole (CDI) at room temperature and in chloroform solution is fast and complete. No unreacted oligomer is present after a few minutes. The PEG–imidazolylformates so obtained, when in chloroform solution, are not water sensitive at room temperature and are not extractable by water. On the contrary, CDI is rapidly eliminated from its chloroform solutions by extraction with water. Consequently, enough CDI to overcome any moisture present in the reaction mixture can be added without harm. This allows us to avoid previous drying of commercial PEG's, which is not a very simple procedure.[21] A large excess of piperazine (20 mol/mol of PEG) is used in the second step. The excess piperazine is eliminated by multiple extractions with 10% potassium nitrate solution and finally with water. The use of the former minimizes losses, and the yields are always high. The purity of the products was checked by ^{1}H NMR, elemental analysis, titration against standard acid, and GPC. All results were consistent with pure, fully substituted products.

Any commercial PEG can be quantitatively functionalized by the above method, which in our opinion compares favorably with all the methods described so far to introduce terminal amino groups in PEG's.

PEG–PAA Block Copolymers. The introduction of I–III as aminic comonomers in the synthesis of PAA's leads to PEG–PAA block copolymers. We have performed this reaction choosing piperazine (X) and 1,4-diacryloylpiperazine (XI) as monomers for the PAA portion (Scheme III). The molar fraction of piperazine in the polymerizing mixture was the same in all cases. Consequently, copolymers XII–XIV are different in the relative length of their PEG and PAA segments, as well as in their PEG content by weight.

The polymerization reactions were performed in water at room temperature, as usual for PAA's, and lasted about 3 days. The final products could be isolated by simply evaporating the reaction mixtures to dryness in vacuo.

For comparison purposes, we have also prepared a PAA homopolymer (XV) with the same recipe, but omitting the addition of I–III. This product was treated with piperidine before isolation in order to saturate the residual double bonds, thus increasing stability. We think that XV can be reasonably considered representative of the PAA blocks within XII–XIV.

PEG–PATA Block Copolymers. We have chosen X and 2,2'-(1,4-piperazinediyl)diethanethiol (XVI) as monomers for the PATA portion.

The polyaddition of bis(β-mercaptoethyl)amines to bisacrylamides is best performed in aqueous solution at slightly acidic pH.[20] Under these conditions, primary and secondary amines do not add to bisacrylamides. Consequently, PEG–PATA copolymers were prepared in two steps. In the first step, amino-terminated PEG's I–III were treated in aqueous solution with excess XI and allowed to react completely. In the second step, the reaction mixtures containing acrylamido-terminated PEG's XVII–XIX together with the excess XI were treated with acetic acid and then with XVI in stoichiometric amount with respect to excess XI (Scheme IV). The reaction mixtures were finally made alkaline and dialyzed. The products were recovered by evaporation to dryness in vacuo. We used membranes with a low molecular weight cutoff, and the yields were always high. However, we cannot exclude that some low molecular weight fractions were lost during isolation.

As in the previous case, a model PATA homopolymer (XXIII) was prepared with the same amounts of XI and XVI as in the copolymers' preparation. Before isolation, an excess of 4-hydroxythiophenol was added in order to transform all terminal acrylamido groups of XXIII into aromatic groups, thus allowing us to approximatively determine its molecular weight by NMR spectroscopy, improving in the meantime its stability. The isolation was performed by precipitating with ammonia solution. Also in this case, we cannot exclude that some low molecular weight fractions are lost during isolation.

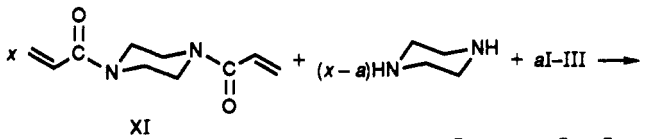
Poly(PEG–amido–amine–urethane). These polymers (XXIV–XXVI) were obtained by direct polyaddition of I–III to XI (Scheme V). The polymerization reaction took place easily in water at room temperature, and the products were isolated by evaporating the reaction mixtures to dryness in vacuo.

It may be observed that in XXIV–XXVI the repeating unit weighs 1420, 2420, and 8420 and the PEG portion is approximately 70, 82, and 95% by weight, respectively. Therefore, as pointed out in the Introduction, even if strictly speaking they are poly(PEG–amido–amine–urethanes), broadly speaking they may be considered as potentially hydrolyzable PEG's containing a few aminic groups along their macromolecular chain.

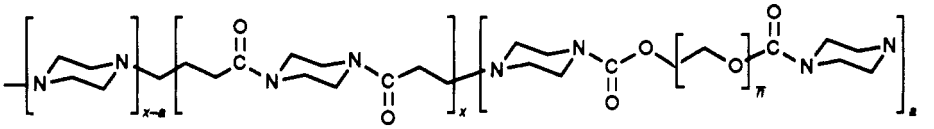
Characterizations. All polymers were characterized by ^{1}H NMR, GPC, elemental analysis, and viscometric measurements. The results are in full agreement with the proposed structures (see Experimental Section).

The results of solubility tests performed on polymers XII–XIV, XX–XXII, and XXIV–XXVI, together with XV and XXIII, and PEG's IV–VI are reported in Table I. It may be observed that all copolymers, apart from XXI and XXII, are soluble in water and phosphate buffer pH 8.0. The latter polymers are only swellable in both solvents, and their swellability increases near the boiling point. On the other hand, XX, characterized by a high PEG content, is completely hydrosoluble. All polymers are soluble in acidic buffers and in chloroform, and all copolymers are soluble in solvents common to both constituent homopolymeric segments. Copolymers XII and XX, deriving from PEG 8000, are more soluble in solvents for the PEG's if compared to copolymers belonging to the same class. Finally, poly(PEG–amido–amine–urethanes) XXIV–XXVI basically show the same solubility properties of the starting PEG's and high molecular weight PEG's.

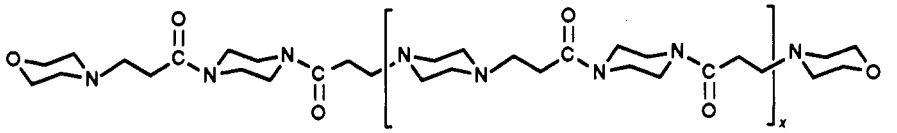
Scheme III



XI

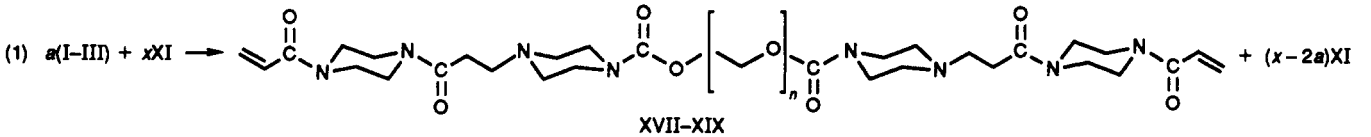


XII: $\bar{n} = 181$, $a = 0.092$
XIII: $\bar{n} = 45$, $a = 0.092$
XIV: $\bar{n} = 22$, $a = 0.092$

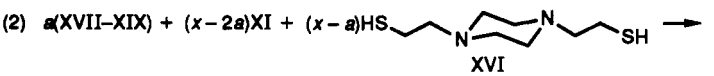


XV

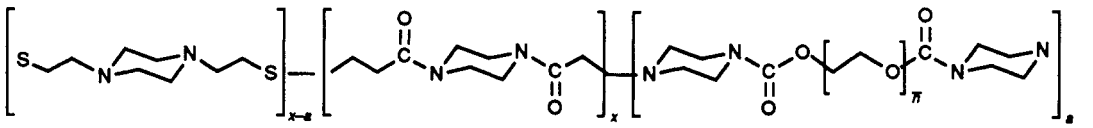
Scheme IV



XVII–XIX

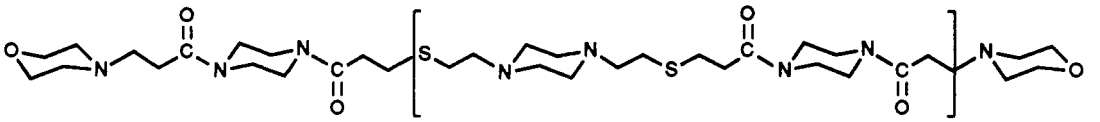


XVI



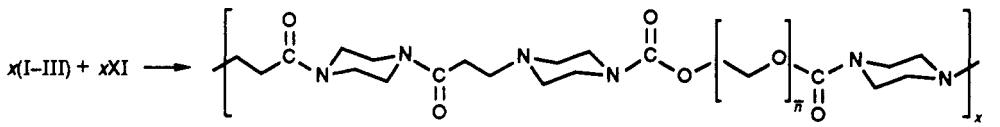
XX–XXII

XVII, XX: $\bar{n} = 181$, $a = 0.124$
XVIII, XXI: $\bar{n} = 45$, $a = 0.124$
XIX, XXII: $\bar{n} = 22$, $a = 0.124$



XXIII

Scheme V



XXIV–XXVI

XXIV: $\bar{n} = 181$
XXV: $\bar{n} = 45$
XXVI: $\bar{n} = 22$

GPC chromatograms were run in phosphate buffer pH 8.0, which, according to our previous experience, was the best mobile phase to elute tertiary amino polymers related to PAA on Bio-Rad columns. However, it was not possible to run chromatograms of XXI, XXII, and model PATA, since they are insoluble in the mobile phase. RI and UV detectors were used in parallel, and the resulting chromatograms were compared for all copolymers. Profiles completely superimposable were obtained in all cases. Chromatograms from the RI detector are reported in Figure 1. For comparison purposes, a standard PEG calibration curve obtained under the same experimental conditions is also reported in Figure 1. Though this calibration curve cannot rigorously fit the PEG copolymers' behavior, it is a fairly reasonable estimation of real behavior, especially for copolymers with a high PEG content. It may be observed that the retention times of all copolymers substantially decrease if compared to those of the starting PEG's, showing a net increase of the molecular weights. Moreover, all peaks are broader than those of the PEG's, as expected for molecular weight distributions of step polyaddition polymers. Finally, in no case do we have evidence of the presence of impurities due to starting polymers or reagents. The presence of starting PEG's or PEG–imidazolylformates in PEG–PAA's, PEG–PATA's, and poly(PEG–amido–amine–urethanes) was excluded by GPC, since their retention times are in all cases widely different. The position and shape of the chromatograms were always similar by both RI and UV detection.

Table I
Solubility Tests[a]

solvent	PEG–PAA block copolymers XII	XIII	XIV	model PAA XV	PEG–PATA block copolymers XX	XXI	XXII	model PATA XXIII	poly(PEG–amido–amine–urethanes) XXIV	XXV	XXVI	starting PEG's IV	V	VI
water	s	s	s	s	s	i[b]	i[b]	i	s	s	s	s	s	s
phosphate buffer, pH 8.0	s	s	s	s	s	i[b]	i[b]	i	s	s	s	s	s	s
acetate buffer, pH 4.6	s	s	s	s	s	s	s	s	s	s	s	s	s	s
formamide	s	sh	sh	s	s	s	sh	i	s	s	s	s	s	s
dimethylformamide	s	i	i	s	s	s	sh	sh	s	s	s	s	s	s
dimethyl sulfoxide	s	i	i	s	s	s	sh	sh	s	s	s	s	s	s
methanol	sh	i	i	i	s	i	i	i	s	s	s	s	s	s
2-propanol	i	i	i	i	sh	i	i	i	sh	sh	sh	sh	s	s
ethyl acetate	i	i	i	i	i	i	i	i	sh	s	s	s	s	s
acetone	i	i	i	i	i	i	i	i	s	s	s	s	s	s
acetonitrile	s	i	i	i	sh	i	i	i	s	s	s	s	s	s
ether	i	i	i	i	i	i	i	i	i	i	i	i	i	i
dioxane	i	i	i	i	i	s	sh	i	s	s	s	s	s	s
chloroform	s	s	s	s	s	s	s	s	s	s	s	s	s	s
toluene	i	i	i	i	sh	i	i	i	s	i	i	s	s	s
cyclohexane	i	i	i	i	i	i	i	i	i	i	i	i	i	i
n-heptane	i	i	i	i	i	i	i	i	i	i	i	i	i	i

[a] s = soluble at room temperature, sh = soluble by heating, i = insoluble. [b] Swells in hot solution.

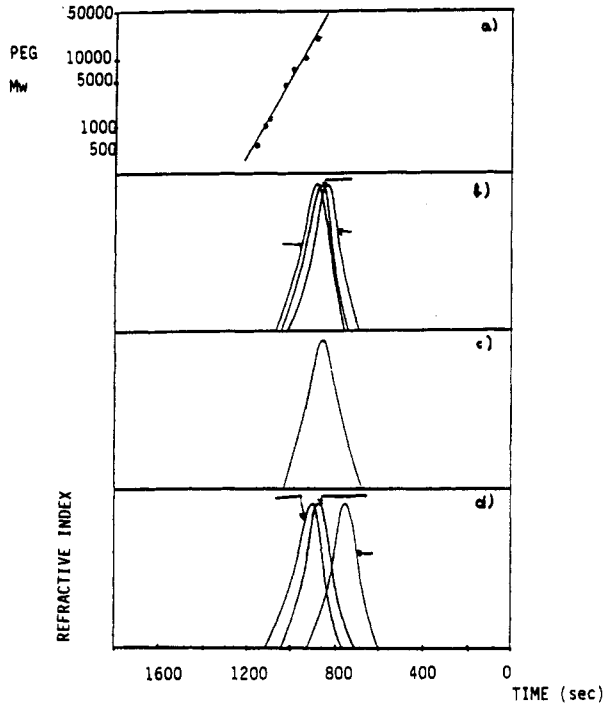


Figure 1. (a) Poly(ethylene glycol) calibration curve; (b) GPC traces of PEG–PAA copolymers; (c) GPC trace of copolymer XX; (d) GPC traces of poly(PEG–amido–amine–urethanes).

These conclusions are confirmed by results of viscometric measurements (see Table II). A dramatic increase in intrinsic viscosity is always observed, passing from both PEG and model PAA and PATA to both PEG–PAA and PEG–PATA copolymers. The viscosity values of poly(PEG–amine–urethanes) are always much higher than that of the starting PEG's.

Conclusions

The above results constitute a synthetic route to new tertiary amino polymeric substances.

It may be observed that all the polymeric substances described in this paper still maintain functional end groups which can be utilized for surface modifications through surface grafting.

Furthermore, it is well-known that an almost endless variety of PAA's and related polymers can be obtained starting from different bisacrylamides, bisamines, and bis(amino thiols). Therefore it may be reasonably supposed that the synthetic method described in this paper is not limited to IV–VI, X, XI, and XVI but is a general one, thus providing the possibility of tailoring for any particular need new PEG-based polymeric substances.

Experimental Section

Measurements. Intrinsic viscosities were measured at 30 °C with an Ubbelohde viscometer. ^{1}H NMR spectra were run at 60 MHz on an EM 360A Varian spectrometer in $CDCl_3$, using TMS as internal reference. Elemental analyses were performed by Redox Co. (Cologno Monzese, Italy). IR spectra were obtained from films cast from $CHCl_3$ on KBr plates with a Jasco 5300 FT-IR spectrophotometer. GPC chromatograms were obtained with Bio-Rad TSK40 and TSK30 columns in series with phosphate pH 8.0 buffer as eluent, flow rate 0.1 mL/min (ERMA Model ERC 2020 instrument), with both a Knauer RI detector and a Knauer UV detector operating at 240 nm. The retention times reported are those corresponding to the peak maximum.

Solubility tests were performed by treating 20 mg of substance with 2 mL of solvent and stirring at room temperature for 2 h. After this period, the system, which was not homogeneous, was gently refluxed 5 min and the results noted.

Materials. Unless otherwise indicated, the starting reagents, including PEG's, were purchased from Fluka and used without further purification. **PEG 8000** was purchased from Aldrich Chemical Co. and used without further purification. **Chloroform** was extracted several times with water, dried over anhydrous calcium chloride, and distilled over calcium hydride. **1,4-Bisacryloylpiperazine** was prepared as previously described.[36] **2,2′-(1,4-Piperazinediyl)diethanethiol** was prepared as previously described.[37]

PEG 8000–Piperazinylformate (I). CDI (4.71 g, 29 mmol) was added at once to a mixture of PEG 8000 (15 g, 1.875 mmol) in chloroform (25 mL). The reaction mixture was stirred 30 min at room temperature, diluted with chloroform (30 mL), and extracted with water (30 mL), vigorously stirring 10 min before phase separation. The chloroform solution was further extracted with water (2 × 20 mL) and rapidly dried over anhydrous sodium sulfate (5 g). After removal of the desiccating agent, a solution of anhydrous piperazine (1.683 g, 20 mmol) in chloroform (10 mL) was added at once. After stirring 2 h at room temperature, the reaction mixture was extracted with 10% aqueous potassium nitrate (8 × 25 mL) and water (2 × 25 mL), dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The residue was finally dried at constant weight at room temperature and 0.05 Torr and stored over potassium hydroxide pellets. Yield: 12.158 g (83%). ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 2 H, NH), 2.75–3.0 (m, 8 H, $CONCCH_2N$), 4.2–4.5 (m, 4 H, CH_2OCON), 3.4–3.9 (m,

Table II
Viscometric Measurements

	PEG–PAA block copolymers			model PAA	PEG–PATA block copolymers			model PATA	poly(PEG–amido–amine–urethanes)			starting PEG's		
polymer	XII	XIII	XIV	XV	XX	XXI	XXII	XXIII	XXIV	XXV	XXVI	IV	V	VI
reduced visc,[a] dL/g	0.39	0.31	0.29	0.08	0.48				0.92	0.30	0.28	0.08	0.04	0.02
					0.82	0.61	0.39	0.165				0.17	0.08	0.06

[a] Upper row: measurement performed in phosphate buffer, pH 8.0, C = 0.1 M; lower row: measurement performed in acetate buffer, pH 4.5, C = 0.1 M.

728 H, all other H). IR: 3350–33310 (ν(N–H), 1700 (ν(C=O), 1100 cm^{-1} (ν(C–O). Anal. Calcd for $C_{372}H_{742}N_4O_{184}$: C, 54.33; H, 9.09; N, 0.68. Found: C, 54.13; H, 9.12; N, 0.70. Titration: calcd 0.243 mequiv/g; found 0.255 mequiv/g. GPC retention time = 950 s.

PEG 2000- and PEG 1000-piperazinylformates (II and III) were prepared in the same way by substituting PEG 2000 (3.75 g, 1.875 mmol) and PEG 1000 (1.875 g, 1.875 mmol) for PEG 8000, respectively, and using 1.539 and 0.770 g of CDI in 8 and 4 mL of chloroform, respectively. Yields: 3.451 (84%) and 1.960 g (86%), respectively.

II: ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 2 H, NH), 2.75–3.0 (m, 8 H, $CONCCH_2N$), 4.2–4.5 (m, 4 H, CH_2OCON), 3.4–3.9 (m, 184 H, all other H). IR: 3350–33310 (ν(N–H), 1700 (ν(C=O)), 1100 cm^{-1} (ν(C–O). Anal. Calcd for $C_{100}H_{198}N_4O_{48}$: C, 53.97; H, 8.97; N, 2.52. Found: C, 53.98; H, 9.01; N, 2.56. Titration: calcd 0.899 mequiv/g; found 0.913 mequiv/g. GPC retention time = 1045 s.

III: ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 2 H, NH), 2.75–3.0 (m, 8 H, $COCCH_2N$), 4.2–4.5 (m, 4 H, CH_2OCON), 3.4–3.9 (m, 92 H, all other H). IR: 3350–33310 (ν(N–H)), 1700 (ν(C=O)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{24.20}H_{79.34}N_{2.18}O_{17.93}$: C, 53.54; H, 8.82; N, 4.62. Found: C, 53.19; H, 9.09; N, 4.56. Titration: calcd 1.634 mequiv/g; found 1.645 mequiv/g. GPC retention time = 1100 s.

PEG 8000–PAA Block Copolymer (XII). I (4.000 g, 0.51 mmol), X (0.196 g, 2.27 mmol), and XI (0.540 g, 2.78 mol) were dissolved in water (8 mL) and allowed to react for 3 days. The reaction mixture was then evaporated to dryness under vacuum and dried to constant weight at 0.1 Torr. Yields were quantitative.

^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.092 × 8 H, CH_2NC, 0.5 × 8 H, CH_2CH_2CO, 0.408 × 8 H, NCH_2CH_2N), 3.2–3.9 (m, 0.092 × 728 H, OCH_2CH_2O, 0.5 × 8 H, CH_2NCOC), 4.2–4.5 (m, 0.092 × 4 H, CH_2OCON). IR: 2700–2980 (ν(C–H)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1400 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{24.20}H_{79.34}N_{2.18}O_{17.93}$: C, 42.25; H, 11.62; N, 4.45. Found: C, 42.03; H, 11.73; N, 4.43. GPC retention time = 870 s.

PEG 2000–PAA and PEG 1000–PAA block copolymers (XIII and XIV) were prepared exactly as XXII by substituting II (1.122 g, 0.51 mmol) and III (0.622 g, 0.51 mmol), respectively, for I and employing 2 and 1.5 mL of water, respectively. Yields were quantitative.

XIII: ^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.092 × 8 H, CH_3NC, 0.5 × 8 H, CH_2CH_2CO, 0.408 × 8 H, NCH_2CH_2N), 3.2–3.9 (m, 0.092 × 184 H, OCH_2CH_2O, 0.5 × 8 H, CH_2NCOC), 4.2–4.5 (m, 0.092 × 4 H, CH_2OCON). IR: 2700–2980 (ν(C–H)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{15.832}H_{29.23}N_{2.184}O_{6.23}$: C, 54.33; H, 8.44; N, 8.74. Found: C, 53.90; H, 8.51; N, 8.68. GPC retention time = 880 s.

XIV: ^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.092 × 8 H, CH_2NC, 0.5 × 8 H, CH_2CH_2CO, 0.408 × 8 H, NCH_2CH_2N), 3.2–3.9 (m, 0.092 × 92 H, OCH_2CH_2O, 0.5 × 8 H, CH_2NCOC), 4.2–4.5 (m, 0.092 × 4 H, CH_2OCON). IR: 2700–2980 (ν(C–H)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{11.6}H_{16.02}N_{2.18}O_{3.3}$: C, 58.33; H, 6.76; N, 12.81. Found: C, 53.89; H, 9.01; N, 12.72. GPC retention time = 890 s.

PEG 8000–PATA Block Coplymer (XX). I (4.000 g, 0.51 mmol) and XI (0.478 g, 0.51 mmol) were dissolved in water (8 mL) and allowed to react for 24 h. Then the reaction mixture was diluted with water (4 mL), and XVI (0.402 g, 1.95 mmol) and acetic acid (0.17 g, 2.83 mmol) were added under stirring until a homogeneous solution was obtained. The reaction mixture was maintained at room temperature for an additional 3 days with occasional stirring, and then it was treated with piperidine (0.50 g, 5.80 mmol), diluted with water (10 mL), and dialyzed against water for 2 days, with a Spectrapore membrane molecular weight cutoff of 1000. Finally, the solution was evaporated under vacuum and dried to constant weight at 0.1 Torr. Yield: 4.636 g (95%).

^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.376 × 16 H, CH_2NC and CH_2S, 0.124 × 8 H, CH_2NC, 0.5 × 8 H, CH_2CH_2CO), 3.1–3.8 (m, 0.124 × 728 H, OCH_2CH_2O, 0.5 × 8 H, $CONCH_2$), 4.2–4.5 (m, 0.124 × 4 H). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{31.7}H_{105.8}N_{2.25}O_{23.82}S_{0.75}$: C, 41.00; H, 11.54; N, 3.41. Found: C, 40.75; H, 11.60; N, 3.37. Retention time = 870 s.

PEG 2000–PATA and PEG 1000–PATA block copolymers (XXI and XXII) were prepared exactly as XX by substituting II (1.122 g, 0.51 mmol) and III (0.622 g, 0.51 mmol), respectively, for I and employing 2 and 1.5 mL of water, respectively. Yields were similar to that for XX. The reaction mixtures, after alkalinization, were not homogeneous. Nevertheless, they were treated in the same way.

XXI: ^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.376 × 16 H, CH_2NC and CH_2S, 0.124 × 8 H, CH_2NC, 0.5 × 8 H, CH_2CH_2CO), 3.1–3.8 (m, 0.124 × 184 H, OCH_2CH_2O, 0.5 × 8 H, $CONCH_2$), 4.2–4.5 (m, 0.124 × 4 H). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{20.41}H_{38.32}N_{2.25}O_{6.95}S_{0.75}$: C, 54.40; H, 8.57; N, 6.99; S, 5.35. Found: C, 53.89; H, 8.66; N, 6.90; S, 5.40.

XXII: ^{1}H NMR ($CDCl_3$): δ 2.2–2.9 (m, 0.376 × 16 H, CH_2NC and CH_2S, 0.124 × 8 H, CH_2NC, 0.5 × 8 H, CH_2CH_2CO), 3.1–3.8 (m, 0.124 × 92 H, OCH_2CH_2O, 0.5 × 8H, $CONCH_2$), 4.2–4.5 (m, 0.124 × 4 H). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{14.70}H_{27.16}N_{2.25}O_{4.1}S_{0.75}$: C, 54.31; H, 8.42; N, 9.68; S, 7.41. Found: C, 53.90; H, 8.51; N, 9.60; S, 7.38.

Poly(PEG 8000–amido–amine–urethane) (XXIV). I (4.000 g, 0.51 mmol) and XI (0.099 g, 0.51 mmol) were dissolved in water (8 mL) and allowed to react for 3 days. The reaction mixture was then evaporated under vacuum and dried to constant weight at 0.1 Torr. Yields were quantitative.

^{1}H NMR ($CDCl_3$): δ 2.3–2.8 (m, 16 H, CH_2NC and CH_2CH_2CO), 3.4–3.8 (m, 728 H, OCH_2CH_2O and CH_2NCO), 4.2–4.5 (m, 4 H, CH_2OCON). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{201}H_{756}N_6O_{186}$: C, 38.72; H, 12.22; N, 1.35. Found: C, 38.49; H, 12.32; N, 1.34. GPC retention time = 740 s.

Poly(PEG 2000–amido–amine–urethane) (XXV) and poly(PEG 1000–amido–amine–urethane) (XXVI) were prepared exactly as XXIV by substituting II (1.122 g, 0.51 mmol) and III (0.622 g, 0.51 mmol), respectively, for I and employing 2 and 1.5 mL of water, respectively.

XXV: ^{1}H NMR ($CDCl_3$): δ 2.3–2.8 (m, 16 H, CH_2NC and CH_2CH_2CO), 3.4–3.8 (m, 184 H, OCH_2CH_2O and CH_2NCO), 4.2–4.5 (m, 4 H, CH_2OCON). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{110}H_{212}N_6O_{50}$: C, 54.62; H, 8.83; N, 3.47. Found: C, 54.29; H, 8.90; N, 3.45. GPC retention time = 870 s.

XXVI: ^{1}H NMR ($CDCl_3$): δ 2.3–2.8 (m, 16 H, CH_2NC and CH_2CH_2CO), 3.4–3.8 (m, 92 H, OCH_2CH_2O and CH_2NCO), 4.2–4.5 (m, 4 H, CH_2OCON). IR: 2870 (ν(CH_2)), 1700 (amidic ν(C=O)), 1650 (urethane ν(C=O)), 1440 (δ(CH_2)), 1100 cm^{-1} (ν(C–O)). Anal. Calcd for $C_{64}H_{122}N_6O_{27}$: C, 54.61; H, 8.74; N, 5.97. Found: C, 54.28; H, 8.81; N, 5.92. GPC retention time = 890 s.

Model PAA (XV). X (0.203 g, 2.36 mmol) and XI (0.564 g, 2.90 mmol) were dissolved in water (2 mL) and allowed to react for 3 days. Piperidine (1 g, 126 mmol) was then added, and the reaction was allowed to proceed for an additional 3 h. The reaction mixture was then evaporated under vacuum and dried under vacuum to constant weight. GPC retention time = 1080 s. Yields were almost quantitative. IR: 2760–2980 (ν(C–H)), 1700 (amidic ν(C=O)), 1440 ($\delta(CH_2)$).

Model PATA (XXIII). XI (0.500 g, 2.57 mmol), XVI (0.400 g, 1.94 mmol), and acetic acid (0.175 g, 2.90 mmol) were dissolved in water (3 mL) and allowed to react for 3 days. 4-Hydroxythiophenol (0.13 g, 13.0 mmol) was then added, and the reaction was allowed to proceed for an additional 3 h. The reaction mixture was then precipitated in 15% ammonia solution, washed exhaustively with water, and then dried to constant weight at 0.1 Torr. Yield: 0.72 g (80%). IR: 2760–2980 (ν(C–H)), 1700 (amidic ν(C=O)), 1440 ($\delta(CH_2)$).

References and Notes

(1) Danusso, F.; Ferruti, P. *Polymer* **1970**, *11*, 88.
(2) Ferruti, P. Biomedical Applications of PAA's. In *Biomedical and Dental Applications of Polymers*; Gebelein, G. C., Koblitz, F. K., Eds.; Plenum Publishing Corp.: New York, 1981; pp 39–57 and references therein.
(3) Ferruti, P.; Marchisio, M. A.; Barbucci, R. *Polymer* **1985**, *26*, 1336.
(4) Ferruti, P.; Barbucci, R. *Adv. Polym. Sci.* **1984**, *58*, 57.
(5) Marchisio, M. A.; Pernis, B.; Vigliani, E. C.; Ferruti, P. *Med. Lav.* **1965**, *39*, 498.
(6) Barbucci, R.; Barone, V.; Ferruti, P.; Oliva, L. *J. Polym. Sci., Polym. Symp.* **1981**, *69*, 49.
(7) Flinterman, M.; Challa, G.; Barbucci, R.; Ferruti, P. *J. Mol. Catal.* **1983**, *18*, 149.
(8) Ferruti, P.; Ranucci, F.; Tempesti, E.; Giuffrè, L.; Arlati, P.; Airoldi, G. *J. Appl. Polym. Sci.*, in press.
(9) Ferruti, P.; Arnoldi, D.; Marchisio, M. A.; Martuscelli, E.; Riva, M.; Provenzale, L. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 2151.
(10) Ferruti, P.; Martuscelli, E.; Nicolais, G.; Riva, F. *Polymer* **1977**, *18*, 387.
(11) Tanzi, M. C.; Fumero, R.; Levi, M.; Tieghi, G. New Heparinizable, Blood Compatible Segmented Polyurethanes: Properties and Stability Tests. In *Polyurethanes in Biomedical Engineering II*; Planck, H., Syré, I., Dauner, M., Egbers, G., Eds.; Elsevier: Amsterdam, 1987; pp 197–212.
(12) Barbucci, R.; Benvenuti, M.; Dal Maso, G.; Ferruti, P.; Nocentini, M.; Russo, R.; Tempesti, F.; Duncan, R.; Bridges, J. F.; McCormick, L. A. A New Material for Biomedical Application. In *Polymers in Medicine III*; Migliaresi, C., Nicolais, G., Giusti, P., Chiellini, E., Eds.; Elsevier: Amsterdam, 1988; pp 3–18.
(13) Ferruti, P.; Domini, I.; Barbucci, R.; Beni, M. C.; Dispensa, E.; Sancasciani, S.; Marchisio, M. A.; Tanzi, M. C. *Biomaterials* **1983**, *4*, 218.
(14) Barbucci, R.; Benvenuti, M.; Casini, G.; Ferruti, P.; Nocentini, M. *Makromol. Chem.* **1985**, *186*, 2291.
(15) Azzuoli, G.; Barbucci, R.; Benvenuti, M.; Nocentini, M. *Makromol. Chem.* **1987**, *8*, 61.
(16) Marchisio, M. A.; Longo, T.; Ferruti, P. *Experientia* **1973**, *29*, 93.
(17) Ferruti, P.; Casini, G.; Barbucci, R.; Tempesti, F.; Mastacchi, R.; Sarret, M. *Biomaterials* **1984**, *5*, 234.
(18) Marchisio, M. A.; Ferruti, P.; Bertoli, S.; Barbiano di Belgioioso, S.; Samour, C. M.; Volter, K. D. A Novel Approach to the Problems of Heparin in Hemodialysis: The Use of a De-heparinizing Filter. In *Polymers in Medicine III*; Migliaresi, C., Nicolais, G., Giusti, P., Chiellini, E., Eds.; Elsevier: Amsterdam, 1988; pp 111–120.
(19) Ranucci, E.; Spagnoli, G.; Ferruti, P.; Sgouras, D.; Duncan, R. *J. Biomater. Sci. Polym. Ed.*, in press.
(20) Ferruti, P.; Ranucci, E.; Depero, L. *Polym. Commun.* **1989**, *30*, 157.
(21) Harris, J. M. *J. Macromol. Sci., Rev. Macromol. Chem. Phys.* **1985**, *C25*, 325.
(22) Cecchi, R.; Rusconi, L.; Tanzi, M. C.; Danusso, F.; Ferruti, P. *J. Med. Chem.* **1981**, *24*, 622.
(23) Zalipsky, S.; Gilon, C.; Zilkha, A. *Eur. Polym. J.* **1983**, *19*, 1177.
(24) Veronese, F.; Boccu, E.; Schiavon, O.; Velo, G. P.; Conforti, A.; Franco, L.; Milanino, R. *J. Pharm. Pharmacol.* **1983**, *35*, 757.
(25) Wieder, K. J.; Palczuk, N. C. *Biochim. Biophys. Acta* **1979**, *254*, 12579.
(26) Suzuki, T.; Ikeda, K.; Tomono, T. *J. Biomater. Sci.* **1989**, *1*, 71.
(27) Nakajima, A.; Hirano, Y., Terai, T.; Goto, K.; Hayashi, T.; Ikada, Y. *J. Biomater. Sci.* **1990**, *1*, 183.
(28) Kimura, Y.; Kirszenstejn, P.; Regen, S. L. *J. Org. Chem.* **1983**, *48*, 386.
(29) Heffernam, J. G.; MacKenzie, W. M.; Sherrington, D. C. *J. Chem. Soc.* **1981**, 514.
(30) Hiratani, K.; Reuter, P.; Manecke, G. *Isr. J. Chem.* **1979**, *18*, 208.
(31) Planck, H.; Egbers, G.; Syrè, I. *Polyurethanes in Biomedical Engineering*; Elsevier: Amsterdam, 1984; Vol. 1.
(32) Lyman, D. J.; Matcalf, L. C.; Albo, D.; Richards, K. F.; Lamb, J. *Trans. Am. Soc. Artif. Intern. Organs* **1975**, *21*, 49.
(33) Boretos, J. W.; Pierce, J. *Science* **1967**, *158*, 1981.
(34) Okano, T.; Grainger, D. W.; Park, K. D.; Nojiri, C.; Fejien, J.; Kim, S. W. *Artificial Heart II*; Koyanagi, H., Akatsu, T., Eds.; Springer-Verlag, in press.
(35) Kim, S. W.; Okano, T.; Park, K. D.; Grainger, D. W.; Nojiri, C. In *Frontiers of Macromolecular Science*, Proceedings of the IUPAC 32nd International Symposium on Macromolecules, Kyoto, Japan, Aug 1–5, 1988.
(36) Ferruti, P. *Makromol. Synth.* **1985**, *9*, 25.
(37) Ferruti, P.; Ranucci, E. *Makromol. Chem., Rapid Commun.* **1987**, *8*, 549.

Registry No. I, 133626-36-5; X, 110-85-0; (X)(XI)(PEG) (block copolymer), 133626-38-7; (XI)(XVI)(PEG) (block copolymer), 133626-40-1; (XI)(PEG) (block copolymer), 133626-42-3; XII (block copolymer), 133626-37-6; XX (block copolymer), 133626-39-8; XXIV (block copolymer), 133626-41-2; PEG, 25322-68-3; CDI, 530-62-1.