Water-Soluble Polyamides as Potential Drug Carriers. VIII. Poly(alkylene oxide)-Grafted Polyaspartamides Bearing Ethylenediamine Side-Group Functions*

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SYNOPSIS

In continuation of previous investigations of aspartamide-type polymers as drug carriers, polyaspartamides featuring hydrosolubilizing poly(alkylene oxide) side chains in addition to ethylenediamine side-group functions as potential drug-binding sites are synthesized from poly-D,L-succinimide by successive aminolytic ring-opening steps. Yields are in the range of 45–55%. Depending on selected feed ratios, the target polymers contain both the poly(alkylene oxide) and the ethylenediamine groups in systematically varied proportions. Compositions are determined microanalytically and from relative band intensities of the ^{1}H-NMR spectra. The polymers dissolve smoothly and completely in aqueous media and thus fulfill the major design requirement of water solubility. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

In previous communications,[1-3] we reported on the conversion of poly-D,L-succinimide (**1**), by aminolytic hetero ring opening, to water-soluble polymeric drug carriers of the polyaspartamide type featuring ethylenediamine side-chain segments. Such segments are of interest as potential ligands for metal (e.g., platinum[3]) coordination and as binding sites for carboxyl- or formyl-functionalized drug models. To achieve a further enhancement of drug-carrying capabilities in aqueous solution, we modified the polyaspartamide structural framework through poly(ethylene oxide) (PEO) side-chain attachment. Poly(ethylene oxides), both short-chain and long-chain varieties, have found wide acceptance in biomedical research on account of their excellent water solubility, paired with biocompatibility and other biologically exploitable properties. As early as 1977, Abuchowski et al.[4] successfully grafted PEO chains onto serum albumin for reduction of immunogenicity, and later (exemplifying) articles dealt with the use of PEO compounds in hydrogels and liposomes for controlled drug release,[5,6] in microcapsules featuring reduced capture by the reticuloendothelial system,[7] in biomaterials with enhanced protein resistance and reduced platelet reactivity,[8-10] as well as in mucoadhesives,[11] drug carriers,[12,13] and immobilized enzyme structures.[14] In this article, we present the results of PEO grafting experiments performed in our laboratory involving partial ring opening and amidation of **1** by monoamine-terminated PEO derivatives.

EXPERIMENTAL

General Procedures

Proton NMR spectra [200 MHz; chemical shifts δ, in ppm, referenced against internal sodium 3-(trimethylsilyl)-2,2,3,3-d_4-propionate; integration error limits ± 15%] were taken on D_2O solutions. Inherent viscosities, η_{inh}, were determined in Cannon-Fenske viscometer tubes at 30.00 ± 0.05°C in H_2O (c = 0.2 g/100 mL) and are given in units of mL g^{-1}. Solid-state IR spectra, obtained on KBr pellets, were recorded over the region 4000–200 cm^{-1}. Dialysis op-

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erations were performed with the aid of cellulose membrane tubing, type Spectra/Por 4, and wet tubing, Spectra/Por 6 (Spectrum Industries Inc., Los Angeles, CA), with molecular mass cutoff limits of, respectively, 12,000–14,000 and 25,000. A Spectra/Por 6 wet tubing with a cutoff limit of 2000 served specifically for the purification of Jeffamine M-1000, and Spectra/Por 3 (cutoff limit, 3500) was used to purify Jeffamine M-2070 (*vide infra*). The stationary, repeatedly exchanged outer dialysis phase was N_2-saturated, deionized H_2O. A Virtis Bench Top 3 freeze-drier, operating at −40°C, 10–15 Pa, was used for freeze-drying of aqueous solutions. The freeze-dried material was subjected to a postdrying treatment in a Sartorius Thermo Control Infrared Drying System with a heating program of 2 × 8 min at 70°C. Microanalyses were performed by Robertson Laboratory, Madison, NJ. Analytical samples were additionally dried for 2 days at 75°C in an Abderhalden apparatus. These mild drying conditions generally left some 2–3% of moisture in the hygroscopic materials. Determinations were made in duplicate and the findings averaged.

Reagents, Reactants, and Solvents

D,L-Aspartic acid, diethylenetriamine, and ethanolamine, all reagent grade, were used as received (Fluka). *N,N*-Dimethylformamide (DMF; 99%) was predried over molecular sieves 4 Å and redistilled under reduced pressure in a faint stream of N_2 (forerun discarded).

The technical-grade PEO derivative, *O*-(2-aminopropyl)-*O'*-(2-methoxyethyl)copoly(ethylene, propylene glycol) 900 (Jeffamine M-1000; Fluka), was purified by aqueous-phase dialysis (5 h) (*vide supra*) and freeze-drying of the retentate. Recovery was 70%.

ANAL: Calcd for $H_2N—CH(CH_3)CH_2O—(CH_2CH_2O)_{18}[CH(CH_3)CH_2O]—CH_2CH_2OCH_3$ ($C_{45}H_{93}NO_{21}$) (984.2): C, 54.91%; H, 9.52%; N, 1.42%. Found: C, 54.97%; H, 9.87%; N, 1.11%.

The second PEO derivative used in this work, *O*-(2-aminopropyl)-*O'*-(2-methoxyethyl)copoly(ethylene, propylene glycol) 1900 (Jeffamine M-2070), was similarly purified by dialysis (7 h); recovery was 63%.

ANAL: Calcd for $H_2N—CH(CH_3)CH_2O—(CH_2CH_2O)_{36}[CH(CH_3)CH_2O]_6CH_2CH_2OCH_3$ ($C_{96}H_{195}NO_{44}$) (2067.5): C, 55.77%; H, 9.51%; N, 0.68%.
Found: C, 55.39%; H, 9.77%; N, 0.60%.

Poly-D,L-succinimide (**1**) was synthesized by high-temperature solution polymerization of D,L-aspartic acid in orthophosphoric acid by the method of Neri and Antoni.[16] Material used in the present project was taken from a master batch obtained from the thoroughly mixed products of approximately equal viscosity stemming from several runs: η_{inh} (DMF), 45 mL g^{-1} (corresponding[17] to a mass-average molecular mass of approximately 44,500). Throughout this article, amounts of polymeric educt and products refer to the recurring unit and, hence, are given as base moles. Accordingly, for the polysuccinimide substrate, the base mole corresponds to structure **1** where $x + y = z = 1$, and for the copolyaspartamide products, it corresponds to structures **2** and **3**, each normalized to $y = 1$.

Polyaspartamides 2 and 3 by Aminolysis of Polysuccinimide 1

The experiment described in the following, affording polyaspartamide **2**(10 : 25 : 65), exemplifies the stepwise ring-opening reactions conducted with Jeffamine M-1000 as the PEO–NH_2 reactant.

To the stirred solution of **1**, 970 mg (10 mmol), in DMF (20 mL) was added a solution of Jeffamine M-1000, 3.3 g (3.3 mmol), in the same solvent (10 mL), while a gentle stream of N_2 was introduced into the liquid phase. The solution was stirred in the stoppered flask for 20 h at 50°C (bath temperature). It was then cooled in an ice bath and resaturated with N_2. With rapid agitation, diethylenetriamine, 258 mg (2.5 mmol), dissolved in DMF (20 mL), was added via a syringe, and stirring was continued for 8 h at 0–5°C and another 15 h at ambient temperature. On addition of ethanolamine, 599 mg (9.8 mmol), stirring was continued again for 6 h at room temperature, and this was followed by slow (1 h) removal of most of the solvent by rotatory evaporation. The polymeric product was precipitated from the residual, highly viscous liquid by excess (35–40 mL) Et_2O, washed well with hot precipitant for extraction of unreacted Jeffamine, and redissolved in H_2O (40 mL). The clear solution was dialyzed for 50 h in Spectra/Por 4 tubing, and the retentate brought to dryness by freeze-drying. The crude solid product was treated with two successive portions (20 mL each) of boiling ether to remove the last traces of admixed Jeffamine and was redialyzed for 30 h in Spectra/Por 6 (25,000 cutoff) tubing. Freeze-drying of the tube contents and postdrying in the IR assembly yielded 1.31 g (50.2%) of cream-colored solid; η_{inh}, 12 mL g^{-1}.

The same procedure, with appropriately varied reactant ratios, was used for the preparation of other members of Series **2**. Experimental data, including

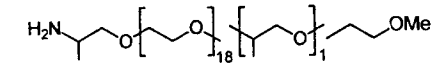
molar feed ratios (expressed here as mol of amine reactants per 100 base mol of **1**), are listed in Table I. Microanalytical and NMR spectroscopic results are in Table II.

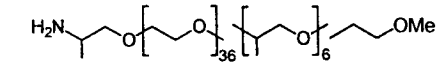
Analogous experiments performed with Jeffamine M-2070 in place of M-1000 gave polyaspartamides of type **3**. Experimental variables and results are summarized in Tables III and IV. All target polymers **2** and **3** were moderately hygroscopic solids, which dissolved smoothly and completely in H_2O over the pH range from 0 to 12.

In selected experiments, the combined aqueous, outer dialysis phases, grossly reduced in volume by rotatory evaporation, were dialyzed in Spectra/Por 3 tubing and freeze-dried. The semisolids obtained were repeatedly washed with boiling Et_2O and, after dissolution in H_2O, were redialyzed in the same type of tubing and freeze-dried, to give lower molecular, water-soluble polyaspartamides in yields of 20–30%; η_{inh}, 6–12 mL g^{-1}. These fractions were not further investigated.

RESULTS AND DISCUSSION

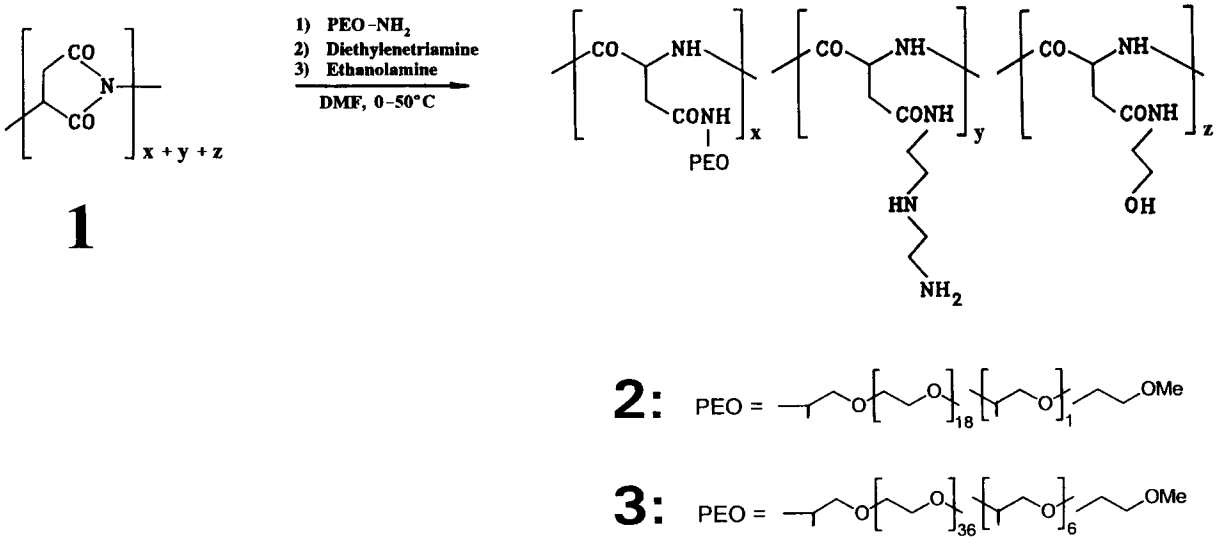
The synthetic pathway chosen is depicted in Scheme 1. Polysuccinimide **1**, dissolved in *N,N*-dimethylformamide (DMF), was treated sequentially with the three amines, PEO–NH_2, diethylenetriamine, and ethanolamine, over various periods of time at 0–50°C, giving terpolymers in which subunits comprising a PEO side chain, the ethylenediamine side-chain segment, and a hydroxyethyl side group were randomly distributed along the chain in predetermined ratios. The amine nucleophile used in the first step, PEO–NH_2, was represented by two PEO derivatives commercially available under the trade names Jeffamine M-1000 and Jeffamine M-2070. These Jeffamines were PEOs containing small proportions of randomly distributed poly(propylene oxide) units, nominal molecular masses being ~ 1000 and ~ 2000, respectively. Each compound was end-capped by a methoxyethyl and a 2-aminopropyl group, with average structures suggested by ^{1}H-NMR data to be as shown:

Jeff-M1000: 

Jeff-M2070: 

Because of a rather sluggish amino-group reactivity, the two Jeffamines failed to interact quantitatively with the imide rings of **1** and, therefore, had to be employed at elevated temperatures and in feed ratios considerably higher than the ratios in which they appeared as backbone constituents of the products (Table I). Not surprisingly, this requirement entailed some run-to-run variability in the percentage Jeffamine incorporated and necessitated accurate determination of Jeffamine contents (^{1}H-NMR) in each polyaspartamide product synthesized.

The amine reactant used in the second step, diethylenetriamine, was chosen, as in previous work,[3] to provide the required ethylenediamine side group. Because of its proven, conveniently high reactivity in imide ring opening reactions,[1-3] this compound



Scheme 1

Table I Feed Ratios and Analytical Data: Polyaspartamides 2[a]

Amine Reactants in Feed (mol %)[b]			Polyaspartamides **2**								
								Anal. Found (Calcd)			
Step 1: M-1000	Step 2: DET	Step 3: EA	Designation[c]	Yield[d] (%)	η_{inh}[e] (mL g^{-1})	Formula[f]	M_{unit}	C	H	N	C/N[g]
16	25	105	**2**(5 : 25 : 70)	51	18	$(C_{34.6}H_{63.2}N_{10}O_{15})_n$	859	47.15 (48.36)	7.62 (7.41)	15.43 (16.30)	3.56 (3.46)
25	25	101	**2**(8 : 25 : 67)	48	13	$(C_{39.76}H_{73.52}N_{10}O_{17.4})_n$	971	47.29 (49.22)	7.69 (7.64)	13.81 (14.44)	3.99 (3.98)
33	25	98	**2**(10 : 25 : 65)	50	11	$(C_{43.2}H_{80.4}N_{10}O_{19})_n$	1044	48.43 (49.70)	7.91 (7.76)	12.93 (13.42)	4.37 (4.32)
47	25	95	**2**(12 : 25 : 63)	47	14	$(C_{46.64}H_{87.28}N_{10}O_{20.6})_n$	1118	48.93 (50.11)	7.99 (7.87)	12.31 (12.53)	4.64 (4.66)
80	25	90	**2**(15 : 25 : 60)	49	13	$(C_{51.8}H_{97.6}N_{10}O_{23})_n$	1229	49.07 (50.64)	8.22 (8.01)	11.01 (11.40)	5.20 (5.18)
85	25	85	**2**(20 : 25 : 55)	47	15	$(C_{60.4}H_{114.8}N_{10}O_{27})_n$	1413	49.99 (51.33)	8.30 (8.19)	9.01 (9.91)	6.47 (6.04)
17	20	113	**2**(5 : 20 : 75)	55	10	$(C_{42.75}H_{77.5}N_{12}O_{19})_n$	1064	46.39 (48.27)	7.52 (7.34)	15.21 (15.80)	3.56 (3.56)
35	20	105	**2**(10 : 20 : 70)	53	12	$(C_{53.5}H_{99}N_{12}O_{24})_n$	1294	48.43 (49.64)	7.87 (7.71)	12.64 (12.99)	4.47 (4.46)
75	20	98	**2**(15 : 20 : 65)	44	14	$(C_{64.25}H_{120.5}N_{12}O_{29})_n$	1525	48.11 (50.59)	8.20 (7.96)	10.51 (11.02)	5.34 (5.35)
18	10	128	**2**(5 : 10 : 85)	48	16	$(C_{83.5}H_{149}N_{22}O_{39})_n$	2085	48.63 (48.09)	7.42 (7.20)	14.23 (14.78)	3.81 (3.80)
34	10	120	**2**(10 : 10 : 80)	46	11	$(C_{105}H_{192}N_{22}O_{49})_n$	2547	47.09 (49.52)	7.71 (7.60)	11.50 (12.10)	4.78 (4.77)
78	10	113	**2**(15 : 10 : 75)	51	13	$(C_{126.5}H_{235}N_{22}O_{59})_n$	3008	47.85 (50.50)	7.98 (7.87)	9.71 (10.24)	5.75 (5.75)

[a] PEO–NH_2 = Jeffamine M-1000. Experiments performed in triplicate; data averaged. Step 1: 20 h, 50°C. Step 2: 8 h, 0–5°C; 15 h, 20–25°C. Step 3: 6 h, 20–25°C; 1 h, 50°C.
[b] Mol of amine per 100 base mol of **1**. M-1000 = Jeffamine M-1000; DET = diethylenetriamine; EA = ethanolamine.
[c] Parenthetic ratio indicates mol % amine residues in **2**.
[d] Main fraction (ultimate retentate in 25,000 cutoff tubing). In addition, 20–30% of lower molecular polyaspartamide (not tabulated).
[e] At 30.00 ± 0.05°C, in H_2O; c = 0.2 g/100 mL.
[f] Composition of repeat unit, defined as structure **2** (Scheme 1) normalized to y = 1.
[g] Carbon/nitrogen atomic ratio.

was added in the same feed ratios (mol per 100 base mol of **1**) as specified for incorporation. Sufficiently high dilution (amine concentrations typically 0.02–0.05M), in conjunction with the prior partial substitution by the bulky PEO side chains in the first step, ensured the diethylenetriamine nucleophile to react monofunctionally despite its potentially multifunctional character, and no cross-linking was observed under the chosen conditions.

In the final step, the third amine reactant, ethanolamine, was employed in excess so as to achieve complete ring opening and substitution of the remaining succinimide units of the substrate polymer. Rigorously anhydrous conditions were required throughout the three reaction steps to prevent concurrent hydrolytic ring opening with resulting generation of carboxylic acid side groups. The polymeric reaction products were isolated as completely water-soluble solids by a sequence of operations including precipitation, dialysis (12,000–14,000 molecular mass cutoff), freeze-drying, rewashing, redialysis (25,000 cutoff), and, again, freeze-drying. This elaborate procedure proved necessary to ensure complete removal of unreacted Jeffamine, which tended to associate with the product polymer and resist diffusion through the dialysis tubing. As a result, yields of ultimate product fractions generally failed to exceed 55%.

In the first series of experiments, Jeffamine M-1000 was the PEO–NH_2 reactant of choice, and the diethylenetriamine contents were held constant at 10, 20, and 25 mol %. These experiments afforded the water-soluble target polymers **2**(x : y : z) (Scheme 1; random placement of subunits, end

Table II ^{1}H-NMR Data for Polyaspartamide 2[a]

	No. Protons Counted[b] (Expected[c])				
Polymer Designation	δ 4.7–4.5[d]	δ 4.1–3.4$_5$	δ 3.4–3.3	δ 3.0–2.5	δ 1.2–1.0
2 (5 : 25 : 70)	4.6 (4)	23 (22)	7.7 (8.2)	14 (14)	1.4 (1.2)
2(8 : 25 : 67)	4.4 (4)	36 (31.6)	8.9 (8.32)	14 (14)	2.0 (1.92)
2(10 : 25 : 65)	4.5 (4)	36 (38)	9.2 (8.4)	14 (14)	2.1 (2.4)
2(12 : 25 : 63)	3.6 (4)	48 (44.4)	7.3 (8.48)	14 (14)	3.1 (2.88)
2(15 : 25 : 60)	3.6 (4)	55 (54)	9.3 (8.6)	14 (14)	3.7 (3.6)
2(20 : 25 : 55)	4.6 (4)	77 (70)	7.9 (8.8)	14 (14)	5.1 (4.8)
2(5 : 20 : 75)	— (5)	29 (28)	11.2 (10.25)	16 (16)	1.5 (1.5)
2(10 : 20 : 70)	5.6 (5)	43 (48)	11.0 (10.5)	16 (16)	2.7 (3)
2(15 : 20 : 65)	6.0 (5)	75 (68)	9.6 (10.75)	16 (16)	4.7 (4.5)
2(5 : 10 : 85)	8.9 (10)	63 (58)	19.7 (20.5)	26 (26)	3.3 (3)
2(10 : 10 : 80)	— (10)	105 (98)	19.1 (21)	26 (26)	6.7 (6)
2(15 : 10 : 75)	9.6 (10)	131 (138)	19.6 (21.5)	26 (26)	8.2 (9)

[a] In D_2O; pD 11–12. Chemical shifts, δ/ppm, referenced against internal sodium 3-(trimethylsilyl)-2,2,3,3-d_4-propionate.
[b] Integration error limits ±15%.
[c] Expected for compositions per designations **2**.
[d] Proton assignments, 4.7–4.5 ppm: methine (α,β-aspartyl); 4.1–3.4$_5$: methine, methylene (Jeffamine and CH_2OH); 3.4–3.3: *O*-methyl (Jeffamine), methylene (CH_2CH_2OH); 3.0–2.5: methylene (remaining groups); 1.2–1.0: C-methyl (Jeffamine).

groups neglected). The parenthetic ratio in this and subsequent product designations reflects the mol % contents of PEO–NH_2, diethylenetriamine, and ethanolamine, in that order. Tables I and II record the molar feed ratios and resulting target polymer compositions, the latter determined by microanalysis and confirmed, within experimental integration error limits, by the ^{1}H-NMR spectra (*vide infra*).

Analogously conducted experiments employing Jeffamine M-2070 as the PEO–NH_2 reactant, with diethylenetriamine contents held constant at 10 and 15 mol %, gave the water-soluble target polymers **3**(x : y : z). Experimental feed ratios and product compositions are compiled in Tables III and IV.

A comparison of feed data with product polymer compositions reveals a nonlinear relationship between the amounts of Jeffamines in the feed and the mol % of PEO-modified aspartamide subunits in the products. Starting from a level of about 10 mol % Jeffamine in the polymer, the relative excess of added Jeffamine necessary to achieve the desired percentage incorporation in these experiments is seen to increase with increasing percentage in the feed, notably so in the Series **3** comprising the longer PEO side chains. In light of the considerable steric hindrance provided to incoming Jeffamine by PEO chains already attached to the backbone, the observed trend agrees well with expectation.

The solid-state IR spectra of both **2** and **3** exhibited the amide I and II bands at 1650 and 1530 cm^{-1} and the Jeffamine ether band near 1100 cm^{-1} as the dominating features. The ^{1}H-NMR spectra (D_2O; pD 11–12) showed two methine proton resonances (α and β peptide forms[15]) of the aspartyl system at 4.7 and 4.5 ppm. The most prominent cluster of signals, ranging from 4.1 to 3.4 ppm, comprised the methylene and methine resonances of the Jeffamine, superimposed on the band due to the hydroxyl-substituted methylene group of the ethanolamine residue. The Jeffamine methoxy resonance emerged as a sharp singlet at 3.38 ppm, partially merging with the second methylene signal (CH_2 adjacent to NH) of the ethanolamine segment at 3.3 ppm. A broad resonance due to the remaining methylene protons appeared at 3.0–2.5 ppm, and the *C*-methyl Jeffamine proton signal was observed at 1.2–1.0 ppm. The compositions established by elemental analysis were corroborated by the relative intensities of these band groups. Tables II and IV contain the expected and found proton counts.

In summary, by a series of aminolytic ring-opening reactions, polysuccinimide **1** was converted to *N*-substituted copolyaspartamides **2** and **3** comprising from 10 to 25 mol % ethylenediamine side groups as potential drug-binding sites. In addition, these polymers possess hydrosolubilizing poly(alkylene oxide) side chains in various proportions and thus dissolve readily and completely in

Table III Feed Ratios and Analytical Data: Polyaspartamide 3[a]

Amine Reactants in Feed (Mol %)[b]			Polyaspartamides 3								
								Anal. Found (Calcd).			
Step 1: M-2070	Step 2: DET	Step 3: EA	Designation[c]	Yield[d] (%)	η_{inh}[e] (mL g^{-1})	Formula[f]	M_{unit}	C	H	N	C/N[g]
21	15	120	**3**(5 : 15 : 80)	49	23	$(C_{73.33}H_{135.33}N_{15.33}O_{33.33})_n$	1765	48.68 (49.89)	7.97 (7.73)	11.98 (12.17)	4.74 (4.78)
43	15	113	**3**(10 : 15 : 75)	55	17	$(C_{104.67}H_{198.01}N_{15.33}O_{47.67})_n$	2434	50.23 (51.64)	8.46 (8.20)	8.53 (8.82)	6.87 (6.83)
79	15	105	**3**(15 : 15 : 70)	51	19	$(C_{136}H_{260.67}N_{15.33}O_{62})_n$	3103	50.78 (52.64)	8.59 (8.47)	6.68 (6.92)	8.87 (8.87)
5	10	134	**3**(1 : 10 : 89)	49	12	$(C_{71.4}H_{124.8}N_{22}O_{33.3})_n$	1824	45.94 (47.01)	7.17 (6.90)	16.41 (16.89)	3.27 (3.25)
8	10	132	**3**(2 : 10 : 88)	46	15	$(C_{80.8}H_{143.6}N_{22}O_{37.6})_n$	2025	46.15 (47.92)	7.23 (7.15)	14.71 (15.22)	3.66 (3.67)
20	10	128	**3**(5 : 10 : 85)	54	18	$(C_{109}H_{200}N_{22}O_{50.5})_n$	2627	48.12 (49.84)	7.82 (7.67)	11.26 (11.73)	4.98 (4.95)
35	10	123	**3**(8 : 10 : 82)	48	13	$(C_{137.2}H_{256.4}N_{22}O_{63.4})_n$	3229	49.96 (51.03)	8.11 (8.00)	9.32 (9.54)	6.25 (6.24)
42	10	120	**3**(10 : 10 : 80)	46	20	$(C_{156}H_{294}N_{22}O_{72})_n$	3630	50.70 (51.61)	8.29 (8.16)	8.44 (8.49)	7.01 (7.09)
56	10	117	**3**(12 : 10 : 78)	50	23	$(C_{174.8}H_{331.6}N_{22}O_{80.6})_n$	4031	51.24 (52.08)	8.39 (8.29)	7.51 (7.64)	7.96 (7.95)
85	10	113	**3**(15 : 10 : 75)	49	16	$(C_{203}H_{388}N_{22}O_{93.5})_n$	4633	51.47 (52.62)	8.61 (8.44)	6.49 (6.65)	9.25 (9.23)

[a] $PEO-NH_2$ = Jeffamine M-2070. Experiments performed in triplicate; data averaged. Step 1: 20 h, 50°C. Step 2: 8 h, 0–5°C; 15 h, 20–25°C. Step 3: 6 h, 20–25°C; 1 h, 50°C.
[b] Mol of amine per 100 base mol of **1**. M-2070 = Jeffamine M-2070; DET = diethylenetriamine; EA = ethanolamine.
[c] Parenthetic ratio indicates mol % amine residues in **3**.
[d] Main fraction (ultimate retentate in 25,000 cutoff tubing). In addition, 20–30% of lower molecular polyaspartamide (not tabulated).
[e] At 30,00 ± 0.05°C in H_2O; c = 0.2 g/100 mL.
[f] Composition of repeat unit, defined as structure **3** (Scheme 1) normalized to $y = 1$.
[g] Carbon/nitrogen atomic ratio.

Table IV ^{1}H-NMR Data for Polyaspartamide 3[a]

	No. Protons Counted[b] (Expected[c])				
Polymer Designation	δ 4.7–4.5[d]	δ 4.1–3.4$_5$	δ 3.4–3.3	δ 3.0–2.5	δ 1.2–1.0
3(5 : 15 : 80)	5.7 (6.7)	63 (66.9)	14.7 (13.7)	19.3 (19.3)	6.3 (7)
3(10 : 15 : 75)	6.3 (6.7)	128 (122.7)	14.2 (14)	19.3 (19.3)	14.6 (14)
3(15 : 15 : 70)	8.0 (6.7)	189 (178.3)	15.0 (14.3)	19.3 (19.3)	22.8 (21)
3(1 : 10 : 89)	10.1 (10)	38 (34.7)	21.6 (20.1)	26 (26)	2.2 (2.1)
3(2 : 10 : 88)	10.7 (10)	49 (51.4)	22.9 (20.2)	26 (26)	3.7 (4.2)
3(5 : 10 : 85)	— (10)	113 (101.5)	23.0 (20.5)	26 (26)	11.3 (10.5)
3(8 : 10 : 82)	10.3 (10)	158 (151.6)	22.6 (20.8)	26 (26)	17.2 (16.8)
3(10 : 10 : 80)	8.3 (10)	169 (185)	21.3 (21)	26 (26)	19.2 (21)
3(12 : 10 : 78)	— (10)	227 (218.4)	26.5 (21.2)	26 (26)	26.1 (25.2)
3(15 : 10 : 75)	9.5 (10)	266 (268.5)	20.9 (21.5)	26 (26)	32.3 (31.5)

[a] In D_2O; pD 11–12. Chemical shifts, δ/ppm, referenced against internal sodium 3-(trimethylsilyl)-2,2,3,3-d_4-propionate.
[b] Integration error limits ±15%.
[c] Expected for compositions per designations **3**.
[d] For proton assignments, see footnote d of Table II.

aqueous media. Selected carriers of types **2** and **3** are currently being platinated, and the results of this study will be presented in a forthcoming publication.

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