Synthesis of a novel star-shaped dendrimer by radial-growth polymerization of sarcosine *N*-carboxyanhydride initiated with poly(trimethyleneimine) dendrimer

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SUMMARY: A novel AB_n-type dendrimer/linear polymer block copolymer, i.e., poly(trimethyleneimine) dendrimer-*block*-(polysarcosine)$_{64}$ (**1**), was synthesized by ring-opening polymerization of sarcosine *N*-carboxyanhydride initiated with the 64-NH_2-terminal poly(trimethyleneimine) dendrimer as a macroinitiator. **1** has narrow molecular weight distributions ($\bar{M}_w/\bar{M}_n = 1.0_1-1.0_3$, by size exclusion chromatography) and controlled polysarcosine chain lengths (by varying the monomer/dendrimer feed molar ratios). Small-angle neutron scattering (SANS) data obtained in D_2O solution of **1** (DP's of polysarcosine = 2.0 and 24) fitted well with a Guinier plot of a spherical particle, and gave diameters of 44 and 100 Å, respectively.

Introduction

Since spherical molecules have some remarkable features such as a molecular capsule and a ball bearing, fullerene, dendrimers[1–3], and microspheres attracted much attention in a wide range of fields from molecular science to materials science. Diameters of common dendrimers (ca. <10 nm) are intermediate between those of fullerene (7 Å) and microspheres (0.1–10 μm). Homodendrimers are generally known to have a limitation of molecular size due to increasing defects of branching or incomplete coupling of high-generational dendrons. Especially, dendrimers with a short interbranch-point distance have a small molecular size, whereas small dendrimers possess attractive characters, e.g., a molecular capsule[4,5] and regulated molecular shape[6–8]. Poly(trimethyleneimine) (PTMI) dendrimer[9], namely poly(propyleneimine) dendrimer[4,5,10,11], is an important dendrimer for the purpose of derivatization to enlarge the globular shape by introducing a block structure.

Among block dendrimers[3], linear polymer/dendrimer block copolymers have an advantage to combine characteristic properties of dendrimers and linear polymers[12–14]. It is noteworthy that the star-shaped block copolymer is conveniently prepared by one-pot reaction with a dendritic initiator, while chemical structure of the products is complicated.

We have already reported that radial-growth polymerization (RGP)[15] of sugar-substituted monomers with poly(amido amine) dendrimers affords a family of sugar balls[16–19] of oligoglycopeptide-type with star-type branches. In this polymerization system, propagating vectors have an order of a radial symmetry initiated by terminal active ends of the dendrimer as an initiator core. The number of linear segments is strictly determined by generation of the dendrimer when the fast initiation system is adopted. Thus, the present multiple polymerization system is different from conventional polymerizations employed for preparation of star polymers[20]. As dendrimer-like star polymers, poly(ε-caprolactone)s[21,22] and poly(methyl methacrylate)s[23] were also reported recently.

This report describes RGP of sarcosine *N*-carboxyanhydride (SarNCA) with PTMI dendrimer. Ring-opening polymerization of SarNCA is known to proceed cleanly without side reactions to afford polysarcosine (poly(Sar)), i.e., poly(*N*-methylglycine)[24]. Besides the synthetic aspect, size and shape of the star-shaped dendrimer are discussed from the results of SANS investigations.

Results and discussion

Ring-opening polymerization of sarcosine *N*-carboxyanhydride (SarNCA), i.e., *N*-methylglycine NCA, with poly(trimethyleneimine) (PTMI) dendrimer of 64-NH_2-terminal-type was carried out in chloroform at 27 °C under a nitrogen atmosphere (Scheme 1). The product was purified by repeated reprecipitations from methanol into diethyl ether. Block copolymer **1** was obtained in 91–99% yields. The results are summarized in Tab. 1. The DP's of the polysarcosine (poly(Sar)) block were determined by ^{1}H NMR spectroscopy, using averaged signal intensity ratios of methyl (3.0–2.9 ppm) and methylene protons (4.4–4.0 ppm) of poly(Sar) to methylene protons of PTMI (1.71 ppm). The evaluated DP's closely agreed with the feed molar ratios of SarNCA to the terminal primary amino groups of PTMI dendrimer. In the ^{13}C NMR spectra, neither signal due to α- and β-methylene

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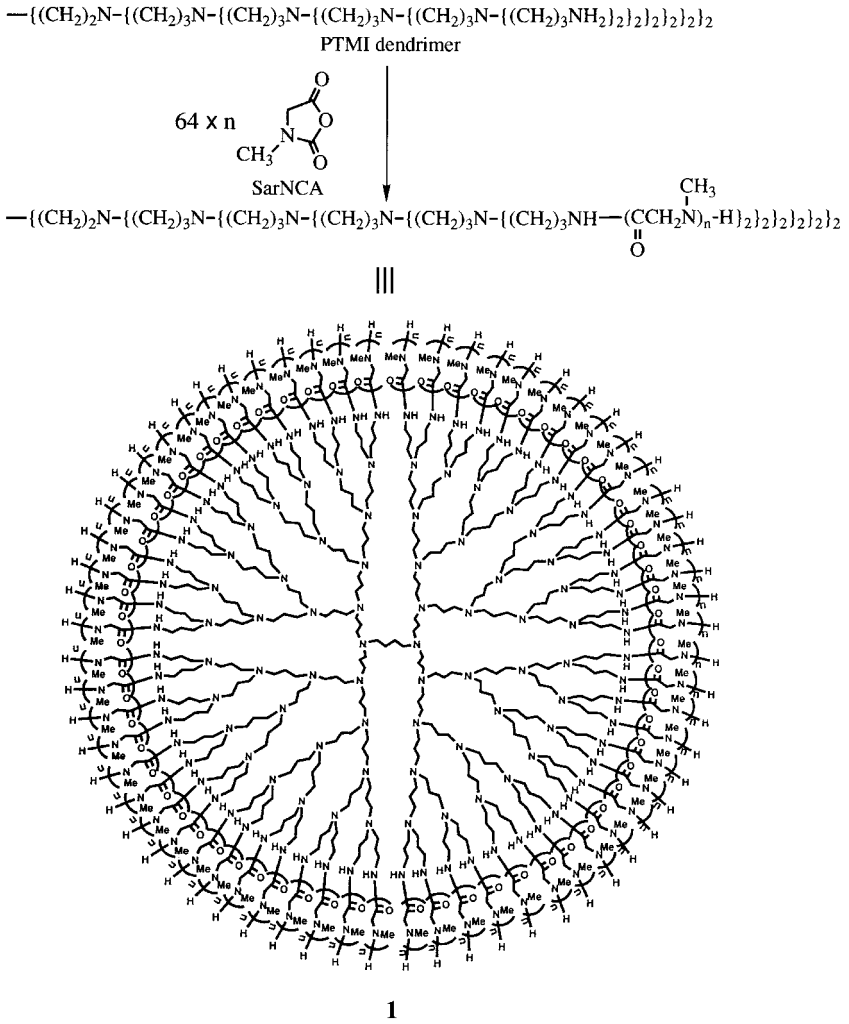
Scheme 1: Synthesis of star-shaped poly(trimethyleneimine) dendrimer-*block*-(polysarcosine)$_{64}$ (**1**)



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Tab. 1. Polymerization of sarcosine *N*-carboxyanhydride initiated with poly(trimethyleneimine) dendrimer[a)]

Run No.	$\frac{[M]_0}{[-NH_2]_0}$ [b)]	Yield in %	DP[c)]	$\bar{M}_n \times 10^4$				$\bar{M}_w/\bar{M}_n$[f)]	$\bar{M}_w/\bar{M}_n$[g)]
				Calc.[d)]	NMR[e)]	SEC[f)]	SEC[g)]		
1	2.1	96	2.0	1.6	1.6	1.1	2.9	1.0_3	1.0_3
2	5.5	99	5.2	3.2	3.1	2.9	7.0	1.0_3	1.0_4
3	22	91	24	11	12	6.0	13	1.0_1	1.0_1
4	49	96	51	23	24	12	24	1.0_4	1.0_3

a) Solvent: chloroform; $[M]_0$: 0.10 mol/L; temperature: 27 °C; time: 20 h; under nitrogen.
b) Feed molar ratio of sarcosine *N*-carboxyanhydride to terminal amino groups of poly(trimethyleneimine) dendrimer.
c) Average degree of polysarcosine, determined by ^{1}H NMR in D_2O at 27 °C.
d) Theoretical molecular weight.
e) Determined by ^{1}H NMR in D_2O at 27 °C.
f) Estimated by size exclusion chromatography (SEC) in 0.05 M K_2HPO_4 aq. solution at 27 °C (pullulan standard).
g) Estimated by SEC in 0.05 M K_2HPO_4 aq. solution at 27 °C (globular protein standard).

moieties of an unreacted terminus of the PTMI initiator was observed. Especially, initiation from all the terminal amino groups occurred even in run no. 1, which indicates that this radial-growth polymerization (RGP) is a fast initiation and slow propagation system. It is reasonable that reactivity of primary amines of the initiator is higher than that of secondary amines of the propagating ends. The $\bar{M}_n$ values estimated by SEC calibrated with pullulan

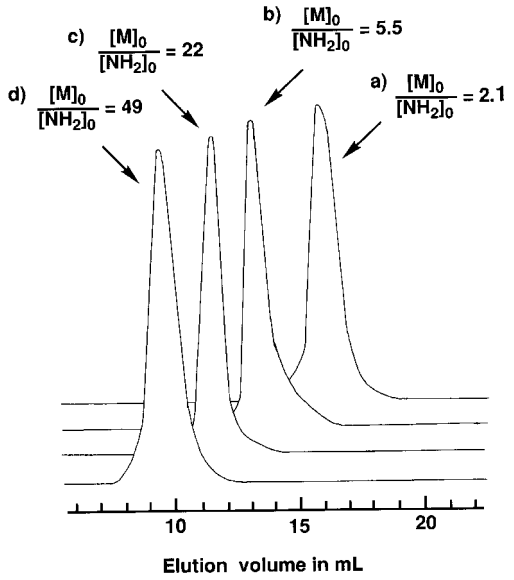

Fig. 1. Profiles of size exclusion chromatography (SEC) of poly(trimethyleneimine) dendrimer-*block*-(polysarcosine)$_{64}$ (**1**); a) run no. 1; b) run no. 2; c) run no. 3; d) run no. 4, in 0.05 M K_2HPO_4 aq. solution at 27 °C

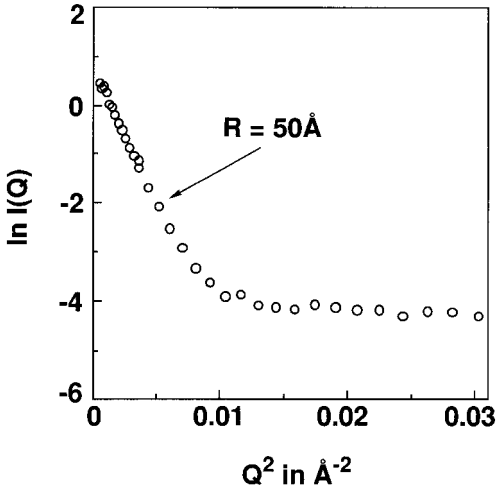

Fig. 2. Guinier plots of small-angle neutron scattering intensity of 1.0 wt.-% D_2O solution of poly(trimethyleneimine) dendrimer-*block*-(polysarcosine (DP = 24))$_{64}$ (**1**) at 25 °C

standards in 0.05 M K_2HPO_4 aq. were lower than those calculated according to the DP's by ^{1}H NMR spectroscopy. The result is logically interpreted as follows. Since **1** has a globular branched structure, the hydrodynamic volume of **1** is smaller than that of linear pullulan having the same molecular weight. On the other hand, $\overline{M}_n$ values of **1** of run nos. 3 and 4 evaluated by using globular protein standards were nearly consistent with those determined by ^{1}H NMR. That the $\overline{M}_n$'s of run nos. 1 and 2 by SEC (globular protein standard) were larger than those by ^{1}H NMR, can be understood by the difference of hydrodynamic volumes of the dendrimer with inner cavities and of globular proteins having a compactly folded structure. The SEC analysis also gave narrow molecular weight distributions ($\overline{M}_w/\overline{M}_n$ =1.0$_1$−1.0$_4$) of **1**, which were obtained for both of the standards. These values are reasonable taking account of the hybridized structure between a dendrimer and a linear polymer. The SEC profiles are shown in Fig. 1. With increasing the feed ratios of monomer to initiator, the unimodal sharp peaks of the resulting polymers shifted toward higher molecular weight region systematically, indicating that controlled RGP of SarNCA proceeded with the dendritic initiator. Different from the case of conventional graft copolymer synthesis by the macroinitiator method, which has a tendency to generate uncontrollable side chains, the present RGP would produce a regulated linear block. It is presumably due to the favorable location of the amino groups of the growing ends on the periphery in the course of RGP on average.

1 was soluble in methanol, dimethyl sulfoxide, and water in a concentration of 1.0 g/L. Poly(Sar) homopolymer was also soluble in these solvents. Contrary to our prediction, **1** was insoluble in dichloromethane and *N*,*N*-dimethylformamide, which are solvents for poly(Sar). It is probably due to formation of a relatively dense shell of poly(Sar) (*vide infra*).

Molecular size and shape of the linear polymer-hyperlinked dendrimer **1** were examined by a small-angle neutron scattering (SANS) study[25,26]. SANS is a powerful methodology to determine size and shape of a nanoscale physical structure. Fig. 2 shows a Guinier plot of SANS data of a D_2O solution of **1** (DP of poly(Sar) = 24) at a concentration of 1.0 wt.-%. We can see that logarithmic $I(Q)$ values decrease linearly with increasing Q^2 at Q = 0.024−0.1 Å^{-1}. From equations for spherical particles described in the experimental section, the radius of **1** (DP = 24) was obtained to be 50 Å (Fig. 3). The calculated values of the radius of **1** were 39 and 89 Å, employing three-dimensionally contracted and extended Corey-Pauling-Koltum (CPK) models, respectively. Therefore, it was found that **1** (DP = 24) had a relatively shrunk structure in aqueous solution. The tendency to form a dense poly(Sar) layer seems to influence the aforementioned insolubility in dichloromethane and *N*,*N*-dimethylformamide. SANS investigations were further undertaken for the PTMI dendrimer and PTMI dendrimer-*block*-oligosarcosine **1** (DP = 2.0), to afford radii of 17 and 22 Å, respectively (Fig. 3). The former value is comparable to that reported by Ramzi et al.[6] (R = 18 Å), and the latter value is acceptable for the PTMI dendrimer with two repeating units of sarcosine.

The results obtained in this study have a fundamental significance that construction of nanometer-scale spherical polymers with narrow size distributions will be easily achieved by the synchronized multiple-propagation with dendritic initiators, instead of conventional living poly-

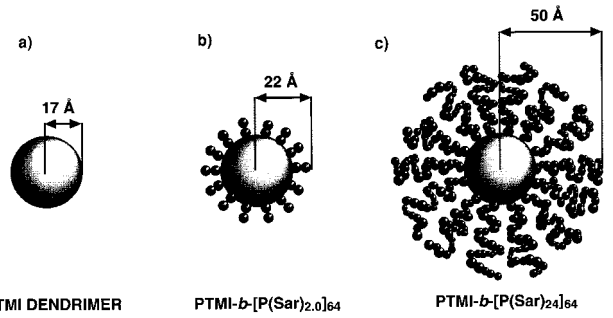

Fig. 3. Schematic illustrations of a) poly(trimethyleneimine) dendrimer and star-shaped dendrimers **1,** b) DP of poly(Sar) = 2.0; c) DP of poly(Sar) = 24, on the basis of the small-angle neutron scattering analysis

merizations producing high-molecular-weight polymers from extra-purified monomers. Furthermore, terminal secondary amino groups of the star-shaped polysarcosine will be utilized by selective derivatizations, which provide a variety of mesoscopic functional materials.

Experimental part

Materials

Poly(trimethyleneimine) (PTMI) dendrimer (Astramol™) was purchased from DSM Co., Geleen, the Netherlands. Sarcosine *N*-carboxyanhydride (SarNCA) was prepared according to the literature[24]. Solvents were dried and purified by distillations under nitrogen. D_2O used for NMR and SANS analyses was purchased from Aldrich Chemical Co., and used without purification.

Typical procedure of preparation of PTMI dendrimer-block-*(polysarcosine)$_{64}$* (**1**)

The procedure of run no. 3 is as follows. In a flask equipped with a three-way stopcock were placed 8.4 mg (1.2 μmol) of PTMI dendrimer (generation = 4.0, 64-terminal-type, 1,4-diaminobutane core) and 16.0 mL of chloroform under nitrogen. To the solution, 0.190 g (1.65 mmol) of SarNCA was added with a gastight syringe, stirred at 27 °C for 20 h. The product was purified by repeated reprecipitations from methanol to diethyl ether. After drying in vacuo, white powdery **1** was obtained in 91.3% yield.

1 (run no. 3, DP of poly(Sar) = 24):

IR (KBr disk): 3477 (ν_{N-H}), 2939 (ν_{C-H}), 1660 ($\nu_{C=O}$), 1494, 1404, 1340, 1300, 1234, 1105 cm^{-1}.

^{1}H NMR (D_2O, ref. MeOH, 27 °C, 400 MHz): δ = 4.40–4.00 (m, 3070H, CH_2 of poly(Sar)), 3.17 (m, 130H, C*H*$_2$NHCO), 3.02–2.88 (m, 4610H, CH_3 of poly(Sar)), 2.64–2.58 (m, 370H, NCH_2 of PTMI), 1.71 (m, 250H, $CH_2CH_2CH_2$ of PTMI).

^{13}C NMR (D_2O, ref. MeOH, 27 °C, 100 MHz): δ = 171.2 (C═O of poly(Sar)), 53.6–50.9 (CH_2 of poly(Sar) and NCH_2 of PTMI), 38.4 (*C*H$_2$NHCO), 36.7–35.0 (CH_3 of poly(Sar)), 25.1 (*C*H$_2$CH$_2$NHCO), 22.8 (CH$_2$*C*H$_2$CH$_2$ of PTMI).

^{1}H NMR data of **1** having oligosarcosine obtained in run no. 1 is as shown below:

^{1}H NMR of **1** (run no. 1, DP of oligo(Sar) = 2.0) (D_2O, ref. MeOH, 27 °C, 400 MHz): δ = 4.34 and 4.03 (m, 250H, CH_2 of oligo(Sar)), 3.17 (m, 130H, C*H*$_2$NHCO), 3.03, 2.99, 2.94, and 2.89 (m, 380H, CH_3 of oligo(Sar)), 2.66–2.50 (m, 370H, NCH_2 of PTMI), 1.68 (m, 250H, CH_2C*H*$_2CH_2$ of PTMI).

Instruments

^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX-400 operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. FT-IR spectra were obtained on a JASCO FT/IR-610. Size exclusion chromatography (SEC) was performed by JASCO PU-980 with an RI detector of JASCO RI-930 (column, Superdex 200 HR 10/30 (Pharmacia Biotech); eluent, 0.05 M K_2HPO_4 aq.; temp., 27 °C; flow rate, 0.5 mL/min.; standard, pulluran or globular proteins (Pharmacia Biotech)).

The SANS measurements were made using the cold neutron small-angle scattering instrument WINK at the High Energy Accelerator Research Organization, Tsukuba, Japan. The instrument was operated at a neutron radiation of 1–16 Å wavelength at 25 °C, using a rectangular quartz cell of dimensions $22 \times 40 \times 2$ mm. The SANS intensities were obtained as a function of scattering vector Q (= $(4\pi/\lambda)\sin(\theta/2)$, where λ and θ are the neutron radiation wavelength and the scattering angle, respectively). The radii were calculated from the slope of a representation of intensity $I(Q)$ versus Q^2 in the Guinier regime ($I(Q) = I_0 \exp(-R_G^2Q^2/3)$) and an equation ($R_G^2 = 3R^2/5$) for a spherical particle model, where I_0, R_G, and R are a constant, the radius of gyration, and the radius of a spherical particle, respectively.

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