(Received 14 July, 2000; Accepted 15 August, 2000)

Synthesis of Lysine-Core Dendrimer Containing Long Pyrrole-Terminated Alkylene Derivative

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Abstract: A new functional pyrrole-terminated lysine core-dendrimer (G3-R) in which the core part and the surface part were hydrophilic and lipophilic, respectively, was synthesized by condensing an amine-terminated third-generation lysine dendrimer with *N*-{{10-{4-[4-(12-carboxyl)dodecyl]phenyleneoxy}decyl}}pyrrole (C12B10P). Structure analysis by ¹H and ¹³C one- and two-dimensional NMR spectroscopy and MALDI-TOF mass spectrometry demonstrated that the condensation gave a fully substituted G3-R with molecular weight of 5926. Phase transitions were determined by DSC and optical polarizing microscope measurements. However, no mesomorphic textures were observed. Molecular force field calculation by use of a Cache3.9 program showed that each C12B10P terminal group points outward three-dimensionally. Pyrrole moiety on the surface of the G3-R might be useful for surface conducting applications.

1. Introduction

Dendrimers or hyperbranched compounds are oligomers or polymers resembling a tree in structure and containing branching points in each structural unit. Since the first report on branched polyamines by Vögtle et al. [1], successful preparations of well-characterized dendritic polymers were independently reported by Tomalia and Newkome et al. [2,3].

Dendrimers can be prepared by two synthetic approaches, i.e., divergent and convergent synthetic methods. In the divergent strategy, dendrimers are built from the central core out to the periphery by a repetitive reaction sequence, increasing the number of reactive sites with each successive generation. In contrast to the divergent strategy, the convergent approach builds the dendrimer from the periphery toward the central core, keeping constant number of

reactive sites throughout the synthesis [4,5]. Dendrimers are characterized by such structural features as i) the initiator core or central core which can affect the dendrimer shape, ii) the nature of the repeating units which determines the microenvironment of the internal cavities, and iii) the nature of the terminal surface groups which are mainly responsible for properties of the dendrimers, i.e., solubility, viscosity, thermal behavior and others. In recent years, dendrimers are attracting a great interest because of unique properties and potential applications in a number of areas, i.e., new catalytic systems [6,7], drug-delivery system [8-10], dendritic building blocks [11,12], and molecular device [13-17]. Especially peptide dendrimers have such potential applications as vaccine and artificial enzymes [18,19].

Conjugated polymers such as polypyrrole and polythiophene have received intense interest due to their practical and potential applications for electrochemical and optical devices [20-22]. Generally speaking, electrical conductivity in solid state is significantly affected by effective π -conjugated length and highly ordered solid-state packing [23,24]. Alkylene spacer and mesogenic units can be utilized for inducing high degree of orientation along the backbone of π -conjugated polymers. It is anticipated that the association of three-dimensional structure of dendrimers with electronic properties of the π -conjugated polymers show interesting new properties. In this study, we report the synthesis and characterization of the pyrrole-modified polylysine dendrimer.

2. Experimental Part

2.1 Materials

1,12-Dodecanedicarboxylic acid, 4-(dimethylamino)pyridine (DMAP) (both from Tokyo Kasei Kogyo Co.), and *N,N'*-dicyclohexylcarbodiimide (DCC) (from Kanto Chemical Co.) were used as purchased. *N*-[10-(4-Hydroxybiphenyleneoxy)decyl]pyrrole was prepared according to the reported procedure [25]. Methyl 3-aminopropionate hydrochloride (H-Ala-OCH₃•HCl) [26], *N,N'*-bis(tertbutyloxycarbon-yl)-L-lysine (Boc-Lys(Boc)-OH) [27], and third-generation lysine dendrimer were prepared according to the literature [28]. The detailed results on the preparation of the lysine dendrimer will be reported elsewhere [29]. The other reagents and solvents were obtained commercially and used as received.

2.2 Characterization

¹H and ¹³C NMR spectra were recorded on a JEOL Lambda-500 spectrometer. The two-dimensional spectra were measured by use of field gradient pulse. Tetramethylsilane (TMS) was used as the internal standard. Differential scanning calorimetry (Mettler DSC 30) was used to determine the phase transition temperature at the heating and cooling rates of 10°C/min. An optical polarizing microscope (Olympus BH-2) equipped with a Mettler FP-82 hot stage and a temperature programmer FP-80 was used supplementary. Matrix-assisted laser-desorption ionization time of flight (MALDI-TOF) mass spectra were recorded on a Bruker Biflex-III instrument in positive ion mode. The matrix was made of *a*-cyano-4-hydroxycinnamic acid (CCA). The weight concentration of sample was 0.1% in chloroform-methanol (9:1).

2.3 Synthesis

N-{[10-{4-[4-(12-Carboxyl)dodecyl]oxy}decyl]pyrrole-

y]biphenyleneoxy}decyl}}pyrrole (C12B10P): A solution of *N*-[10-(4-hydroxybiphenyleneoxy)-decyl]pyrrole (1) (0.50 g, 1.28 mmol), 1,12-dodecanedicarboxylic acid (2) (1.65 g, 6.38 mmol), 4-dimethylaminopyridine (DMAP) (0.16 g, 1.28 mmol) and *N,N'*-dicyclohexylcarbodiimide (DCC) (0.28 g, 1.34 mmol) in 10 ml pyridine was stirred for 39 h at room temperature under nitrogen atmosphere. After work-up, the crude product was purified by column chromatography (silicagel: CH₂Cl₂/methanol = 30:1 as eluent) and then recrystallized from ethanol to yield 0.45 g (56%) of C12B10P.

Pyrrole derivative-terminated lysine-core dendrimer (CH₃O-Ala-Lys-Lys₂-Lys₄-(NH₂)₈-(C12B10P)₈) (G3-R): A solution of C12B10P (300.0 mg, 0.47 mmol), deprotected third-generation lysine dendrimer (67.8 mg, 0.04 mmol), DIEA (113.7 mg, 0.88 mmol), and BOP (322.9 mg, 0.73 mmol) in DMF 15 ml was stirred for 42 h at room temperature under nitrogen atmosphere. After work-up, the crude product was purified by reprecipitation of its chloroform solution into ethanol. Yield 56.6 mg (24%)

3. Results and Discussion

3.1 Synthesis and Characterization of Pyrrole-Terminated Carboxyl Derivative

N-{[10-{4-[4-(12-Carboxyl)dodecyl]oxy}biphenyleneoxy}decyl}}pyrrole (C12B10P) was synthesized by esterification of 1,12-dodecanedicarboxylic acid with *N*-[10-(4-hydroxybiphenyleneoxy)decyl]pyrrole (B10P). The esterification was achieved by direct condensation in the presence of 4-dimethylaminopyridine (DMAP) and *N,N'*-dicyclohexylcarbodiimide (DCC) at room

temperature [30]. The product was purified by column chromatography, followed by recrystallization. The final synthetic step of the pyrrole-terminated carboxyl derivative C12B10P is outlined in Scheme 1.

Scheme 1 Structure of pyrrole-terminated carboxyl derivative C12B10P and pyrrole-terminated lysine core-dendrimer G3-R

The chemical structure of the pyrrole-terminated carboxyl derivative C12B10P was confirmed by use of ¹H and ¹³C NMR spectroscopy and two-dimensional HMQC-FG NMR spectrum, which was used to assign both the ¹H and the ¹³C chemical shifts of carbons. The absorption peak of the hydroxy proton in B10P appeared at 4.7 ppm as a singlet, which completely disappeared in the ¹H NMR spectrum of pyrrole-terminated carboxyl derivative C12B10P after esterification (Fig. 1). C12B10P showed three new peaks at 1.6, 2.3, and 2.6 ppm. These new peaks are attributed to the methylene

protons of 1,12-dodecanedicarboxylic acid moiety. In the ^{13}C NMR spectrum of C12B10P, two peaks due to the pyrrole carbon were observed at 107.7 and 120.6 ppm. Many aromatic and alkylene proton absorptions appeared at 114.7–149.6 and 68.0–24.4 ppm, respectively. In particular, the presence of new peaks at 172.5 and 179.6 ppm due to carbonyl carbon clearly indicates that esterification took place successfully. Above assignment of the ^1H and ^{13}C chemical shifts were carried out by ^1H - ^{13}C correlated two-dimensional HMQC-FG spectrum (Fig. 1). The horizontal and vertical axes show ^1H and ^{13}C spectrum, respectively. Directly coupled C-H's were differentiated by contour from quaternary carbons, i.e., carbonyl (1 and 7) and aromatic carbon (8, 11, 12, and 15) did not show contour. The chemical shift and the integration of resonances were in good agreement with the proposed carboxylic acid derivative C12B10P structure.

Fig. 1 HMQC-FG spectra of pyrrole-terminated carboxyl derivative C12B10P

Thermal properties of the pyrrole-terminated carboxyl derivative C12B10P was examined by optical polarizing microscopy and differential

scanning calorimetry (DSC) measurements. Figure 2 shows a DSC thermogram for the pyrrole-terminated carboxyl derivative C12B10P. The first heating scan (curve A) showed two endothermic peaks at 82.6°C ($\Delta H=29.8\text{J/g}$) and 110.0°C ($\Delta H=72.9\text{J/g}$) on the DSC measurement. However, the first cooling scan (curve B) showed only one exothermic peak at 100.3°C ($\Delta H=78.2\text{J/g}$) and the second heating scan (curve C) also showed only one endothermic peaks at 107.9°C ($\Delta H=77.1\text{J/g}$). This DSC measurement of the pyrrole-terminated carboxyl derivative C12B10P indicating that the thermal transition is reversible and intact during the scan circles. To check the liquid crystallinity of this sample, optical polarizing microscopic observations were performed. However, no mesomorphic textures were observed. There is a transition peak at 82.6°C in the first heating scan, which is probably a solid-solid transition.

Fig. 2 DSC thermograms of pyrrole-terminated carboxyl derivative C12B10P (10°C/min): (A) 1st heating, (B) 1st cooling, (C) 2nd heating

Amine terminated third-generation lysine dendrimer (G3) was prepared from methyl 3-aminopropionate hydrochloride ($\text{H-Ala-OCH}_3 \cdot \text{HCl}$) and *N,N'*-bis(tert-butyloxycarbonyl)-L-lysine (Boc-Lys(Boc)-OH)

Fig 3. COSY-FG 2D ^1H -NMR spectrum of the deprotected lysine dendrimer G3

according to the method reported by Tam et al. [28]. G3 consists of three levels of sequentially branched lysine and eight amino terminals for further reaction ($\text{CH}_3\text{O-Ala-Lys-Lys}_2\text{-Lys}_4\text{-(NH}_2)_8$). In the first step, Boc-Lys(Boc)-Ala-OCH₃ was prepared as an initiator core. In the second step, the Boc groups were removed by treatment with 1:1 trifluoroacetic acid (TFA)/CH₂Cl₂, followed by coupling with Boc-Lys(Boc)-OH. Repetition of the deprotection, coupling, and deprotection led to a lysine dendrimer G3. Boc-Lys(Boc)-OH was used as branching monomer unit in the iterative procedure. In some case, complete removal of absorbed solvent in the dendrimer could not be achieved.

Figure 3 shows a contour plot of the COSY-FG 2D ^1H NMR spectrum of the third-generation lysine dendrimer G3. The sharp absorption peak at 3.6 ppm is due to methyl moiety of the initiator core. Many amide and amine proton absorptions appeared at 7.9–8.6 ppm, which showed coupling as contour with the

neighboring protons. The chemical shift and the integration of resonances were in reasonably agreement with the proposed structure.

3.2 Reaction of Pyrrole-Terminated Carboxyl Derivative with the Lysine Dendrimer

A pyrrole containing lysine dendrimer was synthesized by the condensation of the amine-terminated L-lysine dendrimer G3 with 1.5 equiv. of C12B10P in DMF in the presence of (benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and diisopropylethylamine (DIEA) to give pyrrole derivative-terminated lysine core-dendrimer (G3-R) (Scheme 1). The purification of crude product was accomplished by reprecipitation by use of chloroform-ethanol system. The resulting G3-R showed hydrophobic properties. G3-R was soluble in chloroform, whereas it revealed poor solubility in DMSO, which was a solvent for G3.

^1H and ^{13}C NMR spectra of G3-R measured in

CDCl_3 resembled to those of C12B10P, except for a few differences due to the G3 part on the G3-R.

Fig 4. HMQC-FG spectra of pyrrole-terminated lysine core-dendrimer G3-R

Figure 4 shows two-dimensional HMQC-FG spectrum of the G3-R. In the ^1H NMR spectrum of the G3-R, the methylene peaks neighboring to carboxylic acid group of C12B10P disappeared, while two singlet proton absorptions due to pyrrole moiety and other absorption peaks appeared at almost the same position with those of the C12B10P. Since methyl moiety in the G3 showed singlet absorptions peak at 3.6 ppm, it is reasonable to assign the peak at 3.6 ppm appearing in the ^1H NMR spectrum of G3-R to the methyl moiety of the initiator core. It is interesting to note that the ^1H absorption peaks due to the G3 and C12B10P portions showed intensities corresponding to their contents. Taking into account the relatively low intensity of the G3 peaks relative to that of the C12B10P portion in the G3-R dendrimer, it is suggested that G3 portion exists in the inner side in the solution state. Because of the relatively low

intensity and overlapping of the G3 peaks with C12B10P, the complete assignment was very difficult. However, by comparison with characteristic peaks, it was found that the C12B10P group was introduced almost quantitatively to the 8 amino groups of the lysine dendrimer G3 and the number of C12B10P groups was eight. To support the above NMR analysis, the average molecular weight of the G3-R was measured by MALDI-TOF mass spectrometry (Figure 5). The MALDI-TOF mass spectrum of G3-R (calculated mass 5911 m/z) showed one signal (5926 m/z) that is clearly due to the expected compound, which consists of one lysine dendrimer G3 and eight C12B10P units.

Fig 5 MALDI-TOF mass spectra of pyrrole-terminated lysine core-dendrimer G3-R

Although the mass value was 15 m/z higher than that of the expected, such mass differences might be attributed to errors originating from the solvent, matrix, desorption/ionization efficiency, and the detector response [31,32]. Figure 6 demonstrates the optimized geometry of the pyrrole derivative-terminated lysine core-dendrimer G3-R, as calculated by means of the Cache3.9 molecular force field calculation. It is seen that each C12B10P moiety points outward three-dimensionally. From this figure,

it might be considered that such a configuration does not allow for the compound to express liquid crystalline phase.

Fig 6. Structure of pyrrole-terminated lysine core-dendrimer G3-R calculated in vacuo (Cashe 3.9 molecular force field calculation)

In conclusion, N -{{10-{4-[4-(12-carboxyl)dodecyl-ene-carboxyloxy]biphenyleneoxy}decyl}}pyrrole C12B10P was prepared by reacting N -[10-(4-hydroxybiphenyleneoxy)decyl]pyrrole with 1,12-dodecanedicarboxylic acid. This esterification demonstrated differences in chemical shifts of the aromatic protons. pyrrole-terminated lysine core-dendrimer G3-R was synthesized by the condensation of C12B10B with the third-generation lysine dendrimer identified by MALDI-TOF mass spectrometry. The dendrimer G3-R is an amphiphilic dendrimer in which a hydrophilic lysine dendrimer portion forms a core covered by a liophilic pyrrole derivative portion. The pyrrole-terminated carboxyl derivative C12B10P and the final dendrimer G3-R showed no evidence as thermotropic liquid crystal by means of the optical polarizing microscopic observation and DSC measurement. It is anticipated that terminal pyrrole group might be useful for

electrical applications.

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