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Studies on the orthogonal assembly of β-cyclodextrin-poly (ε-caprolactone) and ferrocene-poly (ethylene oxide)

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ABSTRACT

A biodegradable multi-arm polymer β-cyclodextrin-poly (ε-caprolactone) (CD-PCL) with a "jellyfish-like" structure was obtained, in which flexible and hydrophobic PCL arms were selectively grafted to the wide side of the hydrophilic torus-shaped β-CD. The amphiphilic "jellyfish-like" polymer with a hollow cavity and hydrophobic tails could orthogonally self-assemble into a new amphiphilic supramolecular copolymer CD-PCL/FcPEG with poly (ethylene oxide) end-decorated by ferrocene (FcPEG) in aqueous solution based on terminal hydrophobic interactions. The chemical structures of CD-PCL and CD-PCL/FcPEG were characterized by IR, NMR and UV and their self-assembled structures in water were investigated by transmission electron microscopy (TEM) and dynamic light scattering (DLS). CD-PCL alone self-assembled into nano vesicles in water, while CD-PCL/FcPEG into nanospheres. The supramolecular nanospheres were further investigated by cyclic voltammogram. The results indicated that the ferrocenyl groups which were embedded into the hydrophobic core of the supramolecular nanospheres could not transmit electrons or carry out electrochemical oxidation and reduction reaction.

1. Introduction

Amphiphilic copolymers, especially those with biodegradability and biocompatibility, are widely explored for their ability to self-assemble into nano micellar aggregates with various morphologies as well as their applications in the fields of biotechnology and pharmaceutics (Discher & Eisenberg, 2002; Endres, Beck-Broichsitter, & Samsonova, 2011; Hickey, Haynes, Kikkawa, & Park, 2011; Jain & Bates, 2003; Lee, Zeng, & Dunne, 2005; Liu, Pang, & Huang, 2011; Neiser et al., 2004; Song et al., 2010). The molecular composition and the molecular topological architectures of copolymers are both very important factors in determining the self-assembled morphology. For example, various self-assembled morphologies can be obtained through variation of the block lengths ratio of block copolymers (Terreau, Bartels, & Eisenberg, 2004; Terreau, Luo, & Eisenberg, 2003; Zhang & Eisenberg, 1996). At the same time, not only linear block copolymers but also branched copolymers can self-organize into micelles in selective solvent (Cheng et al., 2010; Liu, Tian, & Hu, 2004; Tan, Hussain, Liu, He, & Davis, 2010; Štepánek et al., 2010; Hu et al., 2002; Xia et al., 2008).

Over the past few years, biodegradable and biocompatible saccharide-based branched amphiphiles have attracted much attention for their applications as biomaterials (Gou et al., 2010aGou, Zhu, & Shen, 2010; Gou et al., 2010bGou, Zhu, Xu, & Shen, 2010; Nouvelet al., 2004; Ouchi, Kontani, & Ohya, 2003; Pang, Zhao, Akinc, Kim, & Lin, 2011; Qiu, Wang, Shen, & Jiang, 2011; Wang, Dong, & Tan, 2003; Wang, Li, & Guo, 2005). β-CD is a kind of cyclic oligosaccharide with seven D-glucose units linked by α-1,4-glucose bonds. This oligosaccharide looks like a truncated cone in which the 7 primary hydroxyl groups are directed to the narrow side of the torus and the 14 secondary hydroxyl groups are to the wide side of the torus. β-CD is not only a suitable backbone for designing functional branched copolymers but also a suitable hydrophilic component with inclusive ability to generate amphiphiles. However reports on β-CD-based copolymers mostly focused on multi-arm star copolymers, in which β-CD with multi-OH groups was only used as a core moiety. The hydrophilicity of its outer surface and the inclusive ability of its hydrophobic cavity were not utilized (Gou, Zhu, & Shen, 2010; Gou, Zhu, Xu, & Shen, 2010; Pang et al., 2011). Kawabata et al. first reported the synthesis and self-assembly of amphiphilic cyclodextrins in 1986 (Kawabata et al., 1986). The hydrophobicity of the primary face of β-CD increased with alkylsulfinyl groups of various lengths. Monolayer formed at the air–water interface with the hydrophilic secondary-OH face oriented towards water and inclusion of cholesterol by the layers was studied. Since then, amphiphilic CDs have been designed to form different supramolecular assemblies (Fernando, Fernández, Pennies, Gil, & De Rossi, 2008; Lemos-Senna, Wouessidjewe, Duchêne, & Lesieur, 1998; Kuo, Tung, & Chang, 2009; Mazzaglia et al., 2009; Nolan, Darcy, & Ravoo, 2003; Wang et al., 2011).

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In general, the polymerizing processes of conventional amphiphilic copolymers based on covalent interaction are very complicated. On the contrary, amphiphilic supramolecular copolymers based on non-covalent interactions such as hydrogen bonding interactions (Binder, Kunz, Kluger, Hayn, & Saf, 2004; Jang, Kramer, & Hawker, 2011; Moughton & O'Reilly, 2010; Ostas et al., 2011), metal-ligand interactions (Fustin, Guillet, Schubert, & Gohy, 2007; Leggio et al., 2007; Meier, Lohmeijer, & Schubert, 2003), and host–guest recognition (Giacomelli, Riegel, Petzhold, Da Silveira, & Stepánek, 2009; Tancini et al., 2010; Yan et al., 2010; Zhang & Ma, 2009), attract wide attention due to easy operation and hierarchical self-assembly of these novel types of copolymers possessing unique characteristics. Ferrocene is of particular research interest in designing supramolecular assemblies due to its unique sandwich structure, hydrophobic character and redox property (Li et al., 2010; Saji, Hoshino, & Aoyagui, 1985). It is reported that ferrocene or its derivative can form a stable inclusion complex with β-CD (Harada, 2001). Recently, Yan et al. (2010) constructed a supramolecular block copolymer β-cyclodextrin-polystyrene/ferrocene-poly (ethylene glycol) (β-CD-PS/FcPEG) in aqueous solution based on terminal host–guest interaction of β-cyclodextrin and ferrocene and obtained voltage-responsive reversible vesicles. However, the application as drug-loaded nanocapsules of the above voltage-responsive supramolecular vesicles is restricted because of the non biodegradablility of PS block. β-CD-based amphiphiles consisting of completely biodegradable components are especially attractive due to their promising applications as biomaterials.

In this paper, a kind of biodegradable "jellyfish-like" polymer CD-PCL with a hollow cavity and hydrophobic tails was designed, in which the hydrophobicity of the secondary face of β-cyclodextrin increased with the introduction of flexible poly(ε-caprolactone) arms. The amphiphile can self-assemble into vesicular micelles in aqueous solution. The polymer CD-PCL can also orthogonally self-assemble into a new amphiphilic supramolecular copolymer CD-PCL/FcPEG with FcPEG based on terminal hydrophobic interaction and the resultant amphiphile forms spherical micelles in aqueous solution. The biodegradable CD-PCL and related self-assembled micelles should be useful as functional biomaterials for many applications such as drug delivery.

2. Experimental

2.1. Materials

β-Cyclodextrin (Beijing Solarbio Science & Technology Co., Ltd., PR China) was recrystallized twice from water and dried at 60 °C under vacuum before use. ε-Caprolactone (CL, Acros Organics, 99%) was dried over CaH_2 for 48 h, distilled under reduced pressure with the fraction collected at 96–98 °C (5 mmHg), and stored under inert atmosphere. Methoxy poly (ethylene glycol) (Aldrich, 99%, PEG, M_n = 2000 g/mol) was dried by azeotropic distillation in the presence of toluene. P-Xylene and DMSO were dried by refluxing over CaH_2 and Na/benzophenone complex was distilled just before use. Stannous octoate ($Sn(Oct)_2$) (Alfa Aesar), Boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$, 48%BF_3), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), dicyclohexylcarbodiimide (DCC, Alfa Aesar, 99%, USA). 4-Dimethylaminopyridine (DMAP, Alfa Aesar, 98%, USA) and ferrocenecarboxylic acid (FcA, Acros Organics, 99%, USA), were utilized as received. All solvents were used as received.

3.1. Synthesis of CD-PCL polymer

The biodegradable "jellyfish-like" polymer CD-PCL was synthesized through a three-step method, as described in our recent publication (Jiang, Guo, Wang, & Wang, 2012).Yield: 98%.

IR (KBr, powder, cm^{-1}): 3440(O—H), 2950(C—H), 2866(C—H), 1730(C=O), 1180–1000 (pyranose). ^1H NMR (600MHz, $CDCl_3$, δ, ppm): 4.1(2H, —CH_2—O—C(O)—), 3.0–4.9(H-1, -2, -3, -4, -5, and -6 of pyranose), 2.3(2H, —O—C(O)—CH_2—), 1.6(4H, —O—C(O)—C—CH_2—, —CH_2—C—O—C(O)—), 1.3(2H, —C(O)—C—C—CH_2—C—C—O—).

3.2. Synthesis of FcPEG polymer

FcPEG was synthesized through a typical esterification between methoxy poly (ethylene glycol) and ferrocenecarboxylic acid according to the procedure described (Yan et al., 2010). Yield: 83%. The degree of the end-functionalization reached 99%, as determined by ^1H NMR and IR.

FT-IR (KBr, powder, cm^{-1}): 2886(C—H), 1736(C=O), 1620(C=C in ferrocene), 1157(C—O). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 4.8(2H, =CHC(COOH)CH=), 4.4(2H, —CH=CH—), 4.2(5H, another cyclopentyl), 3.7(178H, —OCH_2CH_2O—), 3.4(3H, terminal CH_3O—).

3.3. Preparation of CD-PCL polymer micelles

CD-PCL (10 mg) was initially dissolved in a common solvent DMF (10 mL) and dropped into deionized water (30 mL) under vigorous stirring. The solution was stirred for another 2 h and then dialyzed against water to remove the remaining DMF solvent. After 72 h, the volume of the solution was increased to 50 mL with the addition of deionized water to obtain an aggregated solution with a concentration of 0.2 mg/mL for further experiments.

3.4. Preparation of supramolecular copolymer CD-PCL/FcPEG and micelles

CD-PCL (10 mg) was initially dissolved in DMF (10 mL) and dropped into 30 mL FcPEG aqueous solution (1 mg/mL) under vigorous stirring. The solution was stirred for another 2 h and then dialyzed (cut-off molecular weight of dialysis bag is 3500) against water to remove excessive FcPEG and remaining DMF solvent. After 72 h, the volume of the solution was increased to 50 mL with the addition of deionized water to obtain an aggregated solution with a concentration of 0.2 mg/mL for further experiments. A 5 mL CD-PCL/FcPEG supramolecular micellar solution was used to perform cyclic voltammetry studies. For IR and ^1H NMR characterization, the solid specimens of CD-PCL/FcPEG supramolecular copolymer were obtained by freeze drying under vacuum.

3.5. Measurements

^1H NMR analysis was carried out on a JOEL JNM-ECA600 spectrometer in $CDCl_3$, in DMSO-d_6, or in D_2O at room temperature (solvents without TMS). FT-IR measurements were carried out on an AVATAR 360 FT-IR spectrometer (Thermo Nicolet). The samples for FT-IR measurement were prepared by dispersing the powder in KBr and compressing the mixtures to form disks. Molecular weight (M_n) and molecular weight distribution (M_w/M_n) were measured by a Viscotek TDA GPC instrument equipped with tetrahydrofuran (THF) as mobile phase and polystyrene as calibration standard. Fluorescence was measured with a Fluorolog-3, HORIBA Jobin Yvon spectrofluorometer. The critical micelle concentration (CMC) of polymer in water was measured by fluorescent probe method. 5 μL of 6×10^{-3} mg/mL pyrene solution in acetone was added to polymer aqueous solutions with different concentrations respectively and the solutions were sonicated for 10 min before fluorescence emission measurement. The UV–vis spectra and kinetics were recorded on a UV-2550 spectrophotometer (Shimadzu, Japan), using 1 cm path length quartz cuvetts for measurement. Transmission electron microscopy (TEM) was performed on a TECNAI T20 electron microscope. Samples for TEM measurement were