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Transition Metal-Catalyzed One-Pot Synthesis of Water-Soluble Dendritic Molecular Nanocarriers

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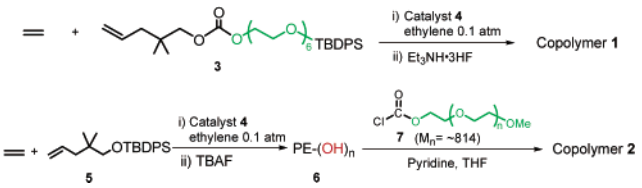
Amphiphilic core−shell structured nanocarriers have attracted much attention recently because of their many potential applications including controlled drug delivery and release,[1] phase transfer,[2] preparation of nanomaterials,[3,4] and catalysis.[5,6] As one example, dendrimers having amphiphilic core−shell structures were shown to have interesting unimolecular micelle properties.[7−9] Because of the unique dendritic architecture and the covalent linkage between the hydrophobic and hydrophilic segments, these unimolecular micelles are much more stable than conventional micelles formed from small molecule amphiphiles, making them attractive candidates as molecular nanocarriers for the above-mentioned applications. Whereas perfect dendrimers offer precise structural control and uniformity, the multistep synthesis involved in their preparations limits their general applicability. It is desirable to develop more efficient syntheses to access dendritic molecular nanocarriers. In addition, most of the reported dendritic unimolecular micelles are reverse micelles soluble only in organic solvents. The general approach for their preparation was hydrophobization of hydrophilic dendrimer cores, such as alkylation of polyamidoamine (PAMAM),[10] poly(propylene imines) (PPI),[11] and hyperbranched polyglycerols.[12,13] Water-soluble unimolecular micelles having hydrophilic shells and hydrophobic cores, although more relevant to biological applications, are less explored due to synthetic difficulties.[1,14−16] Here, we report the first transition metal-catalyzed one-pot synthesis of water-soluble dendritic molecular nanocarriers having a hydrophobic core and a hydrophilic shell (Scheme 1).

By copolymerizing ethylene with a comonomer having a poly(ethyleneglycol) (PEG) tail using the Brookhart palladium-α-diimine chain walking catalyst,[17,18] a core−shell dendritic polymer with a hydrophobic polyethylene (PE) core and a hydrophilic PEG shell was obtained in one step (Scheme 1). We have shown previously that the branching topology of ethylene homo- and copolymers can be systematically tuned in a single synthetic operation by using the chain walking catalyst.[19−22] Linear, hyperbranched, and dendritic copolymers containing a range of functionalities were obtained by changing ethylene pressures for copolymerizations.[22] Because dendritic topology is obtained at low ethylene pressure and the insertion of substituted olefins occurs only when Pd walks to a primary carbon, that is, a chain end,[23] copolymerization of ethylene and an PEG containing olefin at low ethylene pressure will produce a dendritic copolymer with a hydrophobic PE core and a hydrophilic PEG shell (Scheme 1).

The synthesis of the water-soluble core−shell copolymers is shown in Scheme 2. Comonomer **3** with a hexa(ethyleneglycol) tail was prepared by coupling a *tert*-butyldiphenylsilyl (TBDPS) protected mono-alcohol with 2,2-dimethylpent-4-enyl chloroformate. Copolymerization of ethylene and **3** at 0.1 atm ethylene pressure followed by deprotection of TBDPS afforded copolymer **1** in one step. The number-averaged molecular weight (M_n) for copolymer **1** is 9800 g/mol as measured by size exclusion chromatography (SEC) coupled with a multiangle light-scattering

Scheme 1

Scheme 2



(MALS) detector. The comonomer incorporation ratio (r) was determined to be 24 mol % by ^{1}H NMR. A much larger core−shell copolymer **2** was synthesized by a two-step approach (Scheme 2). An ethylene copolymer **6** having many hydroxyl groups was first prepared and subsequently coupled to PEG to afford the copolymer **2**. Copolymer **2** has a much higher molecular weight (M_n = 463 000 g/mol, radius of gyration R_g = 20.8 nm in THF) but a similar comonomer incorporation ratio (r = 26 mol %). Both copolymers **1** and **2** are soluble in water with solubility up to 10 g/L. They form a stable molecular solution in water as evidenced by light-scattering (LS) studies. The hydrodynamic radius (R_h) and R_g for the copolymer **2** in water were measured to be 26.0 and 17.7 nm, respectively. The slight decrease of R_g in water versus in THF was presumably due to contraction of the hydrophobic PE core in water. The ratio of R_h/R_g is around 1.4, which is close to the theoretical value of a filled sphere, 1.3.[24] These data support that the copolymers exist as unimolecular nanospheres in water (see Supporting Information for detailed LS characterizations).

Nile Red, a common hydrophobic dye and an excellent UV/vis and fluorescence probe,[16] was chosen for investigating the unimolecular micellar properties of copolymers **1** and **2** in water. Nile Red is insoluble and does not fluoresce in water, but once it is encapsulated inside micelles, its aqueous solution starts to fluoresce. We monitored the fluorescence intensity as we added different amounts of copolymer **1** or **2** into an aqueous dispersion of Nile Red (16 mg/L). For comparison, a classical small molecule surfactant, sodium dodecyl sulfate (SDS), was also used to encapsulate the dye in water.

Figure 1a shows that the fluorescence intensity of Nile Red increases gradually with the increase of copolymer **1** concentration, indicating copolymer **1** is effective in encapsulating Nile Red. The fluorescence intensities at λ_{max} of excitation spectra for Nile Red were plotted against the concentration of copolymer **1**, copolymer **2**, and SDS, respectively (Figure 1b). For SDS, a typical S-shaped curve was obtained with the deflection point at its critical micelle concentration (CMC = 2.3 mg/mL or 8 mM).[16] At concentrations

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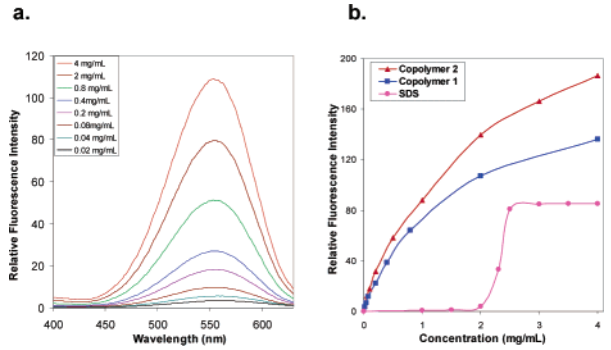

Figure 1. (a) Excitation spectra (λ_{em} = 650 nm) for Nile Red in water at different concentrations of copolymer **1**. (b) Fluorescence intensity at λ_{max} for excitation spectra of Nile Red as a function of concentration of copolymer **1** (blue ■), copolymer **2** (red ▲), and SDS (purple ●), respectively.

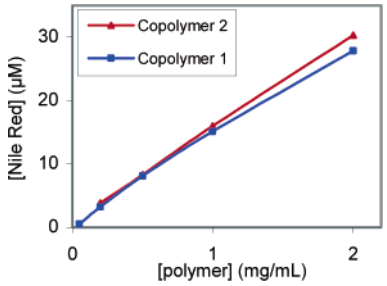

Figure 2. Concentration of encapsulated Nile Red as a function of the concentration of copolymer **1** (blue ■) and copolymer **2** (red ▲), respectively.

below its CMC, there is no micelle formation, and SDS is unable to encapsulate Nile Red. There is a rapid increase in the number of SDS micelles above CMC, causing a sharp increase of encapsulated Nile Red. For the copolymers **1** and **2**, on the contrary, the fluorescence intensity at λ_{max} for Nile Red increases gradually with the concentration of copolymers. No sharp transition was observed because there is no CMC for the covalently linked unimolecular nanocarriers.

To further gain quantitative information of dye encapsulation, UV/vis absorption experiments were conducted. The λ_{max} values for the UV/vis spectra of Nile Red are 554, 551, and 578 nm after addition of the copolymer **1**, **2**, and SDS, respectively. The blue shift in λ_{max} indicates the cores of our copolymers are more hydrophobic than that of the SDS micelle. The concentration of encapsulated Nile Red was obtained from its absorbance at λ_{max} using Beer's Law, which was plotted against the concentration of copolymer **1** or **2** (Figure 2). The nearly linear increase of encapsulated dye with increasing concentration of copolymers indicates the copolymers behave as unimolecular micelles in water.[15] The dye encapsulation capacities for copolymers **1** and **2** were quantified on the basis of the UV/vis data. The amounts of Nile Red being encapsulated by unit amounts of copolymer **1** or **2** are nearly the same, that is, 16 μmol of Nile Red per gram of copolymer or 0.46 wt %. This value is about twice as much as for SDS micelle (0.21 wt % at 4 mg/mL of SDS). Copolymer **1** has a number-of-dye per polymer molecule of 0.15, while copolymer **2** shows a 50-fold increase to 7.6. These values are constant at different copolymer concentrations ranging from 0.2 to 2 mg/mL for both copolymers (Supporting Information Figure S7), indicating that they reflect the inherent property of the copolymers. On the basis of the molecular weights and chemical compositions, it is estimated that the M_n of the hydrophobic core of copolymer **2** (~116 000 g/mol) is about 40 times that of copolymer **1** (~3000 g/mol). The correlation between the number-of-dye per polymer molecule and the molecular structure of the copolymers indicates that the dye encapsulation capacity for our copolymer is mainly determined by the size of the hydrophobic core.

In summary, we have shown the first example of transition metal-catalyzed one-pot synthesis of water-soluble amphiphilic molecular nanocarriers behaving like unimolecular micelles. Using the chain walking catalyst, copolymerization of ethylene and comonomer **3** afforded, in one step, amphiphilic copolymer **1** having a hydrophobic core and a hydrophilic shell. The light-scattering, fluorescence, and UV/vis studies of Nile Red in aqueous solution showed unimolecular micellar properties for the copolymers. Quantitative data indicated that the dye encapsulation capacity is nearly proportional to the M_n of the hydrophobic core. The unimolecular micellar properties coupled with the good water solubility and biocompatibility of PEG make these molecular nanocarriers promising candidates for many applications including drug delivery and controlled drug release.

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Supporting Information Available: Experimental details for the synthesis, light-scattering, and spectroscopic studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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