Synthesis, Self-assembly, and Catalytic Activity of 1H-Imidazole Amphiphiles

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We prepared polycatenar 1H-imidazole amphiphiles having a structure in which a 1H-imidazole head was connected through a benzene ring to a pheny group having two or three oligo(ethylene glycol) chains and studied their supramolecular assembly by fluorescence spectroscopy, transmission electron microscopy (TEM) and atomic force microscopy (AFM). When the aqueous solutions of the amphiphiles (5 × 10^{-5} M ~ 10^{-3} M) were imaged by TEM and AFM. We presume that the structures comprised a chain of the amphiphile dimers formed via successive hydrogen bonding between the 1H of the imidazole group and 3N of the neighboring one. In a solution of pH 4, entangled fibers with diameters of several nanometers were observed by TEM. In a pH 10 solution, film-like aggregates formed exclusively. The 1H-imidazole amphiphiles hydrolyzed tetraethoxysilane to induce gelation to form fibrous and spherical silica structures at neutral pH in aqueous solutions. No silica was formed when imidazole was used instead of the amphiphiles, suggesting that the self-assembled aggregates of the amphiphiles were responsible for the gelation.

Key Words : Self-assembly, 1H-Imidazole, Amphiphile, Catalytic activity

Introduction

Self-assembly of amphiphiles is greatly affected by their head group structures. In particular, the amphiphiles having head groups capable of hydrogen bonding can form bilayers, which further assemble into larger aggregates.\(^1\)\(^2\) Recently, we reported self-assembly of 1H-Imidazole amphiphiles having a hydrophilic imidazole head and one or more hydrophobic alkoxy tails. 1H-Imidazole and its derivatives are known to play important roles in biological systems as the proton donor and/or acceptor. Unlike pyrrole as a proton donor and pyridine as a proton acceptor, a 1H-imidazole has both proton donor and acceptor properties.\(^3\)\(^4\) 1H-Imidazole amphiphiles formed various ordered aggregates in a solution or in bulk. For example, the linear amphiphiles having an imidazole head connected to a hydrophobic alkoxyphenyl group through an ester linkage formed organogels.\(^6\) Polycatenar 1H-imidazole amphiphiles, consisting of a 1H imidazole head connected through a benzene ring to a trialkoxyphenyl tail formed lyotropic liquid crystals showing columnar hexagonal structures and bundles at the surface of silicon.\(^7\) They also exhibited thermotropic transitions of hexagonal columnar phases to cubic phases on heating and vice versa on cooling.\(^8\)

In this paper, we report supramolecular assembly of water soluble 1H-imidazole amphiphiles consisting of a imidazole head, aromatic esters and oligo(ethylene glycol) tails. Synthetic water soluble amphiphilic molecules have been of great interest because many biological systems comprise a variety of amphiphiles, showing three dimensionally ordered phases in aqueous environment. The 1H-imidazole amphiphiles formed twisted suprastructures in aqueous solutions and showed catalytic activity in the sol-gel reaction of TEOS.

Results and Discussion

Synthesis. Polycatenar 1H-imidazole amphiphiles have a structure in which a 1H-imidazole head is connected through a benzene ring to a pheny group having two or three oligo(ethylene glycol) chains (Scheme 1). In the synthesis, 3,4,5-trihydroxybenzoate was first reacted with a tosylate of tri or hexa(ethylene glycol) monomethyl ether in DMF. After hydrolysis, the resulting benzoic acids (3) were converted to the corresponding benzoyl chlorides with thionyl chloride and then reacted with hydroquinone in THF. The 1H-imidazole group was introduced by esterification reaction with 4-chlorocarbonyl imidazole under basic conditions to give compounds 6a and 6b. Compound 6c having two hexa(ethylene glycol) chains was prepared from 3,4-trihydroxybenzoate in the same manner. The structures of these compounds were fully characterized by \(^{1}\)H and \(^{13}\)C NMR spectroscopy and elemental analysis.

Liquid Crystalline Behavior. Compounds 6a were isolated as a waxy solid and 6b and 6c as a viscous oily liquid. At room temperature, compound 6a exhibited a birefringent mesophase with a nonspecific texture when examined with POM (Figure 1(a)). XRD analysis at room temperature showed several reflection peaks in the small angle region, corresponding to \(d\) spacings of 51.9, 25.8, 23.1, 18.2, 14.3, 12.8 and 12.5 Å, which were indexed as the (100), (010), (110), (210), (310), (020) and (120) planes, respectively, of a rectangular columnar lattice with the lattice parameter of \(a = 51.9\) and \(b = 25.8\) Å. The length of the molecule was
calculated to be 25 Å using the MM2 method, which was close to the radii of the corresponding disks determined by X-ray analysis. Judging from these results and the structural motif of a polycatenar molecule, it is very likely that the molecules are arranged in a disk to form a longer mesogen via hydrogen bonding between successive imidazole moieties (Figure 1(b)).

Self-assembly in Water. We investigated the self-assembly behaviors of compounds 6a-c in water by fluorescence spectroscopy, transmission electron microscopy (TEM) and atomic force microscopy (AFM). Compounds 6a-c were dissolved in deionized water. In a very dilute solution state (below $1.00 \times 10^{-6} \text{M}$), the compound showed a weak fluorescence emission. As the concentration was increased, a gradual bathochromic shift from $\lambda_{\text{max}} = 365$ to 376 nm along with the strong enhancement of the integrated fluorescence intensity were observed, suggesting that the molecules were being aggregated into ordered species (Figure 2).

The TEM analysis revealed that most aggregates of compounds 6a-c in aqueous solutions had twisted suprastructures. For the TEM measurement, the solutions of compounds 6a-c ($5 \times 10^{-5} \text{M} \sim 10^{-3} \text{M}$) were sonicated at 40 KHz frequency for 30 min at 30 °C and deposited on a carbon-coated copper grid. The TEM images in Figure 3 show the presence of twisted suprastructures. For compound 6b, grub-like aggregates which were seemingly composed of several vesicles with diameters in the range of 200 to 300 nm were also found, in addition to the major twisted objects. To further confirm the suprastructures, the exact same samples used for the TEM measurement were re-investi-
Synthesis and Self-assembly of 1H-Imidazole Amphiphiles

Gated by AFM. Figures 4(a) and (b) show the height and 3D AFM images of the structure obtained from the aqueous solution of 6b, which corroborate the formation of the twisted suprastructure. The size and diameter of the objects observed by AFM are similar to those visualized by TEM. Previously some helical aggregates of amphiphiles having the imidazole motif have been reported, but all of these amphiphiles were chiral.9-11 For example, Nolte et al. reported that when gluconamide derivatives containing a imidazole group were complexed with copper(II), helical tubular aggregates with diameters of 330 nm were formed.9

Based on the TEM and AFM results, we presume that the suprastructure comprised a chain of the amphiphile dimers formed via successive hydrogen bonding between the 1H of the imidazole group and 3N of the neighboring one. Chain structures of hydrogen bonded imidazole molecules have been observed in both the crystal state and solution states.12-15

The hydrogen bonding ability of 1H-imidazole amphiphiles would be greatly influenced by the pH change. To investigate the morphological changes of 1H-imidazole amphiphile at different pH, two aqueous solutions of pH 4 and 10 of compound 6c were prepared. Figure 5 shows TEM images the compound dried from the aqueous solutions on a carbon coated copper grid. As expected, no twisted structures were found in acidic and basic solutions. In a solution of pH 4 where a 1H-imidazole head group should be protonated, entangled fibrillar aggregates with diameters of several nanometers were observed. In a pH 10 solution, film-like aggregates were formed exclusively.

While investigating self-assembly of 1H-imidazole amphiphiles, we became interested in their potential catalytic activities. Mimicking biological enzymes has been a great challenge for the synthetic chemist due to their high selectivity and efficiency. It is noticeable that many hydrolytic enzymes have histidine moiety for the catalytic site.16 In particular, silicatein protein found in the silica spicules of a marine sponge can hydrolyze and condense tetraethoxysilane (TEOS) to form silica structures. Since TEOS is stable at neutral pH, the enzyme should display hydrolytic activity. It was reported that that histidine and serine residues were required for the hydrolytic activity of this protein.17 Silicate gels can be synthesized by hydrolyzing TEOS in the presence of an acidic or basic catalyst.18 We investigated the 1H-imidazole amphiphile induced silica formation from TEOS without an acidic or basic catalyst. Solutions of amphiphile 6a (8 and 16 mM) in ethanol/deionized water (1/30, v/v) were prepared. TEOS (1.2 g, 5.8 mmol) was added.

Figure 2. Fluorescence emission spectra of compound 6b in water at various concentrations ($\lambda_{ex} = 257$ nm).

Figure 3. TEM images of 6a (a and b), 6b (c and d) and 6c at different magnifications (e and f). The samples were prepared from aqueous solutions ($1.00 \times 10^{-3}$ M) and stained with a uranyl acetate aqueous solution (5 wt %) for 2 h prior to the TEM measurement.

Figure 4. Tapping mode AFM images of 6b [(a) height image and (b) 3D image].

Figure 5. TEM images of 1H-imidazole amphiphile 6c prepared from aqueous solutions of (a) pH 4 and (b) pH 10. The samples were stained with a uranyl acetate aqueous solution (5 wt %) for 2 h prior to the TEM measurement.
Corresponding to Q, MAS NMR spectroscopy showed the broadened peaks. Electron microscopy (SEM) showed that fibrous and spherical phases in the melt state. In aqueous solutions, they formed twisted suprastructures and hydrolyzed TEOS to induce gelation at neutral pH. This interesting catalytic activity was strongly suggested that the self-assembled aggregate of the imidazol amphiphiles exhibited liquid crystalline phases in the melt state. In aqueous solutions, they formed twisted suprastructures and hydrolyzed TEOS to induce gelation at neutral pH. This interesting catalytic activity was strongly suggested that the self-assembled aggregate of the amphiphile was responsible for the hydrolysis and gelation of TEOS.

In summary, we investigated the self-assembly of the polycatenar 1H-imidazol amphiphiles consisting of an imidazole head, aromatic esters and oligo(ethylene glycol) tails. The 1H-imidazol amphiphiles exhibited liquid crystalline phases in the melt state. In aqueous solutions, they formed twisted suprastructures and hydrolyzed TEOS to induce gelation at neutral pH. This interesting catalytic activity was likely associated with self-assembly of the amphiphiles.

**Experimental**

**Materials and Instrumentations.** 4-Imidazole carboxylic acid, triethylene glycol, tri(ethylene glycol) monomethyl ether, p-toluenesulfonyl chloride, thionyl chloride, potassium carbonate, potassium hydroxide, hydrochloric acid, copper(II) chloride and hydroquinone were purchased from Aldrich and used as received. Reagent-grade solvents were dried and purified as follows. Triethylamine (TEA) and methylene chloride (MC) were distilled over calcium hydride. Tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were dried over sodium metal and distilled. Ethanol (EtOH) and methanol (MeOH) were dried over molecular sieves 4 Å and distilled. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 300 and DPX 500 (1H: 300 MHz and 13C NMR: 125 MHz) spectrometer. Fourier transform infrared (FT-IR) measurements were recorded on a PERKIN ELMER Spectrum GX I using KBr pellets. X-ray diffraction (XRD) patterns were recorded by Bruker Xps GADDS (Cu Ka radiation, λ = 1.54 Å). An optical microscopy study was performed by a Leica DM LP equipped with Mettler Toledo FP 82HT heating stage and Mettler Toledo FP 90 central process controller. Elemental analyses were performed at the National Center for Inter-University Research Facilities of Seoul National University, Seoul, Korea. Transmission electron microscopy (TEM) images were obtained by a JEM-200CX instrument operating at 20 kV. Fluorescence spectra were recorded on a RF-5301PC spectrofluorimeter (Shimadzu) with a 150 W Xenon lamp and a 1 cm quartz cell. The excitation and emission band-widths were both 3 nm. UV absorption spectra were obtained using a Scinco S-3150 UV/vis. spectrophotometer. Atomic force microscopy (AFM) images were recorded in ambient atmosphere at room temperature with a Digital Instruments Dimension 3000 atomic force microscope in tapping mode with etched silicon tips (Nanoprobe). Topographic and phase images were obtained simultaneously. The spring constant of the tips was 40-66 N μm⁻¹ as specified by the manufacturer.

**Hexa(ethylene glycol) Monomethyl Ether.** This compound was prepared according to the literature. 20 Triethylene glycol (157 g, 1.00 mol) was stirred under nitrogen at 100 °C while sodium (6.90 g, 1.20 mol) in small portions was carefully added. After all the sodium reacted, the flask content was cooled to 50 °C and then α-(p-toluenesulfonyl)-o-methoxytris(oxyethylene) (80.0 g, 0.25 mol) was added dropwise over 1 h. A white precipitate of sodium tosylate appeared after a few minutes. After stirring for 48 h at 100 °C, the solution was cooled to room temperature and filtered. To the reaction mixture, water (200 mL) was added and the product was extracted with chloroform (3 × 50 mL). The solution was dried over MgSO₄. After filtration and evaporation, the compound was isolated by column chromatography on silica gel [ethyl acetate (EA)] in 50% yield. 1H NMR (300 MHz, CDCl₃) δ 7.34-7.30 (m, 2H, ArH), 7.30 (d, 2H, ArH), 4.16 (t, 2H, SO₂CH₂), 3.69-3.51 (m, 10H, OCH₂). 13C NMR: 125 MHz) spectrometer. Fourier transform infrared (FT-IR) measurements were recorded on a PERKIN ELMER Spectrum GX I using KBr pellets. X-ray diffraction (XRD) patterns were recorded by Bruker Xps GADDS (Cu Ka radiation, λ = 1.54 Å). An optical microscopy study was performed by a Leica DM LP equipped with Mettler Toledo FP 82HT heating stage and Mettler Toledo FP 90 central process controller. Elemental analyses were performed at the National Center for Inter-University Research Facilities of Seoul National University, Seoul, Korea. Transmission electron microscopy (TEM) images were obtained by a JEM-200CX instrument operating at 20 kV. Fluorescence spectra were recorded on a RF-5301PC spectrofluorimeter (Shimadzu) with a 150 W Xenon lamp and a 1 cm quartz cell. The excitation and emission band-widths were both 3 nm. UV absorption spectra were obtained using a Scinco S-3150 UV/vis. spectrophotometer. Atomic force microscopy (AFM) images were recorded in ambient atmosphere at room temperature with a Digital Instruments Dimension 3000 atomic force microscope in tapping mode with etched silicon tips (Nanoprobe). Topographic and phase images were obtained simultaneously. The spring constant of the tips was 40-66 N μm⁻¹ as specified by the manufacturer.

**Compound 1.** To a solution of tri or hexa(ethylene glycol) monomethyl ether (83.0 mmol) in methylene chloride (MC) (100 mL) was added a solution of p-toluenesulfonyl chloride (91.0 mmol) in MC (130 mL) under nitrogen at room temperature. The mixture was stirred for 10 h at room temperature. After filtration and evaporation, the compound was isolated by column chromatography on silica gel [ethyl acetate (EA)] in 50% yield. 1H NMR (300 MHz, CDCl₃) δ 7.80 (d, 2H, ArH), 7.34 (d, 2H, ArH), 6.00 (s, 3H, OCH₃), 2.88 (s, 1H, OH), 2.00 (s, 3H, OCH₃), 3.20-3.00 (m, 10H, OCH₂).
Synthesis and Self-assembly of 1H-Imidazole Amphiphiles

Compound 1. To a solution of 4-imidazole carboxylic acid (2.0 g, 18.0 mmol) in benzene (20.0 mL) was added a solution of thionyl chloride (20.0 mL) slowly. The mixture was refluxed for 10 h. After evaporation, the product was dried and used for the next reaction without further purification. To a solution of compound 1 (2.5 mmol) in DMF (50.0 mL) was added triethylamine (7.0 mmol) under nitrogen. After stirring for 1 h at room temperature, 4-chlorocarboxy imidazole (3.0 mmol) was added. The solution was stirred for 24 h at 80 °C. After filtration and evaporation, the product was isolated by column chromatography on silica gel (MC/MeOH = 11/1 v/v); (51% yield for 6a, 33% yield for 6b and 58% yield for 6c).

Compound 6a: Anal. Calcd for C_{39}H_{39}N_{10}O_{14}: C 57.58, H 7.54, N 3.97. Found: C 57.50, H 7.41, N 3.07. IR (KBr pellet, cm\(^{-1}\)) 3111, 2878, 1735, 1587, 1502, 1431, 1335, 1179, 1122.

Compound 6b: Anal. Calcd for C_{41}H_{39}N_{10}O_{14}: C 56.46, H 7.61, N 2.35. Found: C 56.07, H 7.68, N 2.34. IR (KBr NMR (300 MHz, CDCl\(_3\)) 57.58, H 3.53. Found: C 57.50, H 7.41, N 3.07. IR (KBr pellet, cm\(^{-1}\)) 3111, 2878, 1735, 1587, 1502, 1431, 1335, 1179, 1122.

Compound 6c: Anal. Calcd for C_{41}H_{39}N_{10}O_{14}: C 57.58, H 7.19, N 3.12. Found: C 57.50, H 7.15, N 3.07. IR (KBr NMR (300 MHz, CDCl\(_3\)) 57.58, H 7.19, N 3.12. Found: C 57.50, H 7.15, N 3.07. IR (KBr pellet, cm\(^{-1}\)) 3063, 2876, 1738, 1503, 1487, 1430, 1334, 1179, 1123.

Compound 6d: Anal. Calcd for C_{41}H_{39}N_{10}O_{14}: C 57.58, H 7.19, N 3.12. Found: C 57.50, H 7.15, N 3.07. IR (KBr NMR (300 MHz, CDCl\(_3\)) 57.58, H 7.19, N 3.12. Found: C 57.50, H 7.15, N 3.07. IR (KBr pellet, cm\(^{-1}\)) 3063, 2876, 1738, 1503, 1487, 1430, 1334, 1179, 1123.

Sonication. Compounds 6a-c were dissolved in deionized water (1.00 × 10\(^{-5}\) – 1.00 × 10\(^{-2}\) M). The prepared solutions...
were sonicated on water bath with a JAC-2010 sonifier equipped with a microtip probe and operating at 200 W output and 40 KHz frequency for 30 min at 30 °C. The sonicated solutions were allowed to stand at 25 °C for 3 days.

Sample Preparation for TEM and AFM Measurements. The solutions of compounds 6a-c prepared above were dropped on the carbon-coated copper grid. The samples were stained with an aqueous solution of 5 wt % uranyl acetate and dried in ambient conditions.

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References