Organogels from 1*H*-Imidazole Amphiphiles: Entrapment of a Hydrophilic Drug into Strands of the Self-Assembled Amphiphiles

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Linear 1*H*-imidazole amphiphiles (**1**−**3**) were synthesized by the esterification reaction of 4′-alkyloxy phenol with 4-chlorocarbonyl imidazole. They formed organogels. When 1*N* of the imidazole head was blocked by an ethyl group, however, the compound (**4**) did not self-assemble. The SAX and TEM study revealed that in a dry gel state, the 1*H*-imidazole amphiphiles self-assembled into a fibrous aggregate having a reverse micellar cubic structure. Norfloxacin (NFLX), a fluorescent hydrophilic antibiotic, showed relatively weak fluorescence emission in THF/*n*-hexane (10^{-6} mol/mL) when excited at 280 nm. In the organogel of compound **3** (1.5 wt %) in THF/*n*-hexane, integrated fluorescence intensity of NFLX was enhanced approximately 10 times as compared to that in the THF/*n*-hexane solution or sol state, strongly suggesting that NFLX was trapped in the hydrophilic core of a micellar assembly of compound **3**. The dry gel fibers were also strongly fluorescent under confocal laser scanning microscopy.

Introduction

Synthetic amphiphilic molecules have attracted a great deal of interest, because many biological systems comprise a variety of amphiphiles, exhibiting three-dimensionally ordered phases.[1] Amphiphilic molecules have a tendency to self-assemble into a micelle, cylindrical micellar fibers, and bilayer in an aqueous solution. They form reverse aggregates in nonpolar organic solvents such as a reverse micelle and reverse bilayer. Certain amphiphiles can gelate an aqueous or an organic solvent, resulting in a hydrogel or an organogel, respectively.[2] Gelation of organic solvents as well as water is believed to proceed through self-assembly of gelator molecules into fibers and their entanglement. Hydrogen bonding is the common driving force for organogelation, while hydrophobic forces are most important in gelating aqueous solvents. The hydrogels from low mass molecules have potential uses in biomedical applications. In particular, bicontinuous or micellar cubic phase hydrogels have attracted much attention as drug delivery systems.[3] Organogels are also considered as a potential drug delivery vehicle.[4] However, there has been no report on cubic phase organogels so far.

In this work, we studied self-assembling behaviors of amphiphiles with a 1*H*-imidazole head in organic solvents as well as in bulk. Imidazole and its derivatives have very interesting functionalities such as to play important roles in the biological system, particularly in enzymes, as the proton donor and/or acceptor, ligands of coordination system, and the base of charge-transfer processes.[5,6] Unlike pyrrole as a proton donor and pyridine as a proton acceptor, a 1*H*-

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imidazole has proton donor and acceptor properties simultaneously and thus can form an aggregate by the intermolecular hydrogen bonding. 1*H*-Imidazole amphiphiles studied in this work formed organogels. Interestingly, the SAX and TEM study revealed that in a dry gel state, the 1*H*-imidazole amphiphiles self-assembled into a fibrous aggregate having a reverse micellar cubic structure. We also found that the fluorescence intensity of a hydrophilic drug, norfloxacin (NFLX), was markedly enhanced in an organogel. The strands of the dry organogel were also strongly fluorescent, suggesting that NFLX was trapped in the interior of reverse micelles.

Experimental Section

Materials and Instrumentation. 4-Imidazole carboxylic acid, 1-bromooctane, 1-bromodecane, 1-bromododecane, 1-bromoethane, hydroquinone, and sodium hydride were purchased from Aldrich and used as received. Reagent-grade solvents were dried and purified as follows. Triethylamine (TEA) was distilled over calcium hydride. Tetrahydrofuran (THF) and dimethylformamide (DMF) were dried over sodium metal and distilled. Ethanol was dried over molecular sieves 4 Å and distilled. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 300 (^{1}H and ^{13}C NMR: 300 MHz) spectrometer. Fourier transform infrared (FT-IR) measurements were recorded on a PERKIN ELMER Spectrum GX I using KBr pellets. Transmission electron microscopy (TEM) images were taken by a CX-20 microscope. Scanning electron microscopy (SEM) images were taken by a JEOL JSM6330F microscope. X-ray diffraction (XRD) patterns were recorded by Bruker Xps GADDS (Cu Kα radiation, $\lambda = 1.54$). An optical microscopy study was performed by a Leica DM LP equipped with a 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. 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 bandwidths are both 3 nm. UV absorption spectra were obtained using a scinco S-3150 UV−visible spectrophotometer. Confocal laser scanning microscopy study was performed by a Radiance 2000/MP (Bio-RAD, $\lambda_{ex} = 350$ nm, $\lambda_{em} =$ 450/80 nm), equipped with an IR laser as the light source.

Compound 1. To a solution of 4′-octyloxy phenol (1 g, 4.40 mmol) in DMF (50 mL) were added 4-chlorocarbonylimidazole (0.83 g, 4.84 mmol) and sodium hydride (0.13 g, 4.84 mmol) under nitrogen. The reaction mixture was stirred for 24 h at 90 °C. After removal of precipitates by filtration, the filtrates were concentrated to dryness by evaporation under reduced pressure. The product was isolated by column chromatography on silica gel (THF/*n*-hexane = 3/1); yield 0.93 g (60%).

Anal. Calcd (in wt %) for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.32; H, 7.74; N, 8.84. ^{1}H NMR (DMSO): $\delta =$ 12.82 (s, 1H, NH), 8.03, 7.88 (s, 2H, imidazole ring protons), 7.10, 6.95 (dd, 4H, ArH), 3,96 (t, 2H, $ArOCH_2$), 1.73−1.28 (m, 12H, CH_2), 0.85 (t, 3H, CH_3). ^{13}C NMR (DMSO): δ 164.4, 139.1, 133.6, 120.5, 117.2, 85.3, 75.1, 74.6, 65.6, 31.7, 29.0, 28.7, 22.9, 20.0, 14.5. IR (KBr pellet, cm^{-1}): 3141, 3011, 2920, 2850, 2654, 2593, 1728, 1508, 1449, 1336, 1199, 979.

Compound 2. This compound was prepared by a procedure similar to that described for compound **1** using 4′-decyloxy phenol. The product was isolated by column chromatography on silica gel (THF/*n*-hexane = 2/1); yield 0.92 g (55%).

Anal. Calcd (in wt %) for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.91; H, 8.27; N, 8.27. ^{1}H NMR (DMSO): δ 12.82 (s, 1H, NH), 8.03, 7.88 (s, 2H, imidazole ring protons), 7.10, 6.95 (dd, 4H, ArH), 3,96 (t, 2H, $ArOCH_2$), 1.73−1.28 (m, 12H, CH_2), 0.85 (t, 3H, CH_3). ^{13}C NMR (DMSO): δ 164.4, 139.1, 133.6, 120.5, 117.2, 85.3, 75.1, 74.6, 65.6, 32.2, 29.6, 29.5, 29.3, 28.7, 23.1, 20.0, 14.5. IR (KBr pellet, cm^{-1}): 3141, 3011, 2920, 2851, 2654, 2593, 1729, 1508, 1447, 1338, 1199, 977.

Compound 3. This compound was prepared by a procedure similar to that described for compound **1** using 4′-dodecyloxy phenol. The product was isolated by column chromatography on silica gel (THF/*n*-hexane = 2/1); yield 0.93 g (52%).

Anal. Calcd (in wt %) for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.45; H, 9.04; N, 7.98. ^{1}H NMR (DMSO): δ 12.80 (s, 3H, NH), 8.05, 7.88 (s, 2H, imidazole ring protons), 7.09, 6.96 (dd, 4H, ArH), 3.96 (t, 2H, $ArOCH_2$), 1.70−1.25 (m, 20H, CH_2), 0.86 (t, 3H, CH_3). ^{13}C NMR (DMSO): δ 164.2, 138.9, 133.4, 120.3, 117.0, 85.0, 74.8, 74.4, 65.4, 32.1, 29.8, 29.7, 29.5, 29.3, 29.1, 28.5, 22.9, 19.8, 14.3. IR (KBr pellet, cm^{-1}): 3152, 3010, 2917, 2851, 2654, 2585, 1733, 1507, 1446, 1342, 1199, 982.

Compound 4. To a solution of compound **3** (0.2 g, 0.49 mmol) in DMF (15 mL) were added 1-bomoethane (0.15 mL, 1.47 mmol) and sodium hydride (0.015 g, 0.54 mmol) under nitrogen. The reaction mixture was stirred for 24 h at 90 °C. After removal of precipitates by filtration, the filtrates were concentrated to dryness by evaporation under reduced pressure. The product was isolated by column chromatography on silica gel (EA/*n*-hexane = 2/1); yield 0.19 g (90%).

Anal. Calcd (in wt %) for $C_{24}H_{36}N_2O_3$: C, 71.96; H, 9.06; N, 6.99. Found: C, 71.78; H, 9.02; N, 6.82. ^{1}H NMR (DMSO): δ 7.88, 7.58 (s, 2H, imidazole ring protons), 7.10, 6.90 (dd, 4H, ArH), 4.07 (q, 2H, $N-CH_2$), 3.94 (t, 2H, $ArOCH_2$), 2.17 (t, 3H, $N-CH_2-CH_3$), 1.75−1.27 (m, 20H, CH_2), 0.88 (t, 3H, CH_3). ^{13}C NMR (DMSO): δ 164.5, 139.3, 133.4, 120.4, 117.2, 85.1, 74.8, 74.4, 65.4, 39.9, 32.1, 29.8, 29.7, 29.5, 29.3, 29.1, 28.5, 22.9, 19.8, 16.4, 14.3. IR (KBr pellet, cm^{-1}): 3101, 2923, 2852, 1740, 1506, 1386, 1245, 1191, 1171, 1080, 966.

Compound 5. This compound was prepared by a procedure similar to that described for compound **1** using 4′-dodecyloxy aniline. The product was isolated by column chromatography on silica gel (THF/*n*-hexane = 2/1); yield 0.71 g (40%).

Anal. Calcd (in wt %) for $C_{22}H_{33}N_3O_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 71.26; H, 9.11; N, 11.22. ^{1}H NMR (DMSO): δ 12.82 (s, 1H, NH), 8.03, 7.88 (s, 2H, imidazole ring protons), 7.10, 6.95 (dd, 4H, ArH), 3,96 (t, 2H, $ArOCH_2$), 1.73−1.28 (m, 12H, CH_2), 0.85 (t, 3H, CH_3). ^{13}C NMR (DMSO): δ 160.5, 154.6, 136.8, 135.6, 132.0, 121.2, 119.8, 114.3, 67.5, 31.3, 29.0, 28.9, 28.8, 28.7, 28.6, 25.5, 22.1, 13.9. IR (KBr pellet, cm^{-1}): 3291, 3123, 2919, 2850, 2677, 2604, 1650, 1536, 1470, 1246, 1156, 995, 833, 657.

Results and Discussion

Synthesis. Ester compounds **1**−**3** with a 1*H*-imidazole head were obtained according to Scheme 1. Esterification of 4′-alkyloxy phenol with 4-chlorocarbonyl imidazole was carried out under basic conditions to give compounds **1**−**3**. For comparison, compound **4** was prepared, where 1*N* of the imidazol head was blocked by ethyl group. Amide compound **5** was obtained by amidation reaction of 4′-dodecyloxy aniline with 4-chlorocarbonyl imidazole. The structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Scheme 1

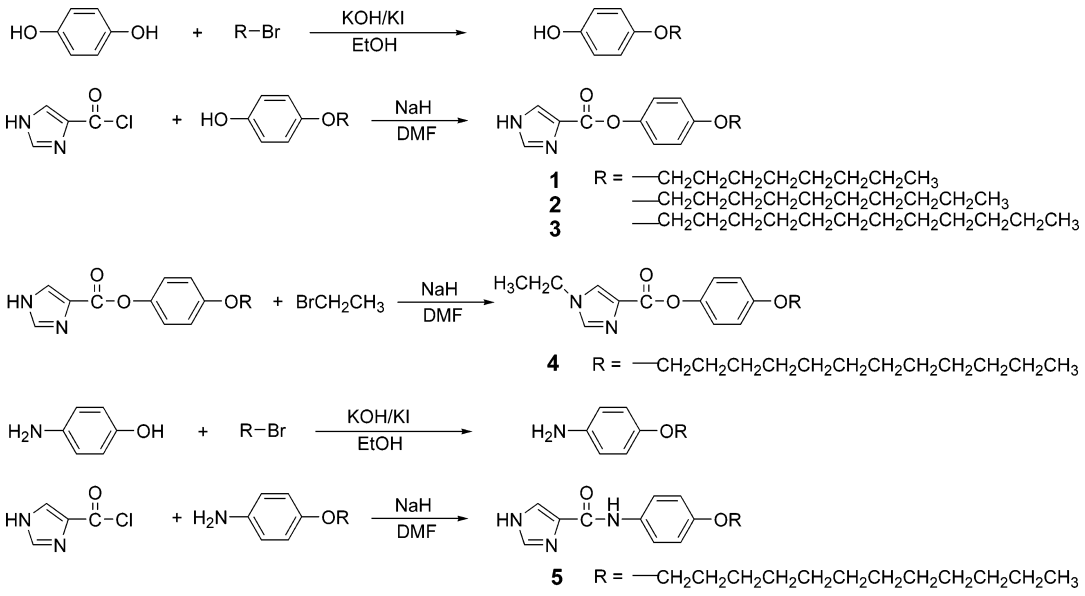

Table 1. Gelation Test Results of 1−5 (1.5 wt %) in Organic Solvents[a]

solvent	1	2	3	4	5
THF/*n*-hexane (2/3 v/v)	G	G	G	S	P
acetone/*n*-hexane (2/3 v/v)	G	G	G	S	P
MC/*n*-hexane (2/3 v/v)	G	G	G	S	P
$CHCl_3$/*n*-hexane (2/3 v/v)	G	G	G	S	P
EA/*n*-hexane (2/3 v/v)	G	G	G	S	P

[a] G = gel at room temperature, P = precipitation, S = soluble.

Gelation Studies. A weighed amount (1.5 wt %) of compounds **1**−**3** in organic solvent (1 mL) was heated in a septum-capped test tube [5 cm (height) × 1 cm (radius)] until the solid dissolved. The solution was then left to cool to room temperature in the air. The state of the phase was confirmed by visual observations. Gel formation was observed while cooling or immediately after the cooling process. However, compound **4** with an ethyl group instead of hydrogen on 1*N* did not form a gel as was expected. Compound **5** having an amide linkage did not show a gelation ability either, probably because the strong hydrogen bonding between amide groups disturbed the assembly of imidazole heads. The gelation results are summarized in Table 1.

Figure 1 shows the sol−gel transition temperatures (T_{gel}) of compound **3** in THF/*n*-hexane (1.5 wt %) as a function of a concentration.[7] T_{gel} was determined by a test tube tilting method. As the concentration of **3** increases to 2 wt %, T_{gel} also increases, which indicates that the stability of the gel is enhanced as the concentration increases. Above the concentration of 2 wt %, **3** in THF/*n*-hexane was precipitated, and below the concentration of 1 wt % (critical gelation concentration), the compound was soluble. If the sol−gel transition is comparable to melting of crystals, the sol−gel transition enthalpy can be estimated by van't Hoff relationship (eq 1). ΔH_{gel} of **3** in THF/*n*-hexane, determined from the slope of ln[concentration of the gelator molecule] versus T^{-1}_{gel}, was 26.1 kJ mol^{-1}.[8]

$$\frac{\mathrm{d} \ln C_g}{\mathrm{d}\, {}^1/_{T_g}} = -\frac{\Delta H_g}{R} \qquad (1)$$

ΔH_{gel} values of compounds **1** and **2** were obtained in the same manner as described for compound **3**, which were 24.7

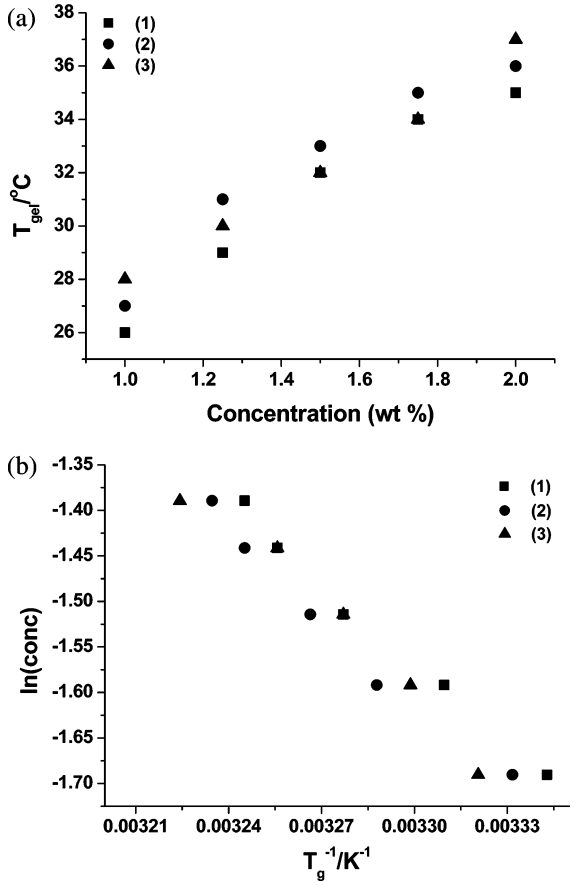

Figure 1. (a) T_{gel} of **1**, **2**, and **3** in THF/*n*-hexane according to concentration and (b) van't Hoff plot of **1**, **2**, and **3** in THF/*n*-hexane.

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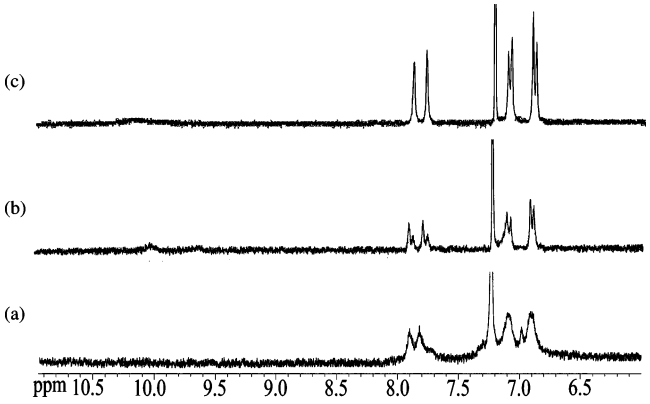

Figure 2. ^{1}H NMR spectra of an organogelator **3** in $CDCl_3$/*n*-hexane-d_{14} (2/3 v/v); (a) 25 °C, (b) 30 °C, and (c) 40 °C.

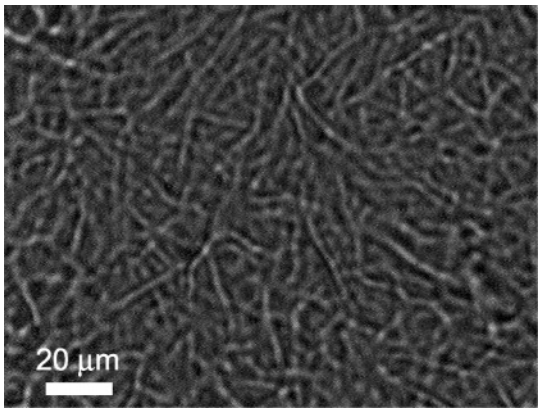

Figure 3. Polarizing optical micrograph of gel **3** [1.5 wt % in THF/*n*-hexane (2/3 v/v)] obtained at room temperature.

and 25.6 kJ mol^{-1}, respectively. The critical gelation concentrations of compounds **1** and **2** were about 1 wt %.

The evidence for the intermolecular hydrogen bonding between 1*H*-imidazole heads in a gel state was provided by ^{1}H NMR analysis. Figure 2 shows the ^{1}H NMR spectra of compound **3** in $CDCl_3$/*n*-hexane-d_{14}. When measured in a gel state at 25 °C without sample spinning, the imidazole proton peaks of only aggregated species of the sample appeared at 7.92 and 7.82 ppm. At 30 °C, the peaks of aggregated and free species were observed simultaneously at 7.92, 7.82 and 7.90, 7.80 ppm, respectively. Upon heating to 40 °C, the imidazole proton peaks corresponding to the aggregated species disappeared with increasing the intensity of free imidazole proton peaks at 7.90 and 7.80 ppm.

The visual images of the molecular aggregates of the organogels in THF/*n*-hexane (1.5 wt %, 2/3 v/v) were investigated by using polarizing optical microscopy (POM) and transmission electron microscopy (TEM). Figure 3 shows the POM image of **3** obtained in a gel state at room temperature. Elongated fibers to form a gel network are seen in the image. The TEM micrographs of the gels dried on the carbon coated copper grids also showed entangled fibers with diameters ranging from 5 to 100 nm for **1** and **2**, and from 5 to 300 nm for **3** (Figure 4).

The structures of the dry organogels in THF/*n*-hexane (1.5 wt %, 2/3 v/v) were investigated by using small-angle X-ray

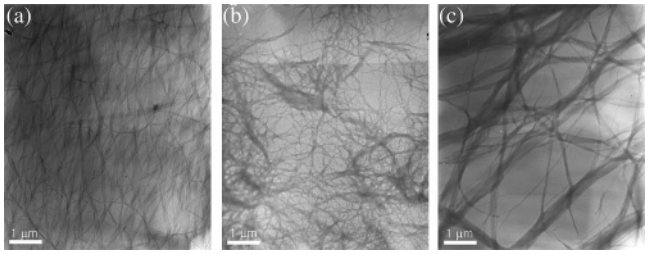

Figure 4. TEM images of dry gels of (a) **1**, (b) **2**, and (c) **3** [1.5 wt % in THF/*n*-hexane (2/3 v/v)].

diffraction (XRD) techniques. In the small-angle X-ray diffractograms of the dry gels of **2** and **3** from THF/*n*-hexane, six reflections corresponding to *d* spacings of 5.04, 3.54, 2.97, 2.66, 2.28, and 2.08 nm for **2** and 5.96, 4.16, 3.38, 3.02, 2.63, and 2.42 nm for **3** were obtained. The relative positions of these reflections are $\sqrt{2}$, $\sqrt{4}$, $\sqrt{6}$, $\sqrt{8}$, $\sqrt{10}$, and $\sqrt{12}$, which is in good agreement with the (110), (200), (211), (220), (310), and (222) reflections of cubic phase with *Im*3*m* symmetry with a lattice constants of 7.13 nm for **2** and 8.43 nm for **3** (Figure 5). In contrary, the dry gel of compound **1** showed only broad peaks resulted from disordered packing. We failed to obtain the XRD patterns of the organogels probably because of low concentration of gelator molecules in the gels. Based on ^{1}H NMR and X-ray analysis results of the dry gels, we presume that compounds **2** and **3** assembled to form reverse micelles in organic solvents. Hydrophilic imidazole heads were aggregated inside micelles through intermolecular hydrogen bonding and three-dimensional networks formed by interactions among peripheral alkyl groups of micelles. There have been reported a few examples for an organogel formed from reverse micelles. In those cases, however, an additive was needed to induce the gelation. For example, organogels were formed by the addition of *p*-chlorophenol or 2,6-dihydroxynaphthalene to the reverse micelles of an anionic surfactant, bis(2-ethylhexyl)sodium sulfosuccinate (AOT), in nopolar organic solvents. The microstructures of the gels were proposed wherein micellar units were networked through *p*-chlorophenol or 2,6-dihydroxynaphthalene.[9]

Hydrophilic drugs can be dissolved in reverse micelles in an organic environment. Norfloxacin (NFLX) is one of the fluoroquinolone antibiotics. It has native fluorescence, which is sensitive to changes in the microenvironment.[10] We investigated fluorescence spectral changes of NFLX in THF/*n*-hexane by the gelation in the presence of compound **3**. Figure 6 shows the fluorescence emission spectra of NFLX obtained in a gel and sol state. NFLX showed relatively weak fluorescence emission in THF/*n*-hexane (10^{-6} mol/mL) when

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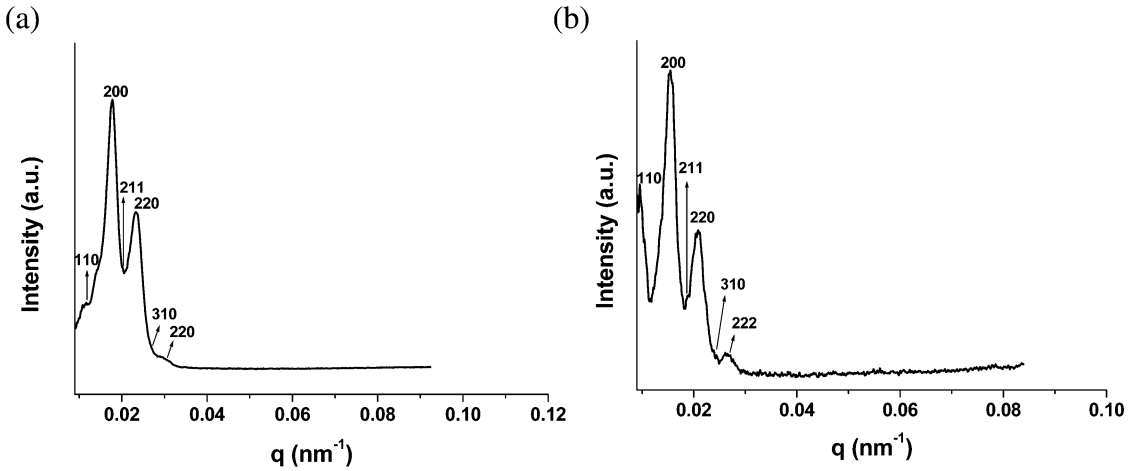

Figure 5. X-ray diffraction patterns of dry gels (a) **2** and (b) **3**.

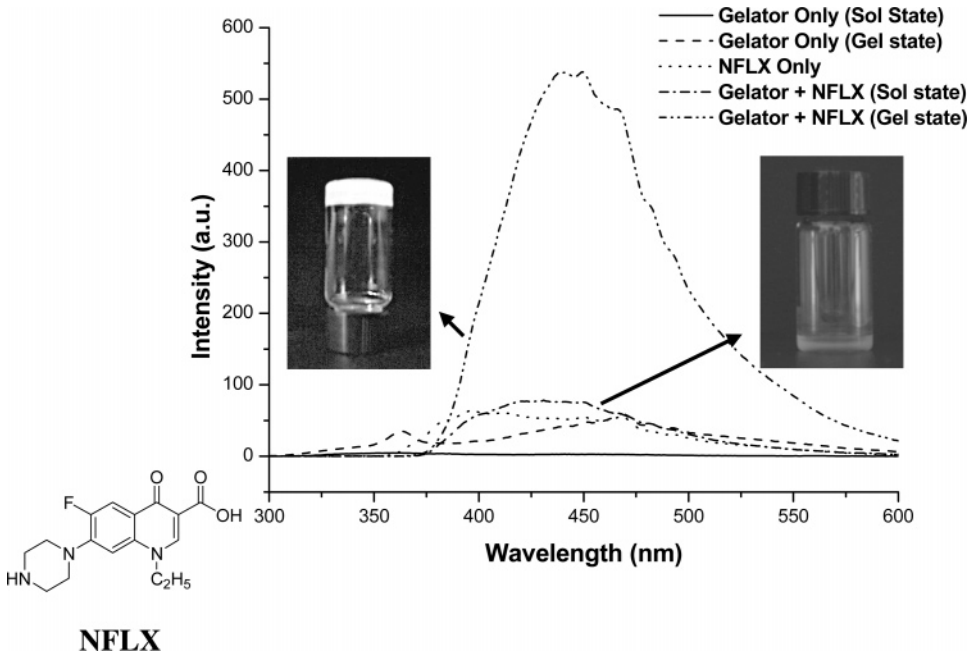

Figure 6. Fluorescence spectra of NFLX in a gel and a sol of compound **3** in THF/*n*-hexane (2/3 v/v) (λ_{ex} = 280 nm).

excited at 280 nm. Compound **3** (1.5 wt %) was added to the NFLX solution at 60 °C. The organogel was formed when the resulting solution was cooled to room temperature and the sol−gel transition was thermally reversible. Integrated fluorescence intensity of NFLX in the gel state was enhanced approximately 10 times as compared to that in the THF/*n*-hexane solution or sol state, strongly suggesting that NFLX was trapped in the hydrophilic core of a micellar assembly of compound **3**. As discussed above, the X-ray analysis showed that the fibrous dry gel had a reverse micellar cubic structure. We performed confocal laser scanning microscopy study on the dry gel to see whether NFLX molecules were present inside the micelle after drying process. Gel slices containing NFLX were put on the slide glass and slowly dried. Figure 7 shows the confocal laser scanning microscopy fluorescence images of the dry organogel. As expected, the gel fibers are strongly fluorescent due to NFLX trapped in the micelles.

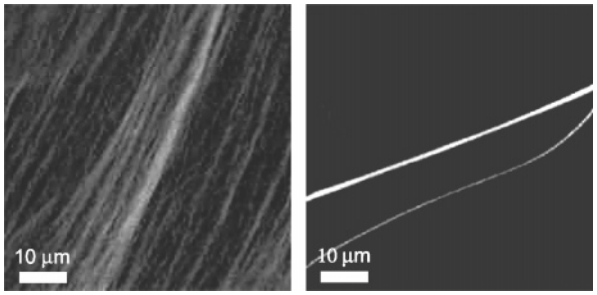

Figure 7. Confocal laser scanning microscopy images of NFLX in dry gel fibers of compound **3**.

Conclusion

We prepared the 1*H*-imidazole amphiphiles where an imidazole head was connected to a hydrophobic alkyloxyphenyl group through an ester linkage. They formed organogels, while the compound with an ethyl group instead of hydrogen on 1*N* did not. In the gel state, the intermolecular hydrogen bonding between 1*H*-imidazole heads was ob-

served by ^{1}H NMR analysis, which could be a driving force for the gelation. When dried, fibrous aggregates having a reverse micellar cubic structure formed. Integrated fluorescence emission intensity of a hydrophilic drug, NFLX, in the gel state was enhanced approximately 10 times as compared to that in the THF/*n*-hexane solution or sol state. Dry gel fibers were also strongly fluorescent. The microstructures of the organogels were not determined, but fluorescence study results in combination with ^{1}H NMR analysis results suggest that the organogels have such micellar properties as to solubilize a hydrophilic drug in nonpolar solvents.

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