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# Versatile Supramolecular Gelling Agents: Unusual Stabilization of Physical Gels by Lithium Ions

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*Dedicated to the memory of the late Professor Chi Sun Hahn*

Supramolecular physical gels,[1–2] which are formed by noncovalent weak interactions among small organic molecular gelling agents, have potential for applications[3] in various fields, such as templates for functional materials,[4] drug delivery,[5] sensors,[6] cosmetics,[7,8] matrixes for tissue culture,[9] separation media,[10] and food processing agents.[8] Hydrogen bonding[11] is the most common interaction for the formation of physical gels due to strong and directional characteristics. Cyclodipeptide moieties[12–14] can be powerful motifs for the formation of a supramolecular assembly because they can provide multiple hydrogen-bonding sites with $C_2$ symmetry. Additionally, the diversity of the amino acid library can provide structural flexibility for molecular design. Ishida and Aida reported supramolecular polymers using xylene-bridged bis(cyclodipeptide), which forms large homochiral supramolecular polymers in solution.[12] Hanabusa et al. synthesized a wide range of cyclodipeptides and examined gelation behavior for various organic solvents.[13] However, only limited cyclodipeptides formed physical gels in some organic solvents with typically a low polarity index. Most cyclodipeptides resulted in precipitation or crystallization in polar solvents due to the hydrophobic side groups. Alternatively, Feng et al. recently reported that cyclo(L-Tyr-L-Lys) can form physical gels in several polar organic solvents and aqueous media, and not with low polarity solvents.[14]

Herein, we report unique and powerful supramolecular gelling agents for a wide range of hydrophobic and -philic solvents, including aqueous media, highlighted by the unusual stabilization of hydrogels with $Li^+$.

A series of oligo(ethylene oxide)-bridged bis(cyclodipeptide) (**1**–**3**) have been synthesized by cyclization reaction of the corresponding dipeptide-conjugated oligo(ethylene oxides), which were prepared by simple alkali-mediated coupling reactions between ditosyl oligo(ethylene oxides) and phenolic OH of the dipeptide moiety and successive deprotection of *tert*-butyloxycarbonyl (Boc) groups. Because cyclodipeptides provide strong and directional hydrogen bonding sites, compounds **1**–**3** may form ordered supramolecular architectures. In fact, compounds **1**–**3** exhibited versatile gelation phenomena. When compounds **1**–**3** were dissolved in $CHCl_3$ (20.0 $g\,L^{-1}$) and incubated for 1 h at room temperature, the formation of stable physical gels was observed. The time required for the physical gel formation was considerably shortened (1 min for 10.0 $g\,L^{-1}$of **3**) with ultrasonic treatment. Notably, gelation occurred in a wide range of organic solvents with very low critical gelation concentrations (CGCs), when the CGCs were predominately less than 1 wt% (Table 1). In general, the strength of hydrogen bonds decreases under polar conditions, however, compounds **1**–**3** showed significant gelation abilities in hydrophilic solvents and polar protic solvents. More interestingly, compounds **1**–**3** formed physical gels also in distilled water

Table 1. CGC values [$g\,L^{-1}$] of **1**–**3** in various solvents.

| Solvent | 1 | 2 | 3 |
|---|---|---|---|
| $CH_2Cl_2$ | 14.0 | 7.5 | 12.7 |
| $CHCl_3$ | 9.4 | 10.0 | 8.8 |
| THF | 9.0 | 9.8 | 17.0 |
| acetone | 7.5 | 7.3 | 12.0 |
| acetonitrile | 5.3 | 4.8 | 6.0 |
| MeOH | 5.5 | 5.6 | 4.6 |
| EtOH | 5.2 | 4.4 | 6.2 |
| propanol | 5.1 | 4.5 | 4.7 |
| butanol | 4.7 | 4.2 | 4.9 |
| pentanol | 4.9 | 3.9 | 7.7 |
| hexanol | 4.3 | 3.9 | 7.4 |
| octanol | 4.0 | 5.0 | 8.0 |
| di(ethylene glycol) | 13.0 | 17.0 | 11.5 |
| tri(ethylene glycol) | 9.0 | 10.9 | 12.0 |
| PEG 400 | 10.6 | 12.0 | 17.5 |

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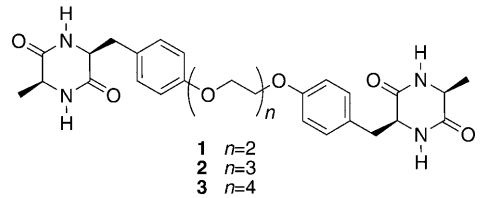
with CGCs of 6.0, 6.0, and 17.0 g L$^{-1}$, respectively. Although many types of low-molecular-weight gelling agents have been reported, limited examples have shown hydrogel formation. But those hydrogelators mostly form precipitates in nonpolar hydrophobic solvents. However, compounds **1**–**3** exhibited versatile gelation ability, which might be due to the existence of amphiphilic characteristics in the oligo (ethylene oxide) chains.




To investigate the structures and morphologies of compounds **1**–**3**, a thin film of the hydrogels was dried in vacuo for 1 h, and then the specimens were examined by field-emission scanning electron microscopy (FE-SEM) and X-ray diffraction (XRD). The FE-SEM images of the dried gel showed a three-dimensional network of nanofibers, in which the average diameter of the elemental fibrils were approximately 60 nm, regardless of the oligo (ethylene oxide) chain length (Figure 1). XRD measurements of dried gels were performed at 25 °C by using a synchrotron in transmission mode. As shown in Figure 2, the three compounds showed similar diffraction patterns, indicating that they have very similar self-assembly patterns in the gel state. In the small-angle region, the diffraction patterns showed lamellar packing of each molecule. For example, compound **3** exhibited three sharp reflection peaks at d spacings of 1.97, 0.98, and 0.65 nm, corresponding to the 100, 200, and 300 planes, respectively (Figure 2b). The diffraction of compounds **1** and **2** also showed similar patterns, however, the d spacings were slightly smaller than those of compound **3** due to the shorter oligo(ethylene oxide) chain length. In contrast to the small-angle diffraction, the wide-angle diffractions showed the same peak patterns without dependence on the length of the oligo(ethylene oxide) chains. Based on the peak patterns, the packing structure of the gelators were oblique structures ($a = 0.643$ nm, $b = 0.594$ nm, $\gamma = 66.3°$), which coincide with crystallographic data from previously reported examples.[13] The assigned crystallographic structure of compound **3** in the gelled state is shown in Figure 2d. The gelators adopt fully extended conformations, regardless of the oligo(ethylene oxide) chain length and form fibrous assembly structures through hydrogen-bonding interaction among cyclodipeptide moieties.

To obtain detailed information on the hydrogen-bonding interactions, infrared absorption spectra were measured for

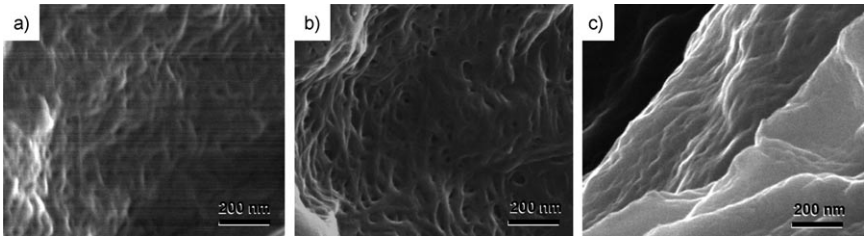



Figure 1. FE-SEM images of dried gels **1** (a), **2** (b), and **3** (c).

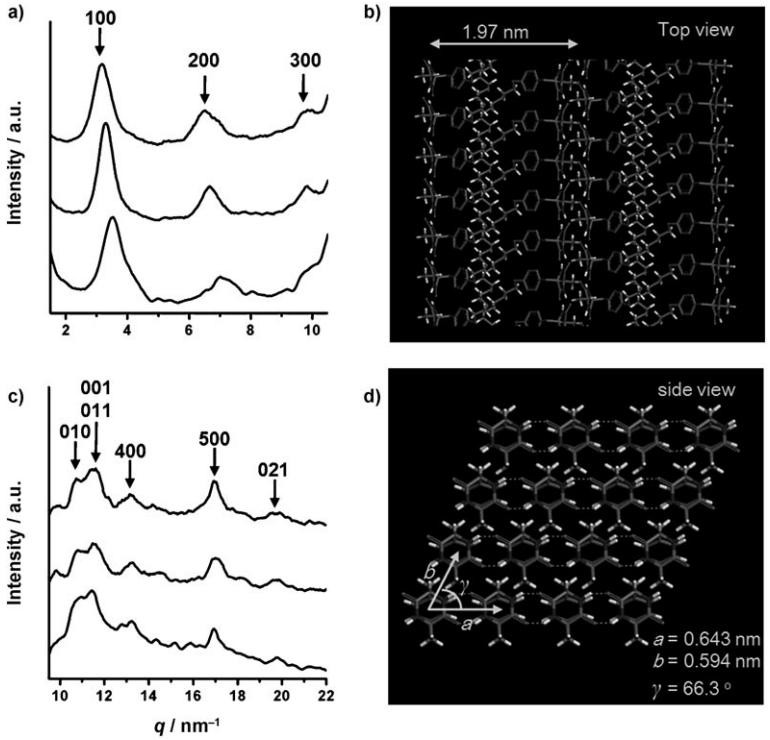



Figure 2. XRD patterns and proposed packing structure model for xerogels. Xerogels were prepared from hydrogels with CGC values of 6.0 (**1** and **2**) and 17.0 g L$^{-1}$ (**3**). a) Small-angle X-ray scattering (SAXS) patterns for **1** (lower), **2** (middle), and **3** (upper). b) Proposed model of **3** from the SAXS pattern. c) Wide-angle X-ray scattering (WAXS) patterns for **1** (lower), **2** (middle), and **3** (upper). d) Proposed model of **1**–**3** from WAXS patterns.

compounds **1–3**. Figure 3 shows the FTIR spectra for gels and solutions of compounds **1–3** in $CHCl_3$. To measure the FTIR spectrum of each solution state, the concentrations of

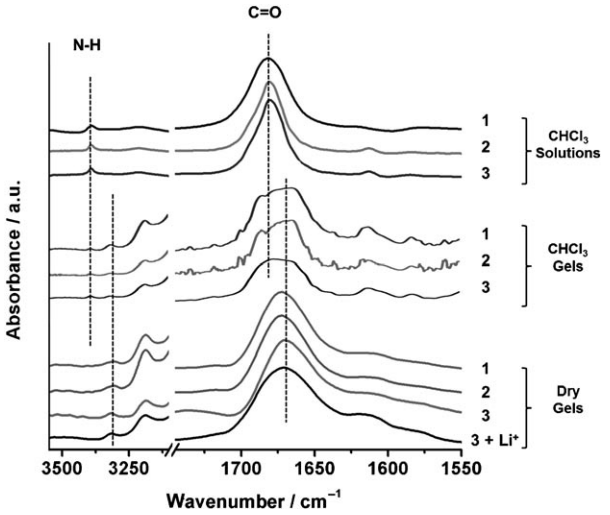



Figure 3. FTIR absorption spectra of **1–3** in $CHCl_3$ and in the dried state.

compounds **1–3** were adjusted to 10 times the diluted conditions of the CGC, and a 1 mm path-length liquid cell was utilized. All three dried gels showed similar IR absorption patterns, regardless of oligo(ethylene oxide) chain length, indicating the packing modes of the gelators were nearly the same. Solutions of compounds **1–3** in $CHCl_3$ exhibited C=O and N−H stretching vibrational bands near 1680 and 3390 $cm^{-1}$, respectively, corresponding to the non-hydrogen bonded states of a cis-type amide. Alternatively, the absorption of C=O and N-H stretching vibration appeared near 1672 and 3310 $cm^{-1}$, respectively, when the dried gels were measured. Gels in $CHCl_3$ exhibited both signals of those observed in solution and dried-state measurements. The strong shifts of the vibrational bands indicate that the hydrogen-bonding interactions among amide bonds play a crucial role for the formation of physical gels.

Alkali-metal ions, such as $Li^+$, $Na^+$, and $K^+$, can be coordinated to the lone-pair electrons on the carbonyl group of the amide. The coordination of metal ions onto the carbonyl group interferes with hydrogen-bonding formation. For example, three-dimensional structures of proteins can be easily denatured upon high ion strength due to the interference in hydrogen-bonding interactions by ion coordination.[15] Therefore, the gelation ability of hydrogen-bonding-based gelators should decrease with the addition of alkali-metal ions. However, a very interesting phenomenon was observed in our system, wherein the gelation abilities of compounds **1–3** were greatly enhanced by the addition of $Li^+$. As previously mentioned, compounds **1–3** have very high gelation ability in distilled water, in which the CGC values were 6.0, 6.0, and 17.0 $g\,L^{-1}$, respectively. By adding a small amount of $Li^+$ to the gelators, the CGC values of compounds **1–3** surprisingly decreased, as summarized in Table 2. The enhancement of gelation by $Li^+$ addition was higher for compound **3** than **1** and **2**. The gelation abilities of compounds

Table 2. CGC values [$g\,L^{-1}$] of **1–3** with various concentrations of $Li^+$.

| $Li^{+[a]}$ | **1** | **2** | **3** |
|---|---|---|---|
| 0 | 6.0 | 6.0 | 17.0 |
| 0.5 | 2.5 | 4.8 | 2.9 |
| 1 | 2.3 | 4.6 | 2.9 |
| 2 | 2.3 | 4.0 | 2.9 |
| 4 | 3.2 | 5.2 | 4.8 |
| 8 | 4.2 | 5.6 | 5.0 |
| 16 | 4.4 | 6.4 | 5.6 |
| 32 | 4.3 | 8.0 | 7.0 |
| 64 | 9.1 | 8.9 | 9.4 |

[a] $Li^+$/gelators (mol/mol).

**1–3** were maximized when the stoichiometry of $Li^+$ to each gelator was 2:1. At higher ratios, the gelation abilities of compounds **1–3** gradually decreased with increasing $Li^+$, possibly due to the interference of hydrogen-bond formation by the coordination of $Li^+$ to the carbonyl groups. The enhancement of gelation may be explained by the coordination of $Li^+$ to oligo(ethylene oxide) chains. As shown in Figure 2b, the gelators form two distinct layers: lamellar sheets of cyclodipeptides and oligo(ethylene oxides) within the fibrous structures.

Therefore, by coordination of metal ions to the oligo (ethylene oxide) chain, terminal cyclodipeptides might move closer and more easily form the hydrogen-bonded-sheet structure of cyclodipeptides (Figure 4). In fact, the IR spectrum of dried gels containing 64 equivalents of $Li^+$ in compound **3** (Figure 3) also exhibited C=O and N−H stretching vibrational bands near 1672 and 3310 $cm^{-1}$, respectively; these values were nearly identical to those obtained from dried gels without $Li^+$ addition, indicating the efficient formation of hydrogen bonds. As a result, the binding affinity of $Li^+$ to the oligo(ethylene oxide) chain is much greater than that to the carbonyl groups of cyclodipeptides.

In conclusion, oligo(ethylene oxide)-bridged bis(cyclodipeptide)s were designed as a new type of supramolecular gelling agents, and exhibited unique and powerful gelation behavior in a wide range of solvents. Unlike other gelators containing cyclodipeptide units, they formed physical gels in nonpolar and polar protic solvents, including aqueous media. Furthermore, the gelation abilities were remarkably enhanced by the addition of $Li^+$. Such unusual characteristics offer potential applications in ion conductive materials.[16] We are currently conducting a new project for the design of ion conductive materials using gel-contained $Li^+$.

## Experimental Section

**Measurements**: Melting points were measured by using a Stuart melting point apparatus SMP3. $^1H$ NMR spectra were recorded from solutions in

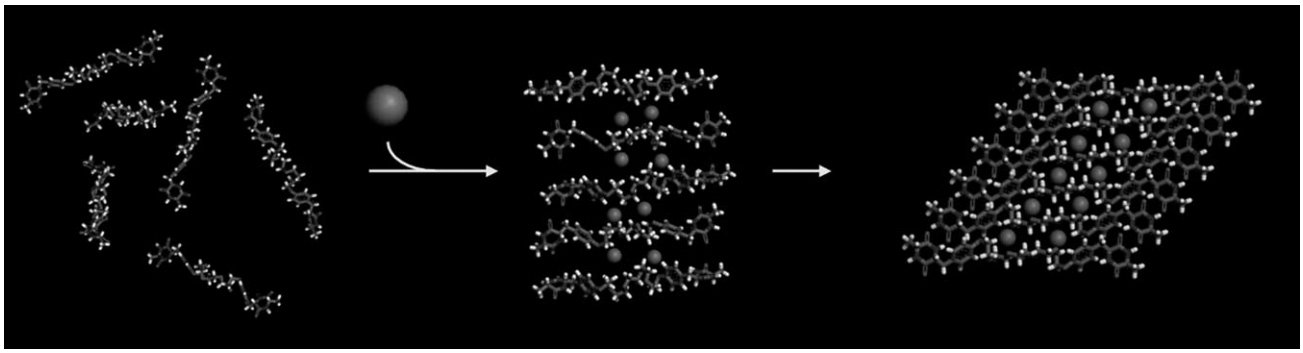


Figure 4. $Li^+$ assisted gelation process.

$CDCl_3$ and DMSO on a Bruker AM 400 spectrometer. Infrared spectra were obtained on a JASCO FTIR 430 spectrometer by using a $CaF_2$ plate or a $CaF_2$ window liquid cell. SEM images were obtained by using a Hitachi S-4300 field-emission scanning electron microscope equipped with a Horiba EMAX 6853-H EDS system (Center for Microcrystal Assembly, Sogang University). X-ray scattering measurements were performed in transmission mode with synchrotron radiation at the 10C1 and 3C2 X-ray beam lines at the Pohang Accelerator Laboratory, Korea.

**Determination of CGC**: Compounds **1–3** were mixed with various solvents in a 5 mL vial with a screw cap and the mixtures were heated until the solid was clearly dissolved. The solution was then cooled to room temperature and the gel was checked visually by inverting the vials.

**Synthesis of dipeptide-conjugated oligo(ethylene oxides)**: The dipeptide-conjugated oligo(ethylene oxides) were prepared by using the same procedure. A representative example is described for bis(Boc-L-Tyr-L-Ala-OMe)tri(ethylene oxide). Di-*p*-toluenesulfonyl tri(ethylene oxide) (2.4 g, 5.2 mmol), Boc-L-Tyr-L-Ala-OMe (4.0 g, 20.9 mmol), and $K_2CO_3$ (3.6 g, 26.0 mmol) were added to acetonitrile (40 mL) and heated at reflux for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined extract was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude products were purified by column chromatography (silica gel) using hexane/ethyl acetate (3:7) as the eluent to yield a colorless liquid (2.7 g, 58%).

**Bis(Boc-L-Tyr-L-Ala-OMe)tri(ethylene oxide)**: Yield 58%; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 8.54$ Hz, 4H; $C_6H_4$ in Tyr), 6.82 (d, $J = 8.54$ Hz, 4H; $C_6H_4$ in Tyr), 6.49 (brs, 1H; NH in Tyr), 4.53 (t, 2H; C-H in Tyr), 4.24 (m, 2H; C-H in Ala), 4.07–4.14 (m, 4H; $OCH_2$ in ethylene oxide), 4.03 (t, $J = 4.35$ Hz, 4H; $OCH_2$ in ethylene oxide), 3.69–3.75 (m, 4H; $OCH_2$ in ethylene oxide), 3.58–3.67 (m, 6H; $CO_2Me$), 2.99 (t, $J = 5.87$ Hz, 4H; C-$CH_2$-Ar in Tyr), 1.41 (s, 18H; Boc), 1.34 ppm (d, 6H; $OCH_3$).

**Bis(Boc-L-Tyr-L-Ala-OMe)tetra(ethylene oxide)**: Yield 62%; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 8.62$ Hz, 4H; $C_6H_4$ in Tyr), 6.82 (d, 4H; $C_6H_4$ in Tyr), 4.52 (t, 2H; C-H in Tyr), 4.24 (m, 2H; C-H in Ala), 3.82–3.87 (m, 6H; $CO_2Me$), 3.67–3.75 (m, 16H; $OCH_2$ in ethylene oxide), 2.99 (d, $J = 6.42$ Hz, 4H; C-$CH_2$-Ar in Tyr), 1.41 (d, $J = 1.83$ Hz, 18H; Boc), 1.35 ppm (d, $J = 7.15$ Hz, 6H; $OCH_3$).

**Bis(Boc-L-Tyr-L-Ala-OMe)penta(ethylene oxide)**: Yield 59%; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 8.54$ Hz, 4H; $C_6H_4$ in Tyr), 6.82 (d, $J = 8.54$ Hz, 4H; $C_6H_4$ in Tyr), 6.49 (brs, 2H; NH in Tyr), 5.00 (brs, 1H), 4.50 (t, $J = 7.17$ Hz, 2H; C-H in Tyr), 4.20 (m, 2H; C-H in Ala), 3.83 (t, $J = 4.81$ Hz, 4H; $OCH_2$ in ethylene oxide), 3.69–3.75 (m, 12H; $OCH_2$ in ethylene oxide), 3.66–3.69 (m, 4H; $OCH_2$ in ethylene oxide), 3.66 (s, 6H; $CO_2Me$), 2.97 (t, $J = 5.87$ Hz, 4H; C-$CH_2$-Ar in Tyr), 1.41 (s, 18H; Boc), 1.34 ppm (d, 6H; $OCH_3$).

**Synthesis of compounds 1, 2, and 3**: Compounds **1**, **2**, and **3** were synthesized by using the same procedure. A representative example is described for **1**. Trifluoroacetic acid (TFA, 15 mL) was added to a solution of tri(ethylene oxide)bis(Boc-L-Tyr-L-Ala-OMe) (2.1 g, 2.6 mmol) in $CH_2Cl_2$ (20 mL) at 0°C and was stirred for 2 h. The resulting solution was concentrated in vacuo to obtain tri(ethylene oxide)bis(L-Tyr-L-Ala-OMe), which was dissolved in butyl alcohol/toluene (15 mL/5 mL) and triethylamine (2 mL) was added to the solution. The reaction mixture was heated at reflux for 12 h and the precipitated mass was separated by filtration with diethyl ether. The crude products were obtained by recrystallization with diethyl ether.

**Compound 1**. Yield 87%; M.p. 233°C (with decomposition); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.06$ (s, 2H; N-H cyclodipeptide), 8.00 (s, 2H; N-H cyclodipeptide), 7.06 (d, 4H; $C_6H_4$ in Tyr), 6.85 (d, 4H; $C_6H_4$ in Tyr), 4.07–3.17 (m, 4H; $OCH_2$ in ethylene oxide), 4.00–4.07 (m, 4H; $OCH_2$ in ethylene oxide), 3.67–3.74 (m, 4H; $CH_2$ in Tyr), 3.49–3.59 (m, 4H; $OCH_2$ in ethylene oxide), 3.06 (m, 2H; -CH in Tyr), 2.79 (m, 2H; -CH in Ala), 0.55 ppm (d, 6H;-$CH_3$ in Ala); ESI-MS: $m/z$: 605.39 [$M$+Na$^+$].

**Compound 2**. Yield 84%; M.p. 213°C (with decomposition); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.05$ (s, 2H; N-H cyclodipeptide), 7.99 (s, 2H; N-H cyclodipeptide), 7.05 (d, 4H; $C_6H_4$ in Tyr), 6.85 (d, 4H; $C_6H_4$ in Tyr), 4.09–4.14 (m, 4H; $OCH_2$ in ethylene oxide), 3.67–3.74 (m, 4H; $CH_2$ in Tyr), 3.63 (d, $J = 7.63$ Hz, 4H; $OCH_2$ in ethylene oxide), 3.47–3.60 (m, 8H; $OCH_2$ in ethylene oxide), 3.06 (m, 2H; -CH in Tyr), 2.78 (m, 2H; -CH in Ala), 0.54 ppm (d, 6H;-$CH_3$ in Ala); ESI MS: $m/z$: 649.41 [$M$+Na$^+$].

**Compound 3**. Yield 85%; M.p. 230°C (with decomposition); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.07$ (s, 2H; N-H cyclodipeptide), 8.00 (s, 2H; N-H cyclodipeptide), 7.06 (d, 4H; $C_6H_4$ in Tyr), 6.85 (d, 4H; $C_6H_4$ in Tyr), 4.07–4.14 (m, 4H; $OCH_2$ in ethylene oxide), 4.03 (t, 4H), 3.69–3.75 (m, 4H; $OCH_2$ in ethylene oxide), 3.58–3.67 (m, 8H; $OCH_2$ in ethylene oxide), 3.17 (dd, 4H; $OCH_2$ in ethylene oxide), 3.06 (m, 2H; -CH in Tyr), 2.79 (m, 2H; -CH in Ala), 0.55 ppm (d, 6H; -$CH_3$ in Ala); ESI MS: $m/z$: 693.49 [$M$+Na$^+$].

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**Keywords:** cyclodipeptides · ethylene glycol · gels · hydrogen bonds · self-assembly

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