Functional organogels from lipophilic L-glutamide derivative immobilized on cyclotriphosphazene core

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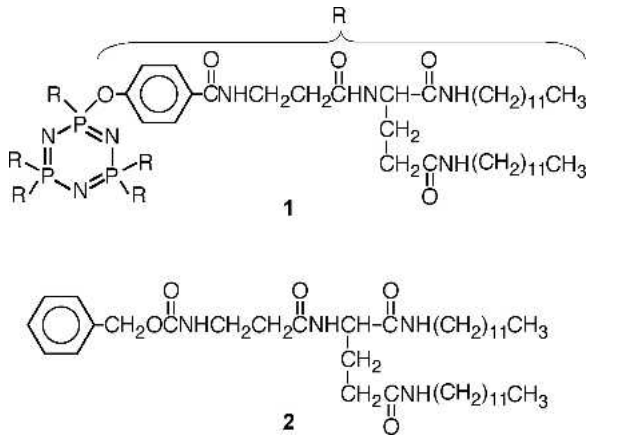
A novel cyclotriphosphazene-based low-molecular weight organogelator was prepared by immobilization of six dialkylated L-glutamide derivatives on a cyclotriphosphazene core, and its ability as a self-assembling organogelator was investigated. The organogelator exhibited enhanced gelation ability and chirality, and thixotropic property for self-restoring to a gel state; this was compared to the corresponding L-glutamide-derived organogelator without the core. The gelation test, transmission electron microscopy observation, and circular dichroism (CD) spectral study showed that the gelation and aggregation ability were enhanced by immobilization onto the cyclotriphosphazene core. Gels in chloroform and cyclohexane-ethanol (95:5) mixture showed an unusual thixotropic property.

I. INTRODUCTION

In the past decade, a considerable amount of research on phosphazene derivatives has been reported because of their thermal and chemical stability, biocompatibility, biodegradability, high conductivity, and many other properties.[1–10] Hexachloro cyclotriphosphazene, one of the inorganic phosphazene representatives, is a nearly planar ring compound that contains alternating phosphorus and nitrogen atoms in its skeleton, and each phosphorus atom contains two chlorine atoms as substituent groups. These six substituents are located at the upward and downward perpendicular positions on a phosphazene ring.[3] These structural properties are suitable for the construction of well-defined hyperbranched polymers and star-shaped polymers because they enable alignment and concentration of various functional side chains on the cyclophosphazene core.[4,5,8–10]

This is the first report on organogels with a cyclotriphosphazene-based compound **(1)** as an inorganic-organic molecular hybrid, which is built up by immobilization of six lipophilic L-glutamide derivatives (R in the scheme) on cyclotriphosphazene. Organogels[11–16] are highly ordered network systems that consist of a solvent trapped in a network of solutes assembled by weak intermolecular forces such as hydrogen bonding, van der Waals forces and π-π interactions. This novel organogel can be characterized by the feature that the six functional substituents are perpendicularly immobilized on the rigid plane, and thus the cylindrical molecular shape yields unique self-assembling behaviors in various organic solvents. As a self-assembled functional organogel, this novel compound is expected to play a role as a chiral organic media for nano-devices and for chemical reaction and chiral separation.



SCHEME: Chemical structures of L-glutamide-derived organogelators.

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II. EXPERIMENTAL SECTION

A. Hexakis[4-(*N′*, *N″*-dodecyl-*N*-aminopropionyl-L-glutamide) phenoxy] cyclotriphosphazene (1)

Hexakis[4-(*N′*, *N″*-dodecyl-*N*-aminopropionyl-L-glutamide) phenoxy] cyclotriphosphazene **(1)** was prepared according to the method reported by the literature.[17] Mp 260.5 °C; ^{31}P-NMR ($CDCl_3$ / TFA = 150/1, 162 MHz): δ (ppm) 10.15 (s); ^{1}H-NMR ($CDCl_3$/TFA = 150/1, 400 MHz): δ (ppm) 0.85–0.88 (t, 36H, J = 6.8 Hz, CH_3), 1.24 (216H, m, CH_2), 1.48 (24H, m, CH_2), 2.010 (6H, m, CH_2), 2.16 (6H, m, CH_2), 2.47 (12H, m, CH_2), 2.77 (12H, t, CH_2), 3.21 (24H, br, CH_2), 3.80 (12H, m, CH_2), 4.555 (6H, m, CH), 6.96 (12H, br, aromatics), 7.43 (6H, br, NH), 7.55 (12H, br, aromatics), 7.84 (6H, br, NH); elemental analysis calculated for $C_{234}H_{414}N_{27}O_{36}P_3$: C, 67.5; H, 9.72; N, 9.08. Found: C, 66.5; H, 9.51; N, 8.74.

B. Hexakis(4-carboxyphenoxy) cyclotriphosphazene

Hexakis(4-carboxyphenoxy)cyclotriphosphazene: Mp 280 °C; ^{31}P-NMR (DMSO-d_6, 162 MHz): δ (ppm) 8.7 (s); elemental analysis calculated for $C_{42}H_{30}N_3O_{18}P_3$: C, 52.7; H, 3.13; N, 4.39. Found: C, 52.6; H, 3.11; N, 4.51.

C. *N′*, *N″*-dodecyl-*N*-[3-(N-benzyloxycarbonyl) aminopropionyl]-L-glutamide (2)

Cyclotriphosphazene-based **(1)** was synthesized by coupling of hexakis(4-carboxyphenoxy)cyclotriphosphazene[17] with *N′*, *N″*-dodecyl-*N*-aminopropionyl-L-glutamide, which was prepared by debenzyloxycarbonylation of **(2)**.[18,19] The coupling reaction was carried out using diethyl phosphorocyanidate with triethyl amine as a promoter. ^{31}P-NMR spectroscopy of **(1)** in $CDCl_3$ indicated a single peak at 10.15 ppm while hexakis(4-carboxyphenoxy) cyclotriphosphazene and hexachloro cyclotriphosphazene provided them at 8.9 (in DMSO-d_6) and 2.3 ppm (in DMSO-d_6), respectively. This is simple evidence indicating the fact that **(1)** has the six equivalent branches on a cyclophosphazene plane. Of course, ^{1}H-NMR spectroscopy proved that these branches consisted of the L-glutamides. *N′*, *N″*-dodecyl-*N*-[3-(*N*-benzyloxycarbonyl) aminopropionyl]-L-glutamide **(2)** was prepared according to the method reported previously.[18,19] Mp 172–175 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.862–0.896 (6H, t, J = 6.8 Hz, CH_3), 1.25 (36H, m, CH_2), 1.49 (4H, m, CH_2), 1.93 (1H, m, CH_2), 2.04–2.09 (1H, m, CH_2), 2.27 (2H, m, CH_2), 2.36 (2H, m, CH_2), 2.46 (2H, m, CH_2), 3.22–3.23 (4H, br, CH_2), 3.80 (12H, m, CH_2), 3.49 (2H, m, CH_2), 4.33–4.34 (1H, m, CH), 5.09 (2H, s, CH_2), 5.44 (1H, br, N–H), 5.85 (1H, br, N–H), 6.83 (1H, br, N–H), 7.43 (1H, br, NH), 7.34 (5H, br, aromatics); elemental analysis calculated for $C_{40}H_{70}N_4O_5$: C, 69.9; H, 10.3; N, 8.16. Found: C, 69.2; H, 10.4; N, 8.06.

III. RESULTS AND DISCUSSION

The obtained **(1)** showed good solubility in various hot organic solvents such as benzene, toluene, tetrahydrofuran (THF), chloroform, and ethanol. The gelation was easily observed when their hot solutions were cooled down to room temperature. A typical example is as follows: 3.5 mg **(1)** was dissolved in 1.0 ml of chloroform at 60 °C (0.84 mM, corresponding to 5 mM per L-glutamide moiety) and then the solution was allowed to stand at 15 °C for 5 min to make a clear gel. Similar gelation was also observed in benzene, toluene, THF and a cyclohexane-ethanol (95:5) mixture (v/v). On the other hand, the L-glutamide derived **(2)**, which was not immobilized on a cyclotriphosphazene core, did not make a gel in chloroform and THF while gelation was also observed in benzene, toluene and a cyclohexane-ethanol (95:5) mixture. No gelation in these solvents is a common observation in lipophilic L-glutamide derivatives[19] because chloroform and THF have relatively high polarity and high solvency to suppress the molecular aggregation. On the other hand, **(2)** at a 5 mM concentration formed sol in DMF and gel in cyclohexane, but **(1)** at a 5 unit-mM concentration was insoluble in both solvents even at 70 °C.

As shown in Table I, only **(1)** provided typical gel-to-sol transitions in all solvents. In addition, the critical gelation concentration (cgc) was determined in a cyclohexane-ethanol (95:5) mixture at 25 °C by an inverse fluid method using a 14 mm sample tube. The cgc of **(1)** (2–3 unit mM; the concentration "unit mM" refers to concentration in mM per L-glutamide moiety) was a little lower than that of **(2)** (3–4 mM). These results indicate that the gelation ability is a little enhanced by immobilization on a cyclotriphosphazene core.

Transmission electron microscopy (TEM) observations showed that both of the gels from **(1)** and **(2)** contained well-developed fibrous aggregates, as shown in Fig. 1. The apparent diameters were 7–30 nm and 10–40 nm, respectively. Therefore, it may be concluded that both of the gels are constructed through three-dimensional network formation with fibrous aggregates. This is a common mechanism in low-molecular organogelators.[11–16,19] However, it should be noted here that the TEM image from **(1)** showed more highly dense network structures than that of **(2)**. This special feature may be

TABLE I. Gel-to-sol transition temperatures determined by an inverse fluid method.

Solvent	1	2
THF	Gel (53 °C)	Only sol
Chloroform	Gel (28 °C)	Only sol
Benzene	Gel (51 °C)	Gel (61 °C)
Cyclohexane-ethanol (95:5)	Gel (46 °C)	Gel (42 °C)
DMF	Insoluble	Only sol
Cyclohexane	Insoluble	Gel (31 °C)

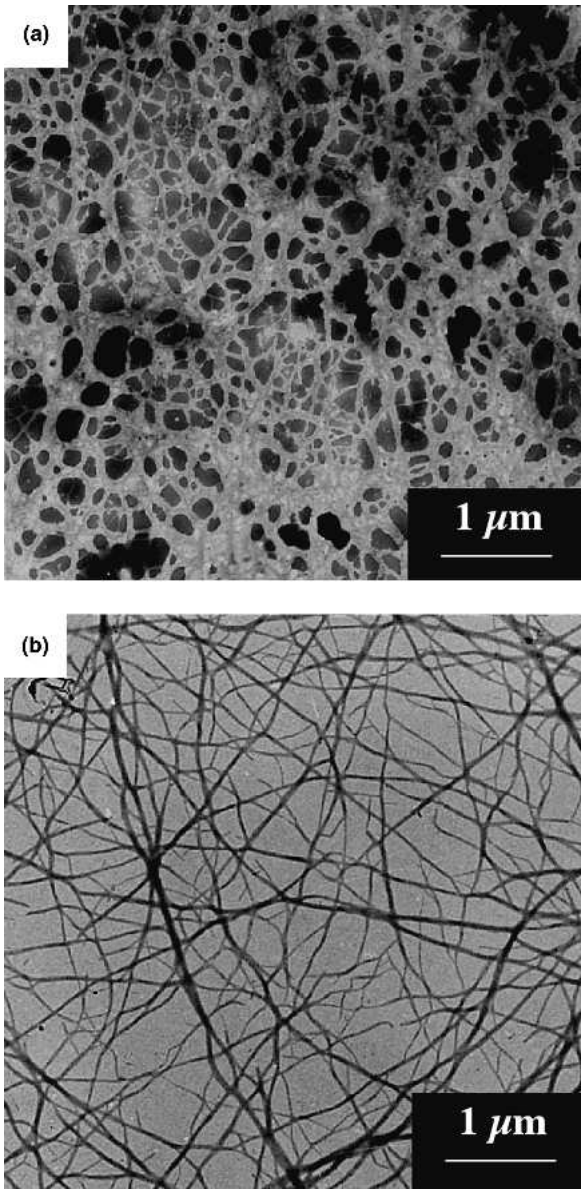


FIG. 1. TEM images of aggregates of (a) **(1)** and (b) **(2)** in benzene; initial concentration of **(1)** (concentration of L-glutamide-derived substituent) = 0.1 unit mM and **(2)** = 0.1 mM; stained by 2 wt% ammonium molybdate.

accompanied by a self-restoring property of the **(1)** gel, which will be discussed later.

Circular dichroism (CD) spectroscopy gave us important information on the aggregation mechanism of **(1)**. As shown in Fig. 2, compound **(1)** (1 unit mM) provided extremely large exciton coupling with -3.6×10^5 deg cm^2 dmol^{-1} at around 242 nm while the intensity almost disappeared at 0.01 unit mM (below 1×10^4 deg cm^2 dmol^{-1}; Fig. 3). This indicates that at 1 unit mM concentration compound **(1)** is in the aggregated state. This was further supported by the trifluoroacetic acid (TFA) experiment. The CD signal was disappeared after adding 2.7 mM

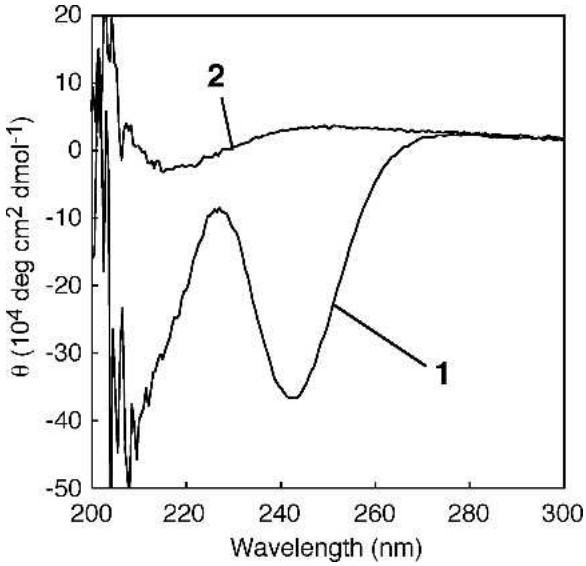


FIG. 2. CD spectra of **(1)** and **(2)** in a cyclohexane-ethanol (95:5) solution at 25 °C by using a 1 mm quartz cell. Concentration of L-glutamide moiety, 1.0 unit mM.

TFA to 1 unit-mM of **(1)** solution. TFA destroys the hydrogen bonds between molecules and as a result, prevents aggregation. Similar enhancement of CD intensity due to aggregation has been detected in aqueous bilayer membrane systems from chiral amphiphiles.[20–23] According to these previous discussions, it is estimated that the **(1)** gel consists of chirally ordered aggregation and undergoes the concentration-dependent transition from ordered-to-disordered states. By using this phenomenon, the critical aggregation concentration (cac) was determined to be 0.045 unit mM in a cyclohexane-ethanol (95:5) mixture at 25 °C, as shown in Fig. 3. The cac value is much

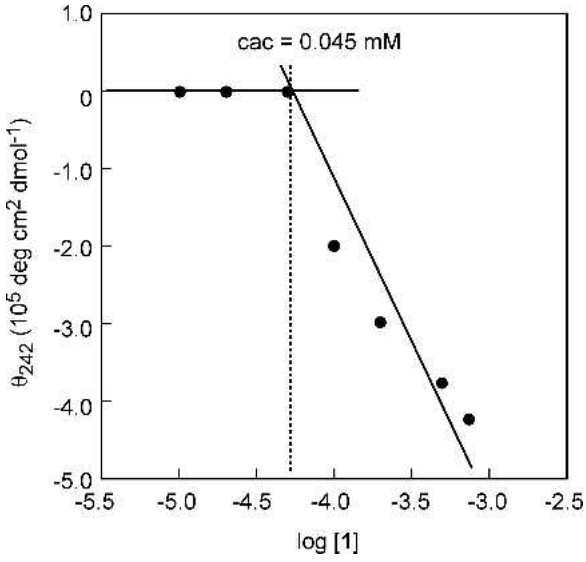


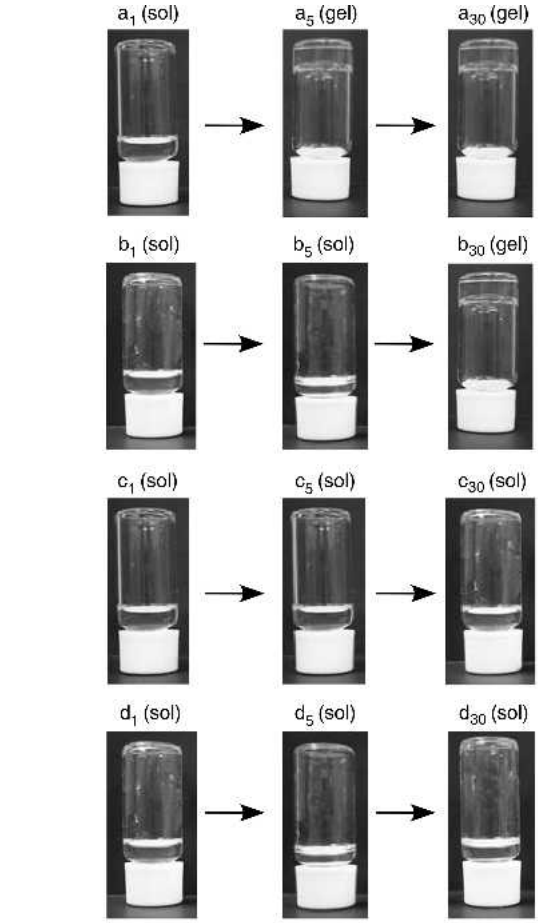
FIG. 3. Concentration dependency of molar ellipticity (θ) of 1 at 242 nm in a cyclohexane-ethanol (95:5) mixture. The cac is determined for per L-glutamide moiety.

smaller than the cgc of **(1)** (2–3 unit mM). This is a proof that the highly ordered aggregates can be formed even in a sol state but the amount of the fibrous aggregates is not enough to create a network formation to a gel state.

Uniqueness of the **(1)** gel should be most emphasized by thixotropy. A typical observation was realized especially in chloroform and a cyclohexane-ethanol (95:5) mixture. In general, organogels from low-molecular compounds such as **(2)** are mechanically weak and not self-restored to a gel without additional heating treatment, but this was not the case for the **(1)** gel. For example, the **(2)** gel state was destroyed to a sol state only by shaking, and then there was no change even after it was allowed to stand at room temperature for 1 h. The most convenient method to regenerate the gel state may be to heat it up again and then cool it down to room temperature. The fractionation of the fibrillar network occurs easily but is difficult to restore to a gel state without reaggregation via a monomeric (or micellar) dispersion state. On the contrary, **(1)** showed the ability to self-restore to a gel state.

Such a phenomenon is sometimes called thixotropy. There are a few reports on organogels but unfortunately almost no quantitative discussion for them.[24–26] In case of **(1)**, mechanical agitation or vortexing at 20 °C turned a gel into a sol, from which the gel state was spontaneously restored within 2–30 min in a cyclohexane-ethanol (95:5) mixture and chloroform, respectively. Additionally, significant information was obtained by CD spectroscopy, showing the fact that the mechanical agitation did not influence the enhanced chirality due to highly ordered aggregation. This explains that the mechanical agitation destroys a macroscopic gel state into a sol state by segmentation of three-dimensional network, but the resultant fragmental aggregates are still based on chirally ordered structures.

Figure 4 shows the viscosity as a function of time for the **(1)** solutions (5 unit mM) in various organic solvents at 20 °C after mechanical agitation for 1 min. The viscosity of all solutions was very low right after agitation, indicating that the system behaviors as a slightly viscous fluid and then distinct viscosity increase was clearly detected in the **(1)** solutions from a cyclohexane-ethanol (95:5) mixture and chloroform. No similar viscosity increase was found in **(2)** in either of the solvents. These big differences between **(1)** and **(2)** are presumably due to those of not only their solubility in organic solvents but also the resultant aggregation morphology. As shown in the TEM images of Fig. 1, the **(1)** gel was constructed by more highly dense fibrillar network compared with the **(2)** gel. This indicates that the **(1)** fibrils can make a chance for fusion between each other because of many reconstructive terminals. On the other hand, the **(1)** gels from THF and benzene did not show self-restoration



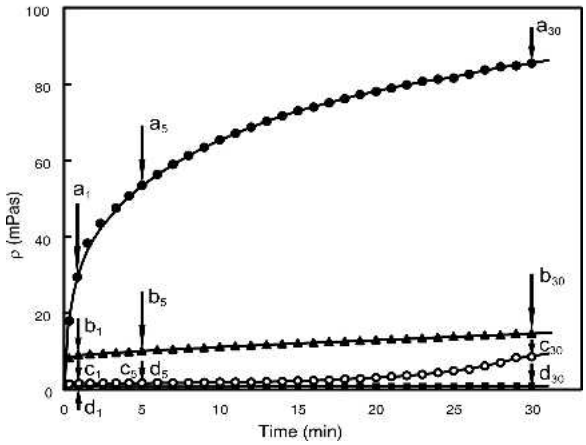


FIG. 4. Time courses of viscosity of **(1)** (a) in a cyclohexane-ethanol (95:5) mixture, (b) in chloroform, and (d) in benzene; and **(2)** (c) in a cyclohexane-ethanol (95:5) mixture at 20 °C after vortexing for 1 min (5 unit mM).

within 1 h. In these solutions, more physically rigid gels were produced compared with the chloroform gel. Regardless of gel formation, it is sure that chloroform is a good solvent for both **(1)** and **(2)**. This suggests that chloroform may provide a delicate environment for **(1)**; e.g., solvation effect for playing a role for fusion between

the fibrils and promotion of intermolecular hydrogen bonding interaction for highly ordered aggregation.

IV. SUMMARY

In conclusion, we have introduced a novel low-molecular weight organogelator, which was prepared by immobilization of six L-glutamide-derived lipids onto a cyclotriphosphazene core, and its ability as a self-assembling organogelator was investigated. The gelator solution showed extremely large enhancement of chirality. The gelation test, transmission electron microscopy (TEM) observation, and CD spectral study showed that the gelation and aggregation ability were enhanced by immobilization onto the cyclotriphosphazene core. Gels in chloroform and cyclohexane-ethanol (95:5) mixture showed an unusual thixotropic property that was not observed in the corresponding L-glutamide-derived organogelator without the core. It implies that immobilization onto cyclotriphosphazene core can lead to induction of new functions. This "immobilization onto cyclophosphazene" strategy can be used to render new functions to common and insipid compounds.

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