Electronic Supplementary Information

N-Alkylamido-D-Glucamine-Based Gelators for the Generation of Thixotropic Gels

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Materials and Methods

D-Glucamine (95%), glycine (99%), glycylglycine (99%), 1-hydroxybenzotriazole monohydrate (HOBt, 97%), palmitotyl chloride (95%) and stearoyl chloride (97%) were purchased from Tokyo Chemical Industry Co., Ltd. and used without further purification. All solvents, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (water soluble carbodiimide (WSC)), hydrochloric acid and sodium hydroxide were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.

^{1}H-NMR and ^{13}C-NMR spectra were acquired using an AVANCE 500 (500 MHz, Bruker BioSpin K. K.) spectrometer. Mass spectra were recorded on an LTQ Orbitrap spectrometer (ESI FTMS, Thermo Fisher Scientific K.K) or a 3100 Mass detector equipped with e2695 Separations module and an s2489 UV/Visible detector (Nihon Waters K. K.). Elemental analysis was performed with a JM10 elemental analyzer (J-SCIENCE LAB CO., Ltd.).

The gelation tests were performed using the vial inversion method. A crystal of alkylamide was placed in a vial with a solvent at a set concentration (wt%) and capped. The vial was heated in a

dry bath of 100 °C until the crystal of gelator was dissolved. Gelator solution was left for 1 h at room temperature, and gelation was checked with naked eyes by inverting the vial.

The thixotropic behaviour was evaluated using the vial inversion method. The Gelator hydrogel in vial was shaken and collapsed by a vortex genie (Scientific Industries, Inc). Then the obtained sol was left for the set time at room temperature, the recovery of the gel state from the sol state was checked with naked eyes by inverting the vial.

Thermal analysis was performed with an EXSTAR6000 differential scanning calorimeter DSC (Seiko Instruments Inc.) using a Ag-made closable sample pan. $T_{gel \rightarrow sol}$ and $T_{sol \rightarrow gel}$ of gels were determined as extrapolated onset temperatures from the DSC curves.

SEM images were recorded with a SU-8000 scanning electron microscope (Hitachi High-Technologies Corporation) at 1.0 kV; the SEM sample (xerogel of hydrogel) was freeze-dried and placed on a conductive tape on the SEM sample stage. Pt, as a conductive material, was used as a coating on the sample (Pt coating is 10-nm thick).

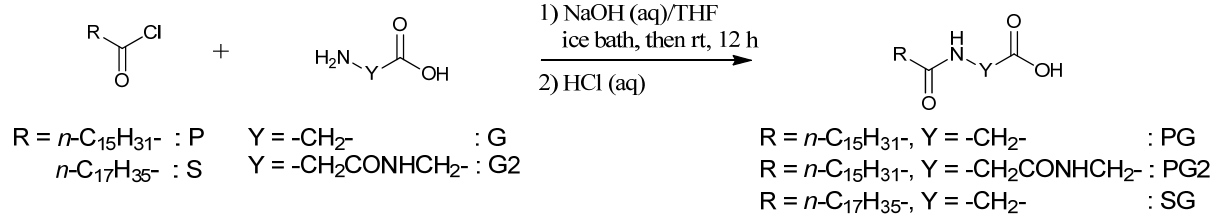
Rheological measurements of frequency sweep were performed with an MCR-301 rheometer (Anton Paar Japan K.K.) with a parallel plate (8 mm diameter) at a gap of 0.50 mm and γ of 0.01 % (measurement temperature: 25 °C). Rheological measurements of strain sweep were performed with an MCR-301 rheometer with a parallel plate (8 mm diameter) at a gap of 0.50 mm and constant angular frequency 1 rad s^{-1} (measurement temperature: 25 °C). For rheological measurements, the hydrogel sample was applied onto the parallel plate and sample stage (the overflow gel was swept). The hydrogel sample for rheological measurements was placed on a parallel plate and a sample stage (the overflow gel was swept). Step-shear measurement was carried out by applying normal strain (strain amplitude 0.01 % and frequency 1 Hz) and large strain (shear rate 3000 s^{-1} for 0.1 s), repeatedly.

X-ray diffraction data were recorded on a D8 Discover X-ray diffractometer (Bruker AXS K.K.) with CuKα at 26 °C (the sample was filled in a quartz glass capillary tube of 1 mm diameter).

Infrared spectroscopy was performed with an FT/IR-620 (JASCO Corporation) using the ATR method (ZnSe prism).

Synthesis of PG-G, PG2-G and SG-G

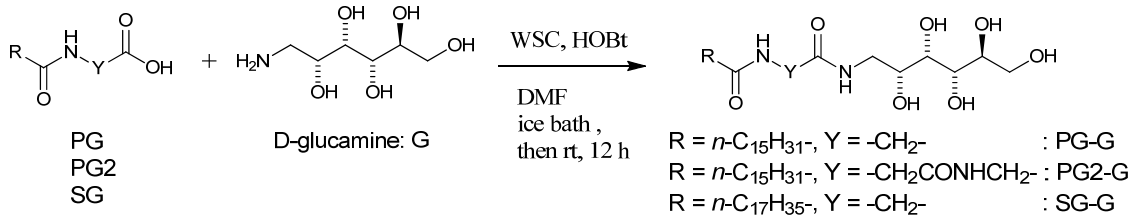
Synthesis of alkyloyl-glycine derivatives (general synthesis 1)



Alkyloyl-glycine derivatives were synthesized according to reported protocol.[1] A solution of alkyloyl chloride (13.82 mmol) in absolute THF (20 mL) was added slowly over a period of 30 min under a N_2 atmosphere to a solution of glycine or glycylglycine (20.73 mmol) in water (40 mL) containing NaOH (2 M) at 0 °C. The solution, along with the generated white precipitate, was stirred in the ice bath for an additional 1 h, and then at rt for 12 h. Water (10 mL) was added to dissolve the precipitate, then HCl (3 M, 20 mL) was added to adjust the pH of the solution to <2. The observed white precipitate was filtered, washed with water and then dried in *vacuo*. The dried precipitate was re-crystallized from MeOH to yield the alkyloyl glycine derivatives.

Synthesis of **SG2-G** was not carried out due to the low solubility of SG2 in Methanol.

Synthesis of alkylaldonamides containing the glycine motif (general synthesis 2)



The synthesis of **PG-G** is described here as a re-presentative example. The synthesis of other gelators followed a similar protocol. Both D-glucamine and WSC (4.21 mmol each) were added under an atmosphere of N_2 to a solution of alkyloyl glycine, **PG**, (3.83 mmol) and HOBt (4.21 mmol) in anhydrous DMF (20 mL) at 0 °C The solution was stirred in an ice bath for 1 h (the solution became opaque), and then at rt for 12 h (the opaque solution became gel-like). DMF was removed in *vacuo* and the white residue was re-crystallized twice in MeOH to yield **PG-G**.

PG: PG (white crystals) was prepared from palmitoyl chloride and glycine according to general synthesis 1 in 48.8% yield. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 8.11 (s (br), 1H), 3.71 (d, 2H, J = 5.7 Hz), 2.10–2.18 (m, 2H), 1.48 (m, 2H), 1.24 (m, 24H) and 0.86 (t, 3H J = 6.9 Hz). LC-MS(ESI): calcd. for $C_{18}H_{35}NO_3$, 313.26; found m/z = 312.0 $[M-H]^-$.

PG2: PG2 (white crystal) was prepared from palmitoyl chloride and glycylglycine according to general synthesis 1 in 65.8 % yield. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 8.18 (t, 1H, J = 5.4

Hz), 7.21 (s (br), 1H), 3.63 (d, 2H, *J* = 6.0 Hz), 3.24 (d, 2H, *J* = 4.1 Hz), 2.12 (m, 2H), 1.53 (m, 2H) 1.24 (m, 24H) , 0.86 (t, 3H *J* = 7.3 Hz). LC-MS(ESI): calcd for $C_{20}H_{38}N_2O_4$, 370.28; found m/z = 369.1 $[M-H]^-$.

SG : SG (white crystal) was prepared from stearoyl chloride and glycine according to general synthesis 1 in 74.8 % yield. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 8.09 (t, 1H, *J* = 5.4 Hz), 3.71 (d, 2H, *J* = 5.7 Hz), 2.10 (m, 2H), 1.48 (m, 2H), 1.24 (s (br), 26H) , 0.86 (t, 3H *J* = 6.8 Hz). LC-MS(ESI): calcd for $C_{20}H_{39}NO_3$, 341.29; found m/z = 340.0 $[M-H]^-$.

PG-G: PG-G (white crystals) was synthesized in 85.8% yield by coupling **PG** with D-glucamine following the protocol described in general synthesis 2. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 7.99 (t, 1H, *J* = 5.2 Hz), 7.68 (t, 1H, *J* = 5.2 Hz), 4.76 (d, 1H, *J* = 4.4 Hz), 4.47 (d, 1H, *J* = 5.7 Hz), 4.39 (d, 1H, *J* = 6.3 Hz), 4.34 (t, 1H, *J* = 5.7 Hz), 4.30 (d, 1H, *J* = 6.6 Hz), 3.66 (d, 2H, *J* = 5.7 Hz), 3.58 (m, 3H), 3.48 (m, 1H), 3.40 (m, 2H), 3.29 (m, 1H), 3.04 (m, 1H), 2.12 (d, 2H, *J* = 7.6 Hz), 1.48 (m, 2H), 1.26 (m, 24H), 0.86 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS, δ, ppm): 172.99, 169.65, 74.40, 72.03, 70.28, 63.81, 42.53, 42,45, 35.68, 31.75, 29.51, 29.47, 29.41, 29.20, 29.16, 25.61, 22.54, 14.39. LC-MS (ESI): calcd for $C_{24}H_{48}N_2O_7$, 476.35; found m/z = 477.35 $[M+H]^+$. Elemental anal. calcd for $C_{24}H_{48}N_2O_7$: C, 60.48; H, 10.15; N, 5.88. Found: C, 60.39; H, 10.12; N, 5.85.

PG2-G: **PG2-G** (white crystals) was synthesized in 44.4 % yield by coupling **PG2** with D-glucamine following the protocol described in general synthesis 2. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 8.10 (t, 11H, *J* = 5.0 Hz), 8.03 (t, 2H, *J* = 5.4 Hz), 7.60 (t, 2H, *J* = 5.0 Hz), 4.79 (d, 1H, *J* = 3.8 Hz), 4.47 (d, 1H, *J* = 5.4 Hz), 4.38 (d, 1H, *J* = 6.0 Hz), 4.34 (t, 1H, *J* = 5.2 Hz), 4.31 (d, 1H, *J* = 6.3 Hz), 3.70 (d, 2H, *J* = 3.2 Hz), 3.59 (m, 3H), 3.47 (m, 1H), 3.41 (m, 2H), 3.32 (m, 1H), 3.05 (m, 1H), 2.13 (d, 2H, *J* = 7.6 Hz), 1.49 (m, 2H), 1.24 (m, 24H), 0.86 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS, δ, ppm): 173.73, 170.21, 169.74, 72.85, 72.45, 70.61, 64.21, 43.03, 42.94, 36.07, 32.15, 29.91, 29.86, 29.81, 29.69, 29.58, 29.55, 25.97, 22.94, 14.80. LC-MS (ESI): calcd for $C_{26}H_{51}N_3O_8$, 533.37; found m/z = 534.37 $[M+H]^+$. Elemental anal. calcd for $C_{26}H_{51}N_3O_8$: C, 58.51; H, 9.63; N, 7.78. Found: C, 58.29; H, 9.57; N, 7.82.

SG-G: **SG-G** (white crystals) was synthesized in 82.0 % yield by coupling **SG** with D-glucamine following the protocol described in general synthesis 2. ^{1}H-NMR (500 MHz, DMSO-d_6, TMS, δ, ppm): 7.99 (t, 1H, *J* = 5.4 Hz), 7.67 (t, 1H, *J* = 4.9 Hz), 4.75 (d, 1H, *J* = 4.4 Hz), 4.46 (d, 1H, *J* = 5.4 Hz), 4.38 (d, 1H, *J* = 6.3 Hz), 4.33 (t, 1H, *J* = 5.4 Hz), 4.27 (d, 1H, *J* = 6.3 Hz), 3.67 (d, 2H, *J* = 5.7 Hz), 3.58 (m, 3H), 3.48 (m, 1H), 3.40 (m, 2H), 3.28 (m, 1H), 3.05 (m, 1H), 2.12 (d, 2H, *J* = 7.6 Hz), 1.51 (m, 2H), 1.25 (m, 28H), 0.86 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS, δ, ppm): 173.41, 170.08, 72.80, 72.45, 70.69, 64.22, 42.93, 42.84, 36.08, 32.15, 29.90, 29.86, 29.82, 29.70, 29.60, 29.55, 26.01, 22.94, 14.79. LC-MS (ESI): calcd for $C_{26}H_{52}N_2O_7$, 504.38; found m/z = 505.38 $[M+H]^+$. Elemental anal. calcd for $C_{26}H_{52}N_2O_7$: C, 61.87; H, 10.38; N, 5.55. Found: C, 61.80; H, 10.31; N, 5.51.

Figs. S1, S2 and Table S1

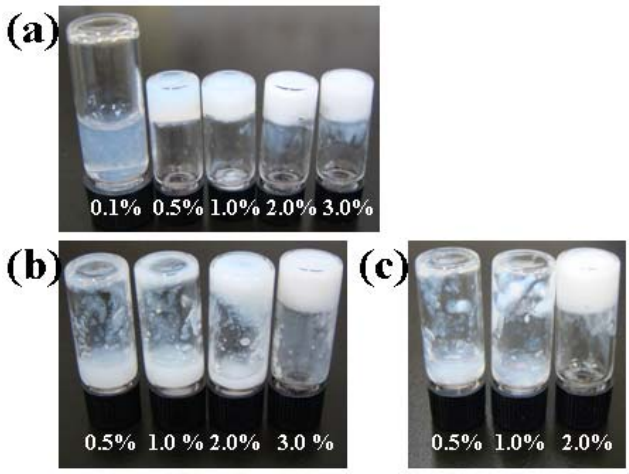


Fig. S1 Evaluation of hydrogels: (a) **PG-G**; (b) **PG2-G** and (c) **SG-G**.

Table S1 Transition temperatures of hydrogels obtained from DSC measurements (heating and cooling rate: 2 °C/min).

Sample	$T_{gel \rightarrow sol}$ /°C (ΔH/mJ mg^{-1})	$T_{sol \rightarrow gel}$ /°C (ΔH/mJ mg^{-1})
PG-G (0.5 wt%)	83, 93* (1.2)	76 (1.0)
PG2-G (3.0 wt%)	107 (4.0)	105 (3.9)
SG-G (3.0 wt%) [Remark 4]	94 (2.6)	81 (1.7)

* Bimodal peak (peak temperatures).

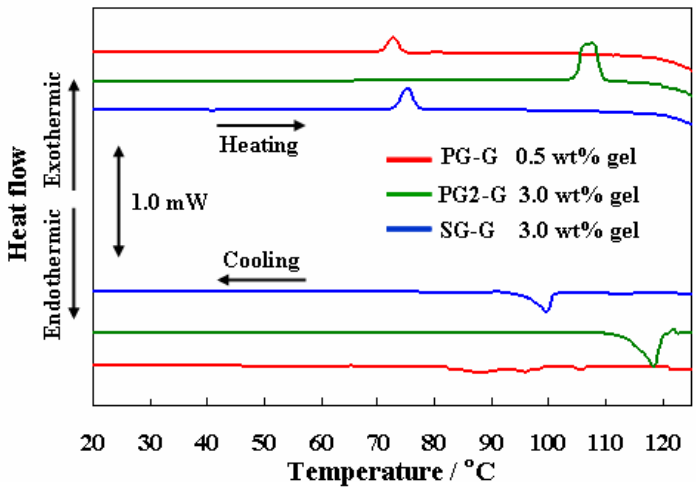


Fig. S2 DSC curves of hydrogels (2 °C/min).

Fig. S3

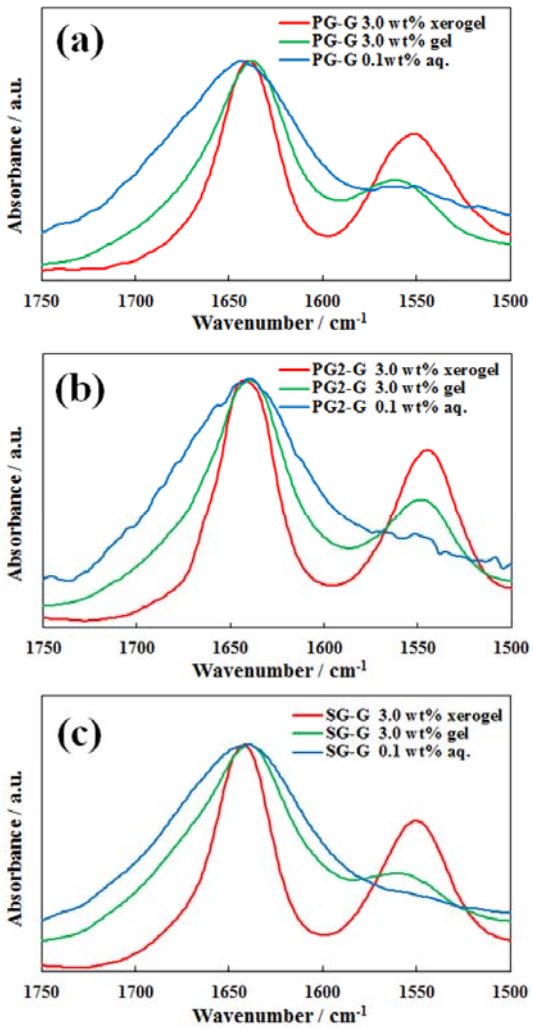


Fig. S3 IR spectra of the hydrogelators in different states in the region of carbonyl stretching: (a) PG-G; (b) PG2-G; (c) SG-G.

To clarify the driving force of the fibre formation of hydrogelators, the infrared (IR) spectrum of hydrogelator systems in different states in the region of the carbonyl stretching were measured (Fig. S3). One of the main absorption peaks of the carbonyl group in the higher wavenumber region (over 1650 cm^{-1}) increases and that of lower wavenumber region (1550 cm^{-1}) decreases when the state changes from solution to gel and from gel to xerogel. The absorption peak of higher wavenumber (over 1650 cm^{-1}) could be attributed to the carbonyl stretching of non-interactive, free molecules and that of lower wavenumber (1650 cm^{-1} and 1550 cm^{-1}) could be attributed to the carbonyl stretching of intermolecular interaction due to hydrogen bonding. This tendency was observed in all hydrogelator systems. From these results, the driving force of the self-assembly tendency probably depends on hydrogen bonding of hydrogelators.

Fig. S4

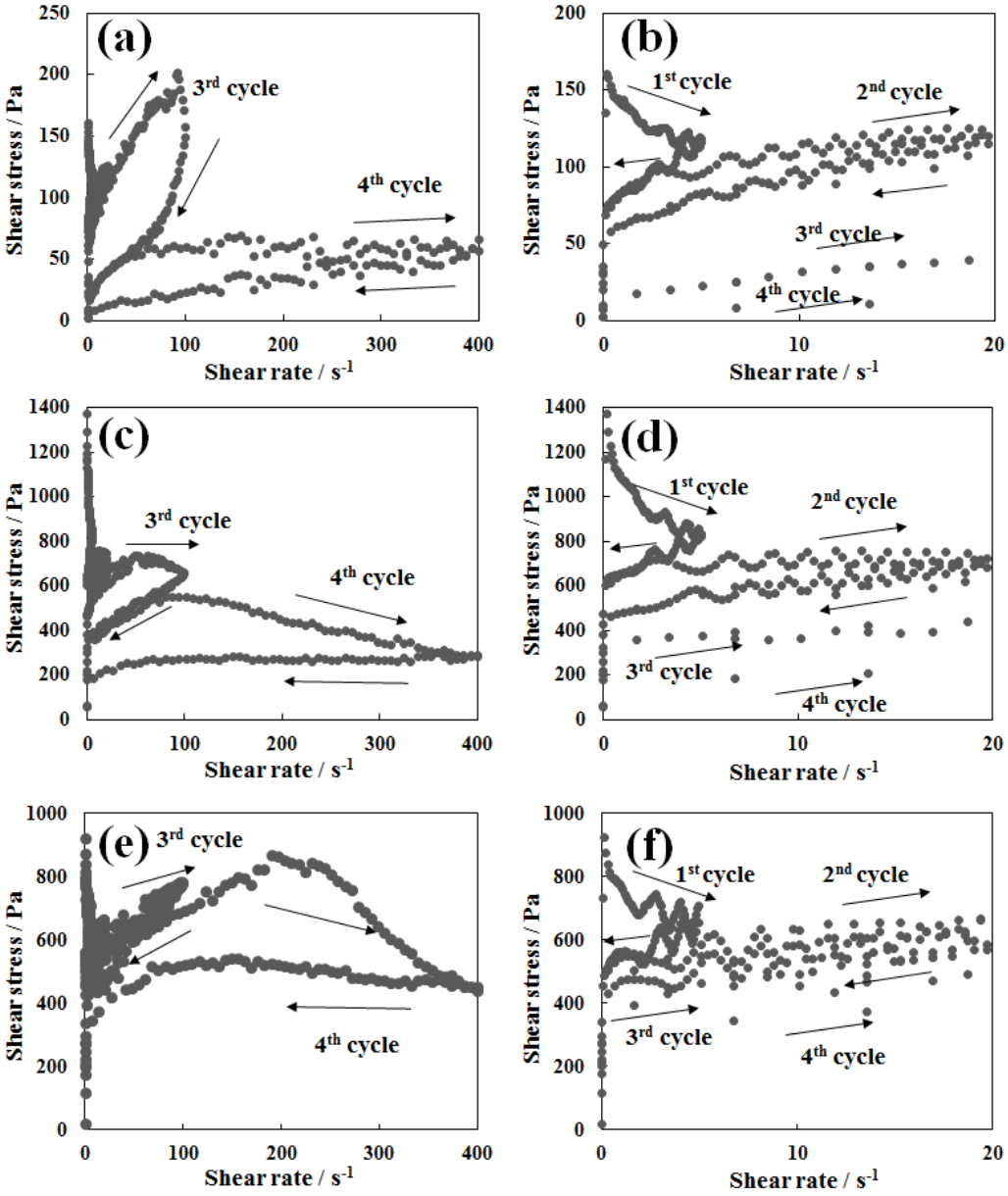


Fig. S4 Thixotropic hysteresis loop of hydrogels: (a, b) PG-G 0.5 wt % hydrogel; (c, d) PG2-G 3.0 wt% hydrogel; (e, f) SG-G 3.0 wt% hydrogel. The test was conducted with 1st cycle: 0.001 s^{-1} - 5.0 s^{-1} - 0.001 s^{-1} (120 s), 2nd cycle: 0.001 s^{-1} - 20 s^{-1} - 0.001 s^{-1} (120 s), 3rd cycle: 0.001 s^{-1} - 100 s^{-1} - 0.001 s^{-1} (120 s), 4th cycle: 0.001 s^{-1} - 400 s^{-1} - 0.001 s^{-1} (120 s), with 1 min intervals between cycles.

Figs. S5 and S6

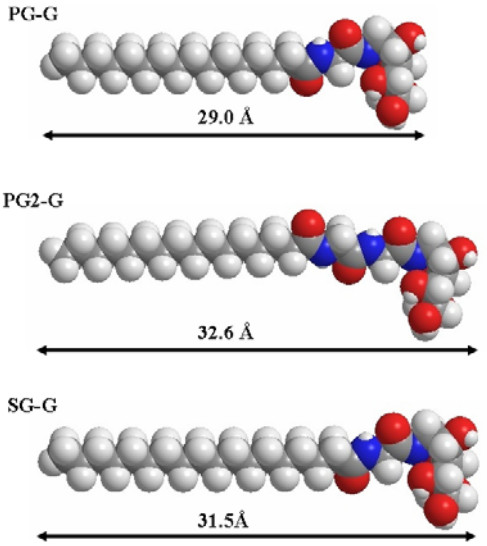


Fig. S5 Contour length of **PG-G**, **PG2-G** and **SG-G** obtained from MM2 calculation in ChemDraw.

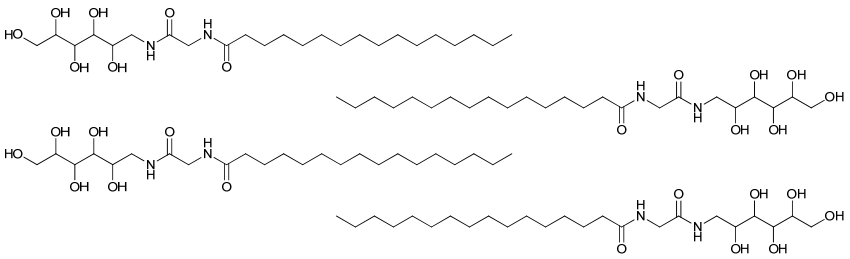


Fig. S6 Schematic illustration of interdigitated lamellar packing in **SG-G**.

Acknowledgments

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Reference

1 Y. M. Osornio, P. Uebelhart, S. Bosshard, F. Konrad, J. S. Siegel, E. M. Landau, *J. Org. Chem.* 2012, **77**, 10583.