Supramolecular Gel Formation and Self-correction Induced by Aggregation-driven Conformational Changes

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**Synthetic procedures:**
Preparation of diamino amides shown below has been previously reported\(^1\):

![Diamino amides](image)

**General procedure for the preparation of N-Boc-protected compounds 1a-c:**
A solution of diamino amide (5.51 mmol) in 100 mL of dry DME was added dropwise over a solution of Boc-L-Pro-OSuc (11.50 mmol) in 100 mL of dry DME. The mixture was stirred at room temperature for 24 h and then at 40 °C for 5 h. Solvent was evaporated under vacuum and the resulting white solid was dissolved in 50 mL of dichloromethane and washed with NaHCO\(_3\) (3 x 15 mL). Afterwards the organic layers were dried (Na\(_2\)SO\(_4\)) and the solvent was evaporated under vacuum to yield N-Boc-protected 1a-c as a white solids.

**N-Boc-protected 1a**

Yield 89 %; m.p. 163 °C; IR (KBr) \(\nu = 3303, 2970, 2876, 1702, 1649, 1545 \text{ cm}^{-1}\); \(^1\)H NMR (500 MHz, DMSO-d6): \(\delta = 0.89 (12 \text{ H, br, m})\), 1.34-1.54 (20H, br, m), 1.76-2.12 (10H, br, m), 3.03-3.23 (4H, br, m), 3.30-3.48 (4H, br, m), 4.11 (2H, dd, \(J = 8.7, 7.9 \text{ Hz}\)), 4.20-4.31 (2H, br, m), 7.72 (2H, br, d, \(J = 7.8 \text{ Hz}\)), 7.90-8.08 (2H, br, m) ppm; \(^{13}\)C NMR (300 MHz, DMSO-d6): \(\delta = 19.157, 19.904, 23.657, 28.670, 29.830, 31.295, 31.790, 36.901, 47.224, 58.599, 60.125, 79.099, 154.055, 171.411, 172.868 \text{ ppm}. \text{ESI-MS} (m/z) = 335.3 \left[\text{M + 2H}\right]^{2+}, 667.6 \left[\text{M + H}\right]^{+}, 689.6 \left[\text{M + Na}\right]^{+}, 705.5 \left[\text{M + K}\right]^{+}.

**N-Boc-protected 1b:**

Yield = 83 %; m.p. 173 °C; IR (KBr) \(\nu = 3299, 2968, 2874, 1702, 1647, 1545 \text{ cm}^{-1}\); \(^1\)H NMR (500 MHz, DMSO-d6): \(\delta = 0.89 (12 \text{ H, br, m})\), 1.26-1.52 (26H, br, m), 1.76-2.21 (10H, br, m), 3.02-3.18 (4H, br, m), 3.30-3.47 (4H, br, m), 4.13 (2H, dd, \(J = 8.1, 7.9 \text{ Hz}\)),

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4.20-4.31 (2H, br, m), 7.68 (2H, br, d, J = 8.5 Hz), 7.90-8.03 (2H, br, m) ppm; $^{13}$C NMR (500 MHz, DMSO-d6): $\delta$ = 19.133, 19.912, 23.643, 26.701, 28.655, 29.650, 31.386, 31.813, 38.961, 47.223, 58.484, 60.177, 79.105, 154.067, 171.255, 172.773 ppm; ESI-MS (m/z) = 709.7 [M + H]$^+$, 731.6 [M + Na]$^+$, 747.6 [M + K]$^+$.

N-Boc-protected 1c:

Yield = 85 %; m.p. = 109 °C; IR (KBr) $\nu$ = 3307, 2968, 2872, 1703, 1644, 1543 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d6): $\delta$ = 0.90 (12 H, br, m), 1.25-1.50 (30H, br, m), 1.75-2.20 (10H, br, m), 2.98-3.16 (4H, br, m), 3.29-3.47 (4H, br, m), 4.13 (2H, dd, J = 8.0, 7.8 Hz), 4.22-4.29 (2H, br, m), 7.67 (2H, br, d, J = 7.9 Hz), 7.87-8.05 (2H, br, m) ppm; $^{13}$C NMR (300 MHz, DMSO-d6): $\delta$ = 19.111, 19.897, 23.650, 26.915, 28.663, 29.303, 29.607, 31.379, 31.798, 38.984, 47.232, 58.469, 60.163, 79.106, 154.062, 171.228, 172.761 ppm. ESI-MS (m/z) = 737.6 [M + H]$^+$, 759.6 [M + Na]$^+$, 775.7 [M + K]$^+$.

Synthesis of N-Boc-protected 2:

A solution of amino amide (6.32 mmol) in 100 mL of dry DME was added dropwise over a solution of Boc-L-Pro-OSuc (6.57 mmol) in 100 mL of dry DME. The mixture was stirred at room temperature for 24 h and then at 40 °C for 5 h. Solvent was evaporated under vacuum and the resulting white solid was dissolved in 50 mL of dichloromethane and washed with NaHCO$_3$ (3 x 15 mL). Afterwards the organic layers were dried (Na$_2$SO$_4$) and the solvent was evaporated under vacuum to yield N-Boc-protected 2c as a white solid.

Yield 84 %; m.p. = 104-105 °C; IR (KBr) $\nu$ = 3298, 2966, 2876, 1703, 1647, 1545 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d6): $\delta$ = 0.86 (9 H, m), 1.39 (9H, s), 1.41-1.51 (2H, m), 1.77-2.23 (5H, m), 3.02-3.16 (2H, m), 3.32-3.52 (2H, m), 4.11-4.19 (1H, dd, J = 8.1, 7.9 Hz), 4.21-4.31 (1H, m), 7.69 (1H, br, d, J = 8.6 Hz), 7.91-8.06 (1H, br, m) ppm; $^{13}$C NMR (500 MHz, DMSO-d6): $\delta$ = 12.016, 19.134, 19.927, 22.949, 23.658, 28.647, 31.394, 31.813, 40.877, 47.232, 58.507, 60.201, 79.113, 154.075, 171.309, 172.782 ppm; ESI-MS (m/z) = 356.4 [M + H]$^+$, 378.4 [M + Na]$^+$, 394.4 [M + K]$^+$.

Synthesis of compounds 1a-c and 2:

N-protected compounds (3.00 mmol) were dissolved in dichloromethane and after addition of 15 mL of TFA the mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum and then the resulting crude oil was dissolved in water (50 mL). The solution was treated with NaOH (pH =12), and extracted with
chloroform (3 x 15 mL). The organic layers were washed with water and dried (Na₂SO₄). Solvent was evaporated under vacuum to yield compounds 1a-c and 2 as white solids.

**Compound 1a:**

Yield 84 %, m.p. 170 ºC; IR (KBr) ν = 3289, 2959, 2870, 1638, 1545 cm⁻¹; ¹H NMR (500 MHz, CD₃CN): δ = 0.89 (12 H, dd, J = 19.9, 6.8 Hz), 1.53-1.60 (4H, m), 1.65-1.72 (4H, m), 1.76-1.84 (2H, m), 2.02-2.14 (4H, m), 2.31 (2H, br, s), 2.84-2.88 (2H, m), 3.12-3.20 (4H, m), 3.69 (2H, dd, J = 8.8, 4.8 Hz), 4.06 (2H, dd, J = 8.8, 5.5 Hz), 6.97 (2H, br, s), 8.08 (2H, br, d, 8 Hz) ppm; ¹³C NMR (500 MHz, CD₃CN): δ = 17.171, 19.071, 26.258, 29.264, 30.752, 30.927, 35.986, 47.141, 58.002, 60.916, 171.720, 175.321 ppm; ESI-MS (m/z) = 234 [M+2]²⁺ C₂₃H₄₂N₆O₄.

**Compound 1b:**

Yield 87 %; m.p. = 190 ºC; IR (KBr) ν = 3285, 2956, 2861, 1641, 1541 cm⁻¹; ¹H NMR (500 MHz, CD₃CN): δ = 0.90 (12 H, dd, J = 19.8, 7 Hz), 1.28-1.34 (4H, m), 1.42-1.49 (4H, m), 1.64-1.71 (4H, m), 1.77-1.84 (2H, m), 2.02-2.10 (4H, m), 2.22 (2H, br, s), 2.82-2.87 (2H, m), 3.00-3.04 (2H, m), 3.12-3.18 (4H, m) 3.65 (2H, dd, J = 4.5, 9.4 Hz), 4.09 (2H, dd, J = 4.5, 9.4 Hz), 6.77 (2H, br, s), 8.08 (2H, br, d, J = 6.70 Hz) ppm; ¹³C NMR (500 MHz, CD₃CN): δ = 17.333, 19.047, 22.706, 26.061, 26.298, 29.219, 30.875, 31.348, 38.672, 47.209, 57.867, 60.903, 171.289, 175.149 ppm; ESI-MS (m/z) = 256 [M+2]²⁺.

**Compound 1c:**

Yield 79 %; m.p. 177 ºC; IR (KBr) ν = 3289, 2957, 2854, 1640, 1540 cm⁻¹; ¹H NMR (500 MHz, CD₃CN): δ = 0.90 (12 H, dd, J = 19.4, 6.9 Hz), 1.25-1.36 (8H, m), 1.40-1.50 (4H, m), 1.65-1.72 (4H, m), 1.78-1.85 (2H, m), 2.03-2.10 (4H, m), 2.29 (2H, br, s), 2.83-2.88 (2H, m), 3.00-3.04 (2H, m), 3.12-3.19 (4H, m) 3.67 (2H, dd, J = 4.6, 9.3 Hz), 4.01 (2H, dd, J = 9.0, 6.2 Hz), 6.77 (2H, br, s), 8.08 (2H, br, d, J = 9.04 Hz) ppm; ¹³C NMR (500 MHz, CD₃CN): δ = 17.289, 19.087, 22.706, 26.291, 26.467, 28.839, 29.289, 30.836, 31.410, 38.955, 47.217, 57.791, 60.896, 171.188, 175.102 ppm; ESI-MS (m/z) = 269 [M+2]²⁺.
Compound 2:

Yield = 79%; m.p. = 127 °C; IR (KBr) ν = 3303, 2963, 2873, 1467, 1518 cm⁻¹; ¹H NMR (500 MHz, CD₃CN): δ = 0.86-0.92 (9 H, m), 1.45-1.52 (2 H, m), 1.66-1.71 (2 H, m), 1.78-1.84 (1 H, m), 2.02-2.10 (2H, m), 2.39 (1H, br, s), 2.83-2.87 (1H, m), 3.00-3.05 (1H, m), 3.07-3.19 (2H, m), 3.67 (1H, dd, J = 9.2, 5Hz), 4.11 (1 H, dd, J =8.9, 6.1 Hz), 6.70 (1H, br, s), 8.07 (1H, br, d, J = 6.70 Hz) ppm; ¹³C NMR (500 MHz, CD₃CN): δ = 10.971, 173.323, 19.032, 22.706, 26.288, 30.878, 31.484, 40.838, 47.205, 57.757, 60.878, 171.231, 175.089 ppm; ESI-MS (m/z) = 256 [M+H]⁺, 278 [M+Na]⁺.
Gelation studies.

Typically, the desired amount of the gelator in the corresponding solvent was heated in a screw-capped vial until it was completely dissolved and, afterwards, it was left to cool by two different methods:

**Spontaneous cooling:**
The sample was cooled at room temperature during 24 h and afterwards it was stabilized at r.t. during 12 h.

**Slow cooling:**
The sample was cooled in a thermoregulated bath (0.5 °C / min) and stabilized at r.t. during 12 h.

To determine the minimum gel concentration values reported, 5-20 mmol of the studied compounds were dissolved in 1 mL of hot solvent in a screw-capped cylindrical glass vial (diameter = 2 cm). The formation of a gel was checked by turning the vial upside down. Thus, when, upon vial inversion, all the solvent remains entrapped within the gel and does not fall-down we consider it as a gel (G).

Table S1. Gelation of compounds 1a-c in different organic solvents after spontaneous cooling at 25 °C.a

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a. G: gel; S: soluble. Minimum gel concentration (mM) in parentheses.
**Scanning Electron Microscopy.** Scanning electron micrographs were taken in a LEO 440I microscope equipped with a digital camera. Samples of the xerogels were prepared by placing the gel on top of a tin plate and, after vacuum drying of the solvent, sputtering with Au/Pd in a Polaron SC7610 Sputter Coater from Fisons Instruments.

**NMR.** $^1$H and $^{13}$C NMR spectra were recorded in a Varian Mercury 300 MHz spectrometer at 30 °C. NOE (1D-NOESY and NOESY) measurements were carried out in a Varian Inova 500 MHz spectrometer. Gel samples were prepared by transferring a hot solution of the gelator in CD$_3$CN to the NMR tube. Upon cooling to room temperature a gel was formed and the sample obtained was analyzed using the same parameters as for solution NMR (except in the case of NOE experiments where the mixing time for gel samples was 20 ms -to avoid spin diffusion- and for solutions 500 ms).

**Molecular modeling.** The models reported were obtained by molecular mechanics calculations performed with MACROMODEL 8.0 using AMBER* as force-field and a GB/SA simulation of chloroform as solvent. The structures of the isolated molecules correspond to minimum energy conformers found after exhaustive Monte Carlo conformational search. The models for the aggregates were energetically minimizied.

**X-ray powder diffraction.** Data collection was performed at room temperature on a Siemens D5000 diffractometer using Cu-K$_\alpha$ radiation. Samples of the powdered solids were placed on a quartz sample holder and data were collected for $2\theta$ values between 3° and 35° with a step size of 0.05° and a time step of 20 s.

**CD spectroscopy.** CD spectra were recorded in a Jasco J-810 spectropolarimeter equipped with a Peltier heating device. The samples were prepared in quartz cuvettes of 1 mm and 0.5 mm of path length.
N-Boc-protected 1a.

$^1$H NMR
500 MHz, DMSO-d$_6$
0.04 M

$^{13}$C NMR
500 MHz, DMSO-d$_6$
0.04 M
N-Boc-protected 1b.

$^1$H NMR
500 MHz, DMSO-d$_6$
0.04 M

$^{13}$C NMR
500 MHz, DMSO-d$_6$
0.04 M
N-Boc-protected 1c.

$^1$H NMR
500 MHz, DMSO-d6
0.04 M

$^{13}$C NMR
500 MHz, DMSO-d6
0.04 M
N-Boc-protected 2.

$^1$H NMR
500 MHz, DMSO-d$_6$
0.08 M

$^{13}$C NMR
500 MHz, DMSO-d$_6$
0.08 M
Compound 1a:

1H NMR
500 MHz, CD$_3$CN
0.01 M

13C NMR
500 MHz, CD$_3$CN
0.01 M
Compound 1b:

$^1$H NMR
500 MHz, CD$_3$CN
0.02 M

$^{13}$C NMR
500 MHz, CD$_3$CN
0.02 M
Compound 1c:

$^1$H NMR
500 MHz, CD$_3$CN
0.02 M

$^{13}$C NMR
500 MHz, CD$_3$CN
0.02 M
Compound 1d:

$^1$H NMR
500 MHz, CD$_3$CN
0.16 M

$^{13}$C NMR
500 MHz, CD$_3$CN
0.16 M
1H-RMN
CD$_3$CN

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$^{13}$C-RMN CD$_3$CN

![Chemical Structure](image)

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Figure S1. SEM images of xerogels of compound 1b: A) CH$_3$CN, spontaneous cooling; B) *idem*, slow cooling; C) toluene, spontaneous cooling.
Figure S2. SEM images of xerogels and crystalline precipitates of compound 1c: A) CH$_2$CN, spontaneous cooling; B,C) *idem*, slow cooling; D) EtOAc, spontaneous cooling.
Figure S3. $\Delta\delta$ vs concentration for the amide signals a and b of compounds 1a-c and 2 (CD$_3$CN, 30 °C)
Figure S4. $\Delta \delta$ vs temperature for the amide signals a and b of compounds 1a-c and 2 (CD$_3$CN, 30 ºC)
Figure S5. Informative NOE contacts for non-aggregated solutions of compounds 1a (CD₃CN, 30 ºC)

Figure S6. Transfer-NOE contacts for gels of compounds 1a (CD₃CN, 30 ºC). Arrows indicate variations from diluted solution.
Figure S7. NOE spectra for a non-aggregated solution (top) and a gel (bottom) of compound 1a (CD$_3$CN, 30 ºC).
Figure S8. Informative NOE contacts for non-aggregated solutions of compounds 1b - c (CD$_3$CN, 30 °C)

Figure S9. Changes in-NOE contacts for gels of compounds 1b-c (CD$_3$CN, 30 °C)
Figure S10. WAXD patterns of xerogels of compound 1a.

Figure S11. WAXD patterns of compound 1b.
Figure S12. WAXD patterns of compound 1c.
Figure S13. Molecular models for compounds 1b and 1c in solution (A) and in aggregates (B). (Macromodel 9, AMBER*, CHCl₃)