Electronic Supplementary Material (ESI) for Soft Matter.

Supplementary Information

Tuning morphological architectures generated through living supramolecular assembly of a helical foldamer end-capped with two complementary nucleobases

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General procedures

Nuclear Magnetic Resonance

1H and 13C NMR spectra were recorded at room temperature on a Bruker AC-200 (200 MHz) and a Bruker Avance III 400 spectrometer (400.13 MHz ^{1}H frequency and 100.62 MHz ^{13}C frequency) instrument using TMS (tetramethylsilane) as the internal reference. The multiplicity of a signal is indicated as s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad. Chemical shifts (δ) are expressed in ppm.

FT-IR absorption

FT-IR absorption spectra were recorded with a Perkin-Elmer 1720X spectrophotometer.

Mass Spectrometry

ESI-MS experiments were performed using an ESI-ToF MarinerTM BiospectrometryTM Workstation of Applied Biosystems by flow injection analysis using MeOH as the mobile phase. Mass spectra were obtained by electrospray ionization on a Perseptive Biosystem Mariner ESI-ToF spectrometer (Foster City, CA). An 1 x 10^{-9} M solution of neurotensin, angiotensin I, and bradykinin in an 1:1 CH_3CN/H_2O mixture, containing 1% formic acid, was used for calibration.

Electronic Circular Dichroism.

ECD measurements were carried out at room temperature, or at controlled temperature using a Jasco J-715 spectropolarimeter equipped with a thermostat. A fused quartz cell of 1-mm path length (Hellma) was used.

Transmission Electron Microscopy

Samples were analyzed on a Jeol 300 PX TEM instrument. A glow discharged carbon coated grid was floated on a small drop of the nanosphere suspension and excess was removed by #50 hardened hatman filter paper.

Scanning Electron Microscopy

A Carl Zeiss Merlin field emission scanning electron microscope operating at 5kV accelerating voltage was used. A small drop of the milk-like aqueous suspension was placed on a microscope glass cover slip and allowed to dry overnight.

Atomic Force Microscopy

AFM experiments were performed on Ntegra Aura (NT-MDT) instrument operating in tapping mode at 200−400 kHz drive frequency and using a single crystal silicon tip coated with TiN (NSG01/TiN, 0.01-0.025 Ω-cm, antimony dope).

Syntheses and characterizations

Materials

1-Hydroxy-7-aza-1,2,3-benzotriazole (HOAt) was purchased from GL Biochem (Shanghai) Ltd. N-(3-dimethylaminopropyl)-N′- ethylcarbodiimide hydrochloride (EDC·HCl) was obtained from Iris Biotech (Germany). Trifluoroacetic acid, N,N'-diisopropylcarbodiimide (DIC), 4-(dimethylamino)-pyridine (DMAP), di-tert-butyl dicarbonate (Boc_2O), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine (TEA), bromoacetic acid and ethyl bromoacetate were obtained from Sigma-Aldrich. The deuterated solvent dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ were purchased from Euriso-Top (France). All other chemicals and solvents are Sigma-Aldrich, Fluka or Acros products and used as provided without further purifications.

Synthesis of thymine-1-acetic acid[1]

Thymine (4.0 g, 31.7 mmol) was dissolved in a solution of KOH (6.82 g, 121 mmol) in 20 ml of water. The solution was warmed at 40°C and a solution of bromoacetic acid (6.25 g, 45 mmol) dissolved in 10 ml of water was added in 30 minutes. The reaction was stirred for another 30 minutes at this temperature. The solution was cooled at room temperature and the pH was adjusted to 5.5 with conc. HCl. The reaction was cooled for 2 h in the refrigerator. After filtration of the precipitate formed, the solution was adjusted to pH 2 with conc. HCl and it was put in the freezer for 2 h. The product was filtrated, washed with water and dried (4.7 g, 85% yield). White solid.

Melting point: 252-255°C

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.75 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 7.49 (s, 1H, CH), 11.35 (s, 1H, NH), 13.18 (s, 1H, OH).

MS (ESI-TOF): [M] calc. = 184.1494 m/z; $[M+H]^+$ found = 185.0567 m/z; [2M] calc. = 368.2988 m/z; $[2M+H]^+$ found = 369.1056 m/z.

IR (KBr): 3178, 3073, 3026, 2962, 1739, 1706, 1664, 1633 cm^{-1}.

Synthesis of ethyl adenine-9-acetate[1]

Adenine (4.0 g, 30 mmol) was suspended in dry DMF (60 ml) and NaH (0.82, 34 mmol, washed with petroleum ether) was added. The reaction was stirred for 2 h at room temperature. After this time, ethyl bromoacetate (6.64 ml, 60 mmol) was added dropwise in 3 h and the solution was stirred for another 3 h. The solvent was removed by evaporation in vacuo. The remaining oil was shaken with water and the resulting white precipitate was isolated by filtration, washed with water and dried (3.7 g, 56% yield).

Melting point: 227-229°C

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.21 (t, 3H, CH_3, J=7Hz), 4.16 (q, 2H, CH_2, J=7Hz), 5.06 (s, 2H, CH_2), 7.25 (s, 2H, NH_2), 8.11-8.13 (2H, CH).

MS (ESI-TOF): [M] calc. = 221.2159 m/z; $[M+H]^+$ found = 222.2057 m/z.

IR (KBr): 3103, 2924, 1741, 1671, 1604, 1582 cm^{-1}.

Synthesis of adenine-9-monoacetyl-ethylendiamino amide[1]

Adenine-9-acetate (0.30 g, 1.35 mmol) was dissolved in ethylenediamine (10 ml, 149 mmol) and DBU was added as catalyst. The reaction was stirred for 2 h at 50°C, then it was allowed to cool the solution at room temperature. The product was precipitated by adding ethyl ether, filtered, washed with ethyl ether and dried (0.278 g, 87% yield).

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 2.59 (m, 3H), 3.08 (m, 3H), 4.83 (s, 2H, CH_2), 7.20 (s, 2H, NH_2), 8.06 (s, 1H, CH), 8.11 (s, 1H, CH),8.26 (s, 1H, NH).

MS (ESI-TOF): [M] calc. = 235.2458 m/z; $[M+H]^+$ found = 236.1578 m/z.

IR (KBr): 3356, 3265, 3098, 1669, 1602 cm^{-1}.

Synthesis of thymine-(aminophenyl) porphyrin[1] (3)

Thymine-1-acetic acid (0.10 g, 0.54 mmol) was dissolved in dry DMF and activated with HOAt (0.073 g, 0.54 mmol) and EDC·HCl (0.104 g, 0.54 mmol) and the solution was stirred for 30 minutes. 5-(4-aminophenyl)-10,15,20-triphenyl porphyrin (0.07 g, 0.11 mmol) was added at the solution and the pH was adjusted to basicity with TEA (100 µl). The reaction was stirred for another 3 h, then water was added to the solution. The resulting precipitate was isolated by mean of a spin-dryer and dried (0.08 g, 90% yield).

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.22 (s, 2H, NH pyrrole), 1.84 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.64 – 8.83 (27H, porphyrinic ring), 10.74 (s, 1H, NH), 11.41 (s, 1H, NH).

MS (ESI-TOF): [M] calc. = 795.8844 m/z; $[M+H]^+$ found = 796.3231 m/z.

IR (KBr): 3314, 1702, 1675 cm^{-1}.

Synthesis of Z-$(Aib)_2$-OCH_3[2]

Z-Aib-OH (3.67 g, 17.5 mmol) was dissolved in dry DCM and activated with HOBt (2.36 g, 17.5 mmol) and EDC·HCl (3.36 g, 17.5 mmol) and the solution was stirred for 20 minutes. In the meanwhile, H-Aib-OCH_3 (5.13 g, 43.8 mmol) was dissolved in dry DCM, the pH was adjusted to basicity with TEA and it was added at the solution of the active ester. The reaction was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with $KHSO_4$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated. The product was precipitate from ethyl acetate and petroleum ether.

^1H NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 1.53 (s, 12H, CH_3 Aib), 3.73 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 5.30 (s, 1H, NH), 6.91 (s, 1H, NH), 7.36 (s, 5H, CH).

^{13}C NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 26.03, 26.24, 53.71, 56.32, 57.85, 67.23, 128.05, 128.95, 129.40, 137.84, 156.87, 175.54, 175.89.

MS (ESI-TOF): [M] calc. = 336.3828 m/z; $[M+H]^+$ found = 337.2547 m/z.

IR (KBr): 3381, 3364, 3318, 3279, 2986, 1727, 1657, 1522 cm^{-1}.

Synthesis of Z-$(Aib)_2$-OH[3]

Z-$(Aib)_2$-OCH_3 (0.30 g, 0.89 mmol) was dissolved in dry THF, then LiOH liquefied in water (0.06 g, 2.67 mmol) was added and the solution was stirred for 2 hours at 40°C. After evaporation of the organic solvent, pH was adjust to 4 with solid $KHSO_4$. The product was extracted with ethyl acetate, then the organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was precipitate from ethyl acetate and petroleum ether.

^1H NMR: (200 MHz, $CDCl_3$, Me_4Si): δ 1.52 (s, 12H, CH_3 Aib), 5.13 (s, 2H, CH_2), 5.24 (s, 1H, NH), 6.91 (s, 1H, NH), 7.37 (s, 5H, CH).

^{13}C NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 25.45, 26.12, 56.53, 57.92, 67.31, 128.11, 129.02, 129.71, 137.96, 157.01, 175.68, 175.91.

MS (ESI-TOF): [M] calc. = 322.3563 m/z; $[M+H]^+$ found = 323.4652 m/z.

IR (KBr): 3430, 3299, 2989, 1722, 1704, 1653, 1534, 1510 cm^{-1}.

Synthesis of Z-$(Aib)_2$-diaminocyclohexane

Z-$(Aib)_2$-OH (0.5 g, 1.55 mmol) was dissolved in dry CH_3CN and activated with HOAt (0.21 g, 1.55 mmol) and EDC·HCl (0.29 g, 1.55 mmol) and the solution was stirred for 20 minutes. *trans*-1,4-diaminocyclohexane was dissolved in dry CH_3CN and added at the solution. TEA was used to basify to pH 8. The reaction was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with $KHSO_4$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated. The product was precipitate from ethyl acetate and petroleum ether and directly used for the next synthetic step, after mass characterization.

MS (ESI-TOF): [M] calc. = 418.5297 m/z; $[M+H]^+$ found = 419.6421 m/z.

Synthesis of peptide foldamer 4

Thymine-1-acetic acid (0.06 g, 0.32 mmol) was dissolved in dry DCM and activated with HOBt (0.044 g, 0.32 mmol) and EDC·HCl (0.062 g, 0.32 mmol) and the solution was stirred for 30 minutes. Z-$(Aib)_2$-diaminocyclohexane (0.14 g, 0.32 mmol) was added at the solution of the active ester and DIPEA was used to basify to pH 8. The reaction was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with $KHSO_4$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated. The product was precipitate from ethyl acetate and petroleum ether.

^1H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.28 (s, 12H, CH_3 Aib), 1.74 (s, 5H, CH_2), 2.07 (s, 1H), 4.22 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 7.06 (d, 1H, NH, J=6Hz), 7.34 (s, 5H, CH), 7.52 (s, 1H, NH), 7.61 (s, 1H, NH), 8.03 (d, 1H, NH, J=5Hz), 11.25 (s, 1H, NH).

^{13}C NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 12.23, 26.14, 30.97, 49.57, 50.15, 51.23, 56.55, 57.16, 66.82, 107.23, 128.42, 128.51, 128.67, 137.25, 141.89, 152.31, 156.37, 164.91, 170.43, 175.39, 175.73.

MS (ESI-TOF): [M] calc. = 584.6639 m/z; $[M+H]^+$ found = 585.2979 m/z; [2M] calc. = 1168.3278 m/z; $[2M+H]^+$ found = 1169.5801.

Synthesis of adenine-capped gold nanoparticles (5)

Adenine-capped gold nanoparticles were synthetized as described in the cited reference.[1] Concisely, the synthesis of A-capped gold nanoparticles initially proceeds *via* the coupling reaction between lipoic acid and adenine-9- ethylenamide amine to form the adenine ligand. Later, ligand (0.105 g, 0.35 mmol) was dissolved in THF (5 ml) and cooled with an ice/water bath. Separately, tetrachloroauric acid (0.069 g, 0.177 mmol) was dissolved in THF (5 ml), cooled and added dropwise to the solution of ligand. The reaction was stirred overnight to allow the complexation. $NaBH_4$ (0.07 g, 17 mmol) dissolved in water

(2 ml) and cooled was added quickly and the solution. After 48 h of aging, the gold nanoparticles were recovered by filtration, washed with CH_3OH and dried.

Synthesis of Boc-$(Aib)_2$-OBzl[4]

Boc-Aib-OH (0.50 g, 2.5 mmol) was dissolved in dry DCM and activated with HOAt (0.34 g, 2.5 mmol) and EDC·HCl (0.47 g, 2.5 mmol) and the solution was stirred for 30 minutes. H-Aib-OBzl (0.57 g, 3 mmol) was added at the solution of the active ester and DIPEA was used to basify to pH 8. The reaction was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with $KHSO_4$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated. The product was precipitate from ethyl acetate and petroleum ether.

^{1}H NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 1.44 (s, 15H, CH_3), 1.57 (s, 6H, CH_3), 4.87 (s, 1H, NH), 5.17 (s, 2H, CH_2), 7.14 (s, 1H, NH), 7.31-7.35 (5H, benzyl ring).

^{13}C NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 26.15, 26.38, 28.73, 56.17, 56.27, 67.35, 80.91, 128.39, 128.49, 128.65, 137.21, 155.61, 175.31, 175.44.

MS (ESI-TOF): [M] calc. = 378.4626 m/z; $[M+H]^+$ found = 379.2315 m/z.

Synthesis of thymine-$(Aib)_2$-OBzl

Boc-$(Aib)_2$-OBzl (0.90 g, 2.4 mmol) was treated with a solution 1:1 dichloromethane/trifluoroacetic acid to remove the *tert*-butyloxycarbonyl protecting group. After evaporation of the solvent, the product was mixed with the active ester of thymine-1-acetic acid (0.50 g, 2.7 mmol) prepared with HOAt (0.37 g, 2.7 mmol) and EDC·HCl (0.52 g, 2.7 mmol), and TEA was added to basify the solution. The reaction was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with $KHSO_4$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated.

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.30 (s, 6H, CH_3), 1.34 (s, 6H, CH_3),1.75 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 7.32-7.35 (5H, benzyl ring), 7.39 (s, 1H, NH), 7.44 (s, 1H, CH), 8.27 (s, 1H, NH), 11.34 (s, 1H, NH).

^{13}C NMR: (400 MHz, $CDCl_3$, Me_4Si): δ 12.25, 26.17, 26.23, 50.13, 56.45, 56.93, 67.37, 107.29, 128.36, 128.51, 128.63, 137.19, 141.79, 152.27, 164.89, 170.35, 175.03, 175.37.

MS (ESI-TOF): [M] calc. = 444.4809 m/z; $[M+H]^+$ found = 445.2761 m/z.

Synthesis of thymine-$(Aib)_2$-OH

Thymine-$(Aib)_2$-OBzl (0.85 g, 1.9 mmol) was dissolved in 10 ml of ethanol. Subsequently, Pd-C 10% and 5 ml of cyclohexene were added under nitrogen. The solution was stirred at 80°C until the reaction finished (seen by thin layer chromatography), then filtered on celite and washed with ethanol, acetonitrile and diethyl ether. The resultant solution was dried *under vacuum* providing the desired compound.

^{1}H NMR: (400 MHz, DMSO-d_6, Me_4Si): δ 1.30 (s, 6H, CH_3), 1.34 (s, 6H, CH_3),1.74 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.44 (s, 1H, CH), 8.35 (s, 1H, NH), 11.35 (s, 1H, NH), 12.06 (br, 1H, OH).

^{13}C NMR: (200 MHz, $CDCl_3$, Me_4Si): δ 12.21, 24.41, 26.03, 50.11, 56.93, 57.12, 107.14, 141.93, 152.25, 164.97, 170.41, 175.32, 179.23.

MS (ESI-TOF): [M] calc. = 354.3583 m/z; $[M+H]^+$ found = 355.6247 m/z.

Synthesis of 1

Thymine-$(Aib)_2$-OH (0.3 g, 0.85 mmol) was dissolved in acetic anhydride (20 ml, 211 mmol) and the solution was stirred for 1 hour at 130°C. The solvent was removed *under vacuum* and the oxazolone is added at adenine-9-monoacetyl-ethylendiamino amide (0.21 g, 0.9 mmol) dissolved in anhydrous DMF. The reaction was stirred overnight. After evaporation of the solvent, the crude product was purified by flash chromatography.

For ^{1}H NMR details and ^{1}H and ^{13}C resonances assignment see the **NMR analysis.**

MS (ESI-TOF): [M] calc. = 571.2615 m/z; $[M+H]^+$ found = 572.2906 m/z.

Synthesis of 2

Peptide foldamer **2** was synthesized using standard solid phase 9-fluorenylmethoxycarbonyl (Fmoc) chemistry on a 2-chlorotrityl chloride resin. For each step, Fmoc deprotection was performed by mixing the resin in a piperidine/N,N-dimethylformamide (DMF) (2:8, *v/v*) solution for 10 minutes (2x), then washing with DMF, MeOH and CH_2Cl_2. For all of the amino acid couplings we used the following protocol: 5.0 eq. (relative to the resin loading) of Fmoc-protected amino acid were activated externally with 4.9 eq. of O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and 15 eq. of diisopropylethylamine (DIPEA) in DMF (2.5 ml/mmol of amino acid). This mixture was then added to a peptide chamber containing the resin and mixed for 3 hours. The resin was then drained and rinsed with MeOH, and CH_2Cl_2, then allowed to dry. All coupling and deprotection

steps were monitored by performing a Kaiser test on a few resin beads, which were removed from the peptide chamber after drying. As a last coupling, thymine-1-acetic acid (5.0 eq.) was used instead of amino acid residue. The resin was prepared for cleavage by washing with CH_2Cl_2 and MeOH then drying under high vacuum. Cleavage from the resin was accomplished by stirring the resin with 10 ml of TFA, water and TIPS (95:2.5:2.5) for 3 hours. The resin was removed by filtration and washed with 3 ml of the cleavage mixture. The filtrate volume was reduced by evaporation under reduced pressure and the peptide was precipitated by the addition of 200 ml cold diethyl ether. The precipitate was filtered and rinsed with cold diethyl ether to obtain the crude peptide. The product was then activated with DIC (0.126 g, 1 mmol) in DMF for 15 minutes, then adenine-9-monoacetyl-ethylendiamino amide (0.47 g, 2 mmol) was added to the mixture. The reaction was stirred at 40°C overnight, then the solvent was evaporated *under vacuum*. The crude product was washed with water, which was evaporated. The product was purified by flash chromatography. For ^{1}H NMR details and ^{1}H and ^{13}C resonances assignment see the **NMR analysis.** MS (ESI-TOF): [M] calc. = 1026.3091 m/z; $[M+H]^+$ found = 1027.5155 m/z.

NMR analysis

NMR experiments were performed at 298 K on a Bruker Avance III 400 spectrometer (400.13 MHz ^{1}H frequency and 100.62 MHz ^{13}C frequency) equipped with a 5 mm multinuclear inverse z-field gradient probe-head. For data processing the Topspin 3.5 software was used.

Foldamer 1 (3 mg) was dissolved in 1 ml of DMSO-d_6 for NMR characterization. The ^{1}H and ^{13}C chemical shifts were reported in ppm and referenced to the ^{1}H residual solvent signal and ^{13}C solvent signal: resonances assignment was obtained using 2D heteronuclear correlation spectroscopy (^{1}H-^{13}C HMQC and HMBC experiments).

^{1}H one-dimensional spectrum was recorded with 8 transients, 14 ppm spectral width, and 32k data points. Exponential multiplication with line broadening of 0.2 Hz was applied prior to Fourier Transform.

The ^{1}H-^{13}C Heteronuclear Multiple Quantum Correlation (HMQC) and the ^{1}H-^{13}C Heteronuclear Multiple-Bond Correlation (HMBC) spectra were acquired with 16 and 200 scans respectively, accumulated for 128 and 180 experiments, and processed with a magnitude calculation; the spectral width was 14 ppm in F2, 180 or 210 ppm in F1. 3.4 ms and 66.7 ms evolution delay were used, respectively for ^{1}H-^{13}C one-bond and ^{1}H-^{13}C long-range coupling constants selection. Zero-filling in

both F1 and F2 dimensions, multiplication with a Gaussian function (in F2) and a squared sine function (in F1) were performed prior to 2D Fourier Transform.

Foldamer 2 (7 mg) was dissolved in 1 ml of H_2O/D_2O solution (10:1) for NMR characterization.
The ^{1}H and ^{13}C chemical shifts were reported in ppm and referenced to DSS: the resonances assignments were obtained using 2D homonuclear (TOCSY and ROESY) experiments and 2D heteronuclear correlation spectroscopy (^{1}H-^{13}C HMQC and HMBC experiments).
^{1}H one-dimensional spectrum was acquired with the 1D gradient NOESY-presat sequence using an inversion recovery delay of 15 ms, accumulating 32 transients of 32k data points and 10 ppm spectral width. Exponential multiplication with line broadening of 0.2 Hz was applied prior to Fourier Transform.
The TOtal Correlation SpectroscopY (TOCSY) spectrum was acquired with WATERGATE sequence for water signal suppression, with a spectral width of 10 ppm. A total of 512 experiments with 16 scans each one were acquired in TPPI mode. The mixing time was 70 ms and the relaxation delay 1.2 s. The Rotating frame nuclear Overhouser Effect SpectroscopY (ROESY) spectrum was acquired with WATERGATE sequence for water signal suppression, with a spectral width of 10 ppm. A total of 512 experiments with 64 scans each one were acquired in TPPI mode. The mixing time was 150 ms and the relaxation delay 1.4 s. The TOCSY and ROESY data were processed with a Gaussian function (in F2) and a squared sine function (in F1) multiplication prior to 2D Fourier Transform, and zero-filling in both F1 and F2 dimensions.
The ^{1}H-^{13}C Heteronuclear Multiple Quantum Correlation (HMQC) and the ^{1}H-^{13}C Heteronuclear Multiple-Bond Correlation (HMBC) spectra were acquired with 128 and 400 scans respectively, accumulated for 128 and 180 experiments, and processed with a magnitude calculation; the spectral width was 10 ppm in F2, 180 and 200 ppm in F1. 3.4 ms and 66.7 ms evolution delay were used, respectively for ^{1}H-^{13}C one-bond and ^{1}H-^{13}C long-range coupling constants selection. Zero-filling in both F1 and F2 dimensions, multiplication with a Gaussian function (in F2) and a squared sine function (in F1) were performed prior to 2D Fourier Transform.

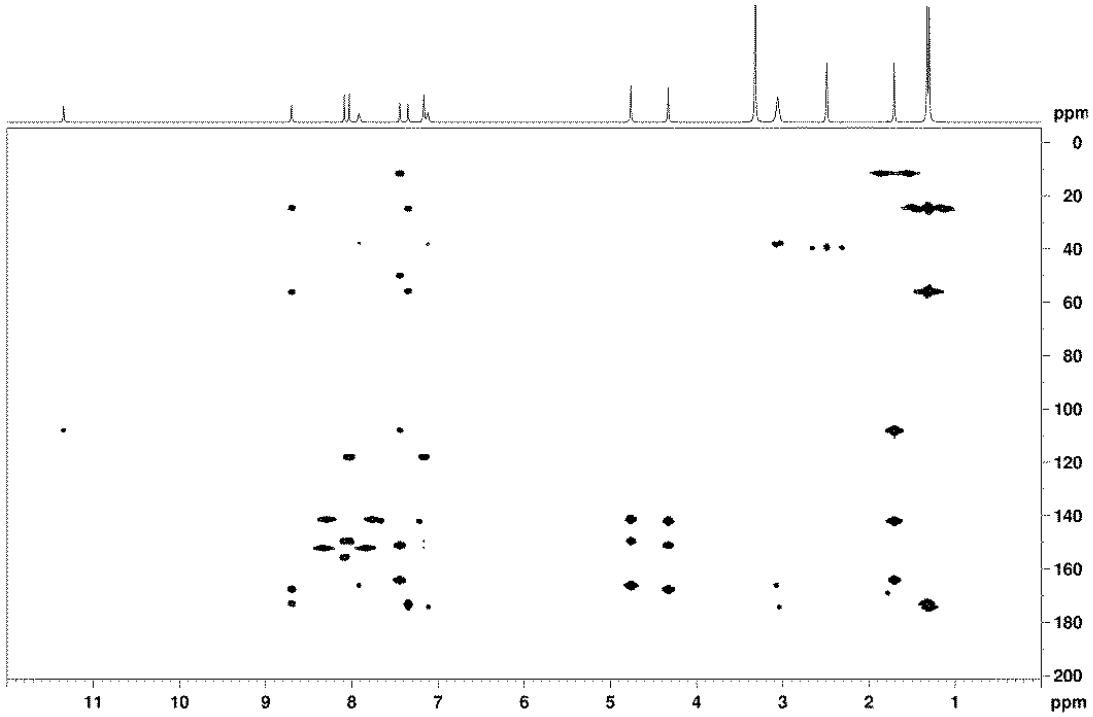

Figure S1: ^{1}H-^{13}C HMBC spectrum of Foldamer **1** in DMSO-d_6.

Thymine	**2**	**3**	**4**	**5**	**6**	**CH_3**
^1H		11.35			7.44	1.71
^{13}C	151.2		164.2	108.0	142.0	11.6
carboxymethylene	**7**	**8**				
^1H	4.33					
^{13}C	49.8	167.75				
Aib 1	**9**	**10**	**11**			**CH_3**
^1H	8.70					1.33
^{13}C		56.3	173.0			24.7*
Aib 2	**12**	**13**	**14**			**CH_3**
^1H	7.35					1.30
^{13}C		55.8	174.4			24.7*
ethylendiamine	**15**	**16**	**17**	**18**		
^1H	7.12	3.06*	3.06*	7.92		
^{13}C		38.3	38.0			
carboxymethylene	**19**	**20**				
^1H		4.76				
^{13}C	166.25	44.7				
Adenine	**22**	**24**	**26**	**27**	**29**	**NH_2**
^1H		8.09			8.03	7.16
^{13}C	149.6	152.1	155.7	118.1	141.5	

Table S1: ^1H and ^{13}C resonances assignment of Foldamer **1** in DMSO-d_6.

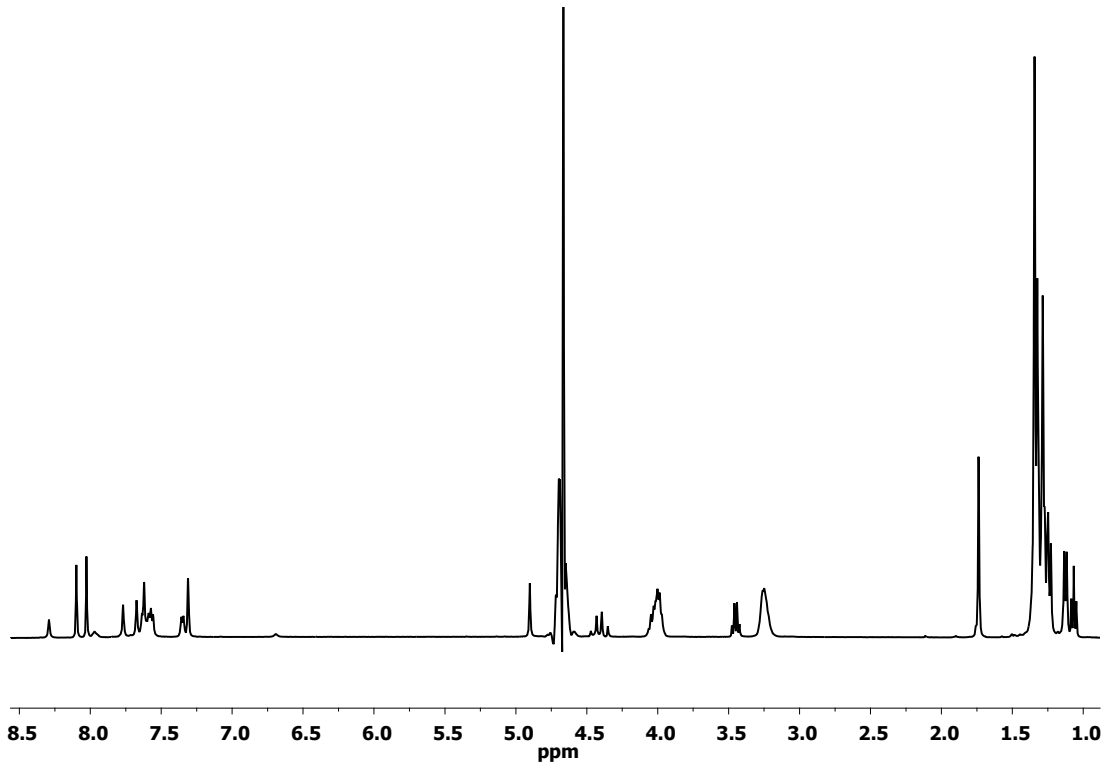

Figure S2: ^{1}H one-dimensional spectrum of Foldamer 2 in H_2O/D_2O 10:1 solution.

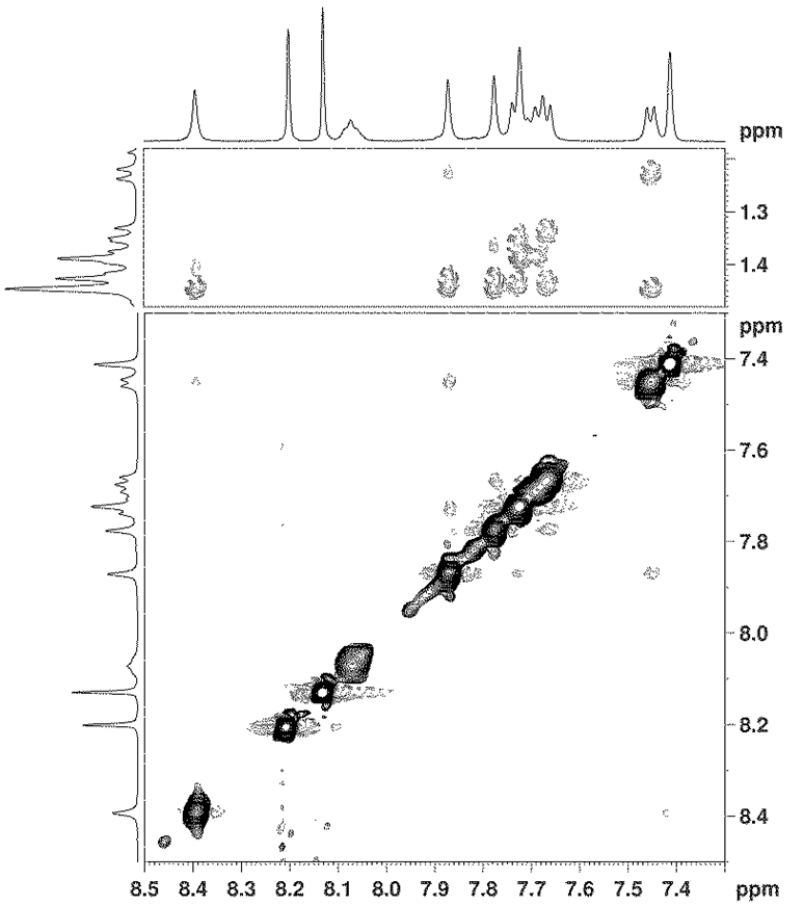

Figure S3: Two sections of the ROESY spectrum of Foldamer **2** in H_2O/D_2O 10:1 solution. NH to NH and NH to CH_3 ROESY connectivities allows the sequential assignment of Aib and Ala residues.

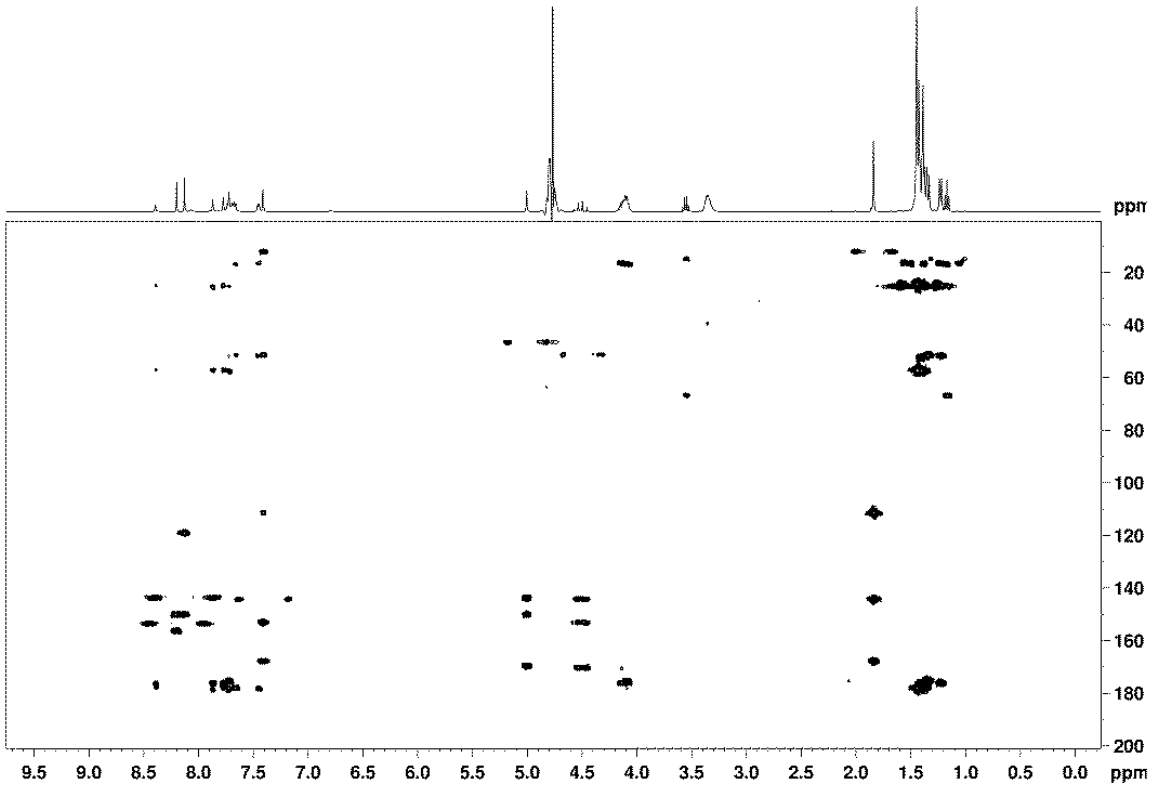

Figure S4: ^{1}H-^{13}C HMBC spectrum of Foldamer **2** in H_2O/D_2O 10:1 solution.

Thymine	**2**	**3**	**4**	**5**	**6**	**CH_3**
^{1}H		nd			7.41	1.84
^{13}C	153.1		167.8	111.4	144.3	12.1
carboxymethylene	**7**	**8**				
^{1}H	4.56-4.47					
^{13}C	51.4	170.4				
Ala 1	**9**	**10**	**11**			**CH_3**
^{1}H	8.75	4.14				1.41
^{13}C		52.3	176.5			16.2*
Aib 2	**12**	**13**	**14**			**CH_3**
^{1}H	8.39					1.45
^{13}C		57.2	178.3			25.0
Ala 3	**15**	**16**	**17**			**CH_3**
^{1}H	7.45	4.10				1.23
^{13}C		51.8	176.1			16.6
Aib 4	**18**	**19**	**20**			**CH_3**
^{1}H	7.87					1.43
^{13}C		57.3	178.5			25.5
Ala 5	**21**	**22**	**23**			**CH_3**
^{1}H	7.73	4.08				1.36
^{13}C		51.9	176.4			16.7*
Aib 6	**24**	**25**	**26**			**CH_3**
^{1}H	7.78					1.45
^{13}C		57.2	177.9			25.1
Ala 7	**27**	**28**	**29**			**CH_3**
^{1}H	7.67	4.11				1.34
^{13}C		51.5	175.5			16.7*
Aib 8	**30**	**31**	**32**			**CH_3**
^{1}H	7.72					1.39
^{13}C		57.6	178.2			25.3
ethylendiamine	**33**	**34**	**35**	**36**		

^{1}H	7.69	3.35*	3.35*	8.07		
^{13}C		39.8*	39.8*			
carboxymethylene	**37**	**38**				
^{1}H		5.00				
^{13}C	169.6	46.5				
Adenine	**40**	**42**	**44**	**45**	**47**	**NH_2**
^{1}H		8.2			8.13	6.79
^{13}C	150.1	153.5	156.4	119.2	143.6	

Table S2: ^{1}H and ^{13}C resonances assignment of Foldamer **2** in H_2O/D_2O 10:1 solution.

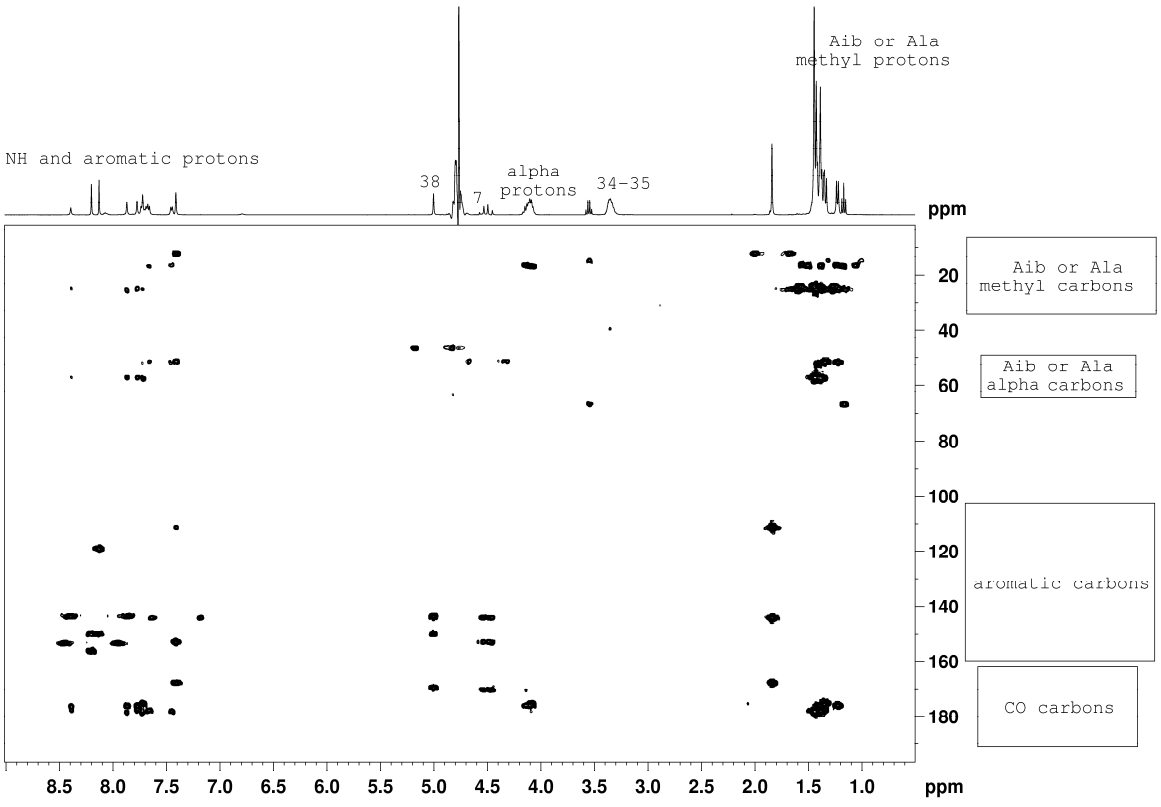

Fig. S5: Example of ^{1}H-^{13}C HMBC spectrum of Foldamer **2** in H_2O/D_2O 10:1 solution with resonances assignment.

X-Ray diffraction

Crystals of foldamers **1** and **4** were grown by slow evaporation from methanol-water and ethanol solutions, respectively. X-Ray diffraction data were collected with a Gemini E four-circle kappa diffractometer (Agilent Technologies) equipped with a 92 mm EOS CCD detector, using graphite monochromated Cu Kα radiation (λ = 1.54178 Å). Data collection and reduction were performed with the CrysAlisPro software (Agilent Technologies). A semi-empirical absorption correction based on the multi-scan technique using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm, was applied. Both structures were solved by ab initio procedures of the SIR 2014 program,[5] and refined by full-matrix least-squares on F^2, using all data, by application of the SHELXL-2014 program.[6] Non-hydrogen atoms were refined anisotropically, except for two, partially occupied, co-crystallized water molecules in the structure of **1**. The asymmetric unit of **4** includes a co-crystallized ethanol molecule, the methyl group of which is disordered and was refined on two positions, with population parameters of 0.65 and 0.35, respectively. H-Atoms were calculated at idealized positions and refined using a riding model. Relevant crystal data and structure refinement parameters, selected torsion angles, and intra-and intermolecular H-bond parameters are listed in Tables S1-S3 for **1**, and in Tables S4-S6 for **4**. CCDC 1535890 and 1535891 contain the supplementary crystallographic data for this paper. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Supporting References

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[2] (a) Leplawy et al., *Tetrahedron*, 1960, **11**, 39; (b) Jones et al., *J. Chem. Soc.,* 1965, 6227; (c) McGahren and Goodman, *Tetrahedron*, 1967, **23**, 2017.

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[4] (a) T. M. Balasubramanian, N. C. E. Kendrick, M. Taylor, G. R. Marshall, J. E. Hall, I. Vodyanoy and F. Reusser, *J. Am. Chem. Soc.*, 1981, **103**, 6127; (b) P. Van Roey, G. D. Smith, T. M. Balasubramanian and G. R. Marshall, *Acta Crystallogr.*, 1983, **C39**, 894.

[5] M.C. Burla, R. Caliandro, B. Carrozzini, G.L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, *J. Appl. Crystallogr.* **2015**, *48*, 306.

[6] G.M. Sheldrick, *Acta Crystallogr. C* **2015**, *71*, 3.

Table S3: Crystal data and structure refinement for foldamer **1** heptahydrate.

Identification code	mc268f	
Empirical formula	$C_{24}H_{33}N_{11}O_6$, 7(H_2O)	
Formula weight	697.72	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 9.11756(10) Å	α= 90°.
	b = 21.6446(2) Å	β= 98.1280(10)°.
	c = 17.9917(2) Å	γ = 90°.
Volume	3514.92(6) Å^3	
Z	4	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.915 mm^{-1}	
F(000)	1488	
Crystal size	0.400 x 0.300 x 0.050 mm^3	
Theta range for data collection	3.213 to 70.887°.	
Index ranges	-11<=h<=11, -26<=k<=26, -21<=l<=21	
Reflections collected	45118	
Independent reflections	6749 [R(int) = 0.0278]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.59078	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6749 / 1 / 432	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R_1 = 0.0565, wR_2 = 0.1647	
R indices (all data)	R_1 = 0.0649, wR_2 = 0.1744	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.549 and -0.427 e.Å^{-3}	
CCDC deposition number	1535890	

Table S4: Selected torsion angles [°] for foldamer **1**.

N1T-C01-C0-N1	145.67(19)
C01-C0-N1-C1A	172.11(18)
C0-N1-C1A-C1	58.0(2)
N1-C1A-C1-N2	27.0(2)
C1A-C1-N2-C2A	178.90(18)
C1-N2-C2A-C2	52.3(3)
N2-C2A-C2-N3	37.5(3)
C2A-C2-N3-C31	-175.73(19)
C2-N3-C31-C32	108.9(2)
N3-C31-C32-N4	-57.3(2)
C31-C32-N4-C33	-84.9(3)
C32-N4-C33-C34	164.4(2)
N4-C33-C34-N9A	170.0(2)

Table S5: Hydrogen bonds for foldamer **1** heptahydrate [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N3-H3...O0	0.86	2.28	3.050(2)	148.4
N4-H4...O1	0.86	2.19	2.857(2)	134.0
N3T-H3T...N1A#1	0.86	2.02	2.884(2)	178.0
N6A-H6A1...O4T#2	0.84	2.12	2.949(2)	168.8
N2-H2...O3#3	0.86	2.57	3.014(3)	112.9
N1-H1...O1W	0.86	2.13	2.980(2)	172.2
N6A-H6A2...O4W	0.90	2.56	3.389(4)	155.1
O4W-H4WA...N7A	0.95	1.88	2.791(3)	159.2
O2W-H2WA...O2	0.75	2.10	2.829(3)	165.6
O3W-H3WA...O2	0.94	1.89	2.824(3)	173.7
O2W-H2WB...N3A#4	0.93	2.07	2.980(3)	164.9
O1W-H1WA...O2W#5	0.87	1.94	2.808(3)	171.3
O1W-H1WB...O4W#6	0.85	2.00	2.821(4)	164.1
O3W-H3WB...O5W	0.95	1.89	2.778(5)	155.3
O4W-H4WB...O5W#7	0.82	1.98	2.807(6)	179.8
O5W-H5WA...O7W	0.84	1.88	2.711(12)	170.4
O6W-H6WB...O3W	0.84	2.01	2.850(8)	178.1
O6W-H6WA...O1W#8	0.84	1.95	2.789(7)	177.8

Symmetry transformations used to generate equivalent atoms:

#1 x-1,-y+1/2,z+1/2 #2 x+1,-y+1/2,z-1/2 #3 x-1,y,z

#4 x,-y+1/2,z+1/2 #5 x-1,-y+1/2,z-1/2 #6 -x,y+1/2,-z+1/2

#7 x+1,y,z #8 x+1,-y+1/2,z+1/2

Table S6: Crystal data and structure refinement for foldamer **4** ethanol solvate.

Identification code	mc258d	
Empirical formula	$C_{29}H_{40}N_6O_7$, C_2H_6O	
Formula weight	630.74	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 10.7942(5) Å	α= 90°.
	b = 18.8139(6) Å	β= 98.486(4)°.
	c = 16.8871(8) Å	γ = 90°.
Volume	3391.9(3) Å^3	
Z	4	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	0.741 mm^{-1}	
F(000)	1352	
Crystal size	0.500 x 0.400 x 0.250 mm^3	
Theta range for data collection	3.538 to 72.983°.	
Index ranges	-13<=h<=13, -23<=k<=23, -20<=l<=19	
Reflections collected	27911	
Independent reflections	6691 [R(int) = 0.0331]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.48756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6691 / 0 / 408	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R_1 = 0.0614, wR_2 = 0.1748	
R indices (all data)	R_1 = 0.0788, wR_2 = 0.1939	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.612 and -0.255 e.Å^{-3}	
CCDC deposition number	1535891	

Table S7: Selected torsion angles [°] for foldamer **4**.

C01-C07-OU-C0	-75.1(3)
C07-OU-C0-N1	170.0(2)
OU-C0-N1-C1A	-177.4(2)
C0-N1-C1A-C1	-58.6(3)
N1-C1A-C1-N2	136.3(2)
C1A-C1-N2-C2A	176.1(2)
C1-N2-C2A-C2	57.0(3)
N2-C2A-C2-N3	30.1(3)
C2A-C2-N3-C31	175.8(2)
C2-N3-C31-C32	-143.8(2)
C2-N3-C31-C36	94.5(3)
N3-C31-C32-C33	-179.0(2)
C36-C31-C32-C33	-56.4(3)
C31-C32-C33-C34	55.4(3)
C32-C33-C34-N4	-177.7(2)
C32-C33-C34-C35	-54.1(3)
N4-C34-C35-C36	177.4(2)
C33-C34-C35-C36	54.6(3)
N3-C31-C36-C35	177.5(2)
C32-C31-C36-C35	56.7(3)
C34-C35-C36-C31	-56.2(3)
C35-C34-N4-C37	117.6(3)
C33-C34-N4-C37	-118.7(3)
C34-N4-C37-C38	178.7(2)
N4-C37-C38-N1T	-147.6(2)

Table S8: Hydrogen bonds for foldamer **4** ethanol solvate [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N3-H3...O0	0.86	2.41	3.098(3)	137.9
N1-H1...O4#1	0.86	2.42	3.234(3)	157.1
C1B2-H1B5...O2T#2	0.96	2.47	3.251(3)	138.8
N2-H2...O2T#2	0.86	2.37	3.190(3)	158.6
N3T-H3T...O4T#3	0.86	2.02	2.860(3)	165.6
O1E-H1OE...O1	0.82	1.97	2.778(3)	167.3
N4-H4...O1E#4	0.86	2.05	2.911(3)	173.8

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 -x+2,-y,-z+1 #3 -x+2,-y-1,-z+1

#4 -x+3/2,y-1/2,-z+3/2

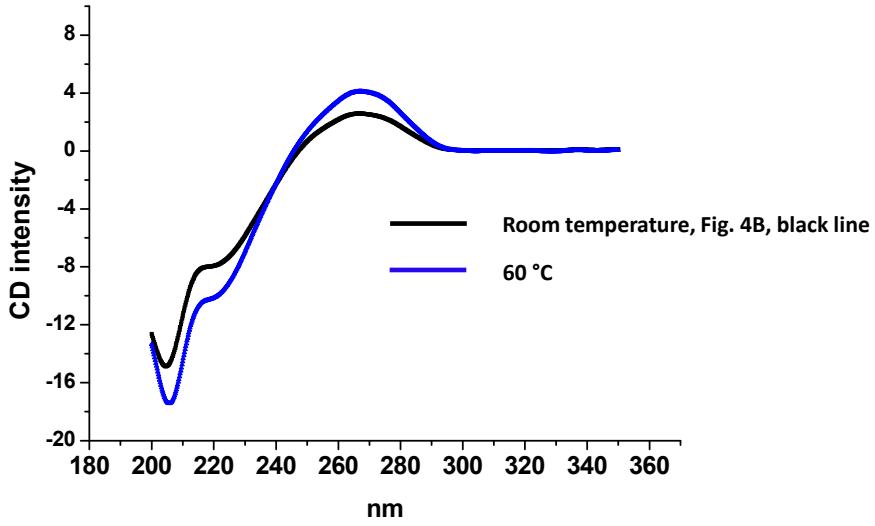

Figure S6: The CD spectrum collected at 60°C (Blue line) is virtually superimposable to that of the monomeric species at 25°C (black line).

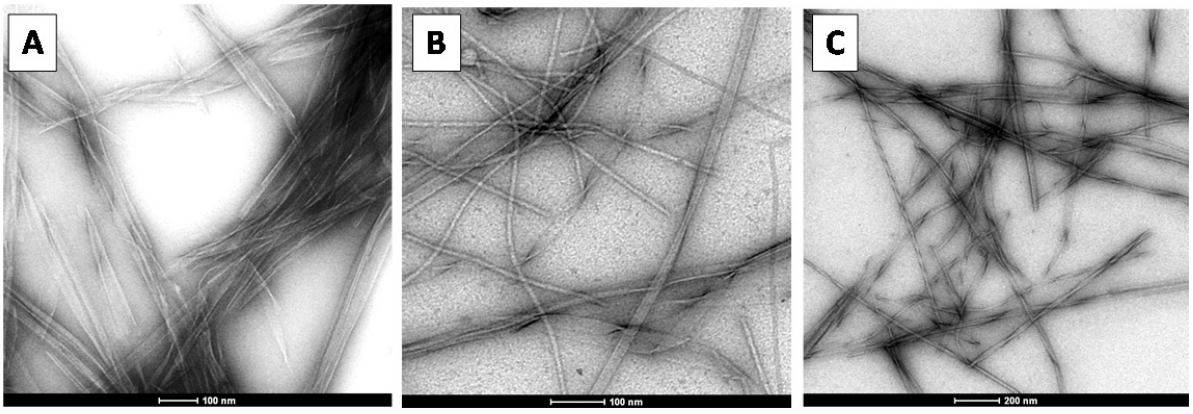

Figure S7: TEM images recorded at three different times (**A** 6 hr, **B** 12 hr, and **C** 18 hr) during the self-assembly of **2** under the conditions reported in main text, Fig 4.