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Supplementary Information

Citric acid encapsulation by a double helical foldamer in competitive solvents

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1. Materials and methods

All reactions were carried out under a dry nitrogen atmosphere. *N,N*-diisopropylethylamine (DIEA) was distilled over calcium hydride. Reactions requiring anhydrous conditions were performed under argon. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 plates and observed under UV light. Column chromatographies were carried out on Merck GEDURAN Si60 (40-63 μm). Analytical grade organic solvents were used for solid phase synthesis. Anhydrous THF and CH_2Cl_2 were dispensed from an MBRAUN SPS-800 solvent purification system. ESI mass spectra were obtained from the mass spectrometry service at the IECB (UMS3033 & US001).

Nuclear Magnetic Resonance

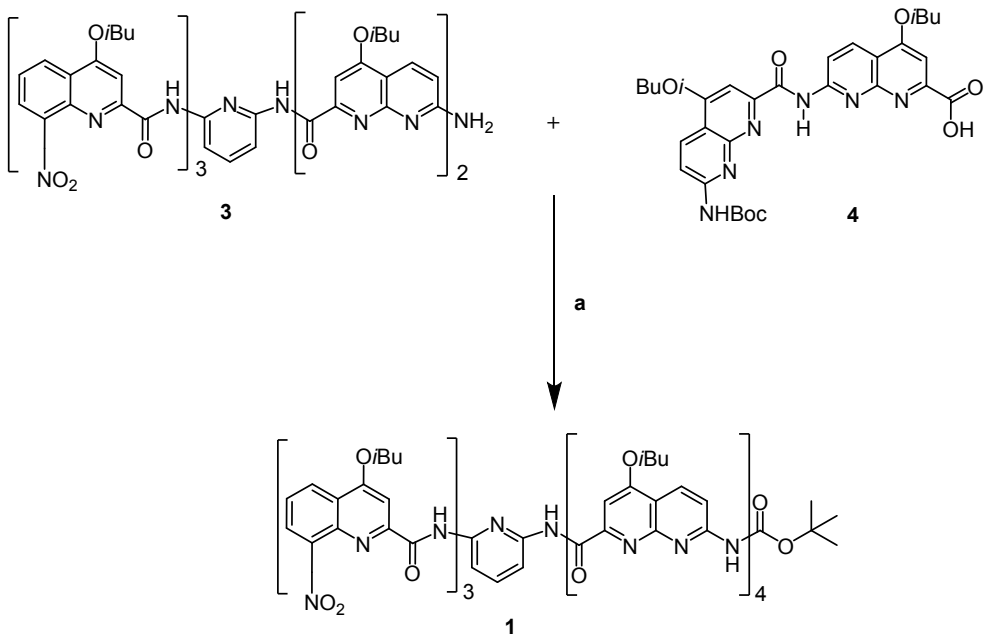
NMR spectra were recorded on 3 different NMR spectrometers: (1) an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7,05T narrow-bore/ultrashield magnet operating at 300 MHz for ^{1}H observation and 75 MHz for ^{13}C observation by means of a 5-mm direct BBO H/X probe with Z gradient capabilities; (2) a DPX-400 NMR spectrometer (Bruker Biospin) with a vertical 9,4T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP $^{1}H/^{13}C/^{31}P/^{19}F$ probe with gradient capabilities. (3) an Avance III NMR spectrometer (Bruker Biospin) with a vertical 16.45T narrow-bore/ultrashield magnet operating at 700 MHz for 1H observation by means of a 5-mm TXI 1H/13C/15N probe with Z gradient capabilities. ^{1}H-NMR spectra were measured at 300, 400 or 700 MHz and ^{13}C-NMR spectra were measured at 75 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of $CDCl_3$ (δ 7.26, 77.2), d_6-DMSO (δ 2.50), CD_3OH (δ 3.31), d_6-acetone (2.05). All coupling constants are reported in hertz (Hz). Signals were abbreviated as s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet, dd, doublet of doublets. Data processing was performed with Topspin 2.0 software.

Crystallography

Crystallographic data on the double helix $(\mathbf{1})_2$ were collected at ESRF on the French CRG Beamline (BM30A) at the wavelength of 0.8726 Å. The XDS package[1] was used to process the data. The structure was solved with SHELXD[2] and refined using SHELXL.[2] Full-matrix least-squares refinement was performed on F^2 for all unique reflections, minimizing $w(Fo^2- Fc^2)^2$, with anisotropic displacement parameters for non-hydrogen atoms on the main chain of the foldamer but not on the isobutoxy side chains. (RESI, AFIX 116 commands were used for the oligomer, RIGU and DFIX restraints on side chains). Hydrogen atoms were included in idealized positions and refined with a riding model, with Uiso constrained to 1.2 Ueq value of the parent atom (1.5 Ueq when CH_3). Crystallographic data on host-guest complex $(\mathbf{1})_2\supset\mathbf{2}$ were collected at the IECB X-ray facility (UMS 3033 CNRS) on a RIGAKU MM07 rotating anodes at the copper k_α wavelength at 150K. The crystal was mounted on cryo-loop after quick soaking on Paratone-N oil from Hampton research and flash-frozen. The CrystalClear suite from RIGAKU (2.0 version from 2009) was used to process the data. The structure was solved using the charge flipping algorithm implemented in SUPERFLIP[3] and refined with SHELXL-2014 following the same strategy as the empty capsule. The SQUEEZE from PLATON[4] procedure was used on both structures

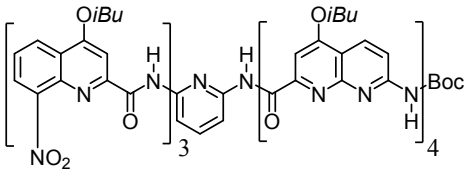
for solvent flattening. Both structures have been measured at medium resolution and as for large molecule structures ALERT A remain in the checkcif test. All the PLAT234, PLAT413 and PLAT430 A alerts are due to the low resolution of the data, high thermal motion factors on floppy side chains atoms. Data statistics for both structures are reported in the tables S1 to S2 and in the cif files with CCDC reference numbers CCDC 1445980 and CCDC 1446002, respectively.

2. Synthetic scheme



Scheme S1. Synthesis of capsule **1**: (a) PyBOP, DIEA, $CHCl_3$, RT then 40°C.

3. Experimental section



1

O_2N-Q_3PN_4-Boc 1: To a solution of hexamer amine[5] **3** (0.074 mmol, 100 mg) and dimer acid **4** (0.089 mmol, 54 mg) in dry $CHCl_3$ (4 mL) were added at room temperature DIEA (0.295 mmol, 0.05 mL) and PyBOP (0.148 mmol, 77 mg). The reaction mixture was heated at 40 °C and let to stir for 24 hours. Then, the solvent was removed under reduced pressure and the residue was precipitated from a minimum amount of MeOH. After filtration, **1** was obtained as a yellow solid in good yield (90%, 129 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 11.50 (s, 1H); 11.19 (s, 1H); 10.89 (s, 1H), 10.20 (s, 1H); 9.98 (s, 1H), 9.63 (s, 1H); 8.88 (s, 1H); 8.58 (d, *J* = 8.79, 1H); 8.46 (m, 2H); 8.21 (d, *J* = 6.83, 1H); 8.16 (d, *J* = 8.14,

1H); 8.03-7.88 (m, 3H); 7.71 (m, 2H); 7.58-7.46 (m, 2H); 7.39 (s, 1H); 7.30 (d, *J* = 7.88, 1H); 7.20 (s, 1H); 7.12-6.77 (m, 6H); 6.64 (d, *J* = 6.00, 1H); 6.37 (d, *J* = 7.71, 1H); 6.23 (s, 1H); 5.96 (t, *J* = 7.70, 1H); 4.36-3.42 (m, 15H); 3.14 (m, 1H); 2.99 (s, 1H); 2.51 (m, 3H); 2.34 (m, 2H); 2.20 (m, 1H); 2.07 (m, 1H); 1.41-1.22 (m, 37H); 1.10-1.06 (m, 13H); 0.66 (d, *J* = 6.45, 3H); 0.42 (d, *J* = 6.27, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 163.8, 163.1, 162.9, 162.5, 162.0, 161.8, 161.6, 160.9, 155.4, 154.8, 154.3, 153.8, 153.7, 153.5, 153.0, 152.9, 152.4, 152.1, 151.9, 151.2, 149.3, 148.6, 148.2, 146.7, 144.7, 138.7, 138.3, 137.4, 136.7, 135.3, 134.3, 134.1, 132.8, 131.9, 131.6, 130.1, 127.5, 127.2, 126.1, 125.5, 125.0, 124.4, 124.0, 123.4, 123.2, 121.3, 119.9, 116.2, 115.7, 115.0, 114.3, 113.6, 113.4, 113.0, 112.4, 110.5, 107.9, 107.6, 100.6, 99.3, 98.7, 98.5, 98.3, 97.8, 97.2, 96.5, 80.7, 79.4, 77.3, 75.9, 75.4, 75.0, 74.5, 31.2, 28.3, 28.0, 27.7, 19.2, 19.1, 18.4. HRMS (ESI^+): *m/z* calcd for $C_{104}H_{108}N_{21}O_{18}$ $[M+H]^+$ 1939.8215 found 1939.8147.

4. NMR studies

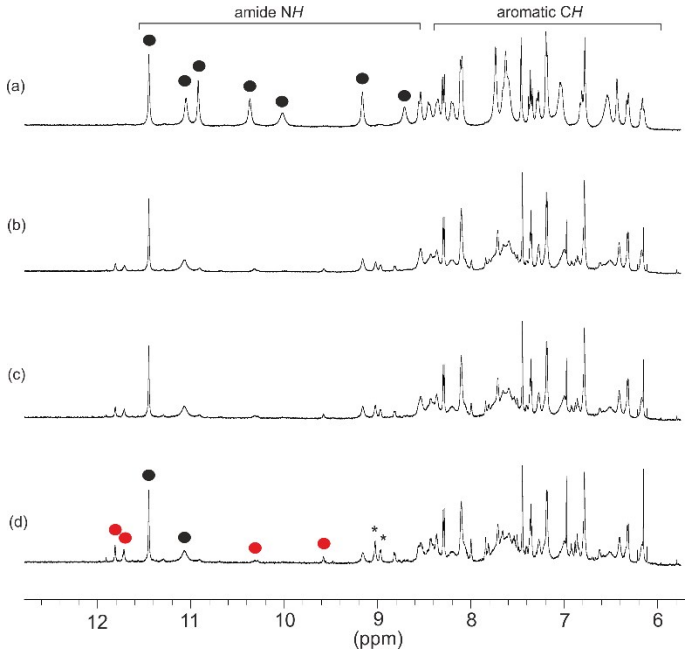


Figure S1. Partial ^{1}H NMR spectra of **1** (700MHz, 298 K) in [D_6]-acetone at: a) 6 mM; b) 1 mM; C) 0.75 mM; d) 0.5 mM. Red and black circles indicate a single or double helix configuration, respectively, and were used to calculate K_{dim} = 6.8 x 10^4 L mol^{-1}.

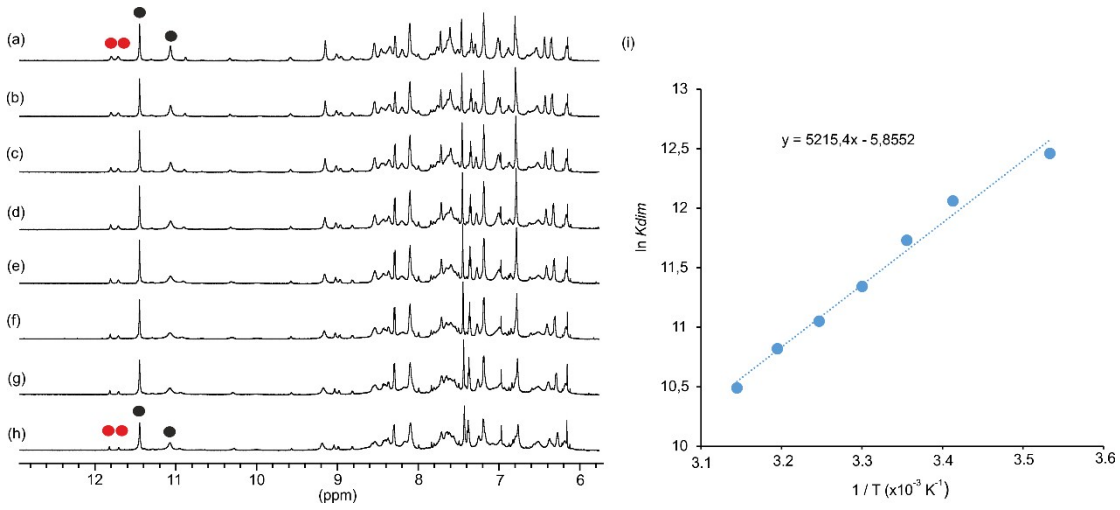


Figure S2. Excerpts of the 700 MHz ^{1}H NMR spectra of capsule **1** (1 mM) [D_6]-acetone at: (a) 323 K; (b) 318 K; (c) 313 K; (d) 308 K; (e) 303 K; (f) 298 K; (g) 293 K and (h) 283 K. Red and black circles denote single and double helix resonances, respectively. (i) Van't Hoff plot of the dimerization of capsule **1**(1 mM) in [D_6]-acetone. Experimental data were fitted to the Van't Hoff equation using linear regression analysis (blue line, R^2=0.9873). ΔH and ΔS were extracted to be -43.3 kJ mol^{-1} and -47.8 J $mol^{-1}K^{-1}$, respectively.

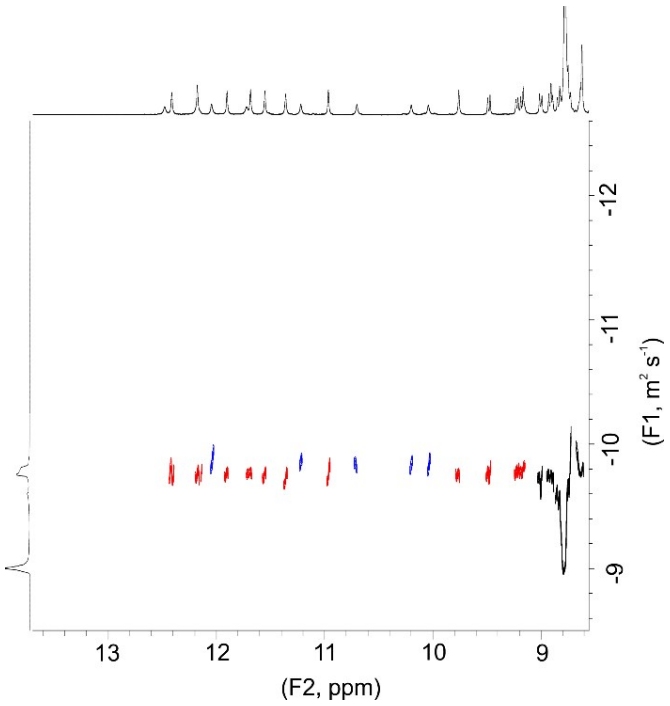


Figure S3. Partial ^{1}H DOSY 400MHz NMR spectra of **1** (6 mM) in [D_5]-pyridine at 298K. Red and blue signals indicate a single or double helix configuration, respectively. Diffusion coefficients for single helical **1** and double helical $(\mathbf{1})_2$ were calculated to be 2.92×10^{-10} and 2.51×10^{-10} m^2 s^{-1}, respectively. K_{dim} = 70 L mol^{-1}.

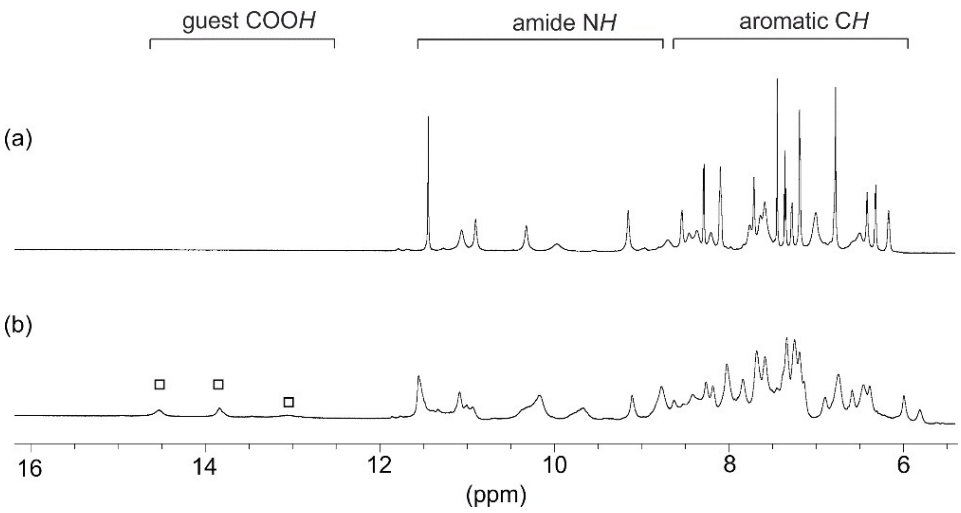


Figure S4. Partial ^{1}H NMR spectrum (700 MHz) at 298K of capsule **1** (6 mM) in [D_6]-acetone in the presence of: a) 0 equiv. and b) 0.5 equiv. of citric acid. Squares denotes the carboxylic acid resonances of the bound guest.

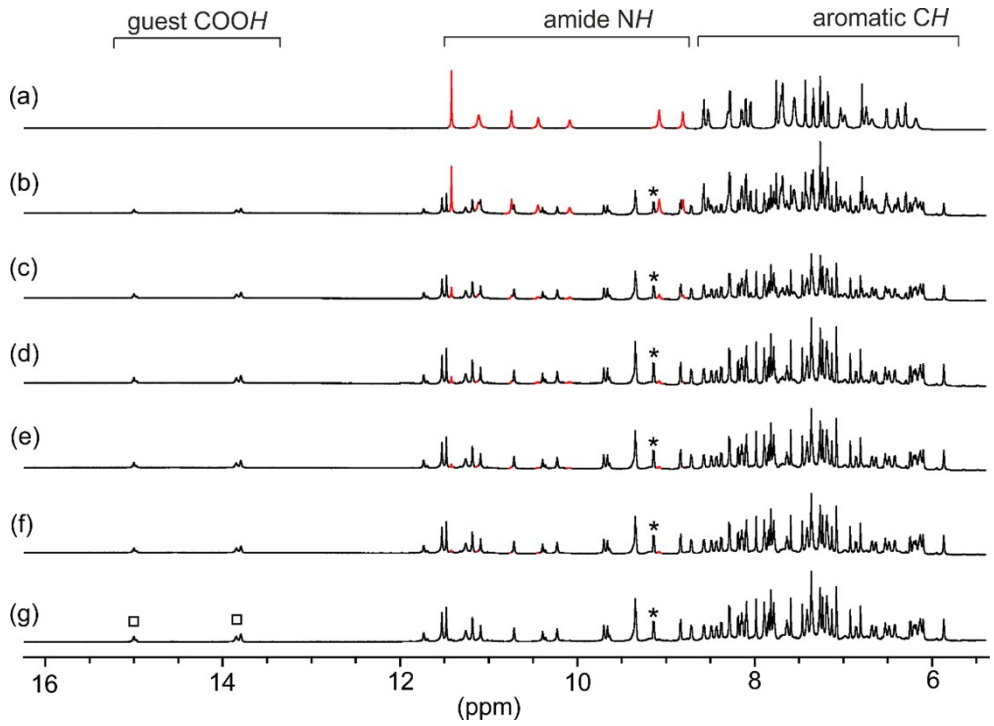


Figure S5. Partial ^{1}H NMR spectrum (700 MHz) at 298K of capsule **1** (6 mM) in a mixture of [D_6]-acetone/CD_3OH (90:10 vol/vol) in the presence of: a) 0 equiv.; b) 0.25 equiv.; c) 0.5 equiv.; d) 0.75 equiv.; e) 1 equiv.; f) 1.5 equiv.; g) 2 equiv. of citric acid. Squares denotes the carboxylic acid resonances of the bound guest. Stars stands for aromatic resonances. K_a = 1300 L mol^{-1}.

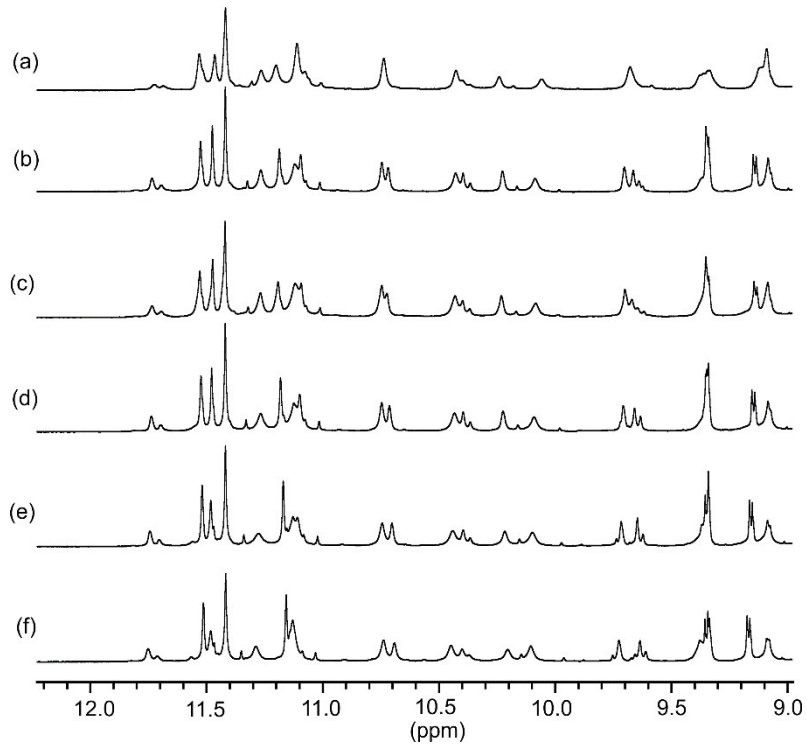


Figure S6. Partial ^{1}H NMR spectrum(700 MHz, 298K) showing the amide region of capsule **1** (6 mM) in a mixture of [D_6]-acetone/CD_3OH (90:10 vol/vol) in the presence of 0.4 equiv. of citric acid at: (a) 323 K; (b) 318 K; (c) 303 K; (d) 293 K; (e) 283 K and (f) 273 K.

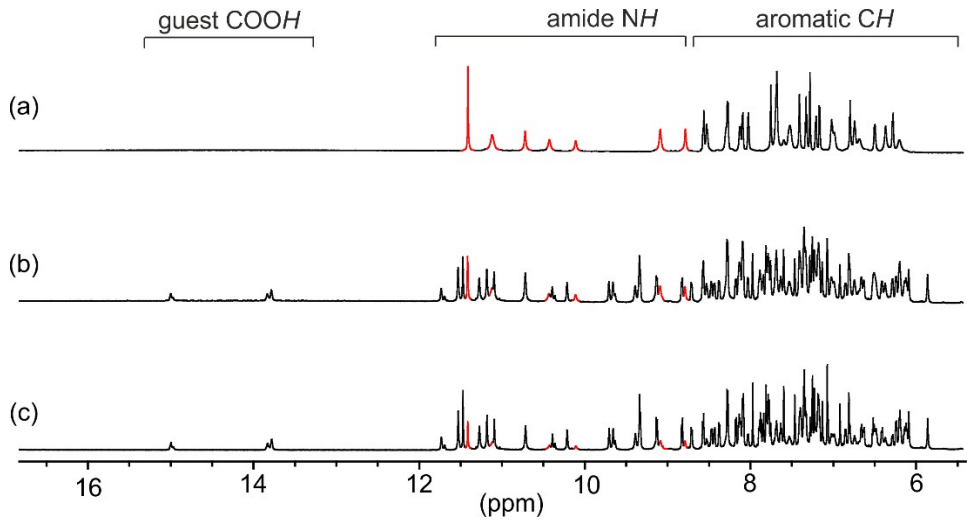


Figure S7. Partial ^{1}H NMR spectrum (700 MHz) at 298K of capsule **1** (6 mM) in a mixture of [D_6]-acetone/CD_3OH (80:20 vol/vol) in the presence of: a) 0 equiv.; b) 0.5 equiv.; c) 0.75 equiv. of citric acid. K_a = 200 L mol^{-1}.

5. Crystallography

5.1 X-Ray crystallographic data for double helix $(\mathbf{1})_2$

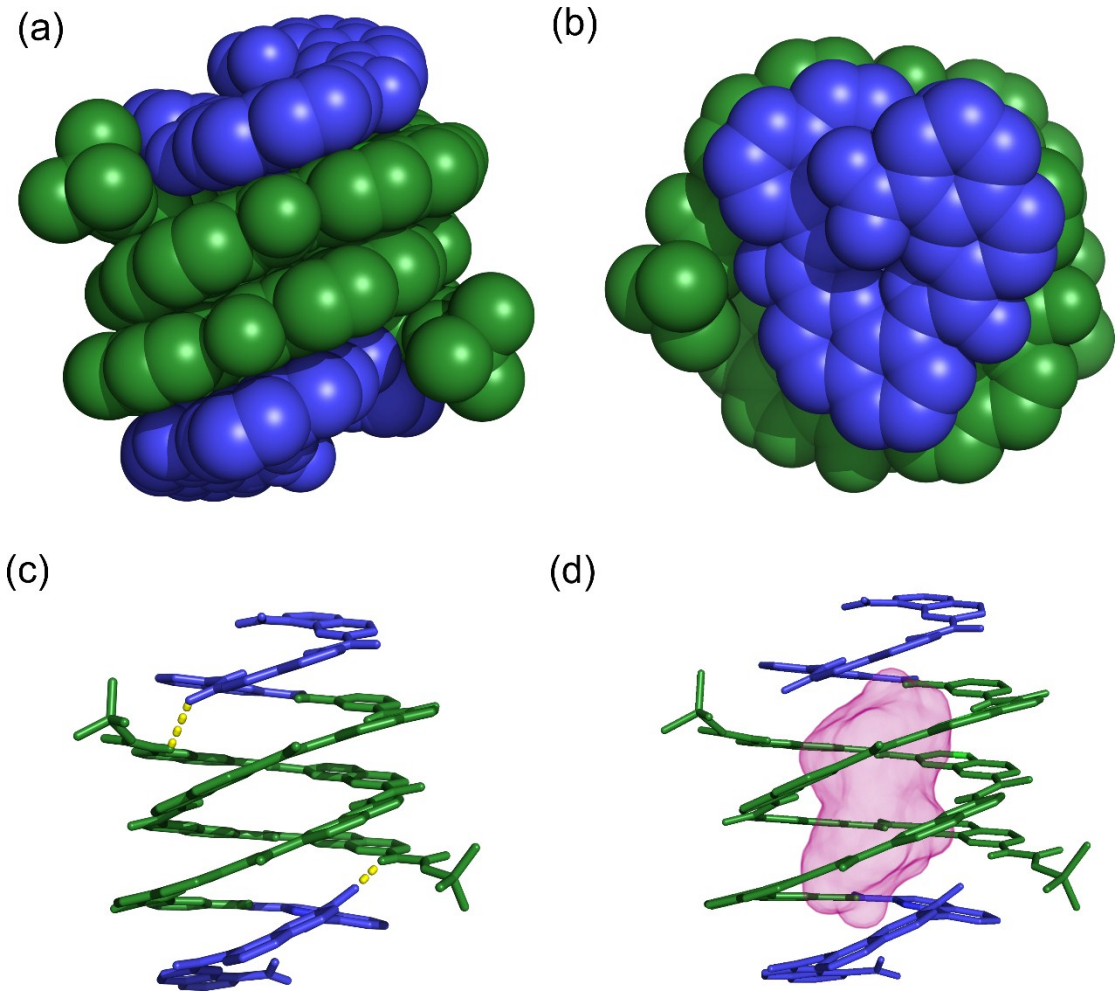


Figure S8. Side view (a) and top view (b) of the crystal structure of $(\mathbf{1})_2$ in CPK representation; monomers are color coded as in Figure 1 of the manuscript (quinoline in blue and naphthyridine in green). Side views (c, d) of the crystal structure of $(\mathbf{1})_2$ in tube representation. In (c) stabilizing intermolecular hydrogen bonds between the two different strands of the capsule are shown as yellow dashes. Isobutyl side chains and solvent molecules have been removed for clarity. In (d) volume of the cavity is shown as a pink transparent isosurface (210 $Å^3$).

Table S1. Crystal data and structure refinement for capsule $(\mathbf{1})_2$

Formula	*C210 H219 N42 O42 S*
M	4035.32
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	34.596(7)
b/Å	23.529(5)
c/Å	32.903(7)
α/°	90
β/°	113.63(3)
γ/°	90
U/Å³	24537(10)
T /K	150
Z	4
ρ/g cm⁻¹	1.092
size (mm)	0.2x0.2x0.01
λ/ Å	0.8726
μ/mm⁻¹	0.139
Total reflections	153923
Unique data	21483
R_{int}	0.0802
parameters/restraints	2406/148
R1, wR2	0.1705/0.4358
goodness of fit	1.728

5.2 X-Ray crystallographic data for host-guest complex $(\mathbf{1})_2 \supset \mathbf{2}$

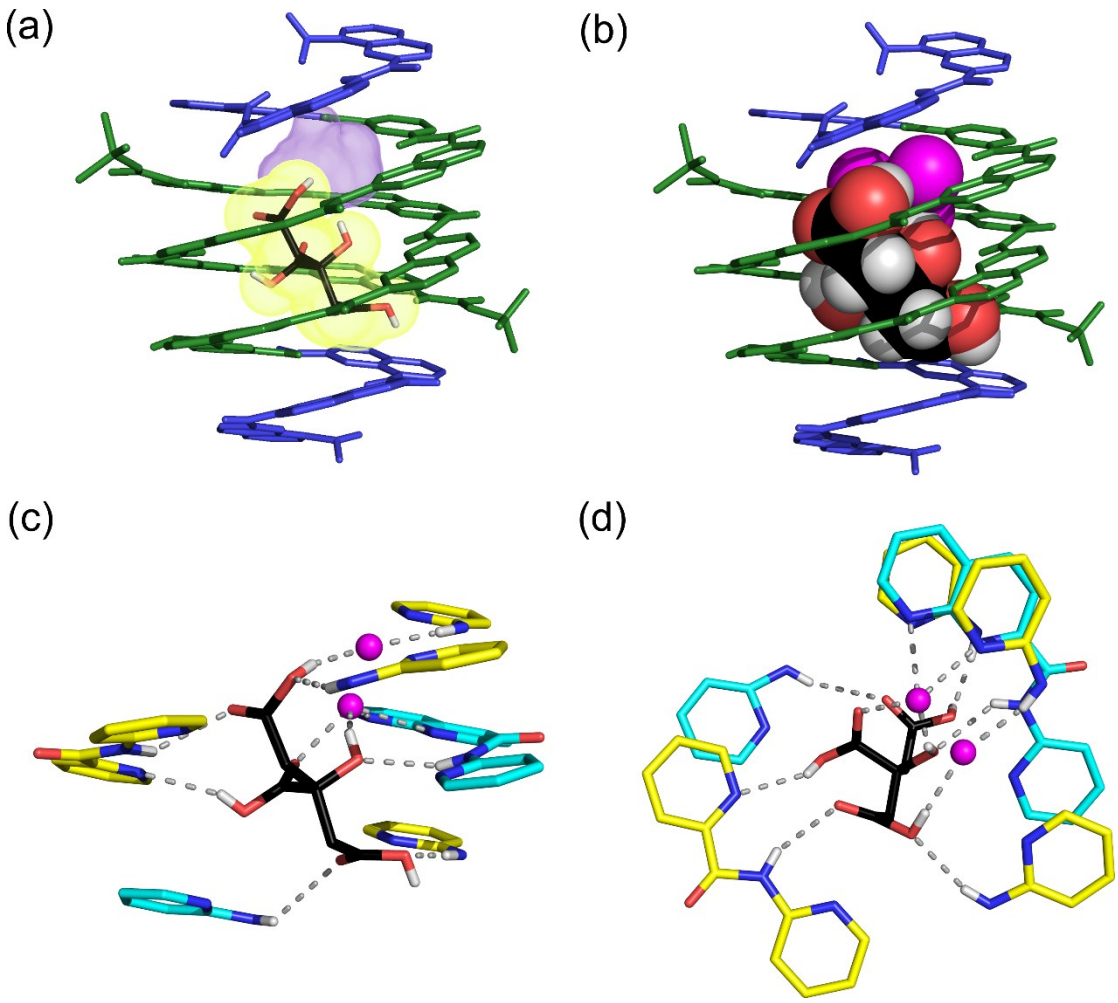


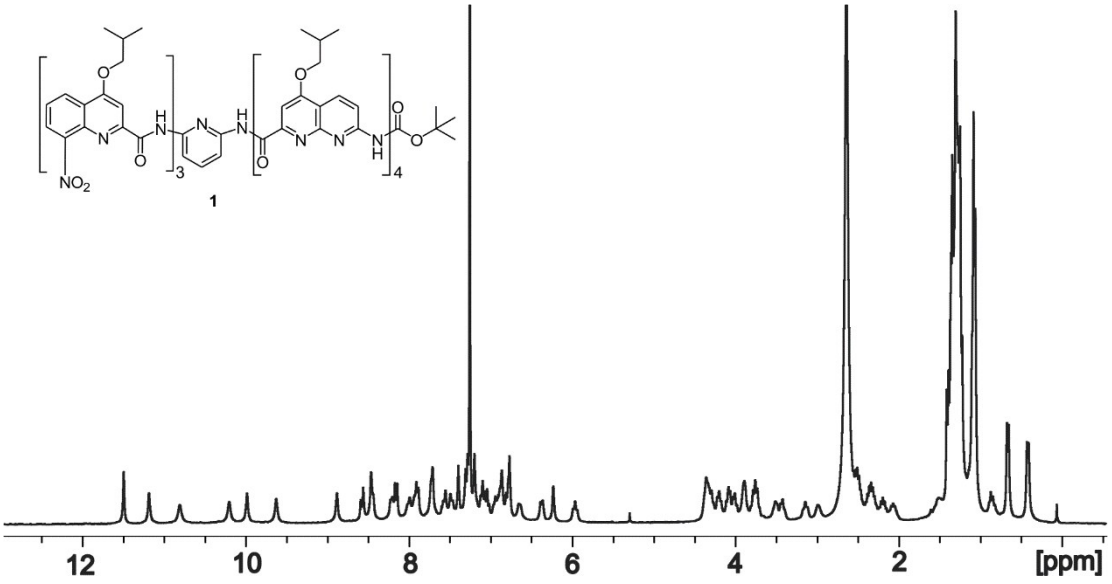
Figure S9. Side views of the crystal structure of complex $(\mathbf{1})_2 \supset \mathbf{2}$ in: (a) tube representation for host and guest; and (b) tube and CPK representations for the host and the guests (citric acid and three water molecules in magenta CPK representation), respectively. In (a) and (b) monomer are color coded as in Figure 1 of the manuscript. In (a) volumes of the empty void in the cavity (after removing water molecules) is shown as a purple transparent isosurface whereas a yellow transparent isosurface denotes the volume of the guest. Enlarged side view (c) and top view (d) of the complex showing the array of 12 hydrogen bonds. Aromatic monomers are color coded in yellow or blue depending of the strand they belong to and shown in tube representation. Two water molecules are shown as magenta balls. Hydrogen bonds are shown as gray dashes. Isobutoxy side chains and solvent molecules have been omitted for clarity.

Table S2. Crystal data and structure refinement for host-guest complex (**1**)$_2$⊃**2**

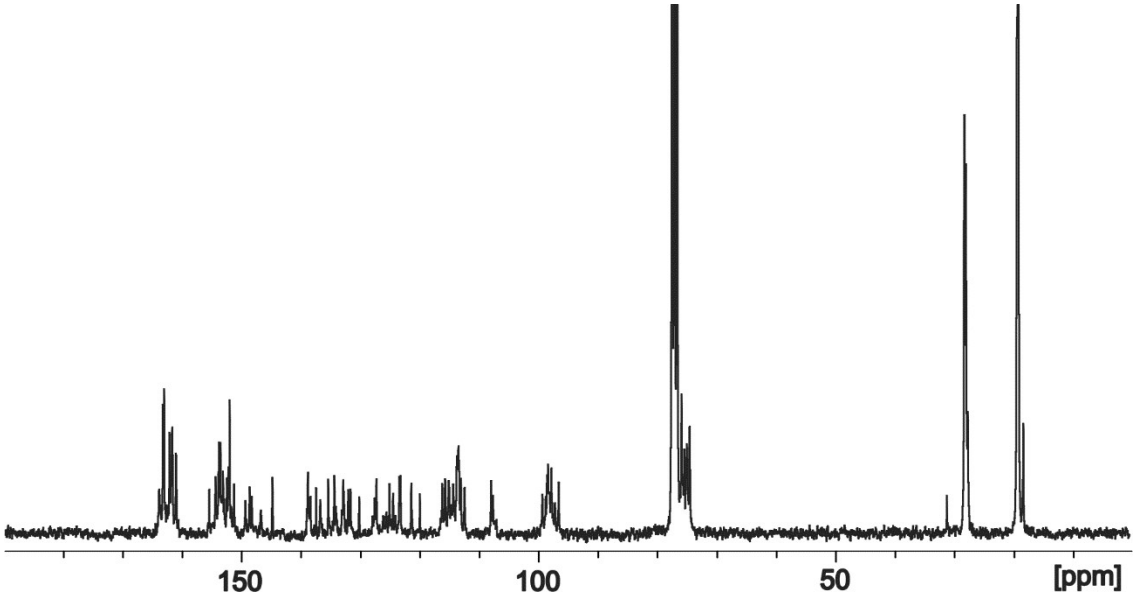
Formula	*C428 H413 N84 O92*
M	8205.40
Crystal system	triclinic
Space group	$P\bar{1}$
a/Å	28.125(6)
b/Å	30.271(6)
c/Å	35.821(7)
α/°	69.22(3)
β/°	80.81(3)
γ/°	88.35(3)
U/Å^3	28134(11)
T /K	150
Z	2
ρ/g cm^{-1}	0.969
size (mm)	0.2x0.2x0.1
λ/ Å	1.54187
μ/mm^{-1}	0.578
Total reflections	272720
Unique data	50700
R_{int}	0.1108
parameters/restraints	4050/323
R1, wR2	0.1928/0.4322
goodness of fit	1.961

6. NMR spectra

^{1}H NMR



^{13}C NMR



7. References

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