Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

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Proteomorphous objects from abiotic backbones

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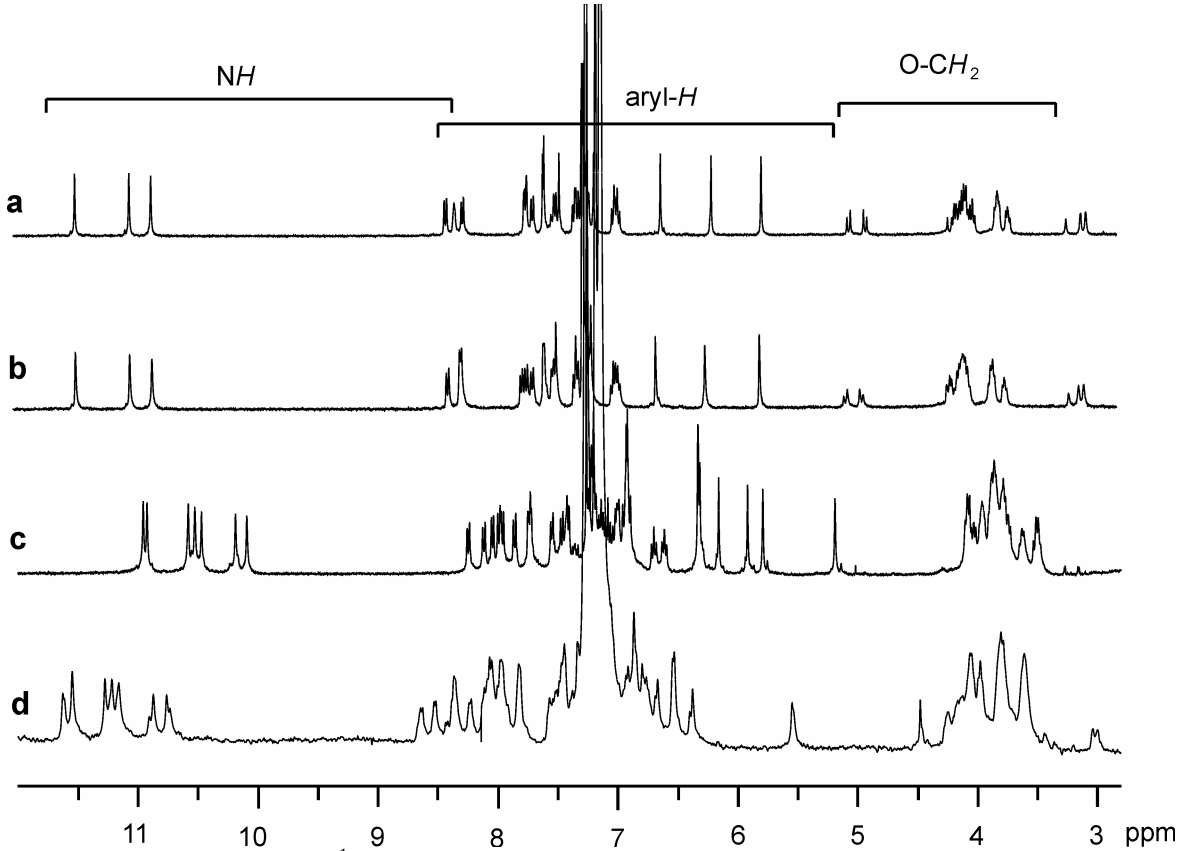

Figure S1. Part of the 400 MHz ^{1}H NMR spectra of **1** and **2**. (a**) 2** in $CDCl_3$ at 25°C. (b) **2** in $CDCl_3$ at 60°C. (c) **1** in $CDCl_3$ at 25°C. (d) **1** in toluene-d_8 at 25°C. The spectra in (a) and (b) are identical but for a few chemical shift variations and a slight line broadening at higher temperature. They show that essentially one species is present in solution. The diastereotopic motifs of the signals of CH_2 benzyloxy and butyloxy protons at 3.5-5 ppm even at 60°C indicate slow exchange on the NMR time scale between P and M helical conformers. The simplicity of the spectrum of **1** in $CDCl_3$ indicates that its structure is symmetrical: its four helical segments are equivalent on average.

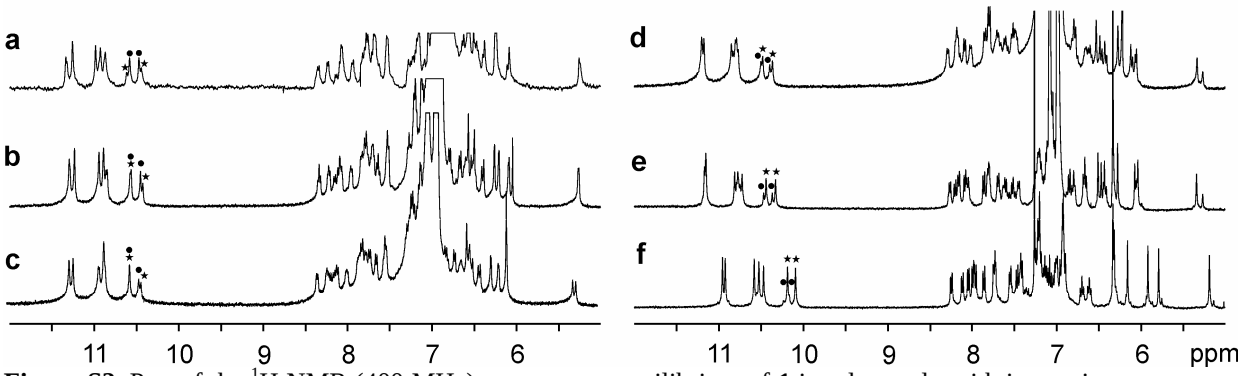

Figure S2. Part of the ^{1}H NMR (400 MHz) spectrum at equilibrium of **1** in toluene-d_8, with increasing amounts of $CDCl_3$ added. (a) in pure toluene-d_8. (b) 5% $CDCl_3$. (c) 9% $CDCl_3$. (d) 18% $CDCl_3$. (e) 33% $CDCl_3$. (f) pure $CDCl_3$. The circles and stars indicate signals assigned individually to the P-M and P-P/M-M conformers of **1**, respectively. The spectra unambiguously show that the P-P/M-M species that prevails in pure toluene is minor in pure chloroform and, reciprocally the P-M species that prevails in chloroform is minor in toluene. Remarkably, the equilibrium is strongly shifted upon the addition of only a small quantity of chloroform.

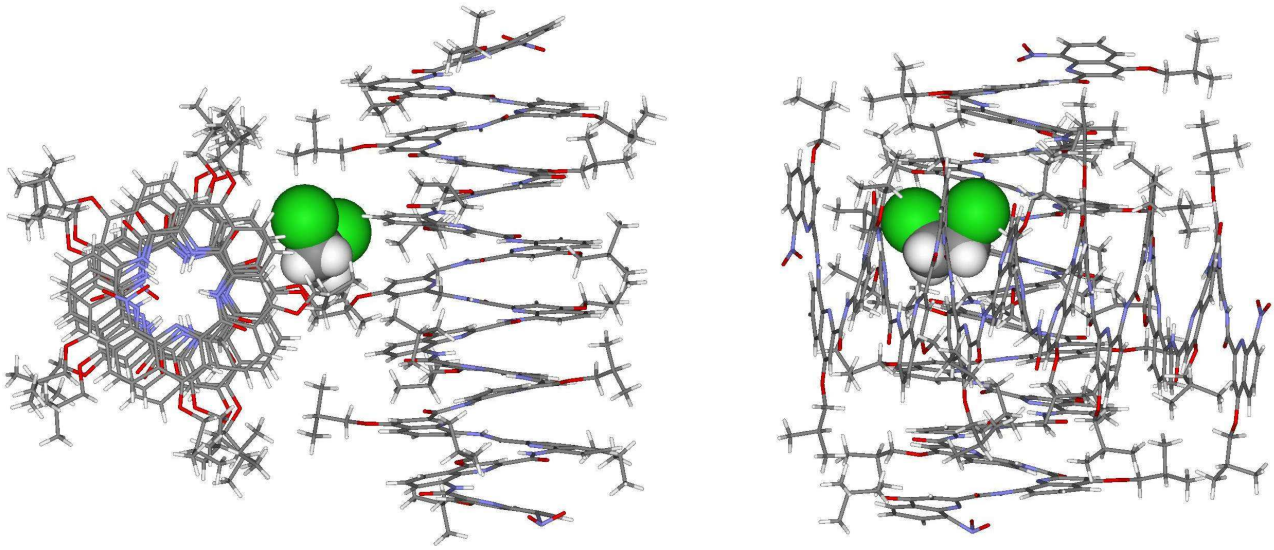

Figure S3. Two views of the crystal structure of **1** showing a dichloroethane molecule (in CPK representation) included in a cavity between the helices. The presence of such molecules may play a role in the relative stability of the P-M and P-P/M-M conformers in various solvents.

Experimental section.

Synthetic procedures.

4-benzyloxy-2,6-bis(*tertio*-butyloxycarbonylaminomethyl)-pyridine 6. In a three necked round bottom flask equipped with a condenser and an addition funnel, 4-benzyloxy-2,6-pyridinedicarboxamide **5**[1] (828 mg, 3.05mmol) was introduced under an inert atmosphere. A solution of BH_3 in THF (50 mL, 1 M, 16 equiv.) was added dropwise at 25°C. The reaction mixture was then heated to reflux for 48h. The solution was cooled to 25°C. and MeOH was carefully added dropwise to quench excess BH_3 until H_2 evolution stopped. After evaporation of the solvent, the crude oil was diluted in MeOH (110 mL) and the mixture was stirred at reflux for 48h. MeOH was removed under vacuum, dichloromethane (100 mL) was added, the organic phase was washed with aqueous NaOH (1

M, 100 mL), dried over Na_2SO_4, filtered and concentrated to yield a yellow oil of 4-benzyloxy-2,6-bis(aminomethyl)-pyridine (742 mg, quant. yield) which was used in the next step without further purification (^{1}H NMR (400MHz, $CDCl_3$) : δ = 7.42-7.34 (5H, m), 6.75 (2H, s), 5.10 (2H, s), 4.64 (4H, broad s), 3.86 (2H, s). The bis(aminomethyl) intermediate (742 mg, 3.05 mmol) was dissolved in anhydrous THF (100 mL) in a round bottom flask. A solution of di-tertbutyl dicarbonate (1.33 g, 6.10 mmol, 2 equiv.) in anhydrous THF (50 mL) was slowly added and the mixture was stirred at 25°C for 5h. Volatiles were evaporated and the solid was taken up in dichloromethane (50 mL), the organic phase was washed with saturated NaCl (50 mL), dried over Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography on silicagel eluting with CH_2Cl_2/MeOH 98:2 vol:vol and obtained as a white solid (1.35 g, 75 % yield). ^{1}H NMR (400MHz, $CDCl_3$) : δ = 7.38 (5H, m), 6.74 (2H, s), 5.42 (2H, bs), 5.08 (2H, s), 4.64 (2H, s), 4.35 (4H, d, *J*=4.8Hz), 1,47 (18H, s). ^{13}C NMR (100MHz, $CDCl_3$) : δ = 166.0, 158.8, 155.9, 135.5, 128.7, 128.4, 127.5, 106.7, 79.5, 69.9, 45.7, 28.4. MS (EI): m/z = 444 (3, $[M+H]^+$), 443 (2, $[M]^+$), 388 (8), 343 (27), 332 (8), 314 (27), 269 (13), 287 (33), 152 (19), 91 (100). HRMS (ESI): calcd for $C_{24}H_{34}N_3O_5$, $[M+H]^+$ 444.2498, found 444.2518.

2,6-bis(*tertio*-butyloxycarbonylaminomethyl)-4-hydroxypyridine. Benzyl ether **6** (362 mg, 0.82 mmol) was dissolved in a mixture of EtOAc (12 mL) and MeOH (4 mL). Palladium black (5 % weight, 36 mg) was added and the reaction mixture was placed under a hydrogen atmosphere, stirred for 12h and filtered through celite. The solvent was removed, the residue was dried in vacuo and purified by chromatography on silicagel eluting with CH_2Cl_2/MeOH 96:4 and then 92:8 vol:vol. The product was obtained as a white solid (212 mg, 73 % yield). ^{1}H NMR (400MHz, $CDCl_3$/CD_3OD, 1:1 vol:vol) : δ = *$CDCl_3$,/CD_3OD, 1/1) :* δ = 10.86 (1H, bs), 6.24 (2H, s), 5.72 (2H, bs), 4.17 (4H, s), 1.45 (18H, s). ^{13}C NMR (100MHz, $CDCl_3$/CD_3OD) : δ = 158.5,113.1, 81.0, 42.5, 28.7. MS (EI): m/z = 354 (20, $[M+H]^+$), 298 (29), 253 (44), 242 (69), 224 (55), 198 (51), 197 (87), 180 (54), 154 (61), 152 (64), 136 (86), 57 (100). HRMS (ESI): calcd for $C_{17}H_{28}N_3O_5$, $[M+H]^+$ 354.2029, found 354.2034.

1,2-*O,O'*-bis(2,6-bis(*tertio*-butyloxycarbonylaminomethyl)-pyridine4-yl)-ethyleneglycol 8. 2,6-bis(*tertio*-butyloxycarbonylaminomethyl)-4-hydroxypyridine (120 mg, 0.34 mmol, 2.2 equiv.) and PPh_3 (122 mg, 0.46 mmol, 3 equiv.) were placed in a round bottom flask under nitrogen. A 0.179 M solution of anhydrous ethylene glycol in anhydrous THF was prepared separately and 862 µL of this solution (0.15 mmol, 1 equiv.) followed by DIAD (91 µL, 0.46 mmol, 3 equiv.) were added to the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 30min then at 25°C for 12h. THF was removed and the residue was purified by chromatography on silicagel eluting with CH_2Cl_2/MeOH 98:2 vol:vol. The product was obtained as a yellowish solid (100 mg, 89 % yield). ^{1}H NMR (400MHz, $CDCl_3$) : δ = 6.68 (4H, s), 5.55 (4H, bs), 4.32 (12H, bs), 1.44 (36H, s). ^{13}C NMR (100MHz, $CDCl_3$) : δ = 165.7, 159.0, 155.9, 106.3, 79.4, 65.8, 45.6, 28.3. MS (EI): m/z = 733 (2, $[M+H]^+$), 632 (4), 532 (4), 432 (6), 314 (14), 153 (8), 59 (100). HRMS (ESI): calcd for $C_{36}H_{57}N_6O_{10}$, $[M+H]^+$ 733.4136, found 733.4112 (3.3ppm).

General procedure for Boc deprotection. The starting *tertio*butyl-carbamate was dissolved in CH_2Cl_2. Trifluoroacetic acid (16 equiv. per amine function) was added. The reaction mixture was stirred at 25°C for 3 hours. CH_2Cl_2 was evaporated and replaced by anhydrous toluene which was then evaporated to azeotrope excess tifluoroacetic acid. This operation was repeated three times to yield an oil which was dried in vacuo. The amine products were used without further purification.

Foldamer 2. Precursor **6** (21 mg, 0.047 mmol) was deprotected according to the general Boc deprotection procedure using TFA (115 µL, 1.50 mmol, 32 equiv.) in CH_2Cl_2 (1 mL). Intermediate diamine **7** was obtained as a yellow oil (22 mg, quant. yield). ^{1}H NMR (400MHz, $CDCl_3$) : δ = 7.42-7.34 (5H, m), 6.75 (2H, s), 5.10 (2H, s), 4.64 (4H, broad s), 3.86 (2H, s). Tetramer acid **3**[2] (105 mg, 0.10 mmol, 2.2 equiv.), HBTU (54 mg, 0.14 mmol, 3 equiv.), HOBT (13 mg, 0.09 mmol, 2 equiv.), anhydrous DMF (1.5 mL) and freshly distilled ethyl diisopropylamine (100 µL, 0.47 mmol, 10 equiv.) were stirred for 30 minutes at 25°C. The amine (22 mg, 0.05 mmol, 1 equiv.) dissolved in DMF (0.5 mL) was added and the reaction mixture was stirred for 12h. A solid precipitate formed and the suspension was filtered to yield 31 mg of the pure product. Toluene (15 mL) was added to the filtrate which was then washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with toluene (2 × 15 mL). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with EtOAC/toluene 2:98 to 10:90 vol:vol to give an additional 38 mg of the desired product (total: 69 mg, yield 65 %). ^{1}H NMR (400MHz, $CDCl_3$) : δ = 11.49 (2H, s), 11.04 (2H, s), 10.85 (2H, s), 8.39 (2H, dd, *J*=7.6Hz, *J*=1.6Hz), 8.31 (2H, bs), 8.26 (2H, d, *J*=7.2Hz), 7.73 (2H, d, *J*=7.6Hz), 7.67 (2H, d, *J*=8Hz), 7.59 (2H, s), 7.58 (2H, s), 7.48 (2H, d, *J*=7.6Hz), 7.45 (1H, s), 7.34-7.20 (10H, m), 7.16 (1H, s), 6.99 (4H, m), 6.60 (2H, s), 6.17 (2H, s), 5.76 (2H, s), 5.03 (1H, d, *J*=11.2Hz), 4.89 (1H, d, *J*=10.8Hz), 4.21-3.99 (10H, m), 3.83-3.69 (6H, m), 3.09 (2H, dd, *J*=17.7Hz, *J*=2.1Hz), 2.27 (8H, m), 1.63 (2H, dd, *J*=17.7Hz, *J*=2.1Hz), 1.31-1.16 (48H, m). ^{13}C NMR (100MHz, $CDCl_3$) : δ = 164.8, 163.7, 162.7, 162.2, 162.0, 161.8, 160.9, 160.1, 159.9, 153.7, 153.4, 150.2, 149.0, 148.0, 144.9, 138.6, 138.0, 137.7, 136.7, 136.2, 133.9, 133.0, 131.5, 128.8, 128.4, 127.6, 127.5, 127.1, 126.1, 125.4, 124.6, 123.7, 121.8, 121.1, 119.8, 117.0, 116.4, 116.0, 115.1, 105.6, 100.1, 98.6, 98.1, 97.3, 75.5, 75.2, 74.6, 69.6, 41.6, 28.3, 28.2, 28.1, 19.6, 19.4, 19.3. MS (MALDI-TOF) : m/z = 2240.71 $[M+H]^+$, 2262.69 $[M+Na]^+$, 2278.66 $[M+K]^+$.

Foldamer 1. According to the general boc deprotection procedure, **8** (33 mg, 0.045 mmol), and TFA (222 µL, 2.88 mmol, 64 equiv.) were stirred for 3h in CH_2Cl_2 (1 mL). The tetra-amine intermediate was obtained as a yellow oil (35 mg, quant. Yield). ^{1}H NMR (400MHz, $CDCl_3$/MeOD 3:1 vol:vol) : δ = 6.72 (4H, s), 4.31 (4H, s), 4.08 (8H, s). Octamer acid **4**[2] (122 mg, 0.06 mmol, 4.4 equiv.), HBTU (32 mg, 0.08 mmol, 6 equiv.), HOBT (8mg, 0.06 mmol, 4 equiv.), anhydrous DMF (1.75 mL) and freshly distilled ethyl diisopropylamine (48 µL, 0.28 mmol, 20 equiv.) were stirred for 30min. The amine (11 mg, 0.014 mmol, 1 equiv.) dissolved in DMF (0.55 mL) was added and the reaction was

stirred for 12h. Toluene (15 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with toluene (2×15mL). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with EtOAC/toluene 2:98 to 10:90 vol:vol. A second chromatographic purification was performed using recycling GPC eluting with $CHCl_3$ to yield 50 mg of **1** (44 %). ^{1}H NMR (400MHz, $CDCl_3$) : δ = 10.96 (4H, s), 10.92 (4H, s), 10.58 (4H, s), 10.53 (4H, s), 10.47 (4H, s), 10.19 (4H, s), 10.09 (4H, s), 8.24 (4H, dd, *J*=7.6Hz), 8.11 (4H, d, *J*=8.0Hz), 8.04 (4H, d, *J*=7.2Hz), 8.00-7.95 (8H, m), 7.86 (4H, d, *J*=8.4Hz), 7.75-7.72 (8H, m), 7.56-7.40 (20H, m), 7.24-6.89 (51H, m), 6.70 (4H, t, *J*=8.0Hz), 6.61 (4H, t, *J*=8.0Hz), 6.33 (9H, s), 6.16 (3H, s), 5.92 (3H, s), 5.79 (3H, s), 5.19 (3H, s), 4.10-3.47 (76H, m), 2.61-2.13 (32H, m), 1.37-1.10 (192H, m). MS (MALDI-TOF) : m/z = 8158.20 $[M+H]^+$.

X-ray crystallography

Data were collected using a Rigaku Rapid diffractometer equipped with an MM007 micofocus rotating anode generator with monochromatized Cu-K_α radiation (1.54178 Å) and varimax optics. The data collection, unit cell refinement and data reduction were performed using the CrystalClear software package. The positions of non-H atoms were determined by the program SHELXS 87 and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier Synthesis. H atoms were included for structure factor calculations but not refined.

Single crystals of **1**, $[C_{464}H_{464}N_{70}O_{74}(C_2H_4Cl_2)_6(H_2O)_{31}(CH_3OH)_{13}]$, were grown from 1,2 dichloroethane/methanol. A single yellow crystal of dimensions 0.2 × 0.15 × 0.15 mm was selected, mounted on a cryloop under oil and frozen into a N_2 stream at 140K. Crystals belong to the triclinic space group P-1 with unit cell dimensions: a = 28.1917 (13) Å, b = 29.8945 (13) Å, c = 36.8224 (17) Å, α = 78.369 (3)°, β = 80.612 (3)°, γ = 71.172 (3)°, V = 28608 (2) Å^3, and Z = 2 (FW is 9773.81, ρ = 1.135 Mg m^{-3}). Reflections were collected from 6.51° ≤ θ ≤ 72.35° for a total of 171148 of which 81044 were unique (R_{int} = 0.1222) having I > 2σ (I); number of parameters is 6203. Final *R* factors were R_1 = 0.1926 (I > 2σ (I)), wR_2 = 0.5214 (all data), GOF = 1.018 from SHELX, maximal residual electron density is 0.749 e Å^{-3}. CCDC deposition # 609462.

Single crystals of **2**, $[C_{126}H_{125}N_{19}O_{21}(CHCl_3)_4(H_2O)_5]$, were grown from chloroform/pentane. A single yellow crystal of dimensions 0.20 × 0.15 × 0.10 mm was selected, mounted on a cryloop under oil and frozen into N_2 stream at 153K. Crystals belong to the triclinic space group P-1 with unit cell dimensions: a = 16.7757 (12) Å, b = 20.1283 (15) Å, c = 23.7478 (17) Å, α = 89.778 (5)°, β = 76.890 (5)°, γ = 68.634 (5)°, V = 7245.6 (9) Å^3, and Z = 2 (FW is 2809.00, ρ = 1.288 Mg m^{-3}). Reflections were collected from 6.56° ≤ θ ≤ 72.37° for a total of 24974 unique reflections having I > 2σ (I); number of parameters is

1694. Final *R* factors were R_1 = 0.1522 ($I > 2\sigma(I)$), wR_2 = 0.4218 (all data), GOF = 1.005 from SHELX, maximal residual electron density is 0.955 e $Å^{-3}$. CCDC deposition # 609463.

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[2] H. Jiang, J.-M. Léger, C. Dolain, P. Guionneau, I. Huc, *Tetrahedron* **2003**, *59*, 8365.