Electronic Supplementary Information

Peptoid Nanotubes: An Oligomer Macrocycle That Reversibly Sequesters Water via Single-Crystal-To-Single-Crystal Transformations

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S1 General Experimental Details

Preparative HPLC was performed on a Delta-Pak C18 (Waters, 15 μm, 100 Å, 25 mm _ 100 mm) with a linear gradient of 30–100% acetonitrile/water (0.1% TFA) over 60 min with a flow rate of 2.5 mL/min using a Beckman Coulter System Gold instrument.

Analytical HPLC was performed on a C18 reversed-phase analytical HPLC column at room temperature (Peeke Scientific, 5 μm, 120 Å, 2.0 mm × 50 mm) using a Beckman Coulter System Gold instrument. A linear gradient of 5–95% acetonitrile/water (0.1% TFA) over 10 min was used with a flow rate of 0.7 mL/min.

LC-MS was performed on an Agilent 1100 Series LC/MSD Trap XCT (Agilent Technologies).

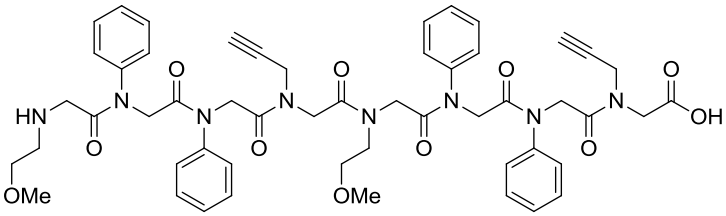
NMR-spectra of peptoids were measured on a Bruker AV 500 high performance digital spectrometer using $CDCl_3$ as solvent. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. All coupling constants (J) are absolute values and are expressed in Hertz (Hz). For assigning signal separation of ^{1}H-NMR spectra the following abbreviations were used: s = singlet, bs = broad singlet, d = doublet, m = multiplet, H_{Ar} = aromatic proton.

S2 Experimental Procedures

General. Solvents and reagents purchased from commercial sources were used without further purification. Abbreviations for reagents are as follows: benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP); trifluoroacetic acid (TFA); 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP); dichloromethane (DCM); *N*,*N*-dimethylformamide (DMF); *N*,*N*-diisopropylcarbodiimide (DIC); diisopropylethylamine (DIPEA); acetonitrile (ACN).

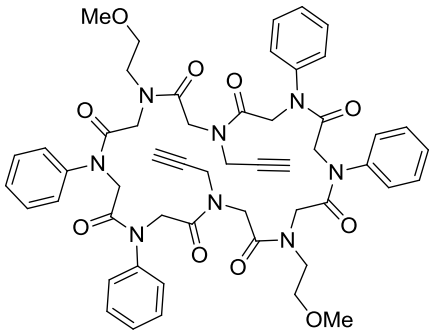
Synthesis of the linear peptoid oligomer

Synthesis of the cyclic peptoid was performed via solid phase peptoid synthesis on 2-Chloro-



trityl chloride resin (Novabiochem, 1.2 mmol/g). 2-Methoxyethyl-amine was used as a submonomer for incorporation of *N*-(methoxy-ethyl)glycine; propargylamine was used as submonomer for the incorporation of *N*-propargyl-glycine and aniline was used as a submonomer for incorporation of *N*-phenylglycine. In a 10 mL fritted plastic syringe, 200 mg of 2-chlorotrityl chloride resin (0.24 mmol, 1.00 equiv.) were washed in 2 mL of DCM, followed by swelling in 2 mL of DCM for 5 min in a fritted syringe. The first submonomer was added by reacting 181 mg of bromoacetic acid (1.30 mmol, 5.40 equiv.) and 214 μL of DIPEA (155 mg, 1.20 mmol, 5.00 equiv.) in 2 mL of DCM on a shaker platform for 40 min at room temperature, followed by washes with DCM (3 × 2 mL) and DMF (3 × 2 mL). Bromoacylated resin was incubated with 2 mL of 1 M amine solution in DMF on a shaker platform at room temperature, followed by washes with DMF (3 × 2 mL). Reaction time was 30 min for propargylamine and 2-methoxyethylamine and 18 h for aniline due to reduced reactivity. The following bromoacetylation was carried out by reacting the resin with 333 mg bromoacetic acid (2.40 mmol, 10.0 equiv.) and 400 µL DIC (326 mg, 2.58 mmol, 10.8 equiv.) in 2 mL DMF. Reaction time was 30 min after incorporation of propargylamine and 2-methoxyethylamine and 2 h after aniline. Coupling steps were continued until the desired peptoid sequence was achieved. After the last amination step, the resin was washed with DMF (2 × 2 mL) and DCM (2 × 2 mL). The linear peptoid was cleaved from the resin using 2 mL 20% HFIP in DCM (v/v) at room temperature for 30 min. The solvent was evaporated under a stream of nitrogen gas. The crude linear peptoid was cyclized without further purification.

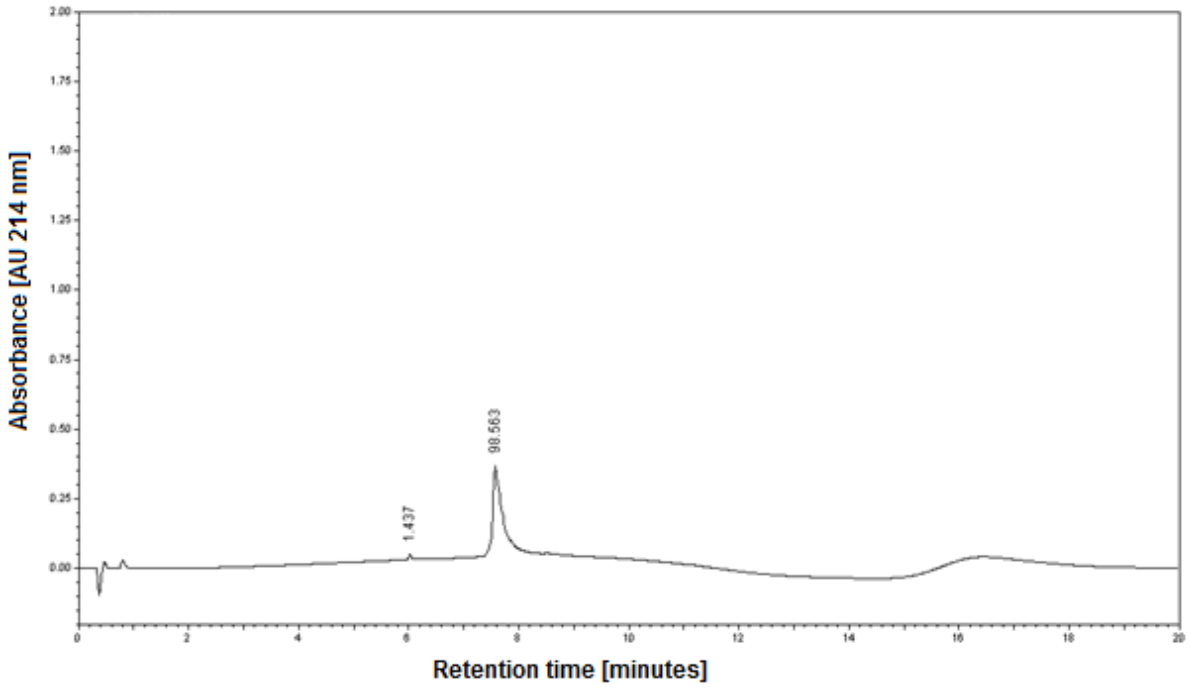
Macrocyclic peptoid



The linear starting material was dissolved in 100 mL dry, deoxygenated DMF to give a 2.4 mM solution. To this solution, 238 µL DIPEA (186 mg, 1.44 mmol, 6.00 equiv.) and 375 mg PyBOP (0.720 mmol, 3.00 equiv.) were added. The reaction was stirred at room temperature for 30 min and the solvent removed under reduced pressure. The crude yellow oil was purified using preparative HPLC (30–100 % ACN in 40 min, retention time: 22.5 min, detection at 230 nm). After purification and lyophilization, 10.8 mg (10.8 µmol, 4.5%) of the product could be obtained as a white powder. Mass calculated: 953.05 g/mol, mass found: 975.0 $[M+Na]^+$. Clear, white, plate-like crystals could be obtained by slow evaporation from methanol at room temperature.

^{1}H-NMR (500 MHz, $CDCl_3$) δ [ppm]: 2.20 (s, 2 H, 2 × C*H*), 3.19 (s, 6 H, 2 × CH_3), 3.23–3.26 (m, 2 H, 2 × OCH_2CHH), 3.36 (bs, 4 H, OCH_2), 3.60–3.63 (m, 4 H, 2 × PhNC*H*HCONCH_2CCH, 2 × OCH_2CHH), 3.72 (d, ^2J=16.8 Hz, 2 H, 2 × HC≡CCH_2NC*H*HCON$(CH_2)_2$OMe), 3.82 (d, ^2J = 17.5 Hz, 2 H, 2 × NC*H*HC≡CH), 3.88–3.92 (m, 2 H, 2 × PhNC*H*HCONPh), 3.99–4.03 (m, 4 H, 2 × MeO$(CH_2)_2$NC*H*HCONPh, 2 × PhNC*H*HCONPh, 4.43 (d, ^2J = 17.7 Hz 2 H, 2 × MeO$(CH_2)_2$NC*H*HCONPh), 4.83 (d, ^2J = 17.1 Hz, 2 H, 2 × PhNC*H*HCONCH_2CCH), 4.93 (d, ^2J = 17.5 Hz, 2 H, 2 × NC*H*HC≡CH), 5.39 (d, ^2J = 16.8 Hz, 2 H, 2 × HC≡CCH_2NC*H*HCON$(CH_2)_2$OMe), 7.33–7.43 (m, 16 H, H_{Ar}), 7.51–7.52 (m, 4 H, H_{Ar}).

HPLC-trace of cyclic peptoid 5



S3 Single Crystal Structure Determination: Experimental Description

A plate-like crystal with the size of 0.55 × 0.54 × 0.16 mm^3 was selected for geometry and intensity data collection with a Bruker SMART APEXII CCD area detector on a D8 goniometer. The temperature during the data collection was controlled with an Oxford Cryosystems Series 700+instrument. Preliminary lattice parameters and orientation matrices were obtained from three sets of frames. Data were collected using graphite-monochromated and 0.5 mm-MonoCap-collimated Mo-K_α radiation (λ = 0.71073 Å) with the ω and ϕ scan method.[S1] Data were processed with the INTEGRATE program of the APEX2 software[S1] for reduction and cell refinement. Multi-scan absorption corrections were applied by using the SCALE program for area detector. The structure was solved by the direct method and refined on F^2 (SHELXTL).[S2] Non-hydrogen atoms were refined with anisotropic displacement parameters. For the structure **1**, **3**, **4**, **6**, and **8**, the occupancy of the water molecule was refined. For the structure **2a**, **2b**, **5**, and **7**, the occupancy refinement of the water molecule resulted in insignificant values, therefore water was removed in the final refinement of these structures. Hydrogen atoms on carbons were placed in idealized positions (C-H = 0.95 or 0.99 Å) and included as riding with *U*iso(H) = 1.2 *U*eq(non-H); the hydrogen atom on oxygen was refined freely. Data collection parameters and refinement results are listed in Table S1.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. 887682 (**1**), 887683 (**2a**), 887684 (**2b**), 887685 (**3**), 887686 (**4**), 887687 (**5**), 887688 (**6**), 887689 (**7**), and 887690 (**8**). Copies of available material can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table S1a. Crystal data for structures **1**−**4**.

Structure #		**1**	**2a**	**2b**	**3**	**4**
Chemical formula		$C_{52}H_{56}N_8O_{10}\cdot(H_2O)_{0.194}$	$C_{52}H_{56}N_8O_{10}$	$C_{52}H_{56}N_8O_{10}$	$C_{52}H_{56}N_8O_{10}\cdot(H_2O)_{0.223}$	$C_{52}H_{56}N_8O_{10}\cdot(H_2O)_{0.438}$
Water content (mol%)*		19.4(6)	0	0	22.3(6)	43.8(7)
Formula weight (M)		956.52	953.05	953.05	957.06	960.93
Crystal system		Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group		*C* 2/*c*	*C* 2/*c*	*C* 2/*c*	*C* 2/*c*	*C* 2/*c*
Temp. (K)		100	295	100	100	100
Z		4	4	4	4	4
Unit cell	***a* (Å)**	26.2161(19)	26.328(2)	26.2136(17)	26.2149(18)	26.236(2)
	***b* (Å)**	8.8142(6)	8.8744(7)	8.8077(6)	8.8110(6)	8.8244(7)
	***c* (Å)**	21.7727(16)	22.0441(17)	21.7438(14)	21.7702(15)	21.8128(17)
	***β* (°)**	106.8540(10)	106.8840(10)	106.8260(10)	106.8700(10)	106.8960(10)
	***V* (Å^3)**	4815.0(6)	4928.6(7)	4805.3(5)	4812.1(6)	4832.0(7)
Total ref. no.		75014	64702	66383	35559	35860
Independent ref. no.		5992	5681	5982	5984	5999
Ref. no. with I > 2σ(I)		5309	4293	5285	4804	4739
R_{int}		0.0401	0.0358	0.0390	0.0482	0.0536
R_1 ***(I > 2σ(I))***		0.0367	0.0451	0.0372	0.0395	0.0410
wR^2 ***(all)***		0.0991	0.1287	0.0990	0.0996	0.1060
S (I > 2σ(I))		1.045	1.033	1.035	1.044	1.055

***** These values are based on the occupancy refinement of the water molecule. When the absolute value is close or smaller than the standard uncertainty, water was removed from the refinement and zero was listed here.

Table S1b. Crystal data for structures **5**−**8**.

Structure #		**5**	**6**	**7**	**8**
Chemical formula		$C_{52}H_{56}N_8O_{10}$	$C_{52}H_{56}N_8O_{10}\cdot(H_2O)_{0.449}$	$C_{52}H_{56}N_8O_{10}$	$C_{52}H_{56}N_8O_{10}\cdot(H_2O)_{0.145}$
Water content (mol%)*		0	44.9(7)	0	14.5(6)
Formula weight (M)		953.05	961.11	953.05	955.66
Crystal system		Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group		*C* 2/*c*	*C* 2/*c*	*C* 2/*c*	*C* 2/*c*
Temp. (K)		295	100	295	100
Z		4	4	4	4
Unit cell	***a* (Å)**	26.331(2)	26.2216(14)	26.3406(11)	26.215(3)
	***b* (Å)**	8.8767(7)	8.8212(5)	8.8751(4)	8.8119(8)
	***c* (Å)**	22.0413(17)	21.8021(11)	22.0453(9)	21.748(2)
	***β* (°)**	106.8470(10)	106.9180(10)	106.8860(10)	106.862(2)
	***V* (Å^3)**	4930.6(7)	4824.7(4)	4931.4(4)	4807.8(8)
Total ref. no.		49128	75423	49912	44922
Independent ref. no.		6136	6005	6126	5991
Ref. no. with I > 2σ(I)		4619	5307	4921	4937
R_{int}		0.0296	0.0321	0.0209	0.0452
R_1 *(I > 2σ(I))*		0.0468	0.0378	0.0483	0.0387
wR^2 *(all)*		0.1365	0.1023	0.1409	0.0498
S (I > 2σ(I))		1.039	1.055	1.047	1.030

***** These values are based on the occupancy refinement of the water molecule. When the absolute value is close or smaller than the standard uncertainty, water was removed from the refinement and zero was listed here.

Table S2. Hydrogen bond geometry [Å].

Structure #	***D*-H…*A***	***D*-H**	**H…*A***	***D*…*A***	**∠*D*-H…*A***
1	O6-H6O···O5	0.88(8)	1.99(8)	2.871(5)	175(6)
3	O6-H6O···O5	0.77(8)	2.11(9)	2.878(5)	173(7)
4	O6-H6O···O5	0.87(5)	2.03(5)	2.885(3)	166(4)
6	O6-H6O···O5	0.85(5)	2.04(5)	2.881(2)	173(4)
8	O6-H6O···O5	0.91(11)	1.97(11)	2.873(7)	173(9)
Average	O6-H6O···O5	0.86(7)	2.03(8)	2.878(4)	172(6)

Table S3. Torsion angles measured according to ref. S3 from the crystal structure of the cyclic peptoid. Due to the C_2 symmetry, the torsion angles are repeated within the macrocycle. Residue numbering is given in Scheme 1 the main text.

Residue	ω	φ	ψ	χ_1
1,5	9.7	87.1	176.6	−56.2
2,6	173.3	−76.8	175.2	89.5
3,7	162.1	−73.3	176.9	−40.3
4,8	16.1	69.8	−175.3	−91.6

Dehydration and hydration experiments:

1) A crystal from the sample was taken (Fig. S1) from the crystallization vial and put under a cold nitrogen stream for X-ray data collection at 100 K. Structure refinement indicated 19.5 mol% water. (Data set: **1**).

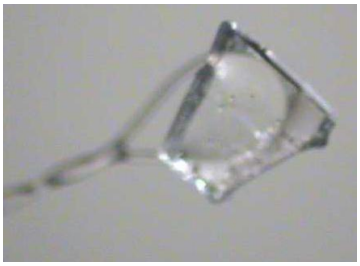


Figure S1. Crystal picked for evaluation of the SCSC-transformation.

2) Afterwards, the crystal was warmed up to room temperature and dried under ambient conditions for 4 h (Fig. S2). The second data set was taken (**2a**) at 295 K showing no residual water in the crystal.

Figure S2. Crystal after drying it at room temperature and the second data collection at 295 K.

3) Another data set was collected at 100 K (Fig. S3) in order to have better refined results for comparison (**2b**). This data also confirmed that after drying no water was left in the crystal.

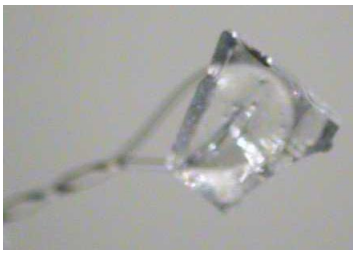


Figure S3. Dried crystal for X-ray analysis at 100 K.

4) The crystal was warmed up to 295 K (Fig. S4). The whole sample with the crystal holder was put into a glass bottle filled with wet paper towels in order to generate a humid environment. The sample holder was kept in this environment for 2 h and was analyzed at 100 K. The collected data (**3**, Fig. S5) showed rehydration to 22.3(6) mol%.

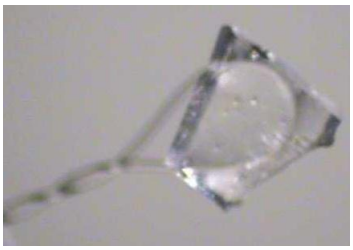


Figure S4. Dried crystal before rehydration experiment.

Figure S5. Rehydrated crystal after 2 h in a humid environment

5) For enhancing the water content, the sample holder with the crystal was put back into the glass bottle and left there for 20 h. Data was collected at 100 K (**4**, Fig. S6) again at 100 K. According to structure refinement the crystal had a water content of 43.8(7) mol%.

Figure S6. Crystal after 20 h in humid environment.

6) Another drying experiment was performed. Therefore, the crystal was dried under ambient conditions for 1 d. Data was collected (**5**, Fig. S7) at room temperature

(295 K) showing complete loss of water after this time period and also complete reversibility of the hydration and dehydration process.

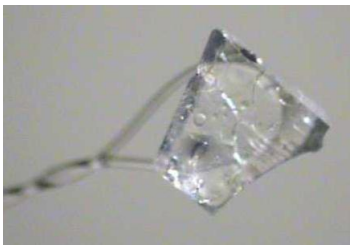


Figure S7. Crystal after 1 d at room temperature showing no residual water in X-ray crystallographic data.

7) For enhancing the water content in the crystal, the sample holder with the crystalline peptoid was put into the glass bottle for 5 d. Data collection at 100 K (**6**) again showed a water content of 44.9(7) mol% indicating that this is about the most water content possible in the crystal lattice (Fig. S8). The crystal had to be moved during the mounting.

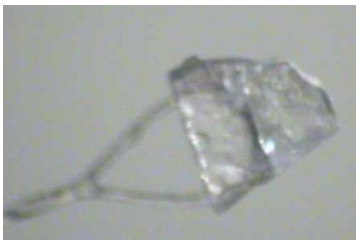


Figure S8. Crystal after hydration for 5 d.

8) Data collection after warming the crystal to room temperature showed complete water loss (**7**, Fig. S9).

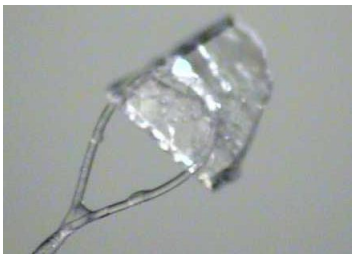


Figure S9. Crystal after warming up to room temperature. Structure refinement showed no remaining water in the crystal.

9) Another experiment for enhancing the water content was performed by placing the dry crystal in an open glass vial which was put into a larger vial filled with 1 mL water. The large vial was closed and heated to 90 °C for 12 h. X-ray data analysis at 100 K (Figure S10) gave a water content of only 14.5(6) mol% (**8**).

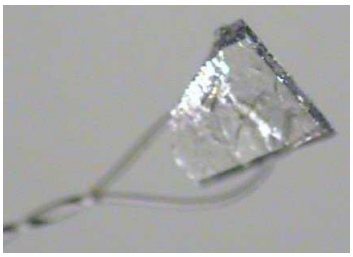
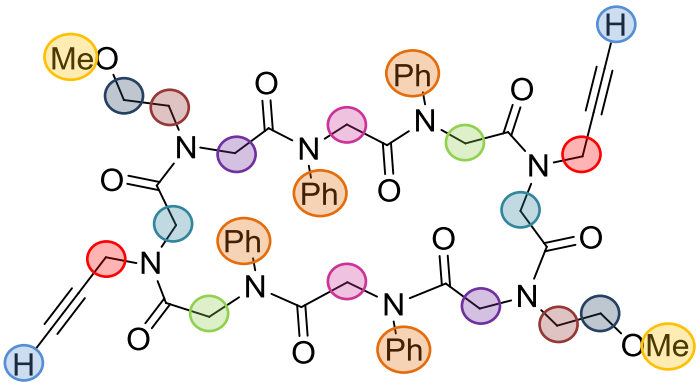
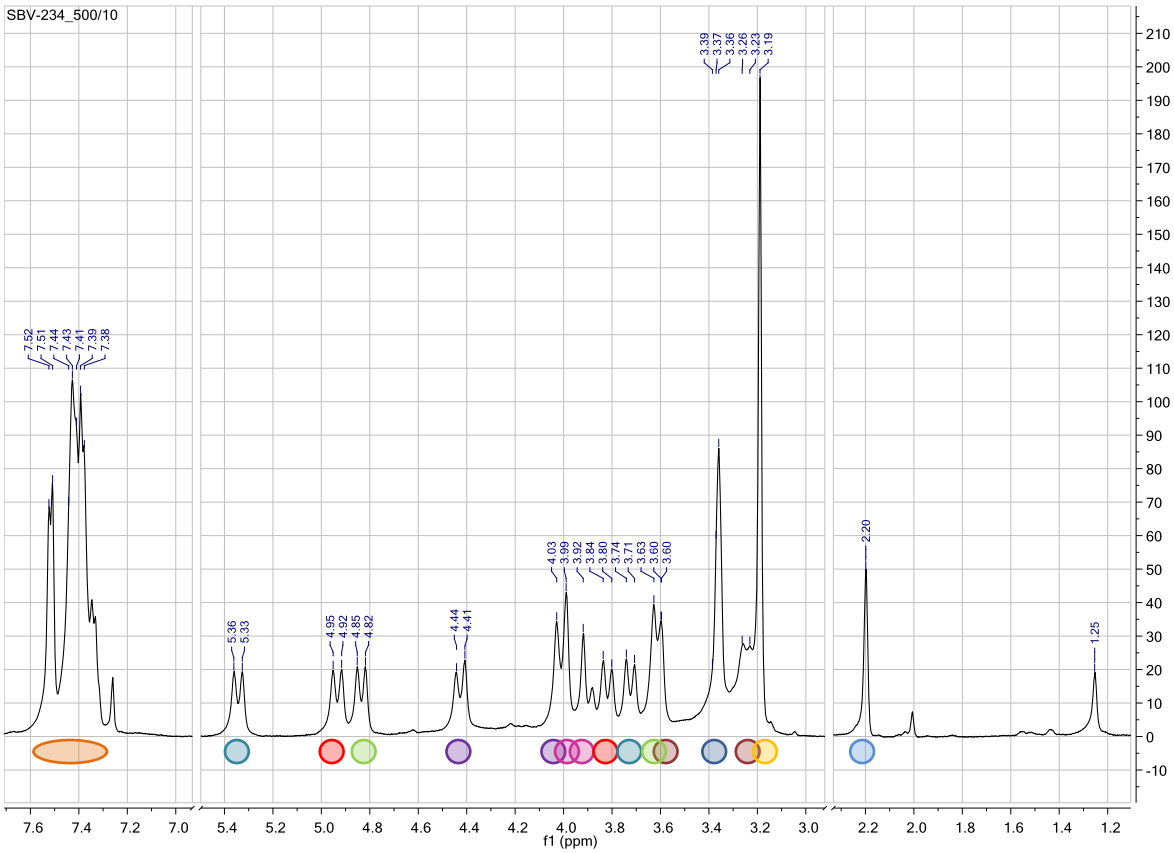


Figure S10. Crystal after 12 h at 90 °C. The water content could not be enhanced further.

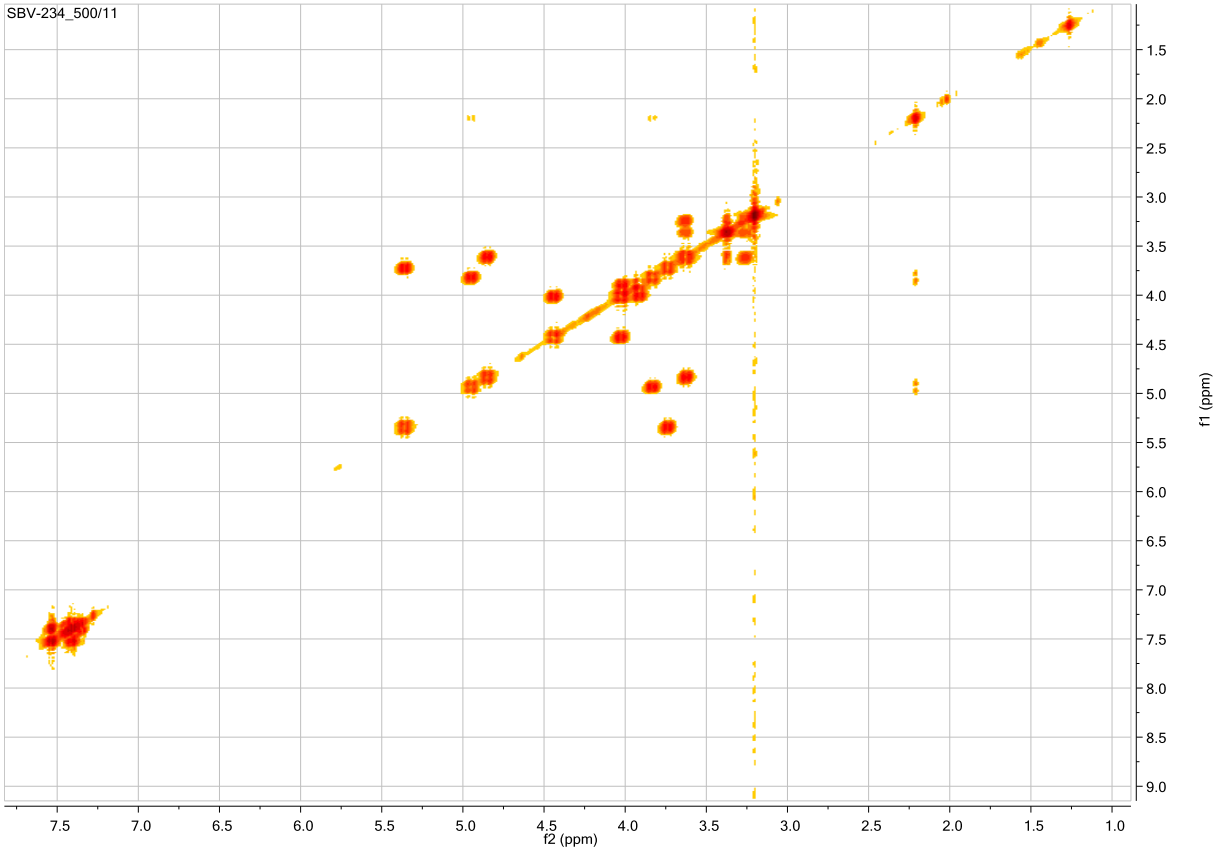
S4NMR-data of macrocyclic peptoid 5

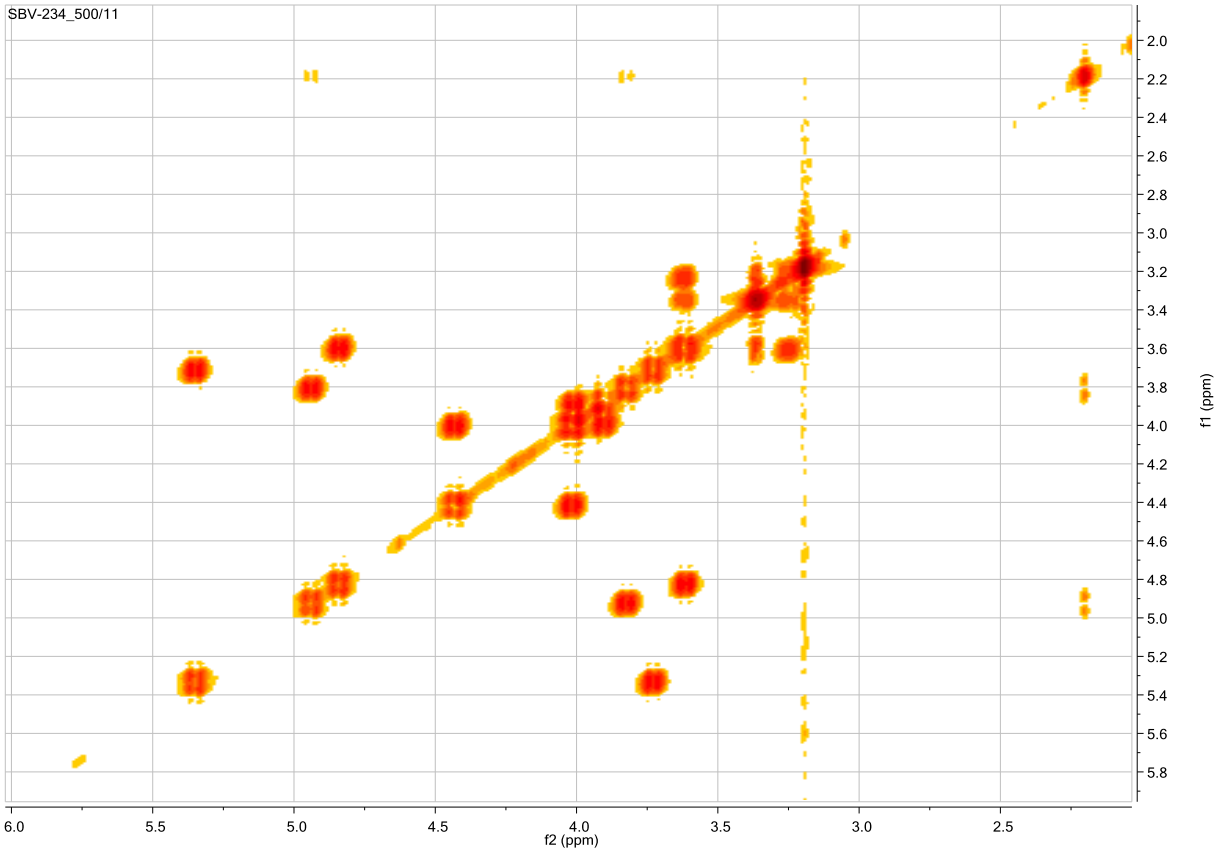
4.1 ^{1}H-NMR



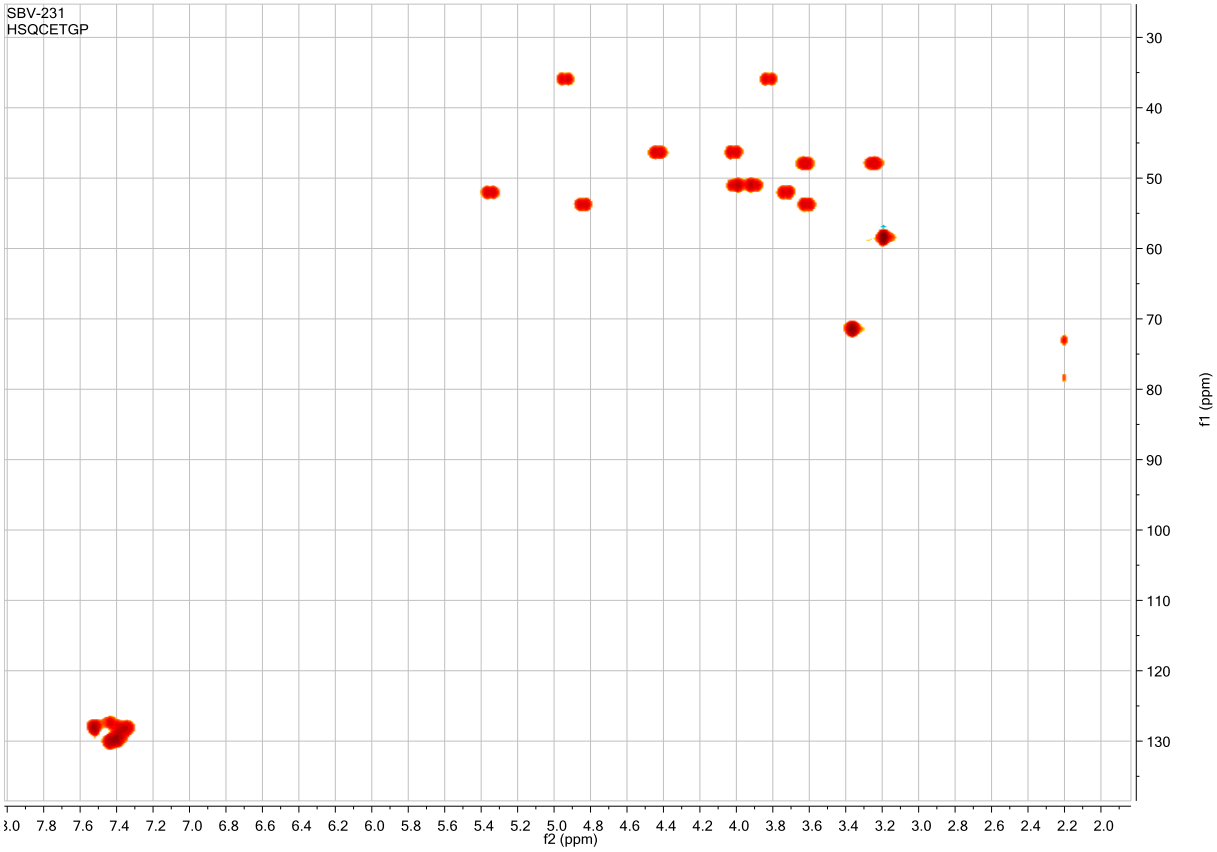


4.2 COSY

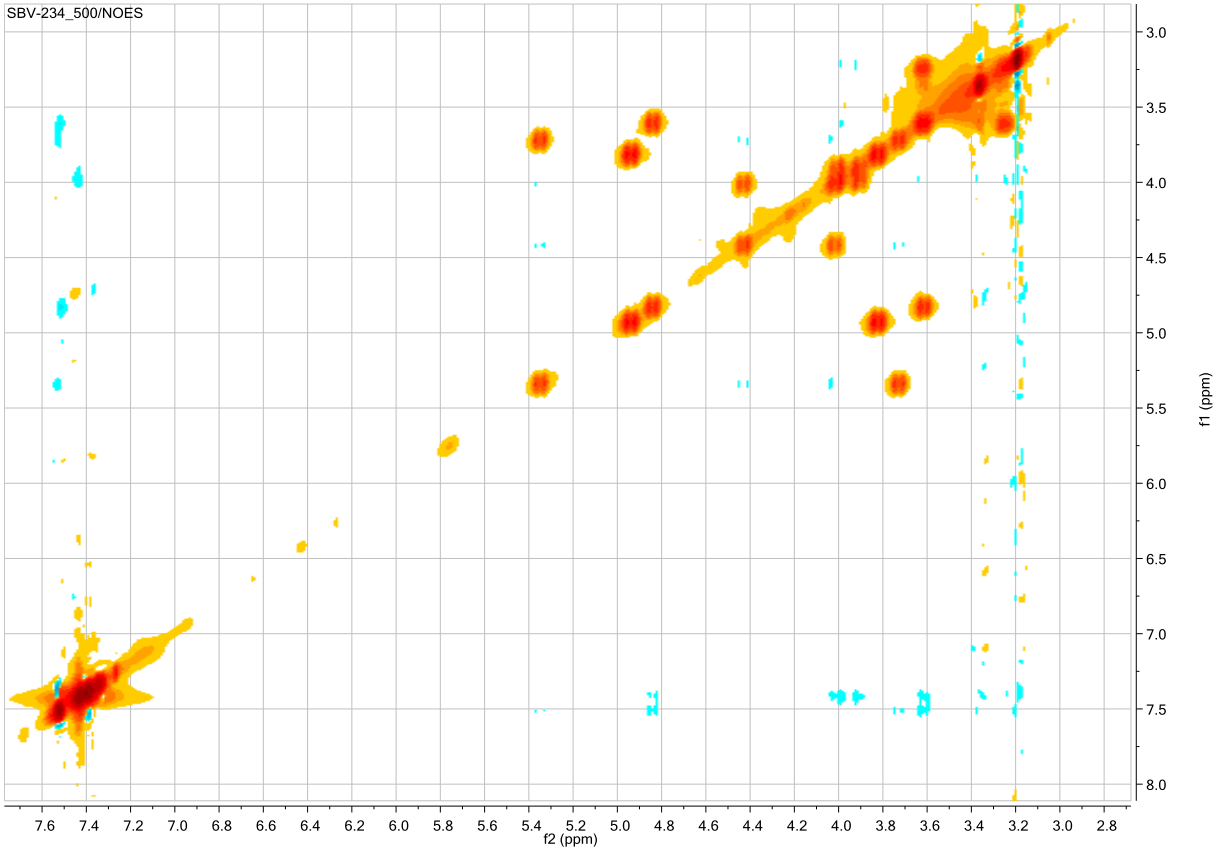




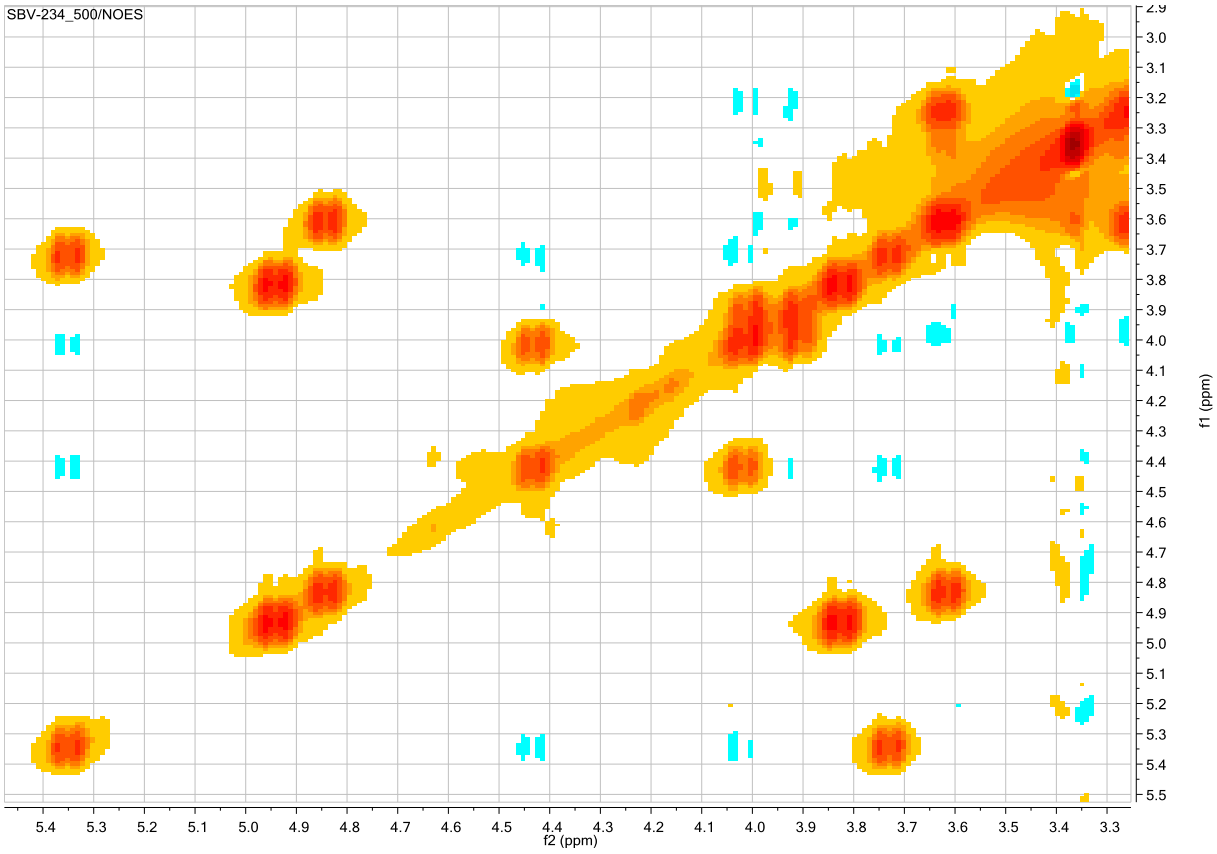
4.3 HSQC



4.4 NOESY



NOESY magnified region for backbone methylene groups.



Magnified region of the backbone methylene groups. Strong signals in orange derive from ^{2}J-coupling of the glycine H. In light blue, the couplings over distance between neighboring glycines are visible.

S5 Literature

S1 APEX2 (version 2009.11-0). *Program for Bruker CCD X-ray Diffractometer Control*, Bruker AXS Inc., Madison, WI, 2009.

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S3 N. H. Shah, G. L. Butterfoss, N. Khanh, B. Yoo, R. Bonneau, D. L. Rabenstein, K. Kirshenbaum, *J. Am. Chem. Soc.* 2008, **130**, 16622–16632.