Supporting Information

A Chiral "Siamese-Twin" Calix[4]pyrrole Tetramer

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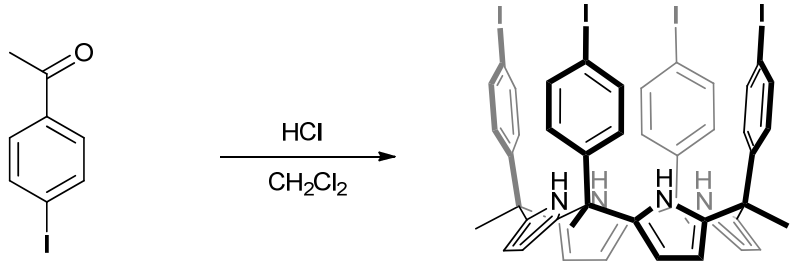
Table of Contents

1. General Methods and Instrumentation

Starting materials and reagents were purchased from Sigma Aldrich and used as received. All reactions were performed under Ar atmosphere unless specified. Anhydrous solvents were obtained from a solvent purification system SPS-400-6 from Innovative Technologies, Inc. All solvents were of HPLC grade quality, commercially obtained and used without further purification. ^{1}H NMR and 2D NMR spectra were recorded on a Bruker Avance II 400 Ultrashield NMR spectrometer. Variable temperature experiments were performed on a Bruker Avance 500 (500.1 MHz for ^{1}H NMR) Ultrashield spectrometer. CD_2Cl_2 and $CDCl_3$ from Sigma Aldrich were used for NMR studies. Chemical shifts are given in ppm, relative to TMS. Mass spectra were recorded on a LCT Premier, Waters-Micromass ESI or Autoflex, Bruker Daltonics MALDI mass spectrometer.

2. Experimental procedures

*Synthesis of Tetraiodo calix[4]pyrrole **10**:*

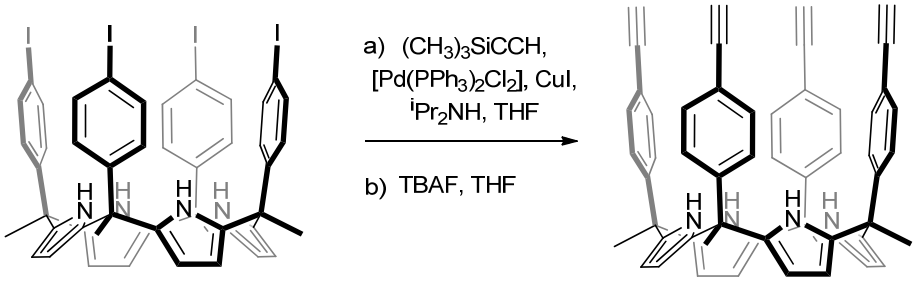


10

In a 500 mL round bottom flask 4'-Iodoacetophenone (10 g, 40.6 mmol) was dissolved in 200 mL of dichloromethane. 1.2 mL of HCl (aq.) (40.6 mmol) was added dropwise followed by the addition over the course of 30 minutes of 1.8 mL of freshly distilled pyrrole (40.6 mmol). The flask was protected from light and the reaction was left stirring 48 hours at room temperature. The precipitated formed was filtered to discard oligomeric pyrrolic by-products and 300 mL of methanol were added to the solution. The solution was concentrated under reduced pressure to remove the dichloromethane and an orange solid precipitated. The solid was filtered and washed with acetonitrile. This crude was recrystallized several times to afford pure α,α,α,α-isomer (1.97 g, 16% yield).

10: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.58 (d, J=8.5Hz, 8H), 7.56 (br, 4H), 6.87 (d, J=8.5Hz, 8H), 5.73 (d, J=2.7Hz, 8H), 1.95 (s, 12H). HRMS-ESI- m/z calcd for $C_{48}H_{39}I_4N_4$ $(M-H)^-$ 1178.9359, found 1178.9338.

*Synthesis of calix[4]pyrrole **5**:*



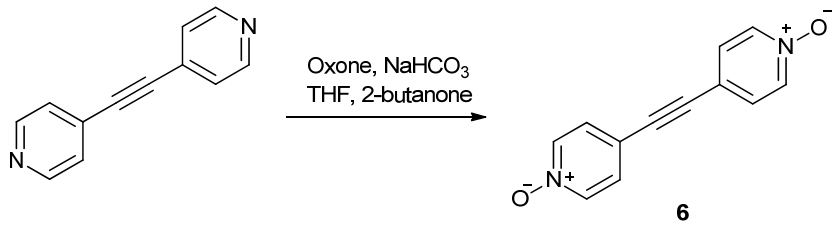
10 **5**

Step 1: A mixture of tetraiodocalixpyrrole **10** (308 mg, 0.261 mmol), $Pd(PPh_3)_2Cl_2$ (36.6 mg, 0.052 mmol), and copper iodide (24.85 mg, 0.130 mmol) was placed in a 50 mL Schlenk tube and dried under high vacuum for one hour. Then, a 1:1 mixture of dry THF:diisopropylamine (20 mL) was added under argon. Finally, trimethylsilylacetylene (293 µL, 2 mmol) was added and the mixture was heated at 80ºC overnight. The reaction crude was concentrated and purified by column chromatography (silica gel, dichloromethane:hexane 1:1) to obtain pure tetra-trimethylsilyl protected calixpyrrole as a white solid (230 mg, 83% yield).

Step 2: The protected calixpyrrole (230 mg, 0.217 mmol) was dissolved in 50 mL of THF in a 100 mL round bottomed flask. Then, tetrabutylammonium fluoride trihydrate was added (383 mg, 2.166 mmol). After three hours the reaction was concentrated and purified by column chromatography (silica gel, dichloromethane) to obtain pure tetraalkyne calixpyrrole **5** almost quantitatively as a white solid.

5: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.64 (br, 4H), 7.39 (d, J=8.2Hz, 8H), 7.08 (d, J=8.2Hz, 8H), 5.74 (d, J=2.6Hz, 8H), 3.06 (s, 4H), 1.98 (s, 12H). HRMS-ESI+ m/z calcd for $C_{56}H_{45}N_4$ $(M + H)^+$ 773.3639, found 773.3639.

*Synthesis of bis-N-oxide **6**:*

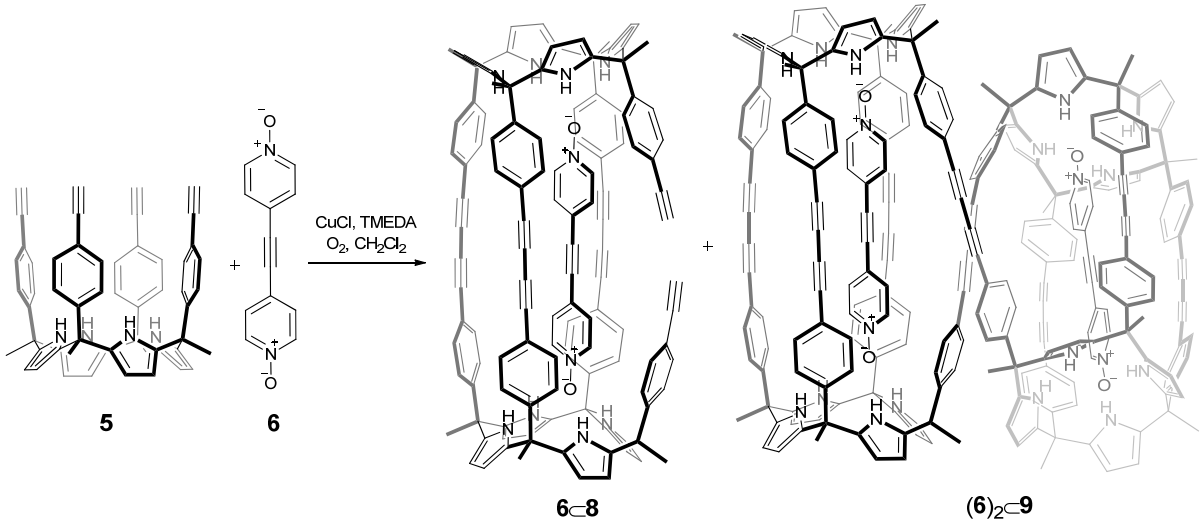


6

1,2-di(pyridin-4-yl)ethyne[1] (108 mg, 0.6 mmol) was dissolved in a 1:1 mixture of water and 2-butanone (60 mL). Under vigorous stirring, sodium bicarbonate (3 g, 36 mmol) was added followed by small additions of Oxone® (2 g, 3.6 mmol). After one hour the reaction was diluted with brine and extracted three times with chloroform. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure to afford the bis-*N*-oxide as a yellowish solid (64 mg, 50% yield).

6: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.19 (d, J=7.4, 4H), 7.39 (d, J=7.4Hz, 4H). HRMS-ESI+ m/z calcd for $C_{12}H_8N_2NaO_2$ $(M + Na)^+$ 235.0483, found 235.0478.

*Synthesis of **8** and **9***:



5 **6** **6⊂8** **(6)$_2$⊂9**

A mixture of calix[4]pyrrole **5** (50.0 mg, 0.065 mmol) and bis-*N*-oxide **6** (6.9 mg, 0.032 mmol) in a 2:1 molar ratio in 25 mL of CH_2Cl_2 was placed in a round bottom flask. Then, CuCl (20 eq) were added in one portion. Finally, 200 μL of TMEDA were added (20 eq). The reaction was stirred at room temperature for 5 hours in the presence of O_2. The organic phase was washed successive times with 10 mL of water until the aqueous layer showed no presence of copper.

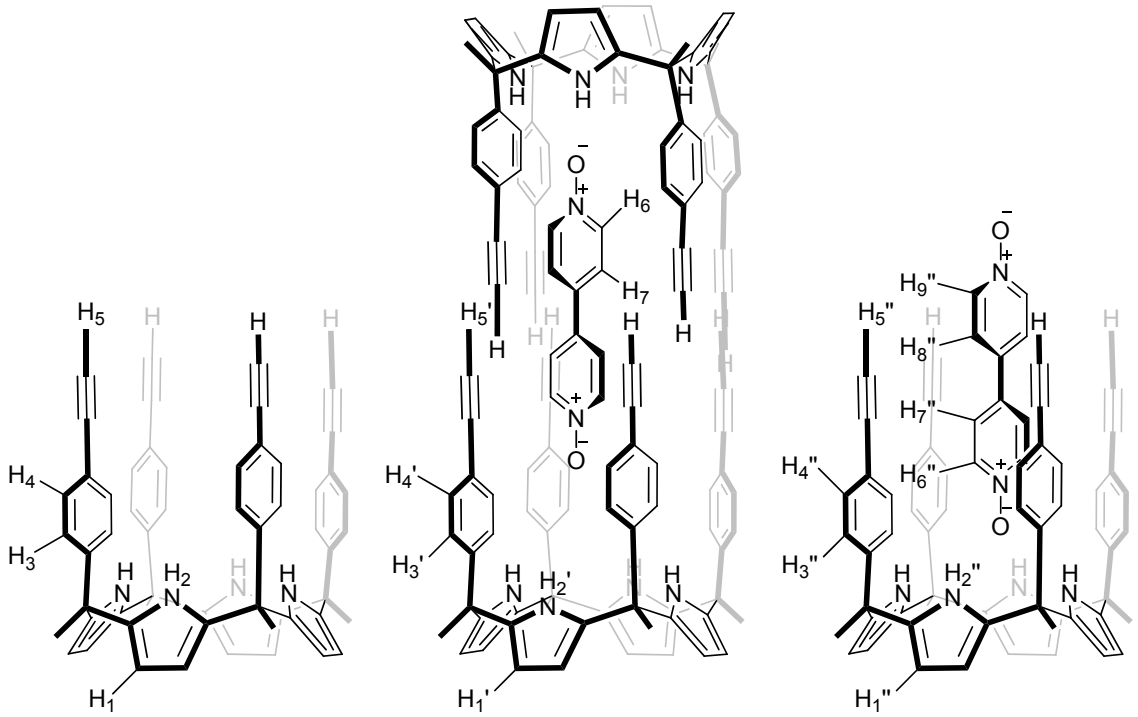
[1] P. Nugent, Y. Belmabkhout, S. D. Burd, A. J. Cairns, R. Luebke, K. Forrest, T. Pham, S. Ma, B. Space, L. Wojtas, M. Eddaoudi and M. J. Zaworotko, *Nature*, 2013, **495**, 80-84.

The organic phase was dried with sodium sulfate and the solvent was concentrated. The resulting mixture of products was passed through a silica column using CH_2Cl_2 : Hexane (6:4) as eluent. Two products were isolated in a 5% (**6**⊂**8**, 3 mg) and 35% ((**6**)$_2$⊂**9,** 20 mg) yield.

6⊂**8:** ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.08 (s, 4H), 9.68 (s, 4H), 7.55 (d, J=8.3Hz, 4H), 7.50 (d, J=8.3Hz, 4H), 7.01 (d, J=8.3Hz, 4H), 6.94 (m, 24H), 6.78 (d, J=7.0Hz, 4H), 6.14 (m, 16H), 4.43 (d, J=7.0Hz, 4H), 3.25 (s, 2H), 1.96 (br, 12H), 1.88 (s, 12H). HRMS-ESI+ m/z calcd for $C_{124}H_{90}N_{10}NaO_2$ $(M + Na)^+$ 1773.7140, found 1773.7136.

(**6**)$_2$⊂**9:** ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.35 (s, 4H), 10.17 (s, 4H), 10.0 (s, 8H), 7.65 (d, J=8.0Hz, 8H), 7.53 (br, 8H), 6.94 (m, 48H), 6.14 (m, 32H), 4.49 (d, J=6.9Hz, 8H), 1.98 (br, 12H), 1.90 (s, 12H), 1.86 (s, 12H), 1.74 (s, 12H). HRMS-ESI+ m/z calcd for $C_{248}H_{176}N_{20}Na_2O_4$ $(M + 2Na)^{2+}$ 1771.6984, found 1771.6972.

3. ^{1}H NMR Titration studies with calix[4]pyrrole 5



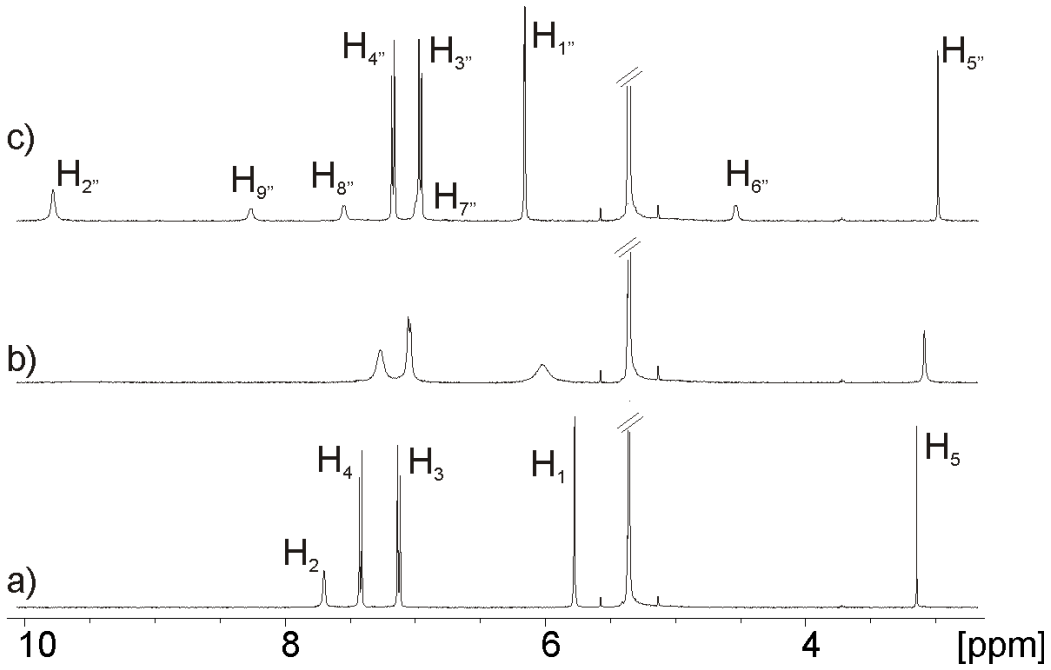


Figure S1. Selected region of the ^{1}H NMR spectra of free **5** (a), 2:1 mixture of **3**:**5** (b) and equimolar mixture of **3**:**5** (c) in CD_2Cl_2.

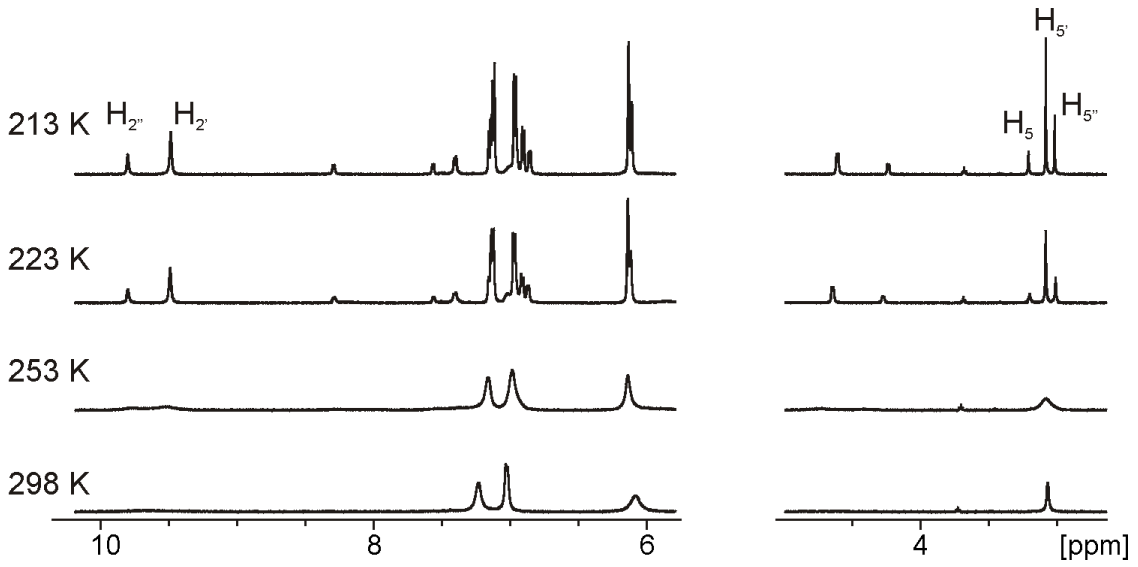


Figure S2. Selected regions of variable temperature ^{1}H NMR spectra of a 2:1 mixture of **3** and **5** in CD_2Cl_2.

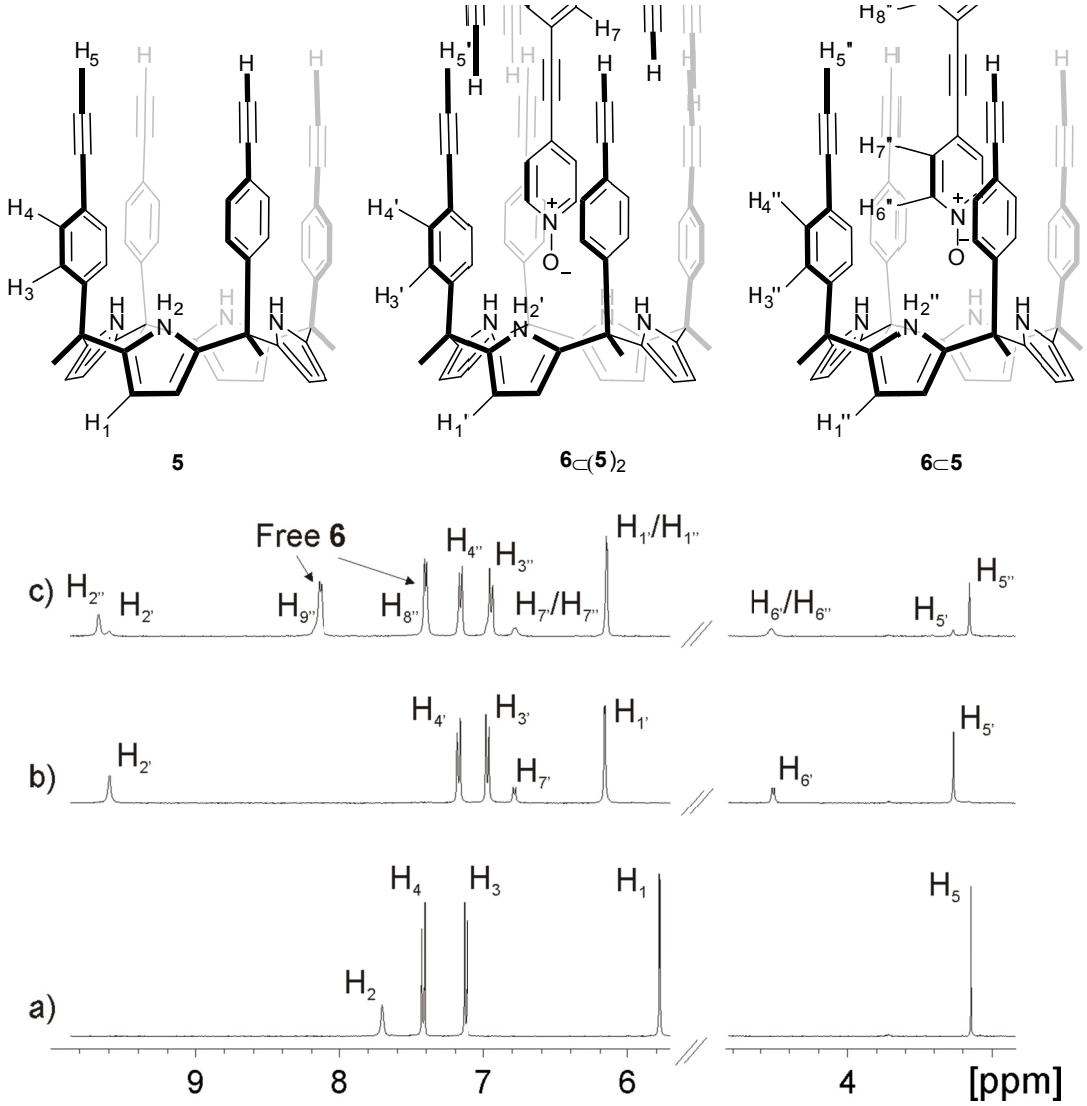


Figure S3. Selected region of the ^{1}H NMR spectra of free **5** (a), 2:1 mixture of **6**:**5** (b) and equimolar mixture of **6**:**5** (c) in CD_2Cl_2.

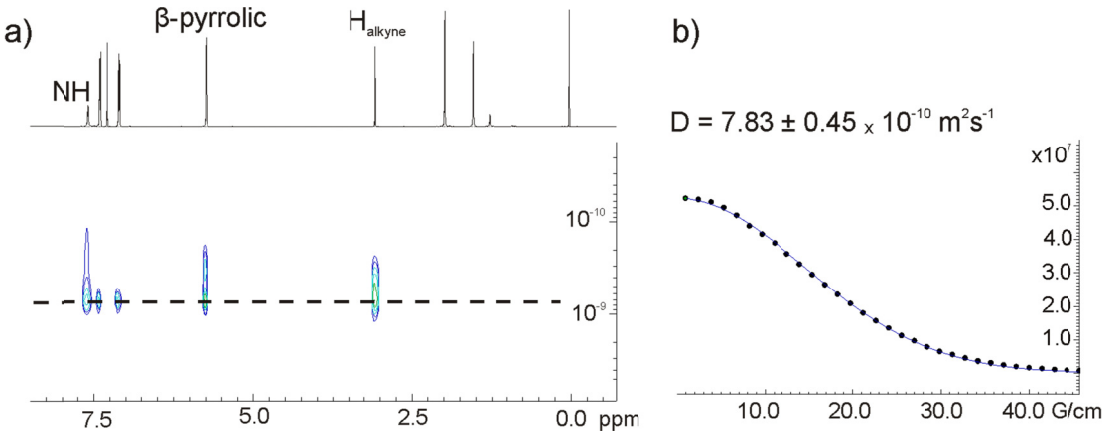


Figure S4. ^{1}H pseudo-2D DOSY profile of calix[4]pyrrole **5** in $CDCl_3$ at 298 K and millimolar concentration (a) and fit of the data to a monoexponential function (b).

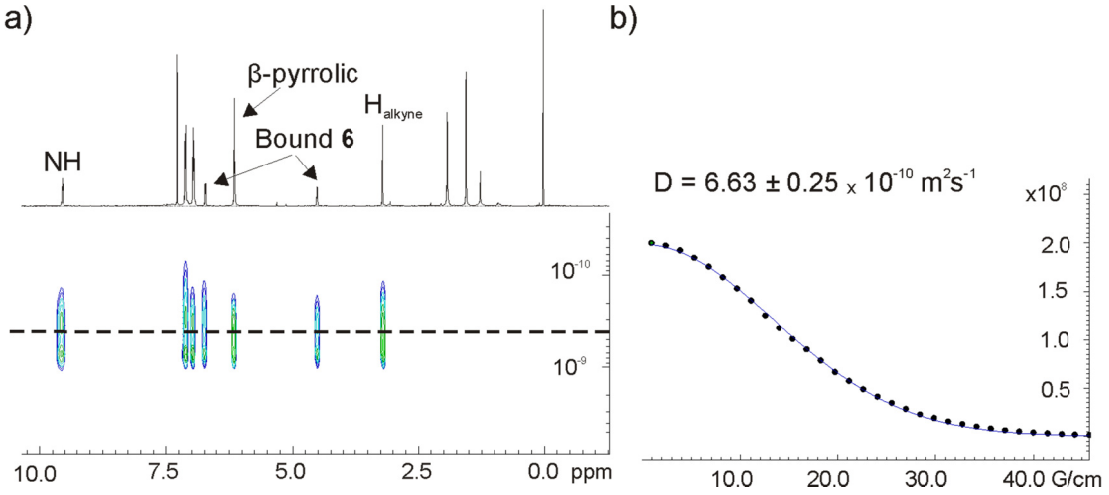


Figure S5. ^{1}H pseudo-2D DOSY profile of a 2:1 mixture of calix[4]pyrrole **5** and bis-*N*-oxide **6** in $CDCl_3$ at 298 K and millimolar concentration (a) and fit of the data to a monoexponential function (b).

4. X-ray crystal structure of homocapsule $6\subset(5)_2$

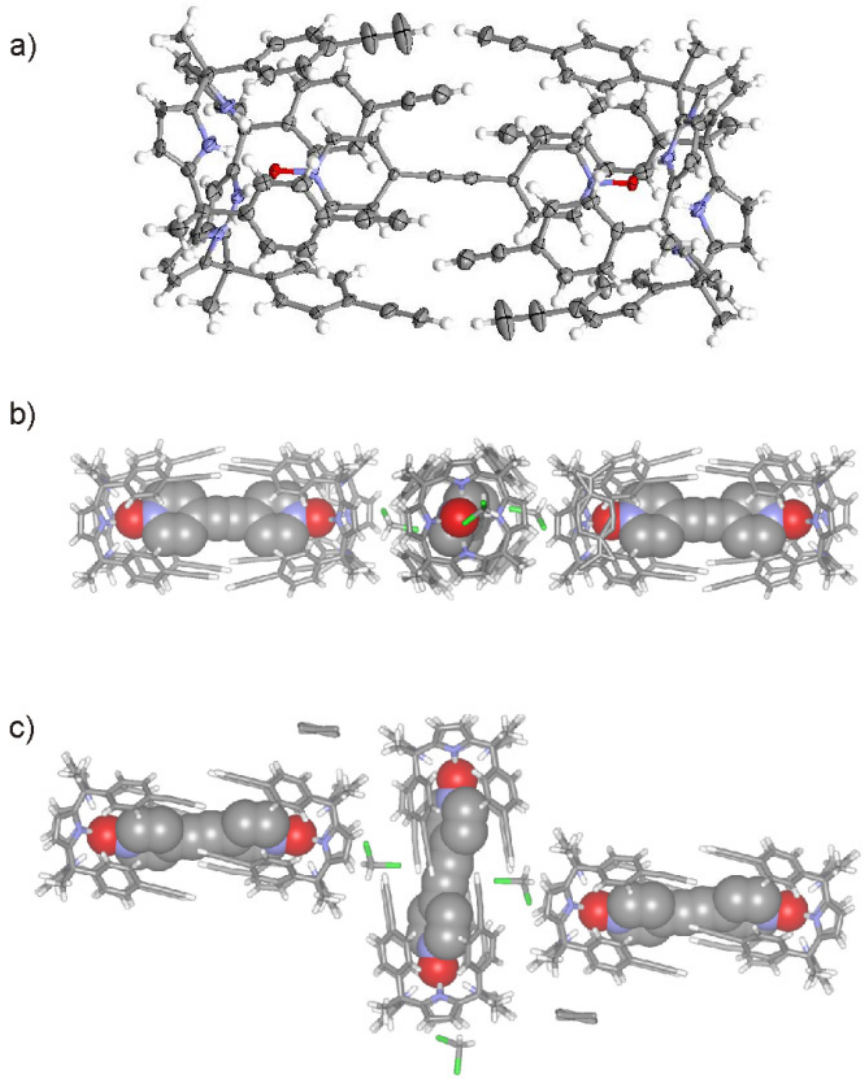


Figure S6. a) X-ray structure of $6\subset(5)_2$ capsule. b) and c) two different views of one layer of packing of the X-ray structure of $6\subset(5)_2$. For clarity, non-polar hydrogen atoms from the guest have been removed. Guest molecules are shown as CPK models and calix[4]pyrrole **5** is depicted in stick representation.

5. Characterization of compounds 6⊂8 and $(6)_2$⊂9

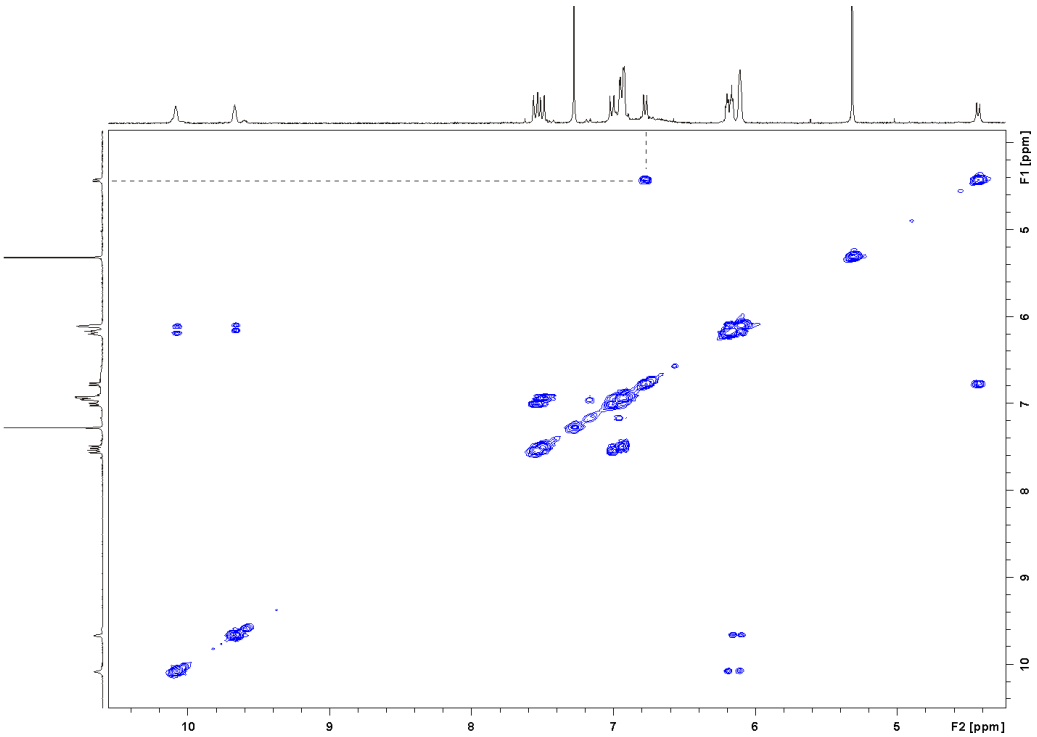


Figure S7. Selected region of COSY NMR spectrum of compound **6⊂8**.

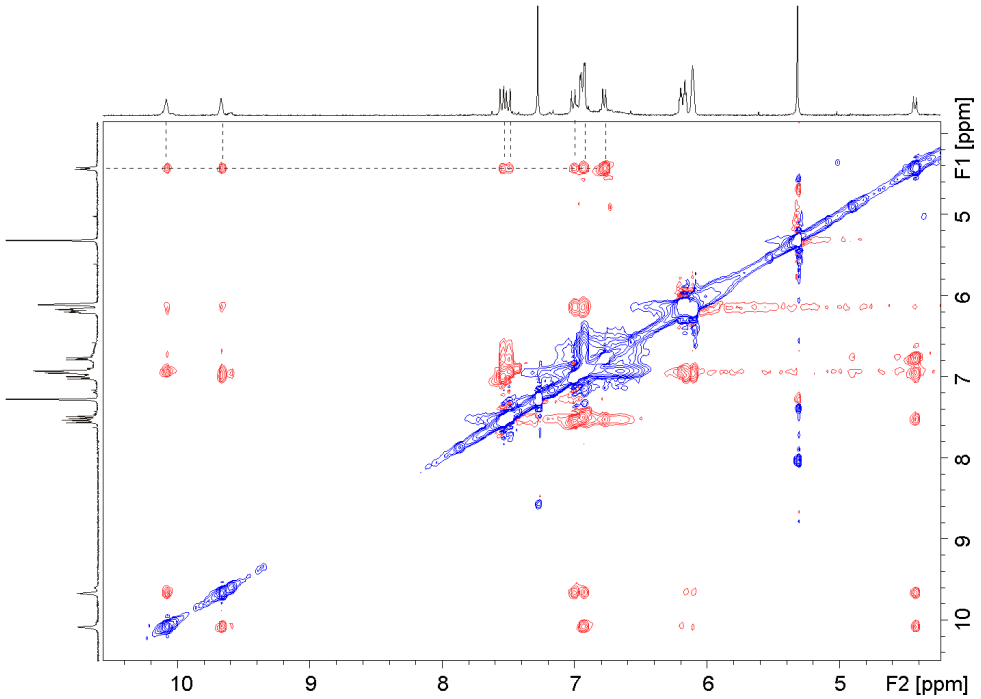


Figure S8. Selected region of ROESY NMR spectrum of compound **6⊂8**.

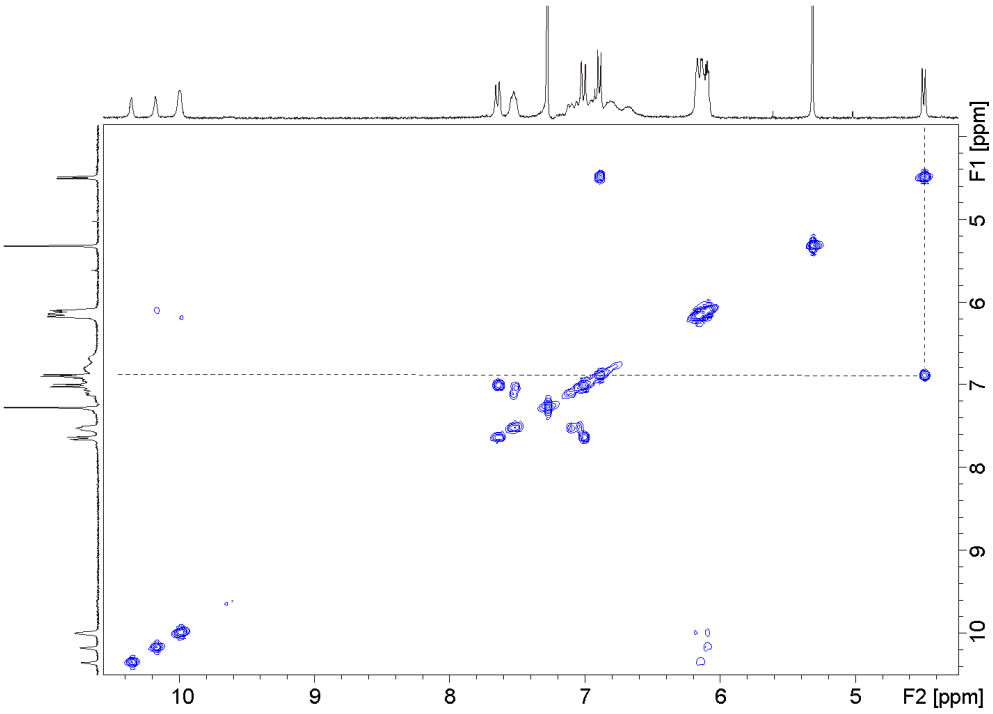


Figure S9. Selected region of COSY NMR spectrum of compound $(\mathbf{6})_2 \subset \mathbf{9}$.

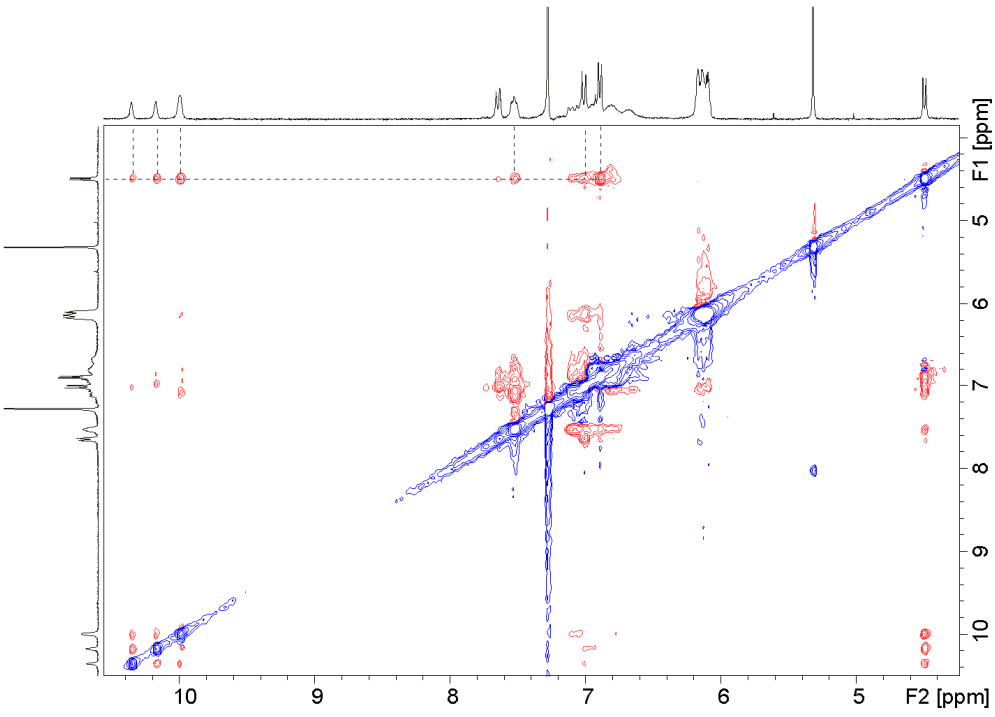


Figure S10. Selected region of ROESY NMR spectrum of compound $(\mathbf{6})_2 \subset \mathbf{9}$.

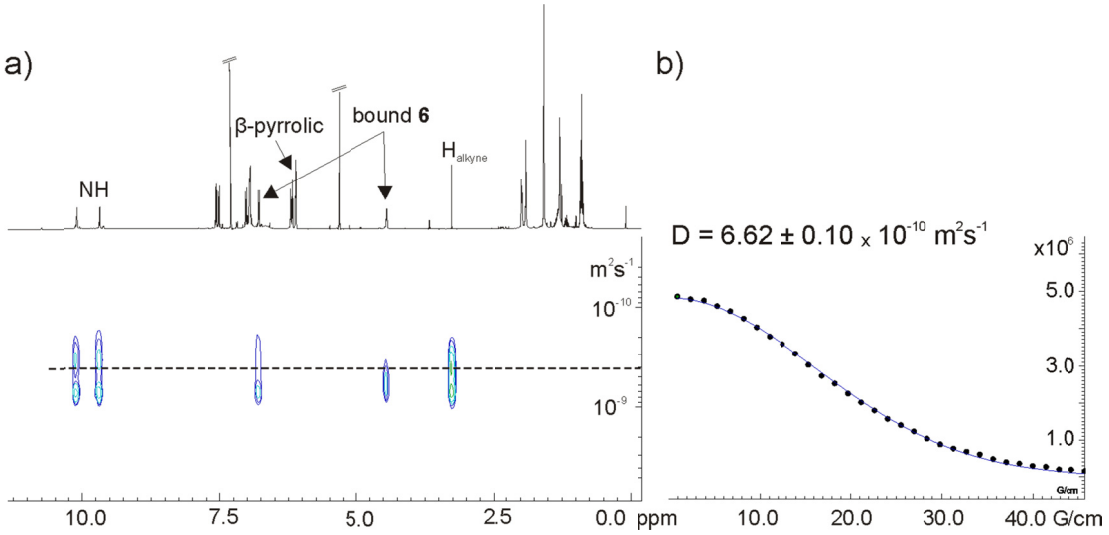


Figure S11. ^{1}H pseudo-2D DOSY profile of molecule **6⊂8** in $CDCl_3$ at 298 K and millimolar concentration (a) and fit of the data to a monoexponential function (b).

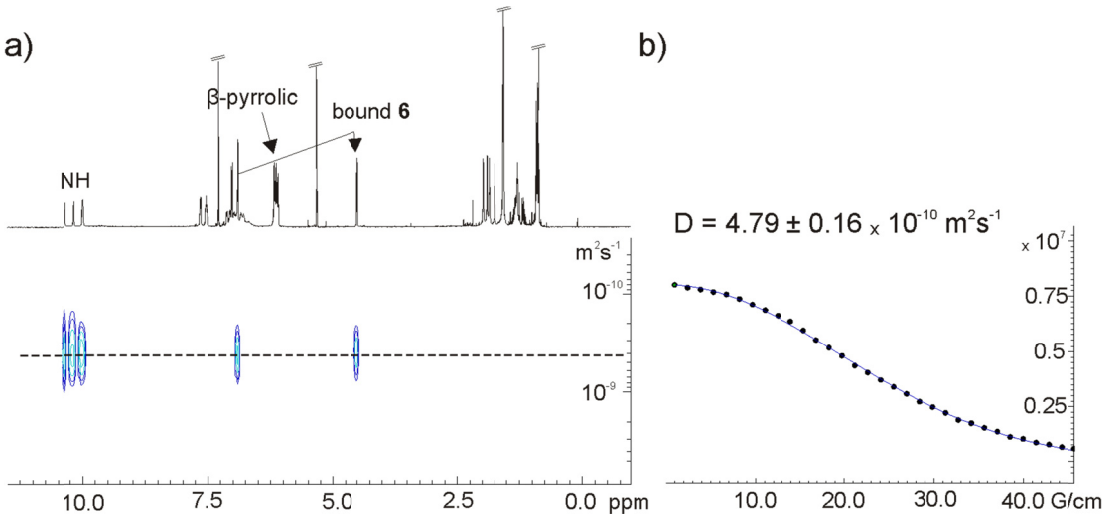


Figure S12. ^{1}H pseudo-2D DOSY profile of molecule $(\mathbf{6})_2$⊂**9** in $CDCl_3$ at 298 K and millimolar concentration (a) and fit of the data to a monoexponential function (b).

6. HRMS spectra

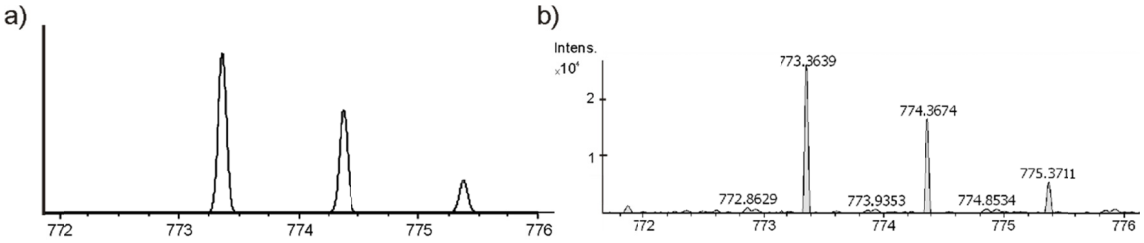


Figure S13. Calculated isotopic pattern of calix[4]pyrrole **5** (a) compared with the experimental one (b).

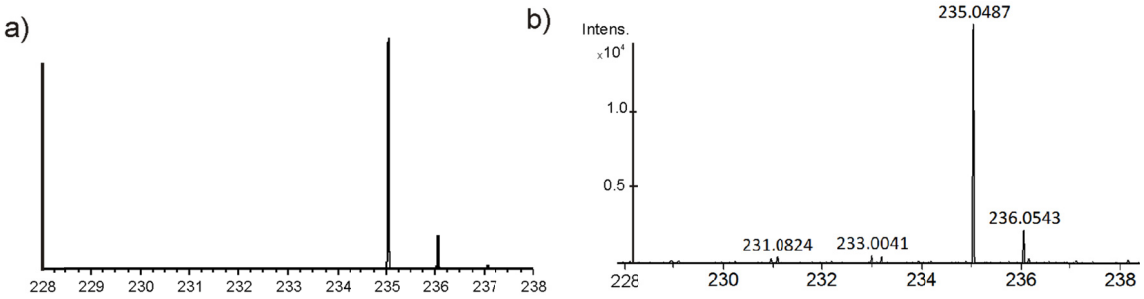


Figure S14. Calculated isotopic pattern of bis-*N*-oxide **6** (a) compared with the experimental one (b).

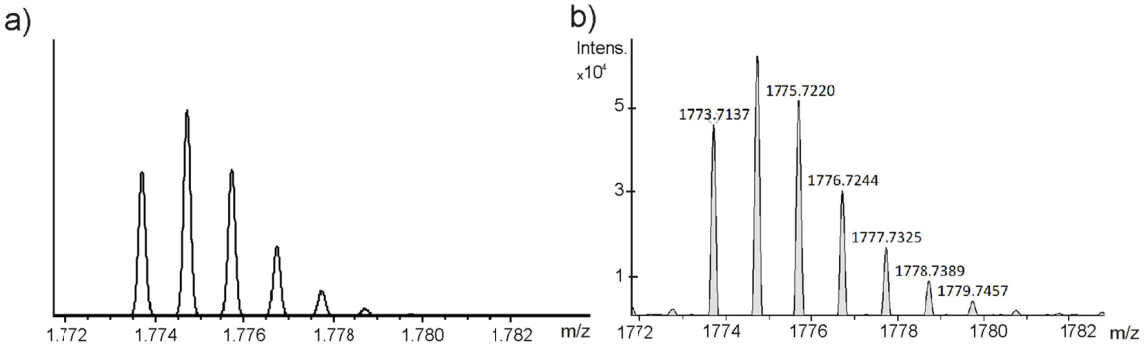


Figure S15. Calculated isotopic pattern of macrocycle **6⊂8** (a) compared with the experimental one (b).

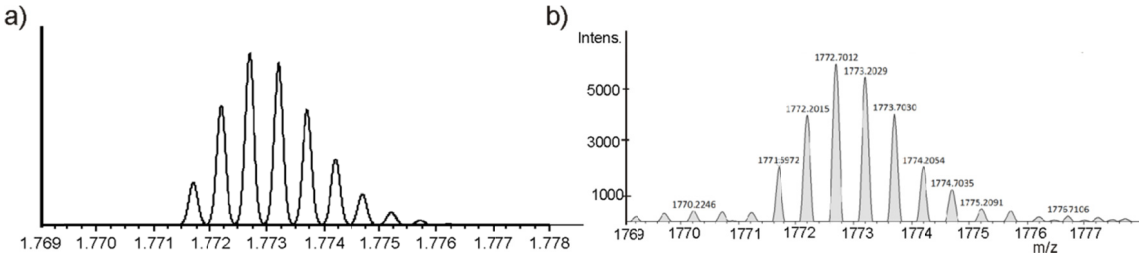


Figure S16. Calculated isotopic pattern of macrocycle $(\mathbf{6})_2\subset\mathbf{9}$ (a) compared with the experimental one (b).

7. Modeling studies

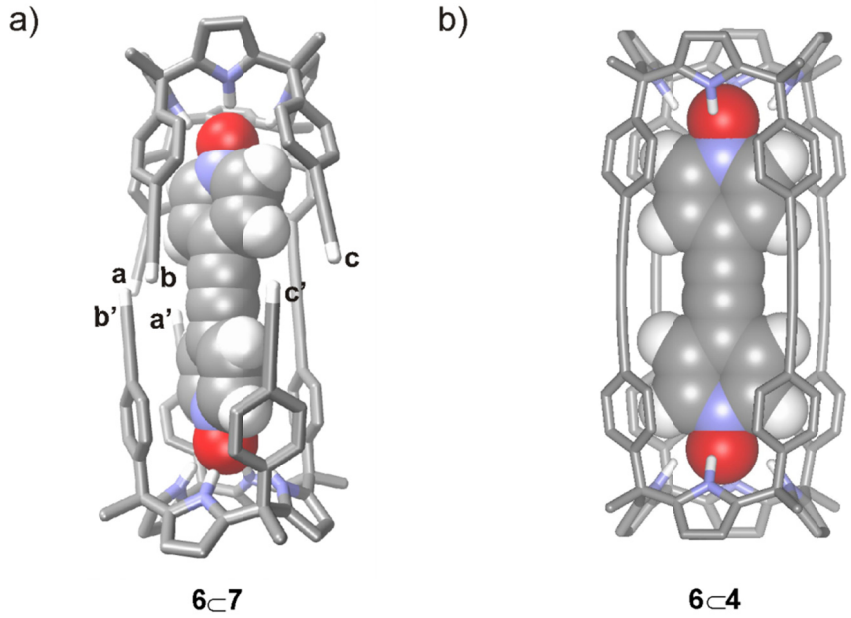


Figure S17. Energy minimized (MM3) structures of the putative **6⊂7** (**a**), and **6⊂4** (b) complexes.

8. Absolute configuration assignment

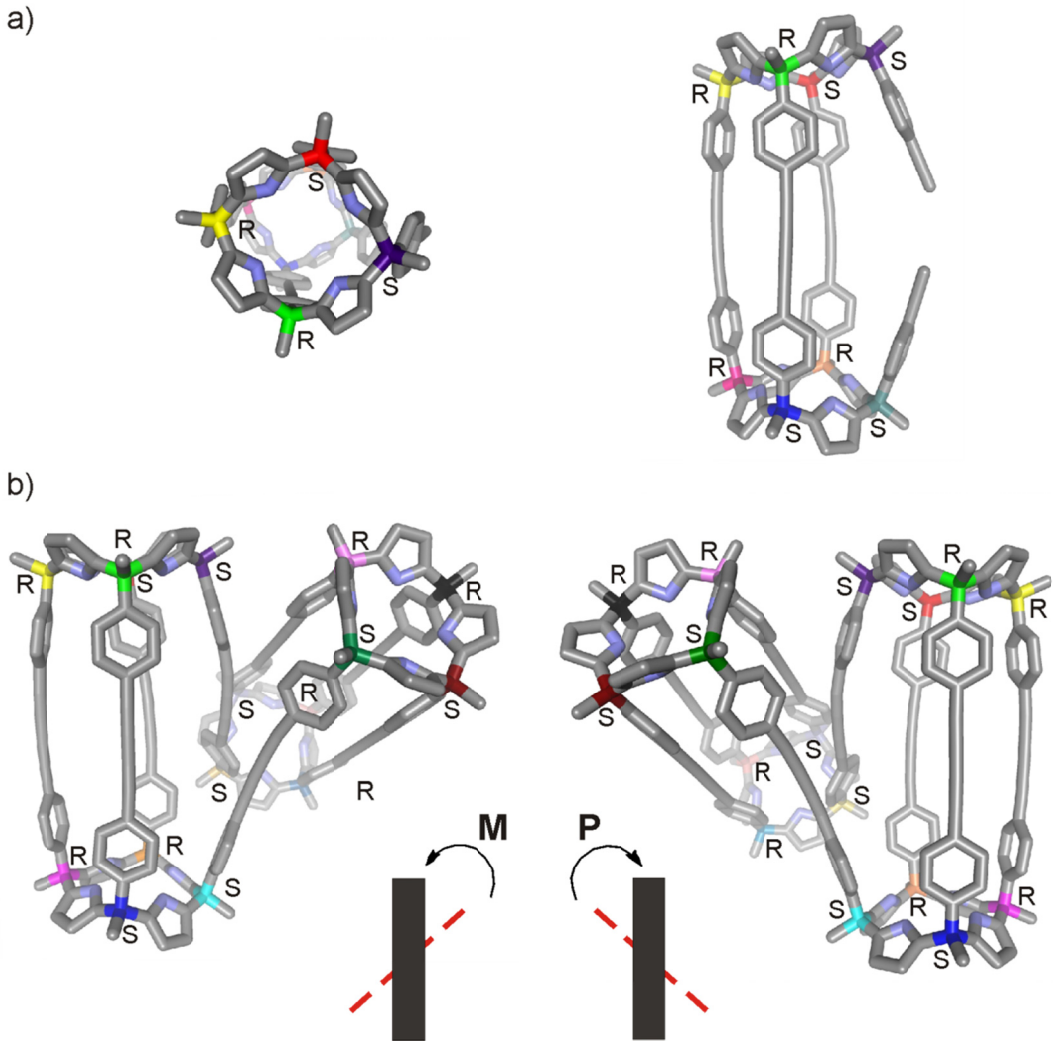


Figure S18. a) Top and side views of compound **8** with the absolute configuration assigned for each stereogenic carbon atom. b) Absolute configuration assignment for each stereogenic carbon of both enantiomeric conformations of compound **9** and schematic representation of the nomenclature (P and M) used for the assignment of absolute configuration of the enantiomeric conformations of **9**. Guests have been omitted for clarity.

9. Study of the interconversion process between the two enantiomeric conformations of $(6)_2\subset 9$

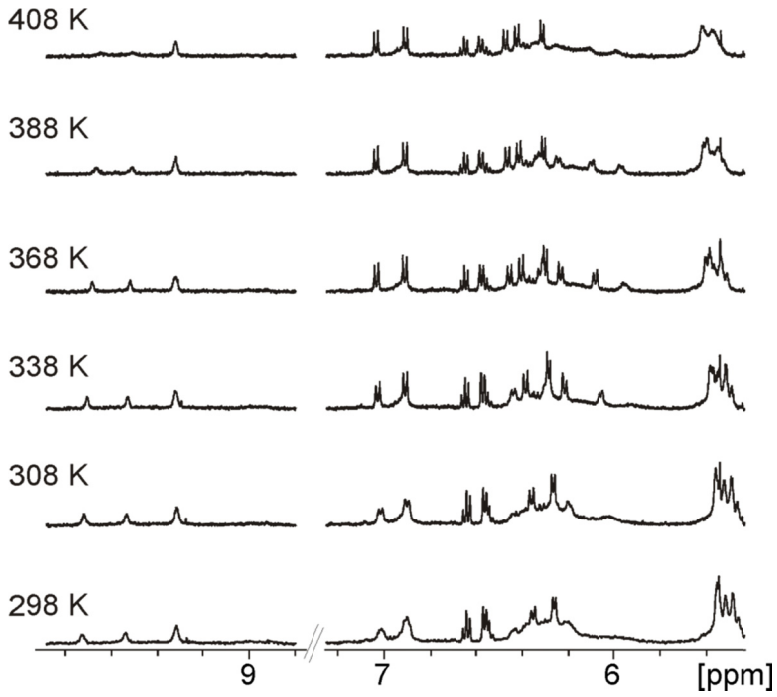


Figure S19. Selected ^{1}H NMR region of the variable temperature experiment of a solution of $(\mathbf{6})_2\subset\mathbf{9}$ in d_2-tetrachloroethane. The racemization barrier was estimated considering the $\Delta\nu$ of the two most downfield shifted diastereotopic pyrrole NH protons at 408 K.

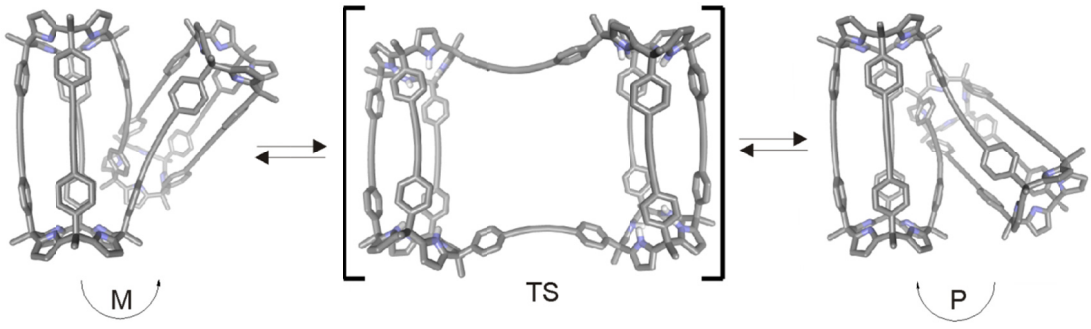


Figure S20. MM3 Energy minimized structures of the two enantiomeric conformations of **9** and of the putative transition state of the interconversion process. Guest molecules and hydrogen atoms are omitted for clarity.