Supporting Information

Efficient self-sorting of a racemic tetra-urea calix[4]pyrrole into a single hetero-dimeric capsule

Marcos Chas,[†] Guzmán Gil-Ramírez,[†] Eduardo C. Escudero-Adán,[‡] Jordi Benet-Buchholz,[‡] and Pablo Ballester[*,§]

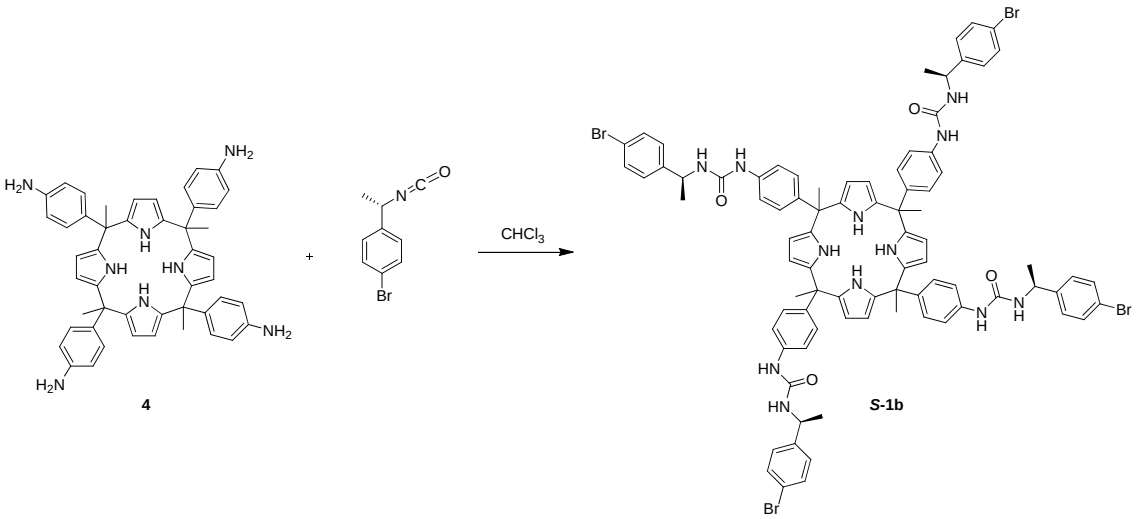
ICREA and Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain.

pballester@iciq.es

Contents for Electronic Supplementary Information

[†] ICIQ
[‡] ICIQ X-Ray Diffraction Unit
[§] ICREA and ICIQ

Synthesis and characterization of chiral tetraureas.



Scheme S1. Synthesis of the chiral urea *S*-**2b**.

(*S*)-(-)-α-Methylbenzyl urea (*S*-1b). Freshly prepared tetraaminocalix[4]pyrrole **4**[1] (58 mg, 0.079 mmol) was dissolved in chloroform (10 mL) and (*S*)-(-)-1-(4-Bromophenyl)ethyl isocyanate (85 mg, 0.378 mmol) was added via syringe. The resulting solution was left stirring under Argon at room temperature overnight. Then, 20 mL of methanol were added to the reaction mixture and the solvents were partially evaporated to 5 mL. The resulting white suspension was left standing for two hours and then filtrated to yield the urea *S*-**1b** as a white solid. Yield 62%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (br s, 4H), 8.31 (s, 4H), 7.51 (m, 8H), 7.26 (d, 8H), 7.18 (d, 8H), 6.76 (d, 8H), 6.55 (d, 4H, *J* = 7.9 Hz), 5.86 (br s, 8H), 4.75 (m, 4H), 1.73 (br s, 12 H), 1.34 (d, 12H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, DMSO-d6) δ 154.7, 145.3, 143.3, 139.1, 137.7, 131.6, 128.6, 127.5, 120.1, 117.7, 105.1, 48.6, 44.0, 23.4. $[\alpha]_D^{25}$ -95.8 ° (*c* 1.0, THF); HRMS (MALDI+/$[M]^+$) calcd. for $C_{84}H_{80}Br_4N_{12}O_4^+$: 1636.3153, found: 1636.2966.

(*R*)-(+)-α-Methylbenzyl urea (*R*-1b). Identical spectra data as obtained for *S*-**1b**. $[\alpha]_D^{25}$ -91.3 ° (*c* 1.0, THF).

[1] Ballester, P.; Gil-Ramirez, G., *Proc. Natl. Acad. Sci. U. S. A.* **2009,** 106, 10455-10459.

Self-assembly of homocapsule 2⊂*S*-1b$_2$ (identical experimental and data for 2⊂*R*-1b$_2$)

Tetraurea *S*-**1b** (1.49 mg, 0.906 μmol) was suspended in CD_2Cl_2 (0.9 mL). To this suspension, 4,4'-Dipyridyl *N*,*N*'-dioxide dihydrate (0.101 mg, 0.453 μmol) was added and the resulting suspension was sonicated for 2 minutes. Then, ^{1}H NMR was run (400 MHz, CD_2Cl_2) δ 10.25 (br s, 4H), 9.83 (br s, 4H), 7.63-7.55 (m, 12H), 7.40-7.32 (m, 20H), 7.16-7.09 (m, 12H), 7.07-6.95 (m, 12H), 6.32-6.18 (m, 16H), 6.18-6.07 (m, 16H), 6.05 (m, 2H), 5.80 (m, 2H), 5.21 (m, 2H), 4.95 (m, 4H), 4.76 (m, 4H), 4.65 (m, 2H), 1.93 (br s, 12H), 1.84 (br s, 12H), 1.68 (d, 12H, *J* = 7.0 Hz), 1.52 (d, 12H, *J* = 7.0 Hz).

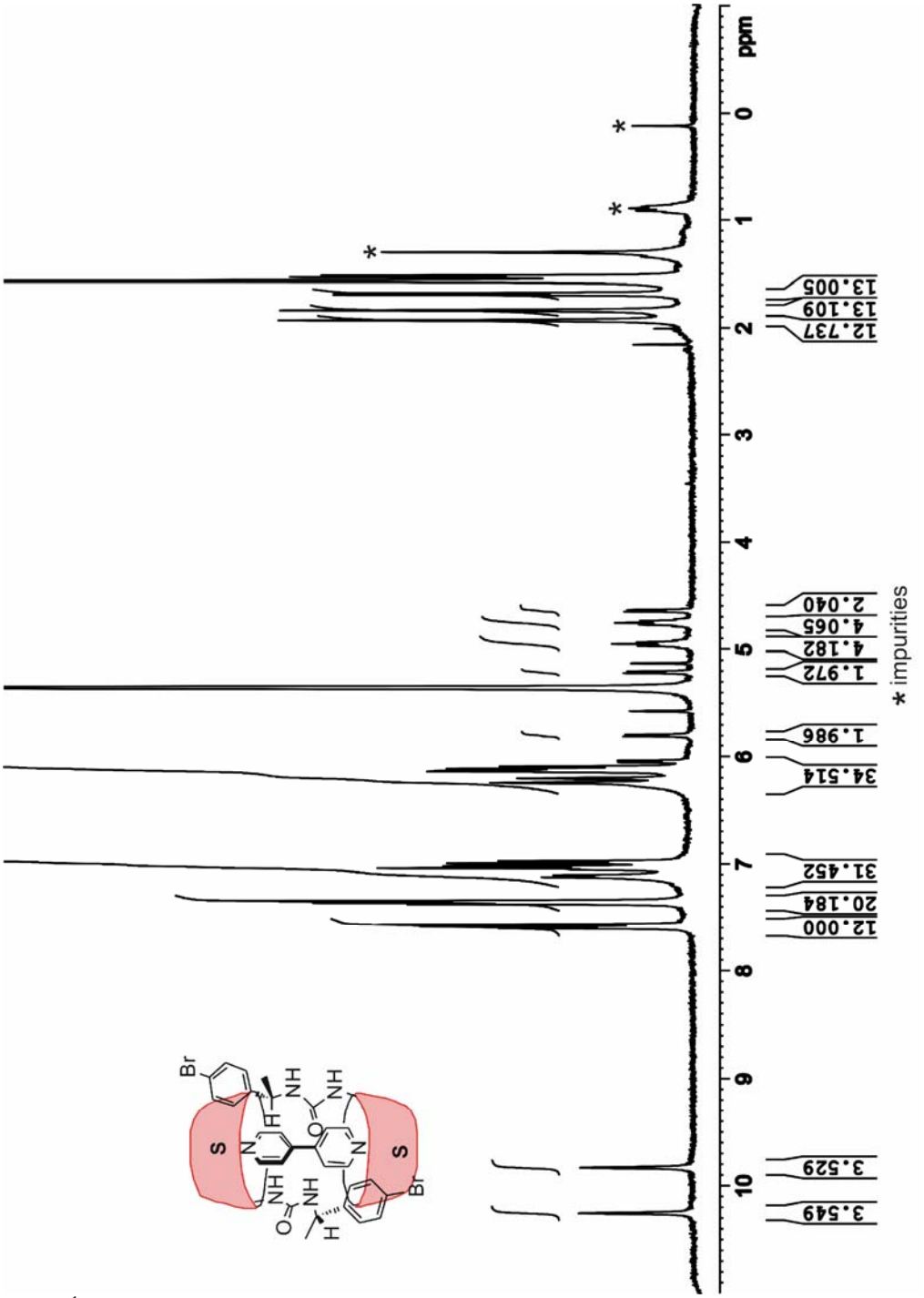


Figure S. 1. ^{1}H-NMR of capsule **2**⊂*S*-**1b**$_2$.

Self-assembly of capsule 2⊂(*S,P·R,M*)-1b$_2$ under homogeneous conditions.

From preformed 2⊂*S*-1b$_2$ and 2⊂*R*-1b$_2$ capsules: Equimolar quantities (0.906 mmol of each) of capsules **2**⊂*S*-**1b**$_2$ and **2**⊂*R*-**1b**$_2$ in CD_2Cl_2 (0.6 mL each) were separately prepared according with the above experiment and mixed. ^{1}H-NMR was performed showing the proton signals corresponding to the mixture of capsules (both capsules being enantiomeric afforded the same spectrum). The solution was placed in an oil bath at 313 K for one week, resulting in the appearance of only a small proportion of the **2**⊂(*S,P·R,M*)-**1b**$_2$ heterocapsule (see figure S. 2).

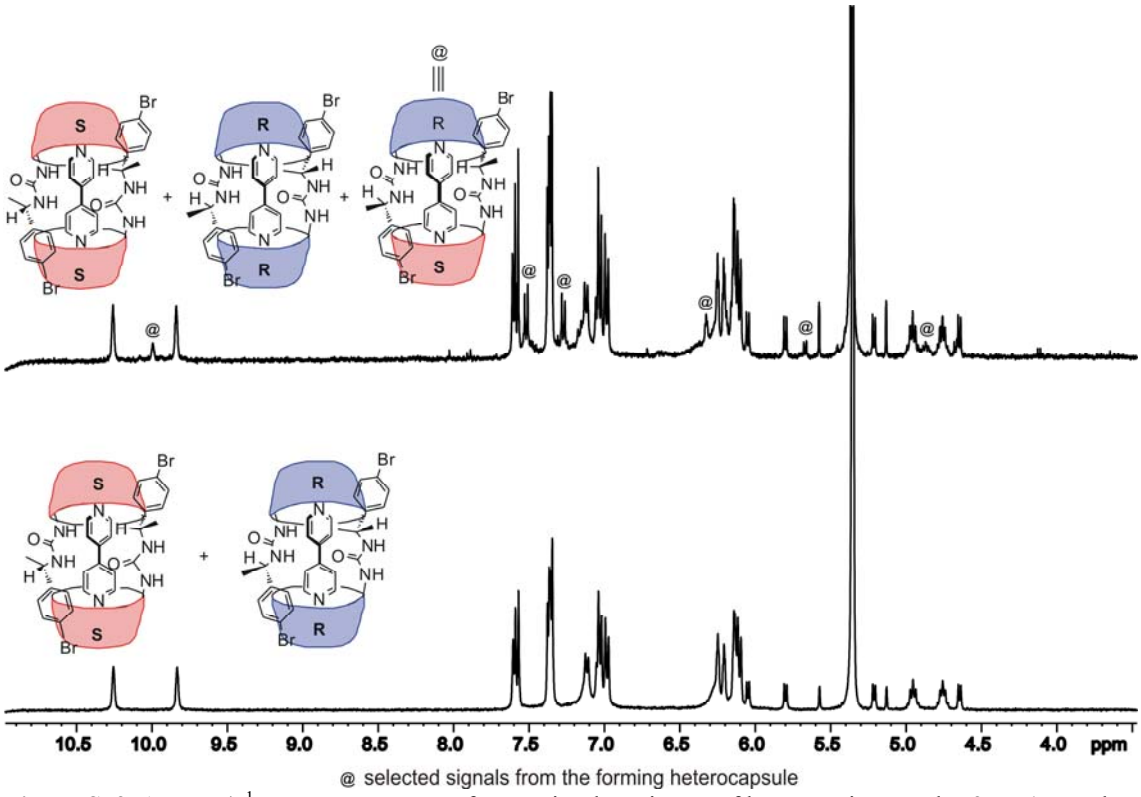


Figure S. 2. (Bottom) ^{1}H NMR spectrum of an equimolar mixture of homomeric capsules **2**⊂*S*-**1b**$_2$ and **2**⊂*R*-**1b**$_2$. (Top) ^{1}H NMR spectrum of the same equimolar mixture heated at 313 K for 7 days. The proton signals marked with the @ sign correspond to the heterocapsule **2**⊂(*S,P·R,M*)-**1b**$_2$**.**

Self-assembly of capsule 2⊂(*S,P·R,M*)-1b$_2$ under heterogeneous conditions.

Tetraurea *S*-**1b** (0.82 mg, 0.50 μmol) and tetraurea *R*-**1b** (0.82 mg, 0.50 μmol) were suspended in CD_2Cl_2 (0.5 mL). To this suspension, 4,4'-Dipyridyl *N*,*N*'-dioxide dihydrate (0.094 mg, 0.50 μmol) was added and the resulting suspension was sonicated for 2 minutes and complete dissolution occurs. Then, ^{1}H NMR (400 MHz, CD_2Cl_2) was run, resulting in the mixture of capsules shown in figure S. 3.

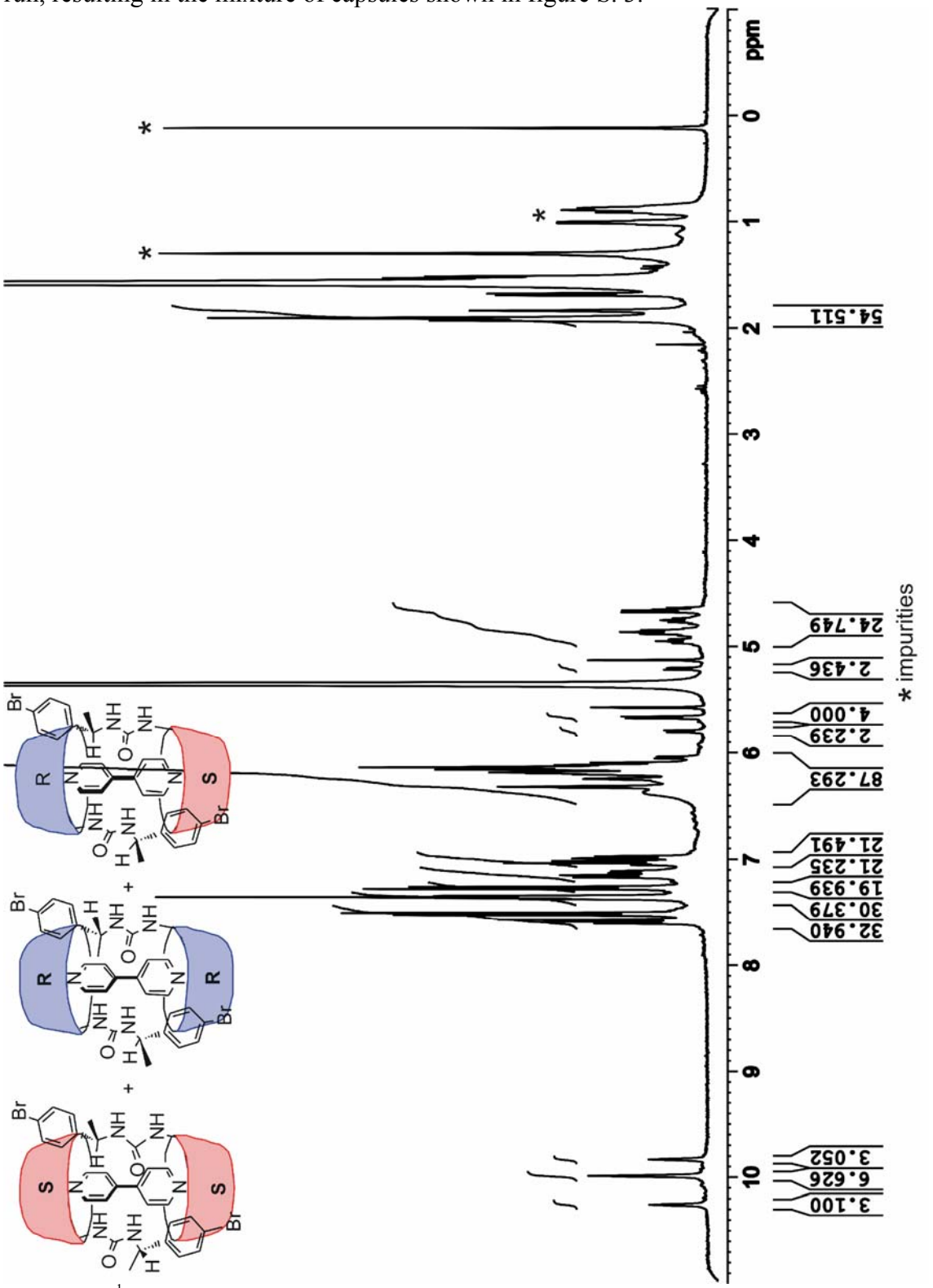


Figure S. 3. ^{1}H NMR spectrum of the mixture of capsules obtained under heterogeneous conditions.

Self-assembly of capsule 2⊂(*S,P·R,M*)-1b$_2$ under heterogeneous conditions followed by the addition of THF.

Tetraurea *S*-**1b** (0.99 mg, 0.60 μmol) and tetraurea *R*-**1b** (0.99 mg, 0.60 μmol) were suspended in CD_2Cl_2 (0.6 mL). To this suspension, 4,4'-Dipyridyl *N*,*N'*-dioxide dihydrate (0.114 mg, 0.60 μmol) was added and the resulting suspension was sonicated for 2 minutes and complete dissolution occurs. ^{1}H NMR was run, showing the expected mixture of capsules (see previous experiment). Then THF-d_8 (0.06 mL) was added to the NMR tube and the resulting solution was left standing at room temperature for two days. After this time, the analysis of the mixture by ^{1}H NMR revealed that the **2**⊂(*S,P·R,M*)-**1b**$_2$ capsule was the almost exclusive component. (400 MHz) δ 9.99 (br s, 8H), 7.51 (m, 16H), 7.36 (br s, 8H), 7.26 (m, 16H), 7.17 (d, 8H, *J* = 7.9 Hz), 6.43-6.29 (m, 24H), 6.21-6.11 (m, 24H), 5.66 (m, 4H), 4.86 (m, 8H), 4.67 (m, 8H), 1.90 (s, 24H), 1.57 (d, 24H, *J* = 6.5 Hz); MS (ESI/[M+Na]$^+$) calcd. for $C_{178}H_{168}Br_8N_{26}O_{10}Na$: 3493.6, found 3493.7.

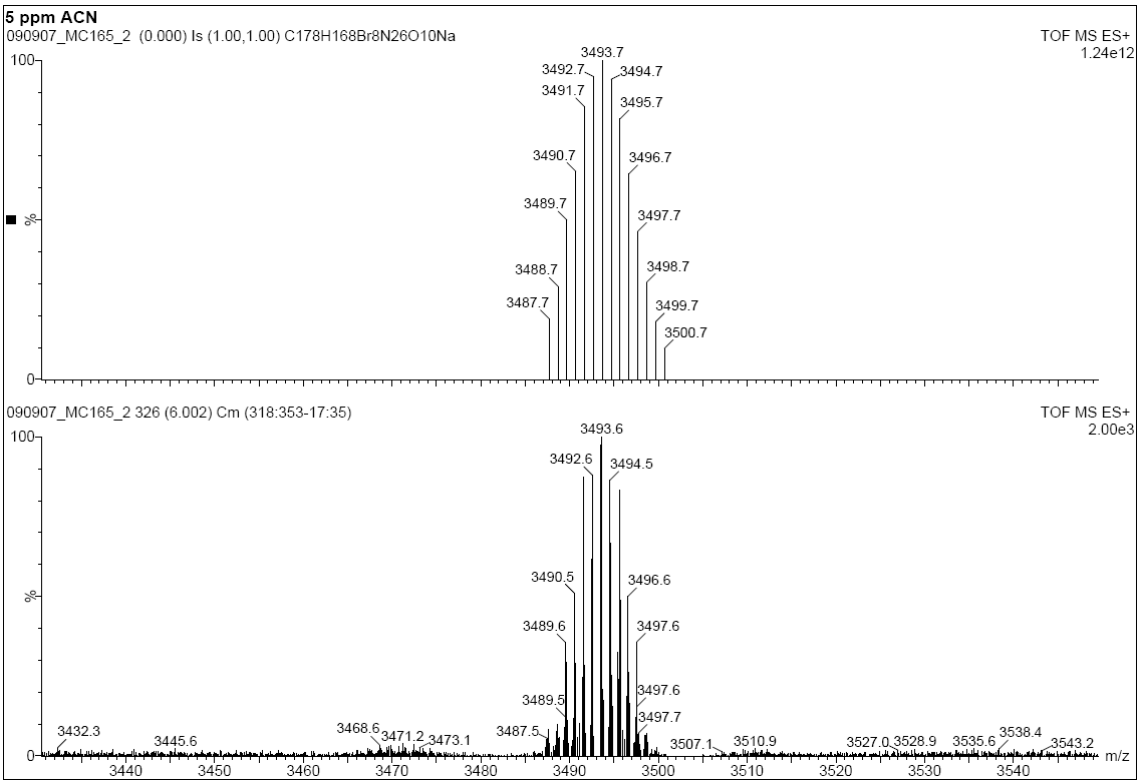


Figure S. 4. HRMS (ESI+ 50 ppm acetonitrile) for capsule **2**⊂(*S,P·R,M*)-**1b**$_2$; theoretical (top) and experimental (bottom) isotopic distribution pattern for $[M + Na]^+$ ($[C_{178}H_{168}Br_8N_{26}O_{10}Na]^+$).

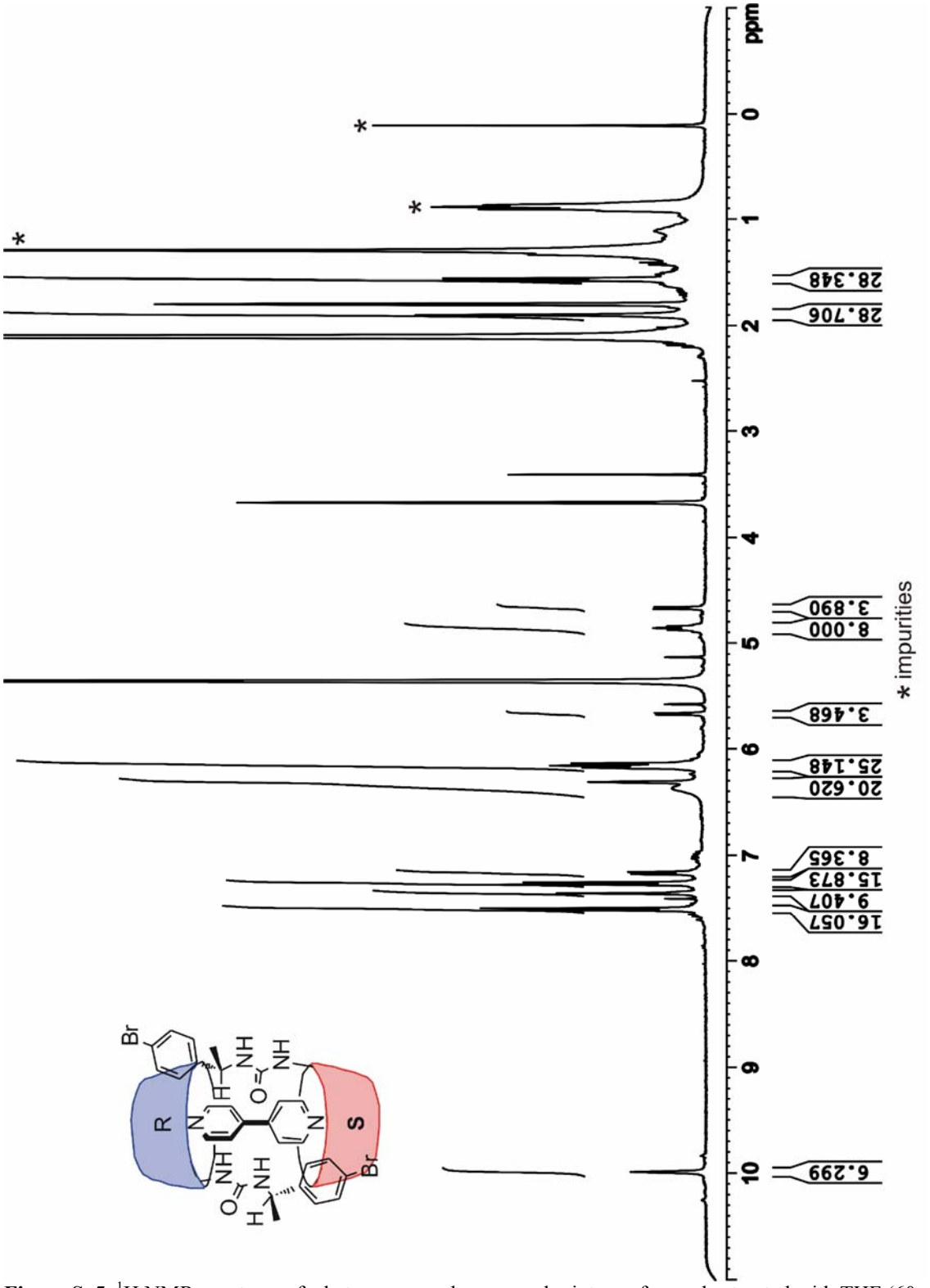


Figure S. 5. ^{1}H NMR spectrum of a heterogeneously prepared mixture of capsules treated with THF (60 μL) and left to stand at rt for two days.

Self-assembly of capsule 3_2⊂*S*-$1b_2$ (identical experimental and data for 3_2⊂*R*-$1b_2$)

Tetraurea *S*-**1b** (1.80 mg, 1.10 μmol) was suspended in CD_2Cl_2 (0.6 mL) under inert atmosphere (glove box). To this suspension, trimethylamine N-oxide (0.082 mg, 1.10 μmol) was added and the resulting suspension, in a sealed NMR tube, was sonicated for 2 minutes. Then, ^{1}H NMR was run (600 MHz, CD_2Cl_2) δ 10.16 (br s, 4H), 9.78 (br s, 4H), 8.45 (m, 8H), 7.98 (m, 4H), 7.58 (m, 8H), 7.44 (m, 8H), 7.40-7.33 (m, 12H), 7.17 (m, 8H), 7.05 (m, 4H), 6.90 (m, 4H), 6.54 (m, 4H), 6.29-6.06 (m, 36H), 5.22-5.06 (m, 8H), 1.89 (br s, 12H), 1.77 (br s, 12H), 1.68 (d, 12H, *J* = 6.9 Hz), 1.52 (d, 12H, *J* = 6.9 Hz), 0.63 (br s, 9H), 0.30 (br s, 9H).

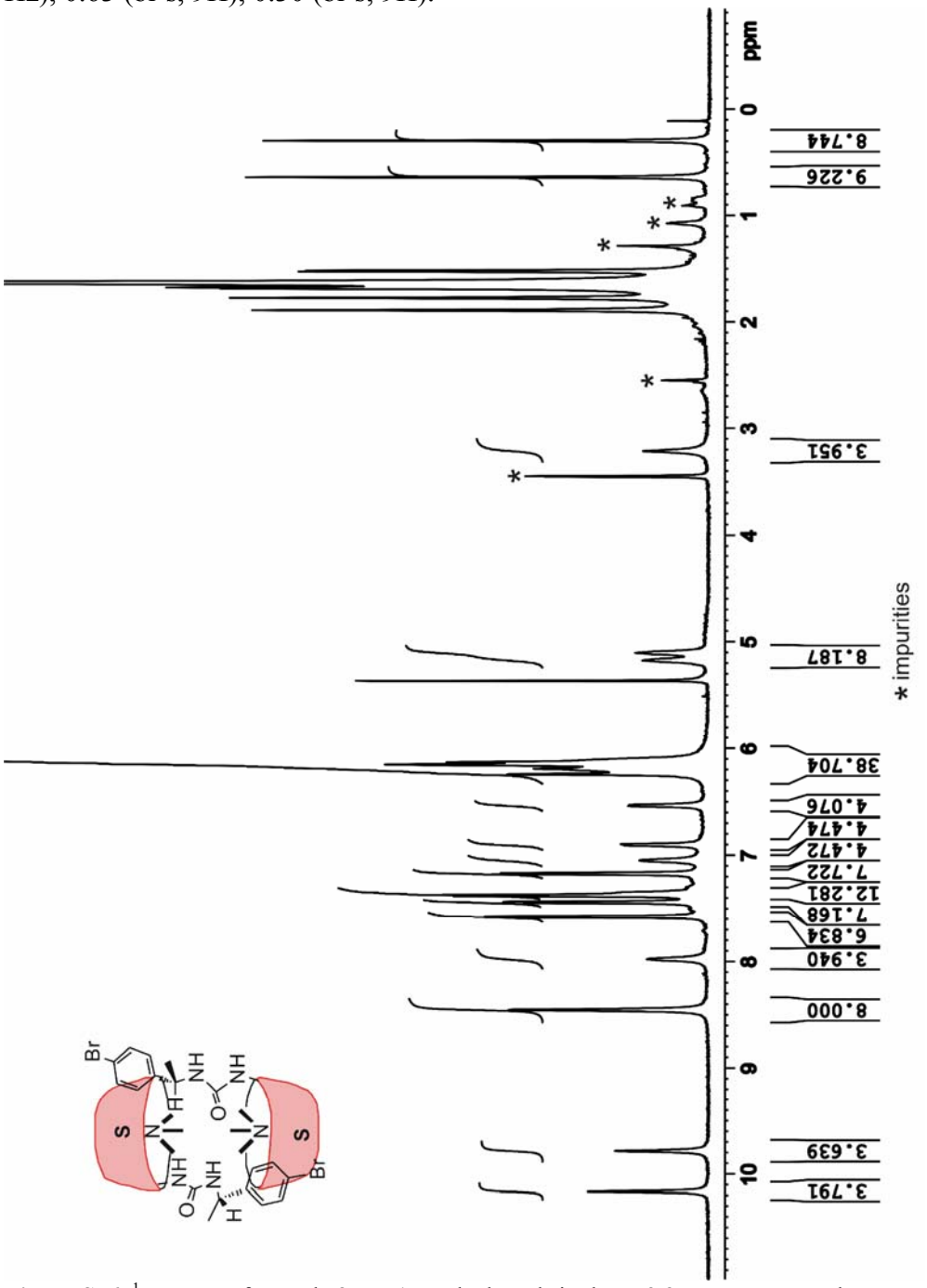


Figure S. 6. ^{1}H-NMR of capsule 3_2⊂*S*-$1b_2$. The broad singlet at 3.2 ppm corresponds to an excess of trimethylamine *N*-oxide **3**.

Self-assembly of capsule 3_2⊂(*S,P·R,M*)-$1b_2$ under homogeneous conditions

Equimolar quantities of capsules **3**⊂*S*-**1b**$_2$ and **3**⊂*R*-**1b**$_2$ (0.55 μmol in 0.6 mL of CD_2Cl_2 each) were separately prepared as described above and mixed in a NMR tube. ^{1}H NMR (400 MHz) was run δ 9.80 (br s, 8H), 8.35 (br s, 8H), 7.53 (m, 16H), 7.44 (d, 8H, J = 7.1 Hz), 7.29 (m, 16H), 6.31-6.06 (m, 48H), 5.16 (m, 8H), 1.83 (br s, 24H), 1.58 (24H, obscured by the water signal).

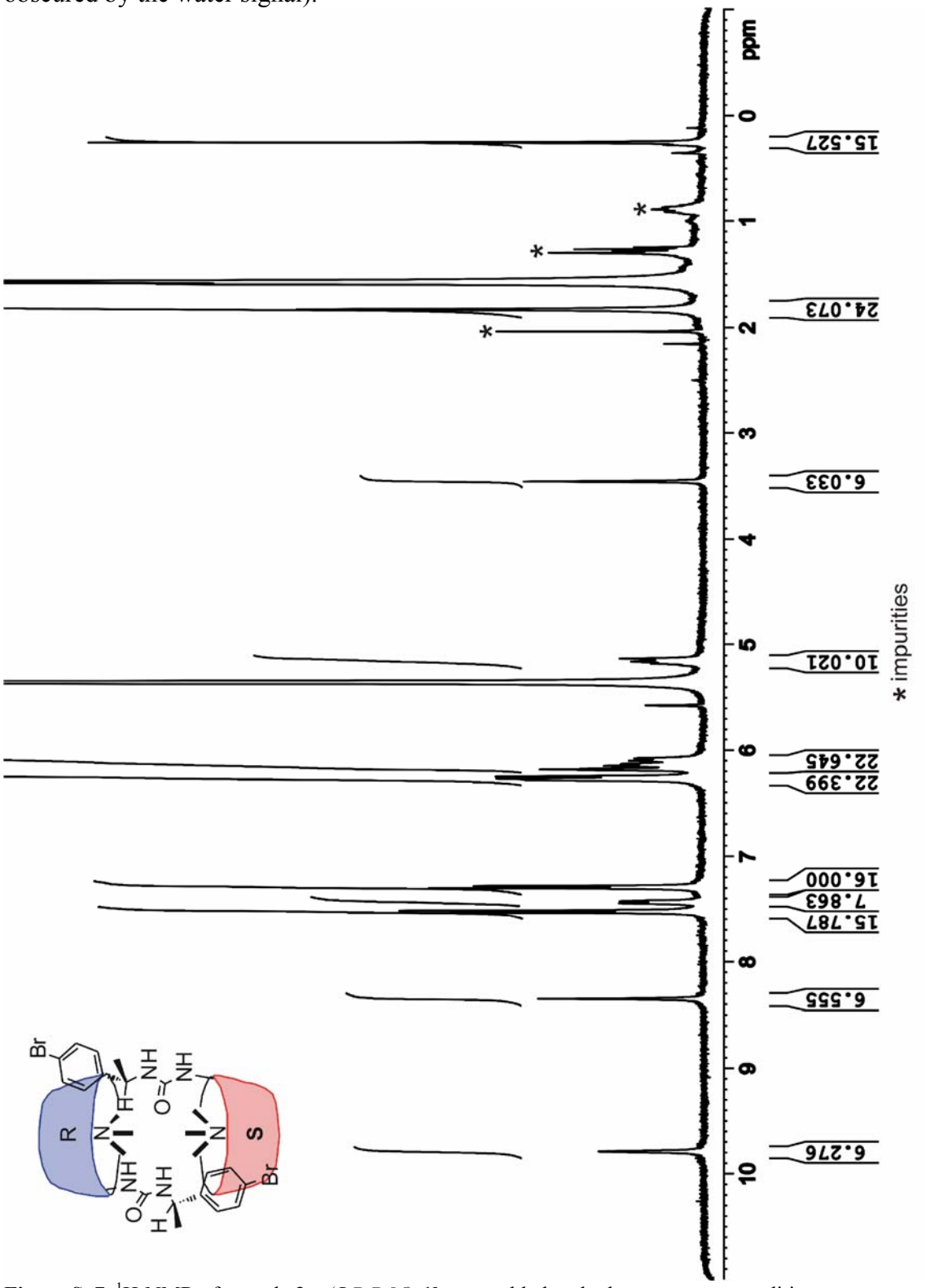


Figure S. 7. ^{1}H-NMR of capsule **3**$_2$⊂(*S,P·R,M*)-**1b**$_2$ assembled under homogeneous conditions.

Self-assembly of capsule 3_2⊂1a·*R*-1b:

Equimolar quantities (0.340 mmol of each) of capsules $\mathbf{3}_2\subset\mathbf{1a}_2$ and $\mathbf{3}_2\subset$*R*-$\mathbf{1b}_2$ in CD_2Cl_2 (0.6 mL each) were separately prepared according with the above experiments. Then, ^{1}H NMR was run (400 MHz, CD_2Cl_2) δ 10.02 (br s, 4H), 9.83 (br s, 4H), 8.44 (s, 4H), 8.37 (s, 4H), 7.73 (m, 4H), 7.55-7.44 (m, 12H), 7.35-7.16 (m, xH), 6.79 (m, 4H), 6.61 (m, 4H), 6.35 (m, 4H), 6.32-6.02 (m, xH), 5.10 (m, 4H), 4.77-4.68 (m, 4H), 4.61-4.52 (m, 4H), 2.45 (s, 12H), 1.83 (m, xH), 0.49 (s, 9H), 0.34 (s, 9H).

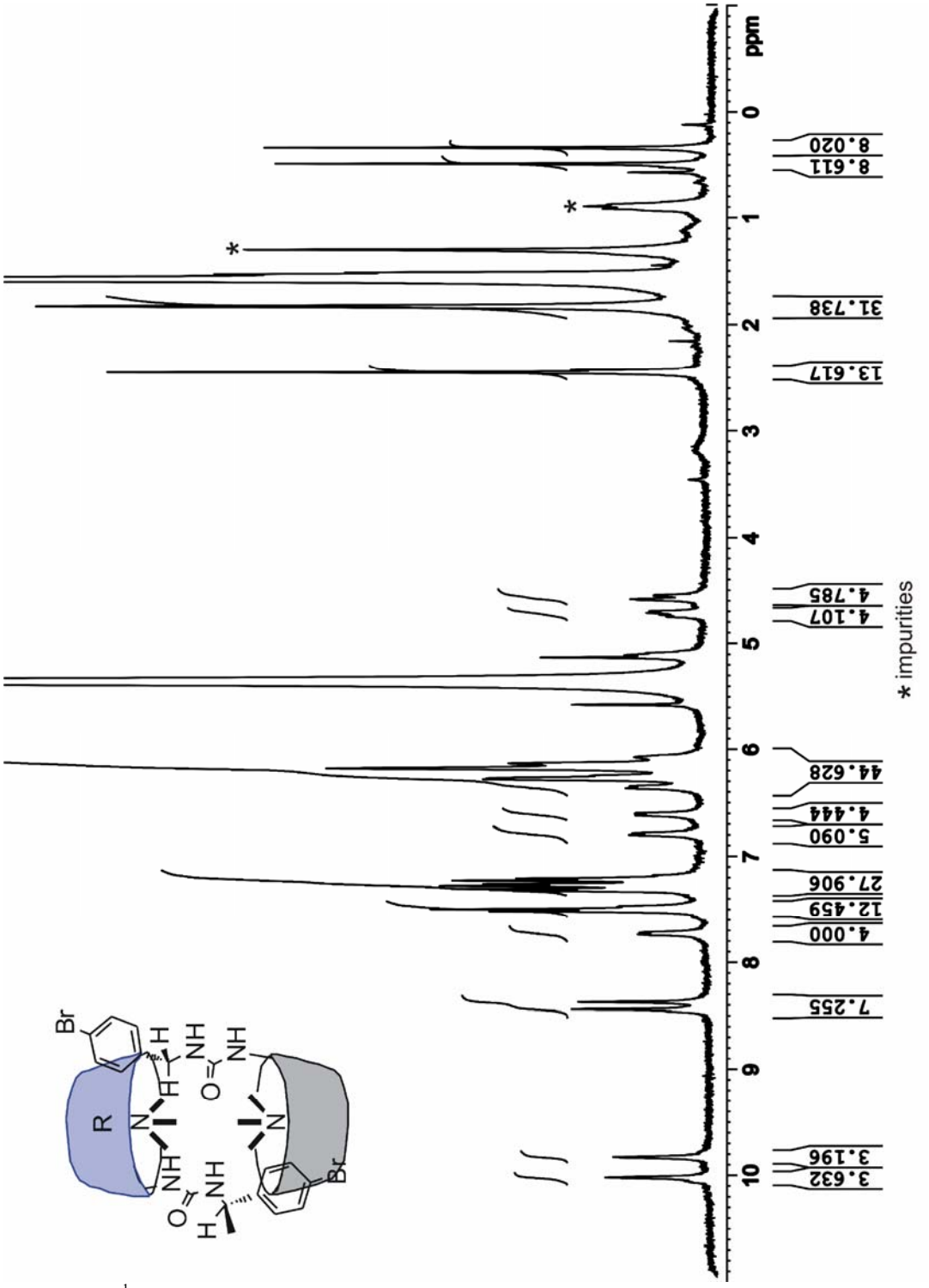


Figure S. 8. ^{1}H-NMR of capsule $\mathbf{3}_2\subset$**1a·*R*-1b**.

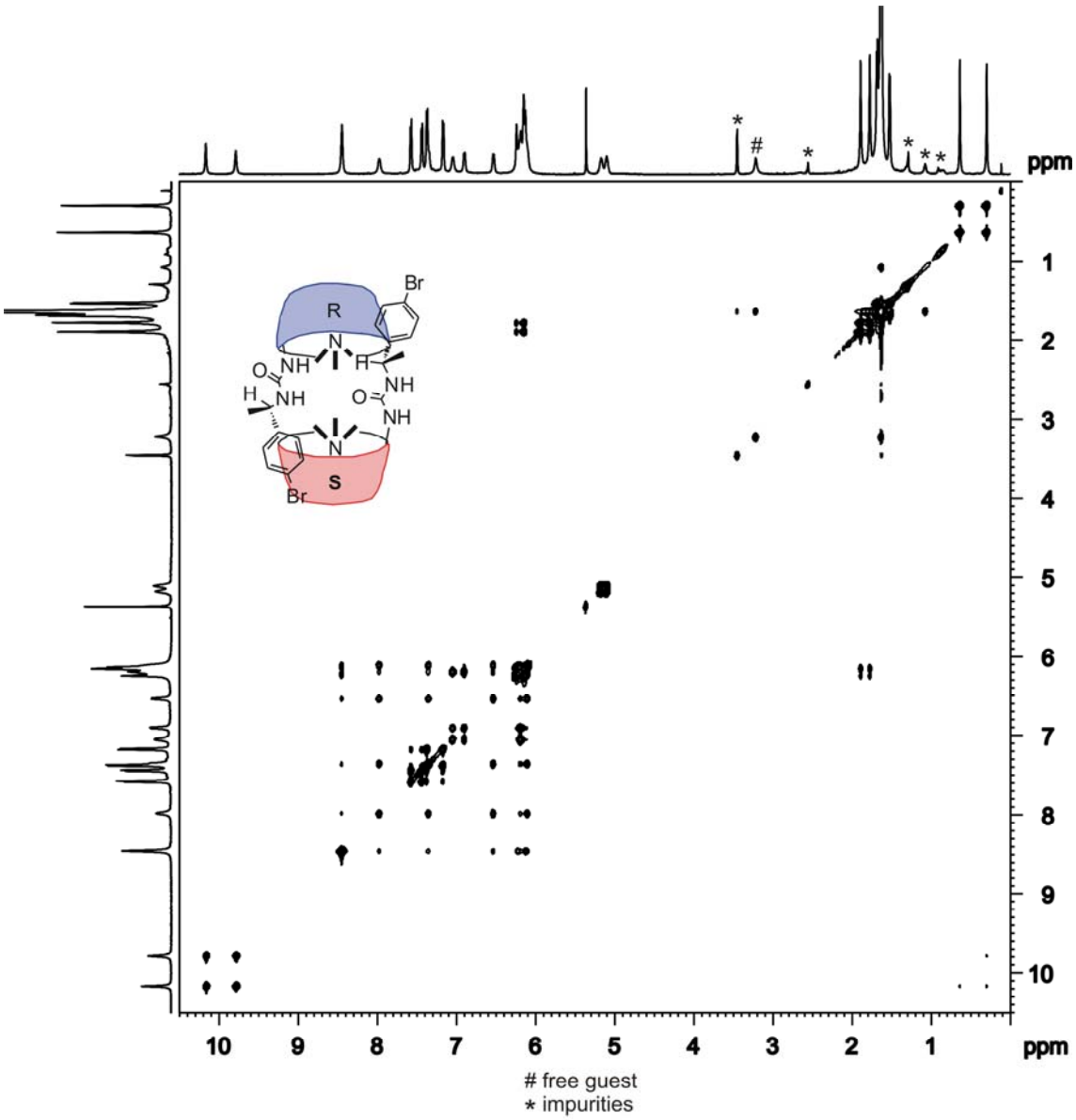


Figure S.9. ^{1}H-^{1}H-NOESY NMR (600 MHz, CD_2Cl_2) of capsule $\mathbf{3}_2 \subset R\text{-}\mathbf{1b}_2$. The signals used to calculate the energy barrier for the change of the direction of the urea belt were those of the pyrrolic NH protons at δ = 10.16 and 9.78 ppm.

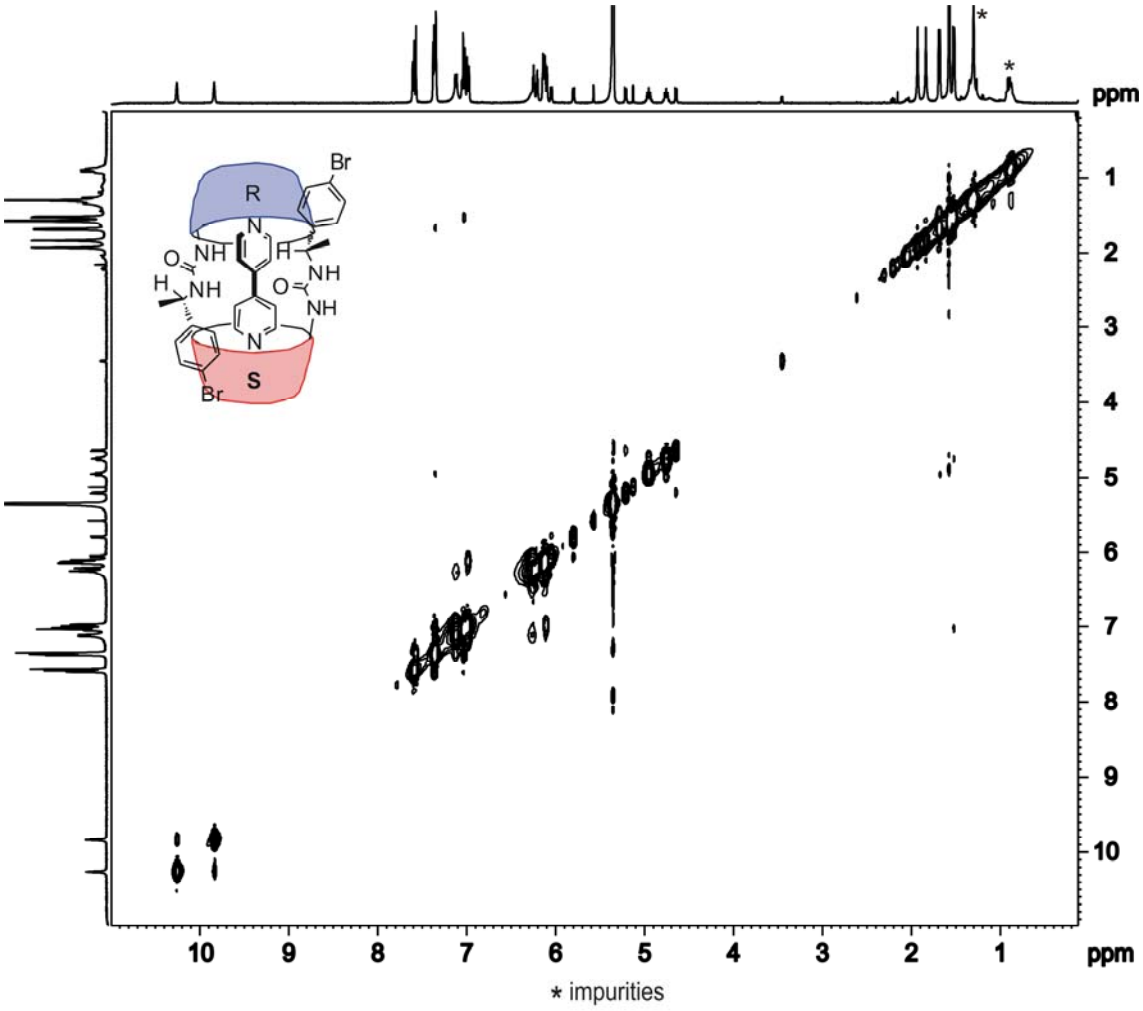


Figure S.10. ^{1}H-^{1}H-NOESY NMR (400 MHz, CD_2Cl_2) of capsule **2**⊂*R*-**1b**$_2$. The signals used to calculate the energy barrier for the change in the direction of the urea belt were those of the pyrrolic NH protons at δ =10.25 and 9.83 ppm.

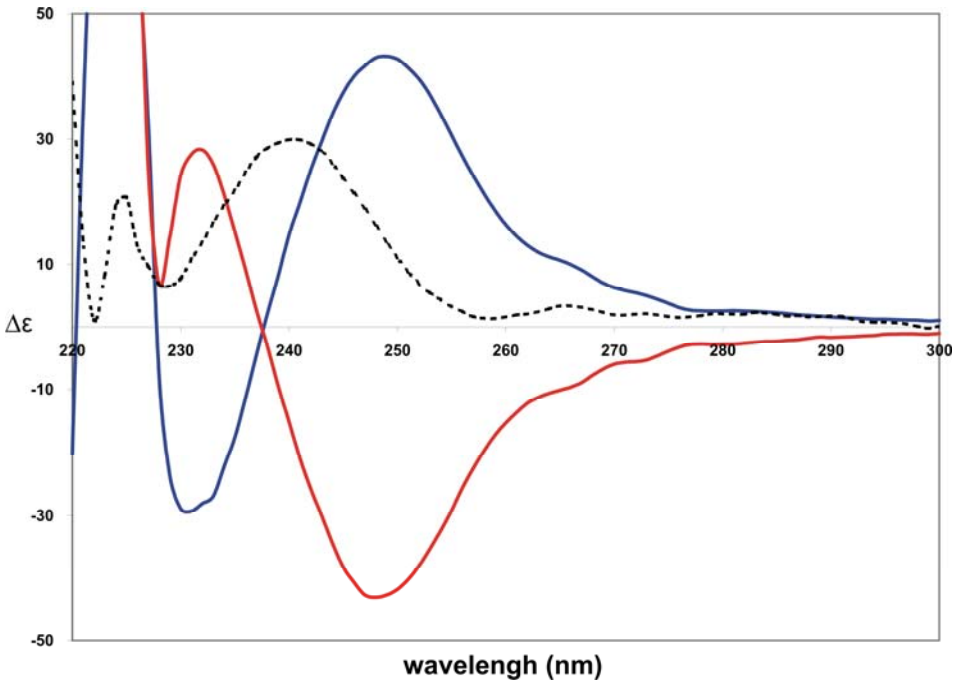


Figure S. 11. Circular dichroism (CD) spectra of: (blue line) a solution of *N*-oxide **3** ($2 \cdot 10^{-5}$ M), **1a** (10^{-5} M) and *R*-**1b** (10^{-5} M) in CH_2Cl_2; (red line) a solution of *N*-oxide **3** ($2 \cdot 10^{-5}$ M), **1a** (10^{-5} M) and *S*-**1b** (10^{-5} M) in CH_2Cl_2; (black dashed line) a solution of *R*-**1b** (10^{-5} M) in CH_2Cl_2.

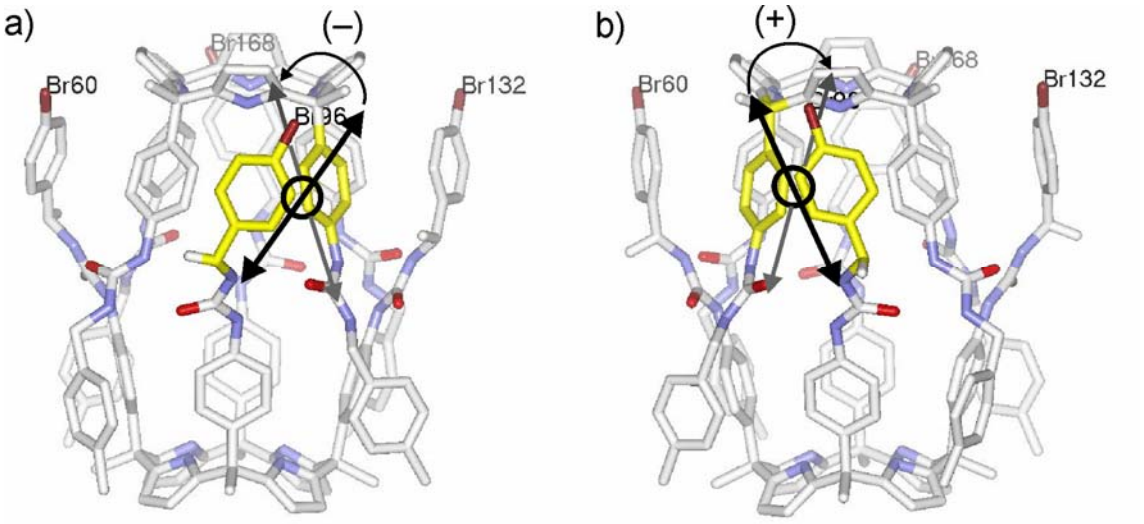


Figure S. 12. Homology construct structures, based on the X-ray structure of **2**⊂**1a**$_2$, of the two possible absolute configurations for the heterodimer **1•1b** a) (*M*•*R*,*P*)-**1•1b** and b) (*P*•*R*,*M*)-**1•1b**. In the heterodimer (*P*•*R*,*M*)-**1•1b** the transition dipoles (arrows) of the two chromophores (highlighted in yellow) intersect at a positive torsion angle. In accordance with the exciton chirality rule, this absolute configuration is responsible of the positive chirality observed for the first Cotton effect in the CD of the capsule. The hydrogen atoms and the encapsulated guests are removed for clarity.

The solid state structure of **2**⊂**1a**$_2$ was solved using ab inito methods XM implemented in the SHELXTL interface and refined as a pseudo-merohedral twin of two domains related by the twin law 0 0 1 0 1 0 0 0 1 with an approximate contribution ratio of 62:38.
The bis *N*-oxide molecules **2** are disordered in two different positions with an occupation ratio of 70:30 for C1CA > C10H and 65:35 for C1F > C10F. One calix-Pyrrol presents also disordered walls that are modeled as follow:
N5D > C41D, C55D > C62D, O2E > C41E, C12 > C13E are disordered in two positions with an occupation ratio of 63:37. C14E > C21E are disordered in three different positions with occupations of 24%, 38% and 38%.
Four solvent molecules are modeled as disordered. C1SK, C1SD and C1SE are in two different positions with occupations ratio of 63:37 while C1SH has three different sites with occupations of 28%, 40% and 38%.

Explanations of A alerts returned by the checkcif program.

Alert level A

PLAT432_ALERT_2_A	Short Inter X...Y Contact	N3E	..	C14E	..	2.36	Ang.
PLAT432_ALERT_2_A	Short Inter X...Y Contact	C13E	..	C14E	..	1.59	Ang.
PLAT432_ALERT_2_A	Short Inter X...Y Contact	C13E	..	C15E	..	2.47	Ang.
PLAT432_ALERT_2_A	Short Inter X...Y Contact	C13E	..	C19E	..	2.67	Ang.
PLAT432_ALERT_2_A	Short Inter X...Y Contact	C7SE	..	C467#	..	2.73	Ang.
PLAT773_ALERT_2_A	Suspect C-C Bond in CIF:	C18"	--	C6K'	..	1.78	Ang.

All this distances are between atoms of disordered groups. NE-C14E, C13E-C15E, C13E-C19E belong to the same molecule and are not Intermolecular distances. C7SE-C467# (C8H') and C18"-C6K' are distances between atom sites that are not occupied at the same time in the crystal.

We thank Professor G. M. Sheldrick for providing us the necessary source to perform this refinement.

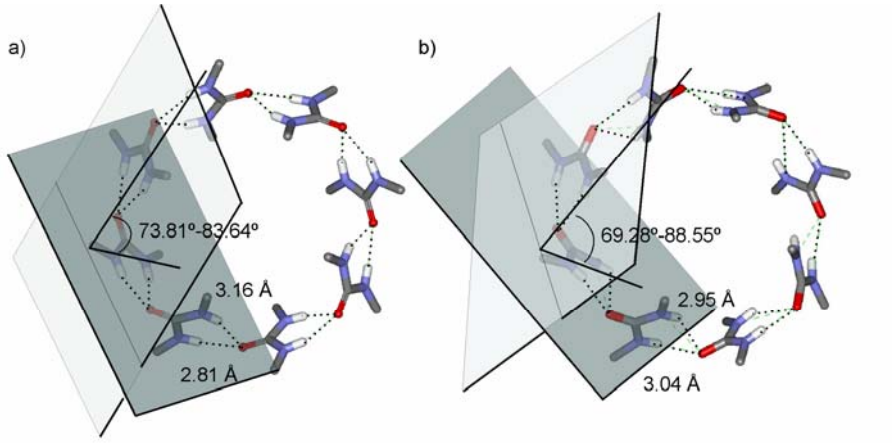


Figure S.13. X-ray structures of the rings formed by the eight urea structures, which are alternatively connected to a) the two calix[4]arenes halves[2] and b) the two phenyl extended calix[4]pyrroles halves[3]. The belt of the urea functions forms the hydrogen-bonding system holding the the capsular assemblies. Hydrogen bonds are depicted by dashed lines. Selected reported distance for the hydrogen bonds are measured between heteroatoms (N···O=C). The range of values of the dihedral angles of the planes defined by the N-CO-N atoms of adjacent urea units is also indicated.

[2] Mogck, O.; Paulus, E. F.; Bohmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533-2534.
[3] X-ray structure of **2**⊂**1a**$_2$ capsular assembly reported in this work.

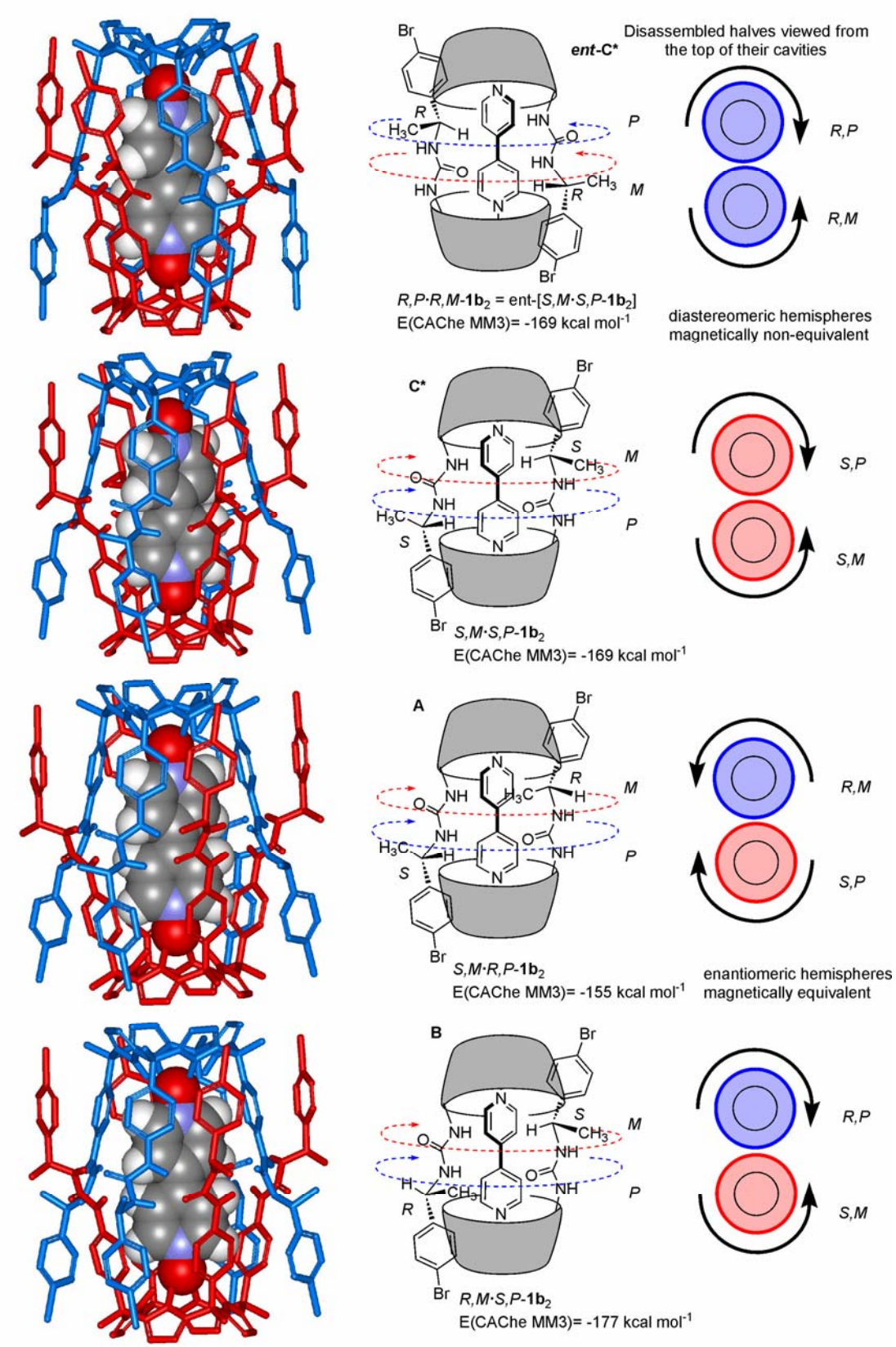


Figure S.14. CAChe[4] MM3 minimized structures of the three expected diastereoisomeric capsules resulting from the self-assembly of racemic **1b** induced by encapsulation of **2** and their corresponding schematic representations.

[4] CAChe WorSystem Pro Version 6.1.12.33. Copyright© 2000-2004 Fujitsu Limited.