Supporting Information

Influence of the solvent in the self-assembly and binding properties of [1 + 1] tetra-imine bis-calix[4]pyrrole cages

Chiara F. M. Mirabella,[a,b] Gemma Aragay,[a] Pablo Ballester[a,c]

[a] *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology (BIST), Avgda. Països Catalans, 16, 43007 Tarragona, Spain.*
[b] *Universitat Rovira i Virgili, Departament de Química Analítica i Química Orgànica, c/Marcel·lí Domingo,1, 43007 Tarragona, Spain.*
[c] *ICREA, Passeig Lluís Companys, 23, 08010 Barcelona, Spain*

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1. *General information and instruments*

Reagents were purchased from commercial suppliers and used without further purification. All reactions were performed under Ar atmosphere unless otherwise specified. All solvents were of HPLC grade quality, commercially obtained and used without further purification except pyrrole which was distilled and freshly used. Anhydrous solvents were obtained from a solvent purification system SPS-400-6 from Innovative Technologies.

Routine ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR), Bruker Avance 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) or Bruker Avance 500 with cryoprobe (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR). Deuterated solvents (Sigma Aldrich) used are indicated in the characterization and chemical shifts are given in ppm. Residual solvent peaks were used as reference. $CDCl_3$ from Sigma Aldrich was passed through a column of basic alumina and dried with activated 3 A˚ molecular sieves for the preparation of the dynamic covalent cages. All NMR J values are given in Hz. COSY and ROESY experiments were recorded to help with the assignation of ^{1}H signals.

Mass spectrometric experiments were performed in a Synapt G2-S HDMS (Waters Co., Milford, MA, USA) travelling wave ion mobility mass spectrometer. All ions were generated by electrospray ionization (ESI) in the positive and negative mode. The parameters were optimized to obtain the maximum abundance of the ions of interest.

Crystal structure determinations were carried out using a Rigaku MicroMax-007HF diffractometer equipped with a PILATUS 200K detector and a Bruker Apex II Duo equipped with an APEX II detector, both using Mo Kα radiation. Crystal structure solution was achieved using VLD and Patterson methods as implemented in SIR2014 v14.10. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELX-2018/3.

2. *Synthesis and characterization data*

Tetra-formyl calix[4]pyrrole **3** and tetra-amine derivatives **2a** and **2b** were synthesized using reported procedures.[1,2,3]

2.1. Synthesis of imine cage complexes **4⊂1**

A 2 mM equimolar mixture of tetra-amino calix[4]pyrrole **2a** or **2b**, 4',4'-bipyridyl *N,N'*-dioxide **4** and tetra-formyl calix[4]pyrrole **3**, was prepared in $CDCl_3$ and placed in a NMR tube.

The equimolar mixture of **2a**, **4** and **3** initially formed a suspension most likely due to the poor solubility of **2a** in $CDCl_3$. After 24h at room temperature the solution was clear and the ^{1}H NMR showed the diagnostic peaks for the formation of the cage. 1,3,5-trimethoxybenzene was added as internal standard (i.s. final concentration = 2 mM). By integration of selected proton signals of the cage complex and those of the i.s. we determined a yield for the assembly of the complex around 45%.

In contrast, the equimolar mixture of the more lipophilic tetra-amino calix[4]pyrrole **2a**, with **4** and **3** immediately formed a clear solution. The ^{1}H NMR of the reaction mixture acquired after 3h at room temperature already showed sharp and well-defined proton signals. We calculated

a yield 65% for the assembly of the cage complex according to the integrals of the protons of the cage and the i.s.

4⊂1a: ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.28 (br s, 4H), 8.26 (br s, 4H), 7.69 (s, 4H), 7.35 (d, *J* = 8.4 Hz, 8H), 7.12–7.06 (m, 18H), 6.96 (d, *J* = 8.5 Hz , 8H), 6.74 (d, *J* = 7.3 Hz, 2H), 6.14 (d, *J* = 2.6 Hz, 8H), 6.13 (d, *J* = 2.6 Hz, 8 H), 5.18 ppm (d, *J* = 7.3 Hz, 2H), 5.08 (d, *J* = 7.3 Hz, 2H), 1.96 ppm (s, 12H), 1.94 (s, 12H). MS (ESI TOF) m/z: $[M+K]^+$ Calculated for $C_{118}H_{92}N_{14}O_2K^+$ =1775.7159; Found 1775.8545.

4⊂1b: ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.36 (br s, 4H), 8.06 (br s, 4H), 7.70 (s, 4H), 7.36 (d, *J*= 8.3 Hz, 8H), 7.14–7.05 (m, 18H), 6.99 (d, *J* = 8.3 Hz, 8H), 6.77 (d, *J* = 7.3 Hz, 2H), 6.15 (d, *J* = 2.6 Hz, 8H), 6.04 (d, *J* = 2.6 Hz, 8H), 5.29 (d, *J* = 7.3 Hz, 2H), 5.05 (d, *J* = 7.3 Hz, 2H), 4.10 (q, *J* = 7.1, Hz 8H), 2.44–2.36 (m, 8H), 2.25 (t, *J* = 7.3 Hz 8H), 1.94 (s, 12H), 1.51–1.41 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 12H). HR MS (ESI TOF) m/z: $[M+Cl]^-$ Calculated for $C_{138}H_{124}N_{14}O_{10}Cl^-$=2171.93188; Found 2171.9070.

2.2. Synthesis of imine cage **1b** in 9:1 $CDCl_3$:CD_3CN solvent mixture

A 2 mM equimolar mixture of tetra-amino calix[4]pyrrole **2b** and tetra-formyl calix[4]pyrrole **3** was prepared in a 9:1 $CDCl_3$:CD_3CN solvent mixture and placed in a NMR tube. The ^{1}H NMR of the reaction mixture after 3 hours at r.t. shows the signals corresponding to the formation of the capsule solvate $(CD_3CN)_2$⊂**1b**. 1,3,5-trimethoxybenzene was added as internal standard (i.s. final concentration = 2 mM). By integration of selected proton signals of the tetra-imine cage and those of the i.s. we determined a yield for the assembly of the complex around 65%.

$(CD_3CN)_2$⊂**1b:** ^{1}H NMR (500 MHz, 9:1 $CDCl_3$:CD_3CN) δ(ppm): 7.86 (s, 4H), 7.36 (d, *J* = 8.2 Hz, 8H), 7.34 (bs, 4H), 7.32 (bs, 4H), 7.05 (d, *J* = 8.5 Hz, 8H), 6.94 (d, *J* = 8.5 Hz, 8H), 6.91 (d, *J* = 8.2 Hz, 8H), 5.99 (d, *J* = 2.6 Hz 8H), 5.89 (d, *J* = 2.6 Hz 8H), 3.98 (q, *J* = 7.1 Hz 8H), 2.27–2.24 (m, 8H), 2.15 (t, *J* = 7.2, Hz, 8H), 1.83 (s, 12H), 1.42–1.35 (m, 8H), 1.12 (t, *J* = 7.1 Hz, 12 H). HR MS (ESI TOF) m/z: $[M+H]^+$ Calculated for $C_{128}H_{116}N_{12}O_8Cl^-$=1949.91121; Found 1949.9166.

2.3. Synthesis of imine cage **1b** in chloroform

A 2 mM equimolar mixture of tetra-amino calix[4]pyrrole **2b** and tetra-formyl calix[4]pyrrole **3**, was prepared in $CDCl_3$ and placed in a NMR tube. The ^{1}H NMR of the reaction mixture after 48 hours at 308 K shows the signals corresponding to the formation of the capsule. 1,3,5-trimethoxybenzene was added as internal standard (i.s. final concentration = 2 mM). By integration of selected proton signals of the cage complex and those of the i.s. we determined a yield for the assembly of the complex around 48%.

$(CDCl_3)_2$⊂**1b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.92 ppm (s, 4H), 7.41 (bs, 4H), 7.41 (d, *J* = 8.3 Hz, 8H), 7.38 (bs, 4H), 7.09 (d, *J* = 8.2 Hz, 8H), 7.00 (d, *J* = 8.3 Hz, 8H), 6.94 (d, *J* = 8.2 Hz, 8H), 6.17 (d, *J* = 2.5 Hz, 8H), 6.05 (d, *J* = 2.6 Hz, 8H), 4.11 (q, *J* = 7.1 Hz, 8H), 2.46–2.37 (m, 8H), 2.26 (t, *J* = 7.3 Hz, 8H), 1.95 (s, 12H), 1.55–1.45 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 12H).

2.4. Synthesis of imine cage **1b** in dichloromethane

A 2 mM equimolar mixture of tetra-amino calix[4]pyrrole **2b** and tetra-formyl calix[4]pyrrole **3**, was prepared in CD_2Cl_2 and placed in a NMR tube. The ^1H NMR of the reaction mixture after 72 hours at 303 K shows the signals corresponding to the formation of the capsule. 1,3,5-trimethoxybenzene was added as internal standard (i.s. final concentration = 2 mM). By integration of selected proton signals of the cage complex and those of the i.s. we determined a yield for the assembly of the complex around 48%.

$(CD_2Cl_2)_2$⊂**1b:** ^1H NMR (500 MHz, CD_2Cl_2) δ(ppm): 7.93 (s,4H), 7.48 (d, *J* = 8.1 Hz, 8H), 7.3 (bs, 4H), 7.17 (bs, 4H) 7.14 (d, *J* = 8.3 Hz, 8H), 7.02 (d, *J* = 8.3 Hz, 8H), 6.98 (d, *J* = 8.1 Hz, 8H), 6.19 (d, *J* = 2.6 Hz, 8H), 6.09 (d, J = 2.6 Hz, 8H), 4.08 (q, *J* = 7.1 Hz, 8H), 2.43–2.37 (m, 8H), 2.29 (t, *J* = 7.4 Hz, 8H), 1.99 (s, 12H), 1,55–1.45 (m, 8H, overlapped with water), 1.25 (t, *J* = 7.1 Hz, 12H).

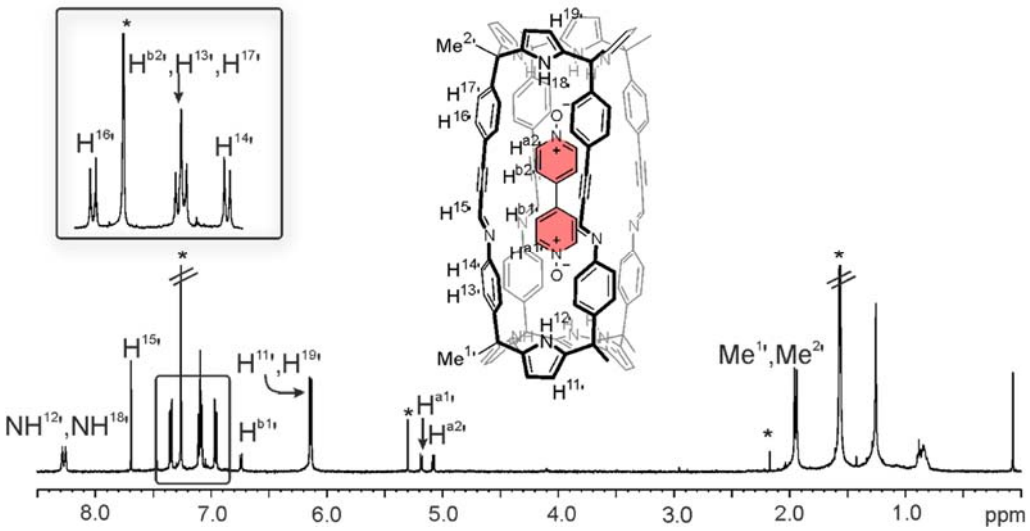


Figure S 1. ^1H NMR spectrum (500 MHz, at 298 K, $CDCl_3$) of a 1:1:1 equimolar mixture of tetra-formyl calix[4]pyrrole **3**, tetra-amino calix[4]pyrrole **2a** and **4** after 3h at r.t. (tetra-imine cage complex **4**⊂**1a**). (*) Indicates residual solvents.

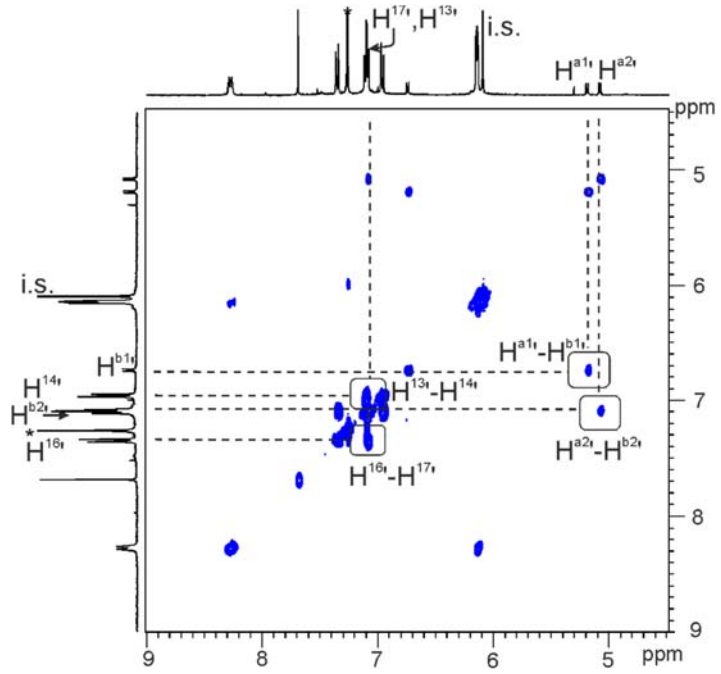


Figure S 2. Selected region of 2D COSY NMR (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage complex **4**⊂**1a**. See Figure S 1 for protons assignment. (*) Indicates residual solvents.

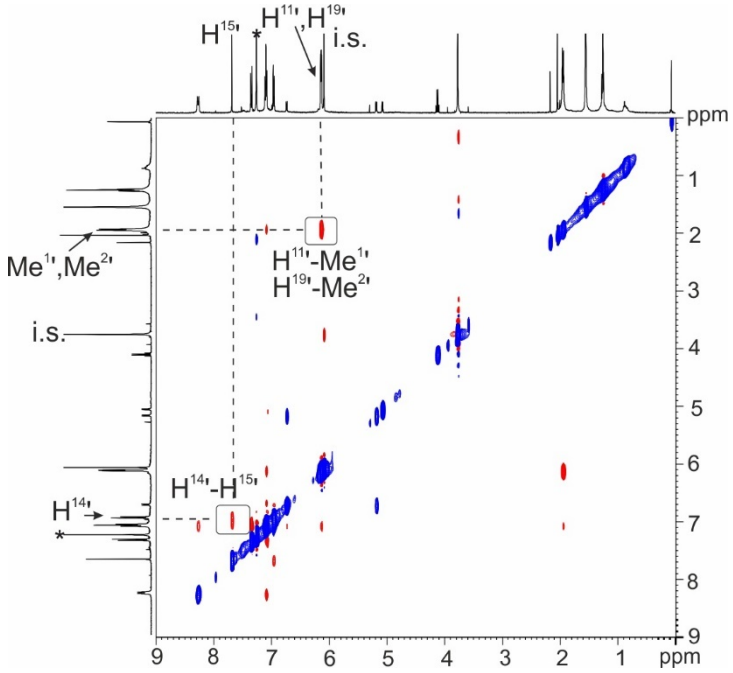


Figure S 3. Selected region of 2D ROESY NMR (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage complex **4**⊂**1a**. See Figure S 1 for protons assignment. (*) Indicates residual solvents.

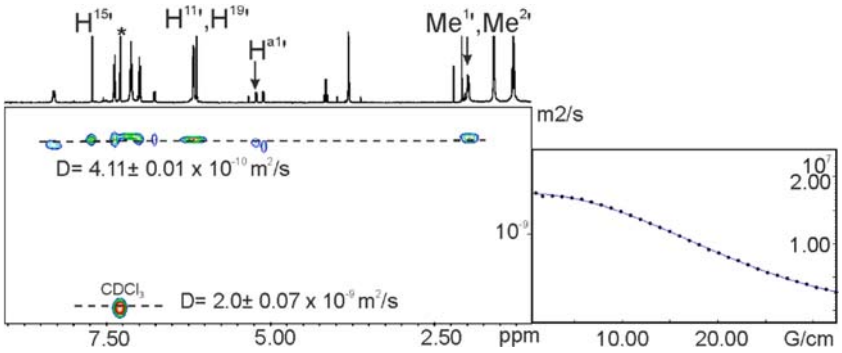


Figure S 4. ^{1}H pseudo-2D plot of DOSY NMR (400 MHz, at 298 K, $CDCl_3$, D20 = 0.15 s, P30 = 0.001 s) of a solution containing tetra-imine cage complex **4⊂1a**. See **Figure S 1** for protons assignment. (*) Indicates residual solvents.

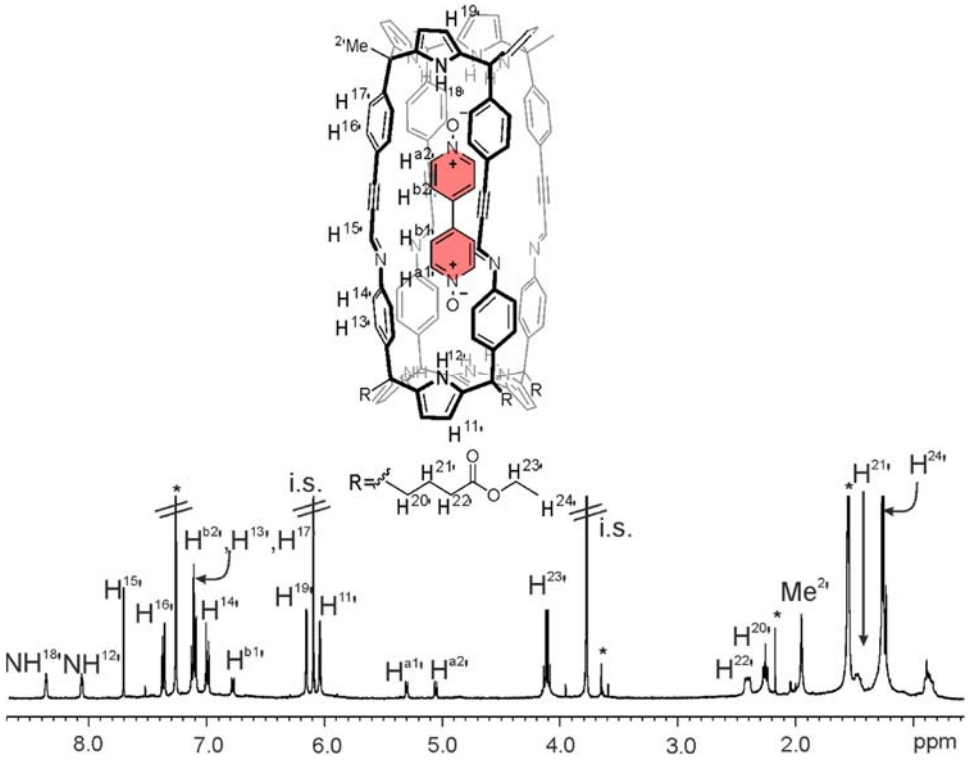


Figure S 5. ^{1}H NMR spectrum (500 MHz, at 298 K, $CDCl_3$) of a 1:1:1 equimolar mixture of tetra-formyl calix[4]pyrrole **3**, tetra-amino calix[4]pyrrole **2b** and **4** after 3h at r.t. (tetra-imine cage complex **4⊂1b**). (*) Indicates residual solvents.

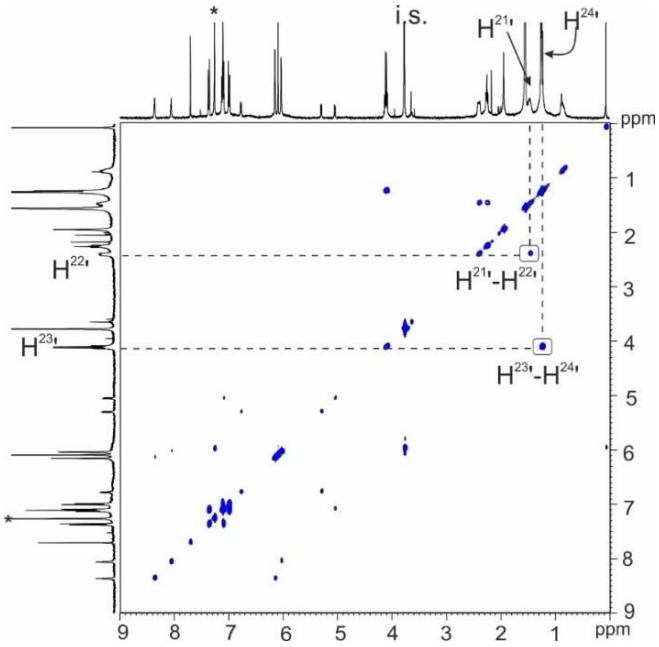


Figure S 6. 2D COSY NMR (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage complex **4⊂1b**. See **Figure S 5** for protons assignment. (*) Indicates the residual solvents.

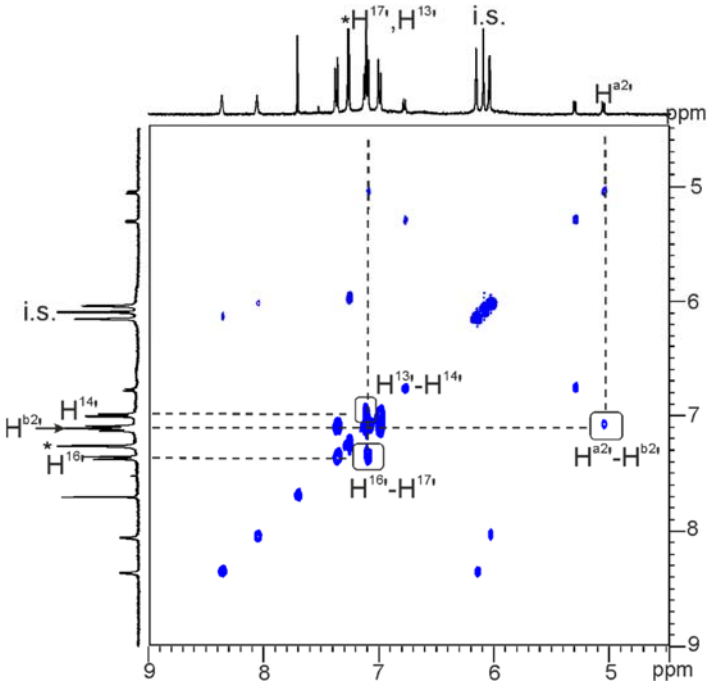


Figure S 7. Selected region of the 2D COSY NMR (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage complex **4⊂1b**. See **Figure S 5** for protons assignment. (*) Indicates the residual solvents.

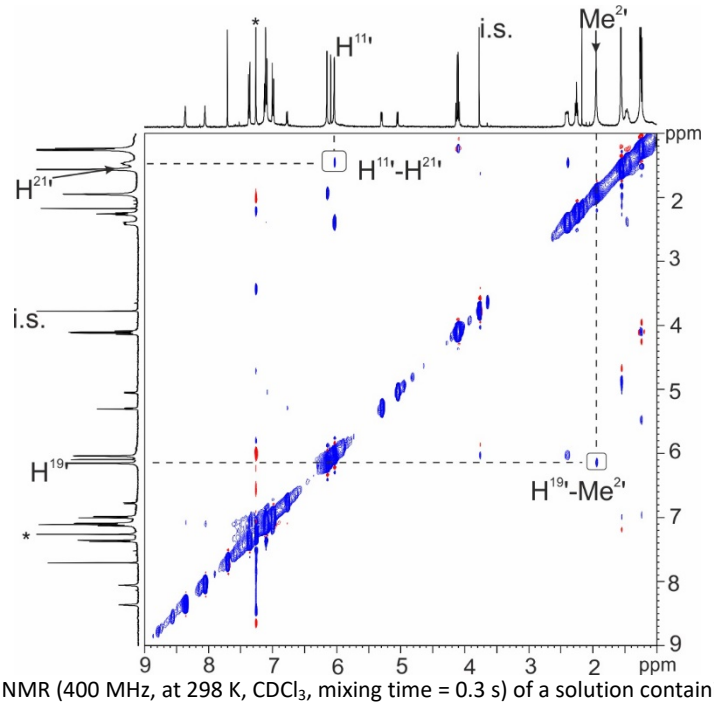


Figure S 8. 2D NOESY NMR (400 MHz, at 298 K, $CDCl_3$, mixing time = 0.3 s) of a solution containing tetra-imine cage complex **4**⊂**1b**. See **Figure S 5** for protons assignment. (*) Indicates the residual solvents.

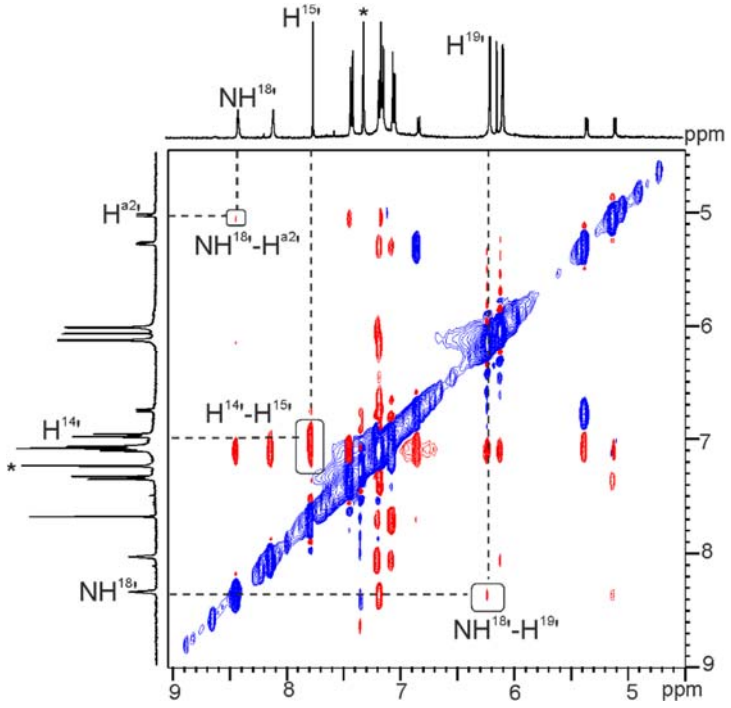


Figure S 9. Selected region of 2D ROESY NMR (400 MHz, at 298 K, $CDCl_3$, p15= 0.3 s) of a solution containing tetra-imine cage complex **4**⊂**1b**. See **Figure S 5** for protons assignment. (*) Indicates the residual solvents.

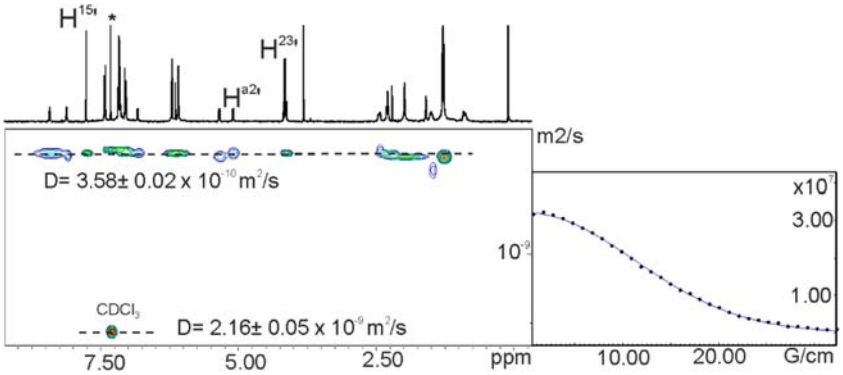


Figure S 10. ^{1}H pseudo-2D plot of the DOSY NMR (400 MHz, at 298 K, $CDCl_3$, D20 = 0.1 s, P30 = 0.002 s) of a solution containing tetra-imine cage complex **4⊂1b**. See **Figure S 5** for protons assignment. (*) Indicates the residual solvents.

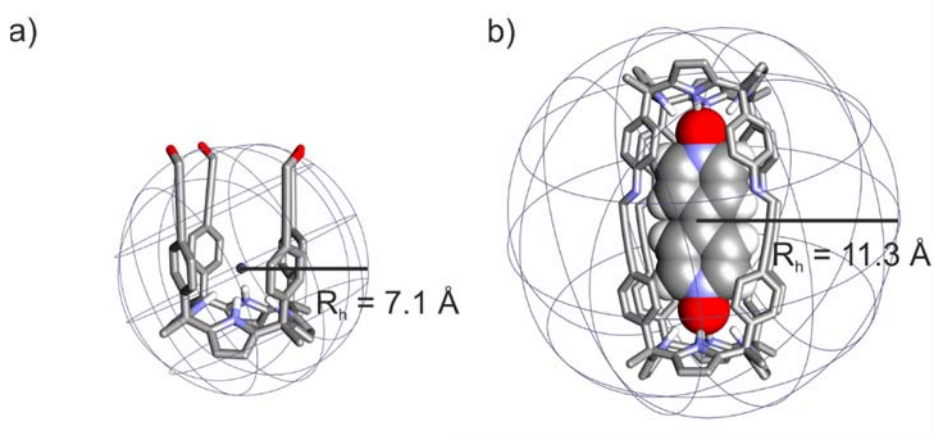
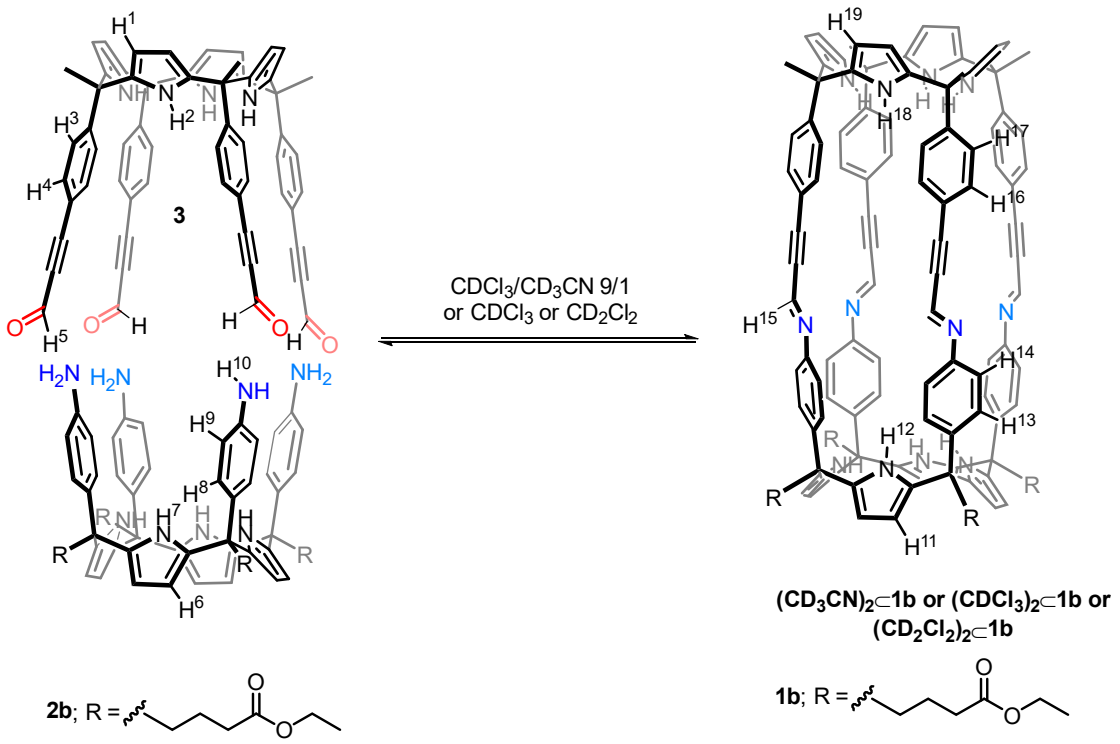


Figure S 11. MM3 Energy minimized structures of tetra-formyl calix[4]pyrrole **3** (a) and tetra-imine complex **4⊂1** enclosed within a sphere of 7.1 and 11.3 Å, respectively. Non-polar hydrogens of the hosts have been removed and ester chains at the lower rim were pruned to methyl groups for clarity.



Scheme S 1. Equilibrium of the [1 + 1] condensation reaction between the "four wall" tetra-amine calix[4]pyrrole **2b** and tetra-formyl counterpart **3** assisted by solvent (CD_3CN, $CDCl_3$ and CD_2Cl_2).

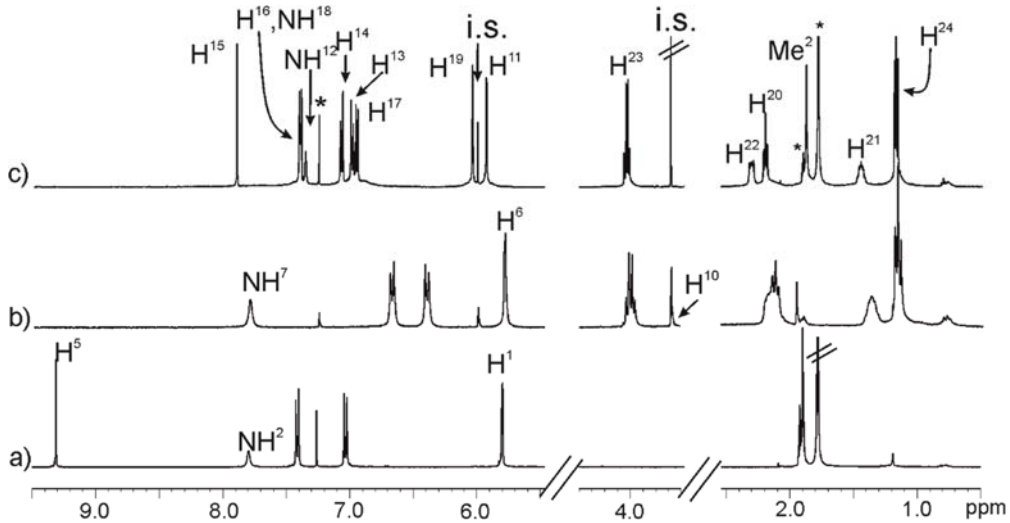


Figure S 12. Selected regions of ^{1}H NMR spectra (400 MHz, at 298 K, $CDCl_3$:CD_3CN 9:1 mixture) of (a) **3**, (b) **2b**, (c) an equimolar mixture of **3** and **2b** after 3h at r.t. (tetra-imine cage $(CD_3CN)_2$⊂**1b**). See **Scheme S 1** for protons assignment. (*) Indicates the residual solvents.

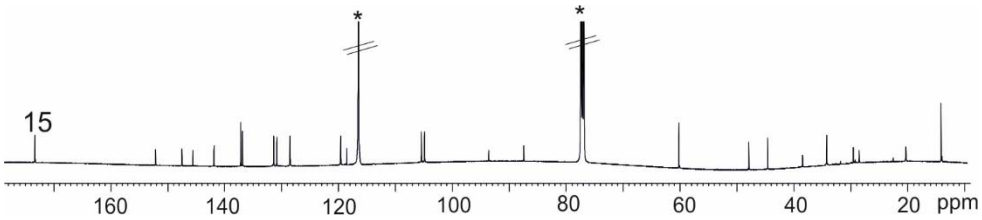


Figure S 13. ^{13}C NMR (120 MHz with cryprobe,298 K, $CDCl_3$:CD_3CN 9:1 mixture) of a solution containing tetra-imine cage $(CD_3CN)_2\subset$**1b**. Imine carbon is indicated as 15. (*) Indicates residual solvents.

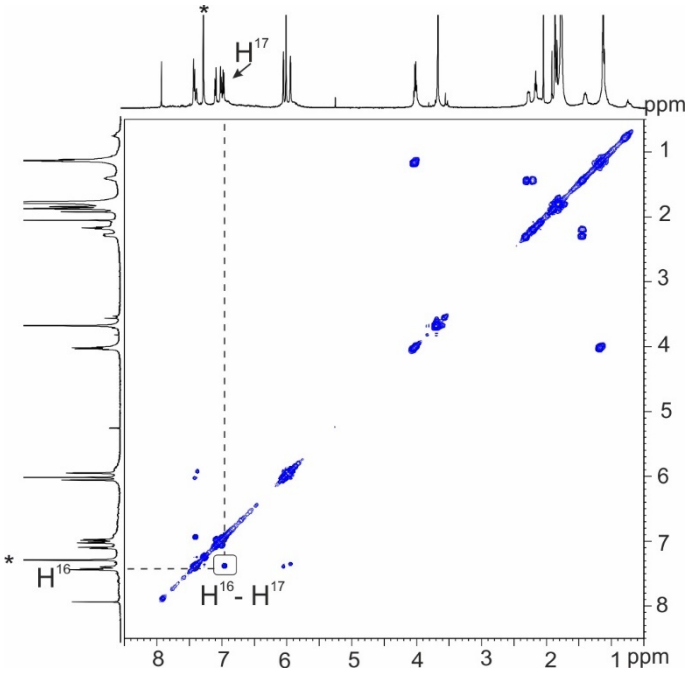


Figure S 14. 2D COSY NMR (400 MHz, at 298 K, $CDCl_3$:CD_3CN 9:1 mixture) of a solution containing tetra-imine cage $(CD_3CN)_2\subset$**1b**. See for **Scheme S 1** protons assignment. (*) Indicates residual solvents.

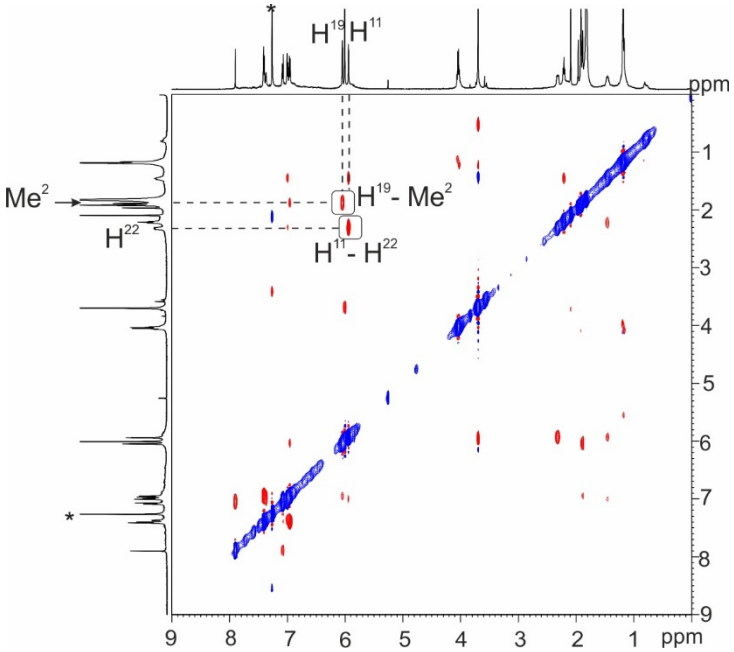


Figure S 15. 2D ROESY NMR (400 MHz, at 298 K, $CDCl_3$:CD_3CN 9:1 mixture, mixing time= 0.3 s) of tetra-imine cage $(CD_3CN)_2\subset$**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

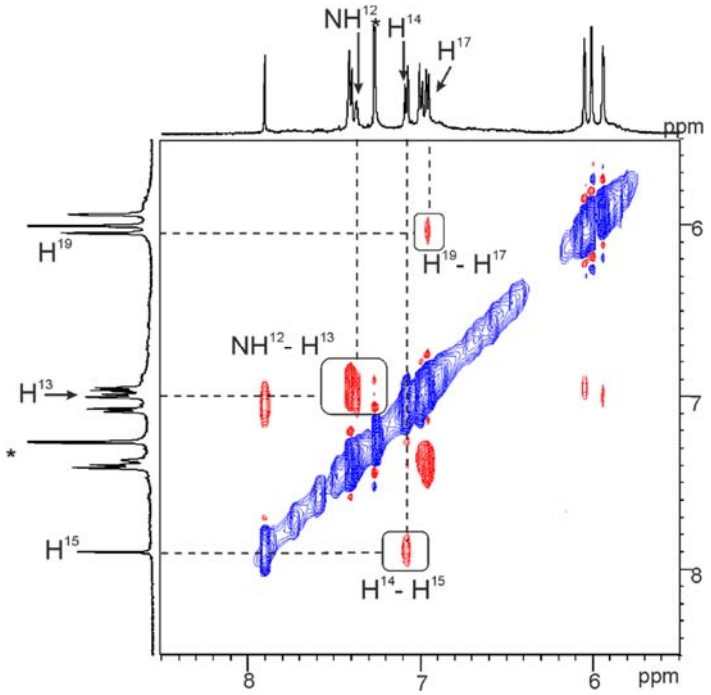


Figure S 16. Selected region of 2D ROESY NMR (400 MHz, at 298 K, $CDCl_3$:CD_3CN 9:1 mixture, mixing time = 0.3 s) of tetra-imine cage $(CD_3CN)_2\subset$**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

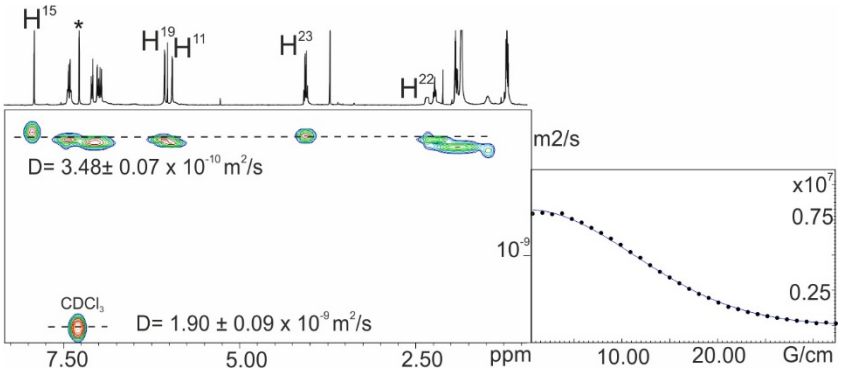


Figure S 17. ^{1}H pseudo-2D plot of the DOSY NMR (400 MHz, at 298 K, $CDCl_3$:CD_3CN 9:1 mixture, D20 = 0.1 s, P30 = 0.002 s) of tetra-imine cage $(CD_3CN)_2\subset$**1b**. See **Scheme S 1** for protons assignment (*) Indicates residual solvents.

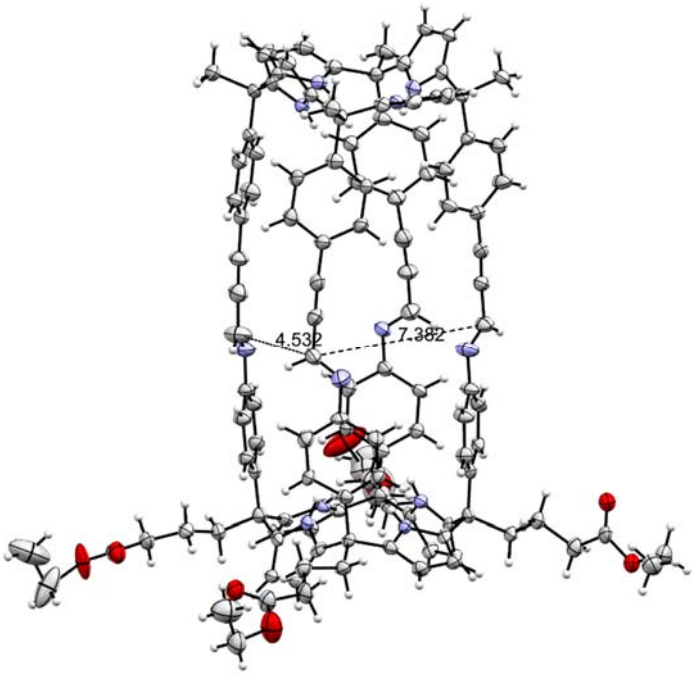


Figure S 18. X-ray crystal structure of tetra-imine cage **1b**. The structure is shown in ORTEP view with thermal ellipsoids set at 50% probability. Hydrogen atoms are shown as fixed-size spheres of 0.3 Å radius. Included guest and solvent molecules are omitted for clarity.

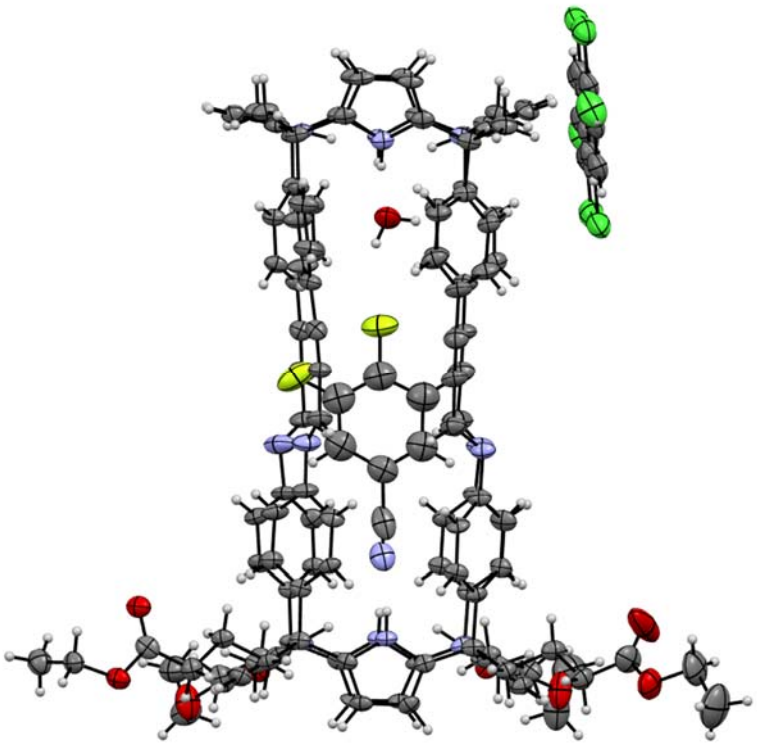


Figure S 19. X-ray crystal structure of tetra-imine cage **1b** with one water molecule and one molecule of 3,4-difluorobenzonitrile included in the cavity. The structure is shown in ORTEP view with thermal ellipsoids set at 50% probability. Hydrogen atoms are shown as fixed-size spheres of 0.3 Å radius. The obtention of single crystals of **1b** suitable for X-ray diffraction analysis required the addition of different halogenated aromatic solvents (i.e., 1,2-difluorobenzene, trichlorobenzene, etc.) to the initial 9:1 $CDCl_3$:CD_3CN solution of tetra-imine cage **1b**. In turn, the resulting mixture of solvents were heated for prolonged amounts of time at different temperatures.

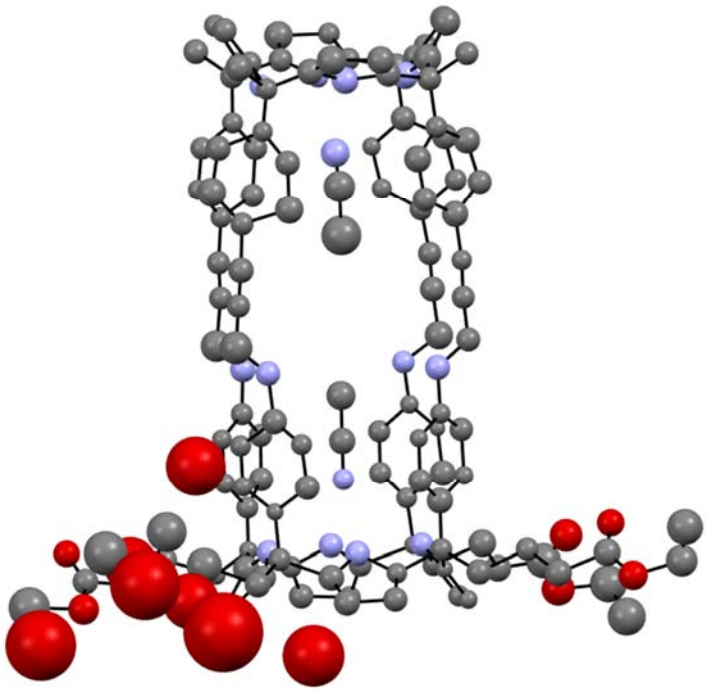


Figure S 20. Preliminary solution of the diffracted data of a single crystal obtained from a 9:1 $CDCl_3$:CD_3CN solvent mixture of tetra-imine cage **1b** showing two molecules of acetonitrile included in the cavity.

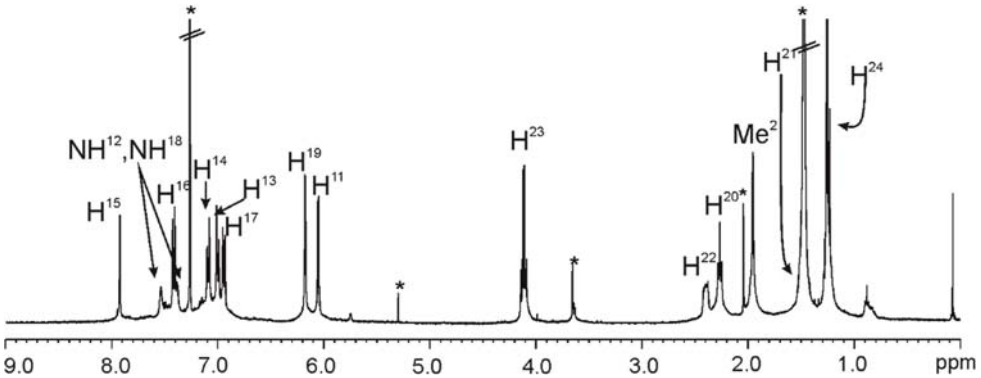


Figure S 21. ^{1}H NMR spectrum (400 MHz, at 298 K, $CDCl_3$) of an equimolar mixture of tetra-formyl calix[4]pyrrole **3** and tetra-amino calix[4]pyrrole **2b** after 48h at 308 K (tetra-imine cage $(CDCl_3)_2\subset$**1b**). See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

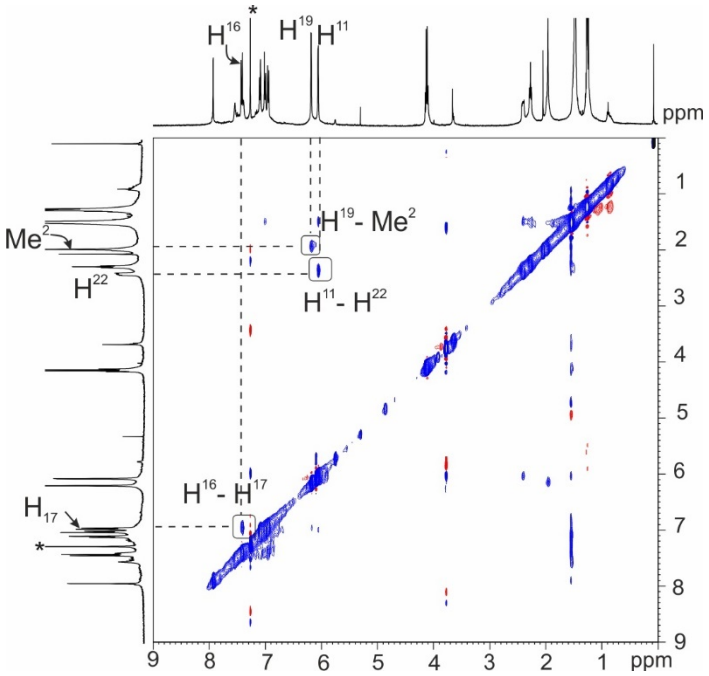


Figure S 22. 2D NOESY NMR (400 MHz, at 298 K, $CDCl_3$, mixing time = 0.3 s) of a solution containing tetra-imine cage $(CDCl_3)_2$⊂**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

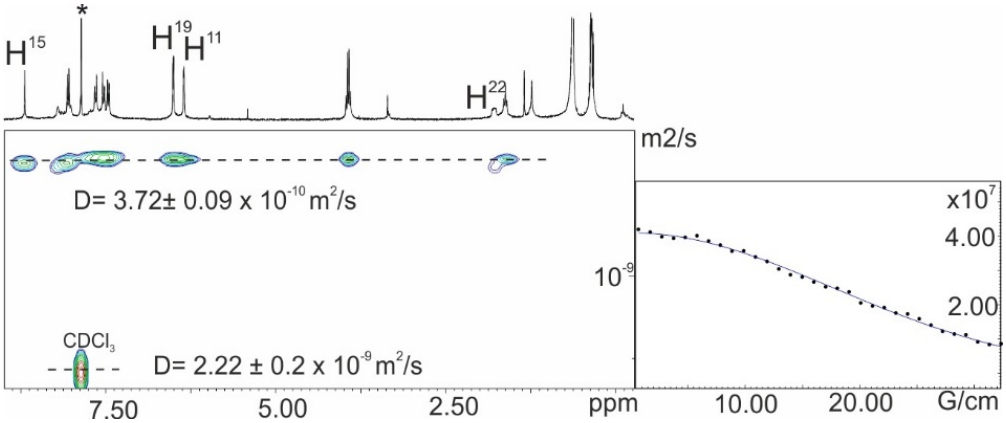


Figure S 23. ^{1}H pseudo-2D plot of the DOSY NMR (400 MHz, at 298 K, $CDCl_3$, D20 = 0.15 s, P30 = 0.001 s) of a solution containing tetra-imine capsule $(CDCl_3)_2$⊂**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

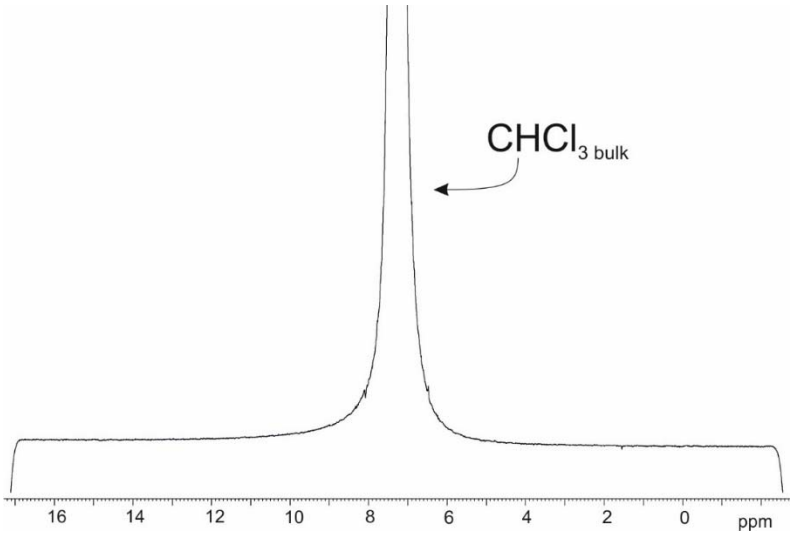


Figure S 24. GOESY NMR experiment (500 MHz, at 298 K) using a 95:5 $CHCl_3$:$CDCl_3$ solution of cage **1b** with selective excitation of the signal of chloroform at 7.28 ppm. The absence of exchange peaks suggests that most likely, the chemical exchange between the free and bound $CHCl_3$ was fast on the chemical shift timescale.

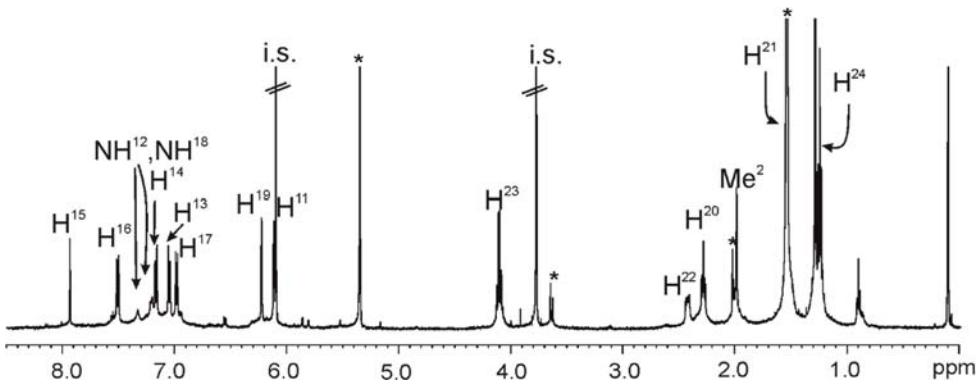


Figure S 25. ^{1}H NMR spectrum (500 MHz, at 298 K, CD_2Cl_2) of an equimolar mixture of **3** and **2b** after 72h at 303 K (tetra-imine cage $(CD_2Cl_2)_2$⊂**1b**). See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

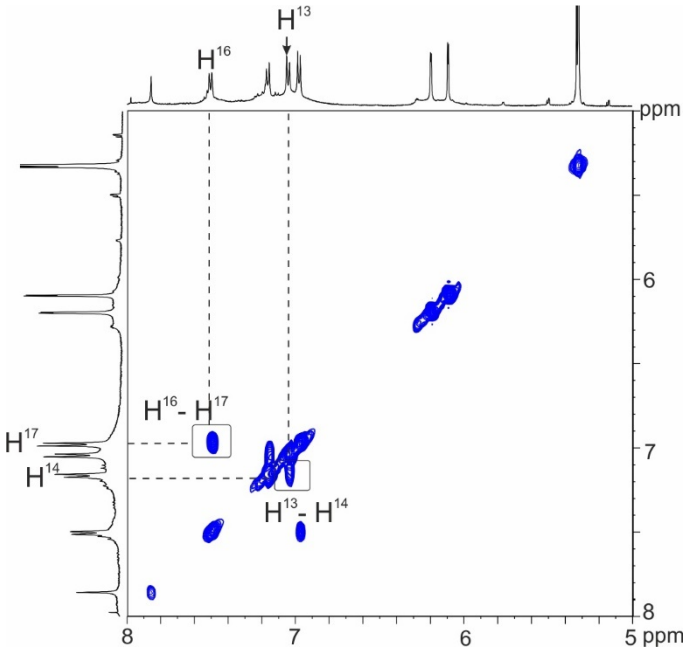


Figure S 26. Selected region of 2D COSY NMR (400 MHz, at 298 K, CD_2Cl_2) of a solution containing tetra-imine cage $(CD_2Cl_2)_2$⊂**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

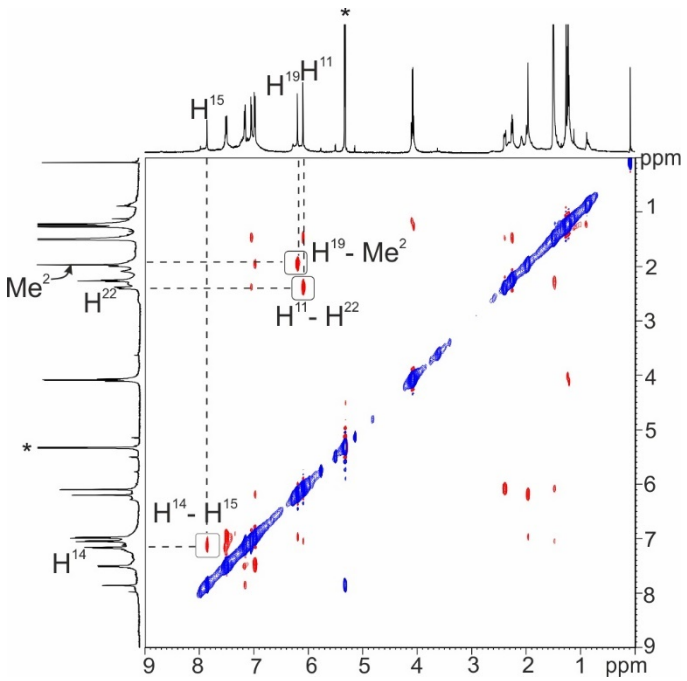


Figure S 27. Selected region of 2D ROESY NMR (400 MHz, at 298 K, CD_2Cl_2, mixing time = 0.3 s) of a solution containing tetra-imine cage $(CD_2Cl_2)_2$⊂**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

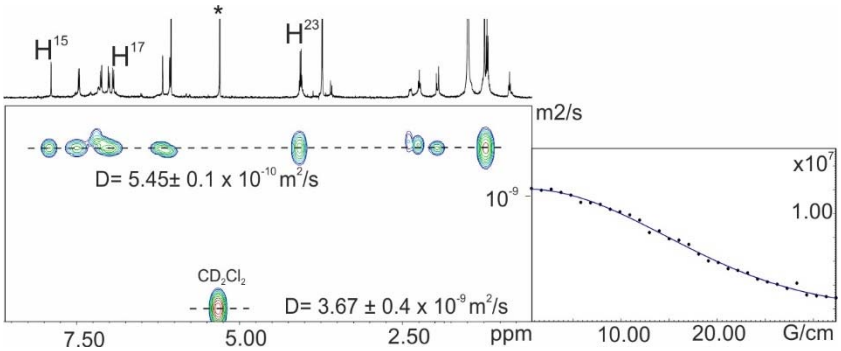


Figure S 28. ^{1}H pseudo-2D plot of the DOSY NMR (400 MHz, at 298 K, CD_2Cl_2, D20 = 0.15 s, P30 = 0.001 s) of a solution containing tetra-imine cage $(CD_2Cl_2)_2\subset$**1b**. See **Scheme S 1** for protons assignment. (*) Indicates residual solvents.

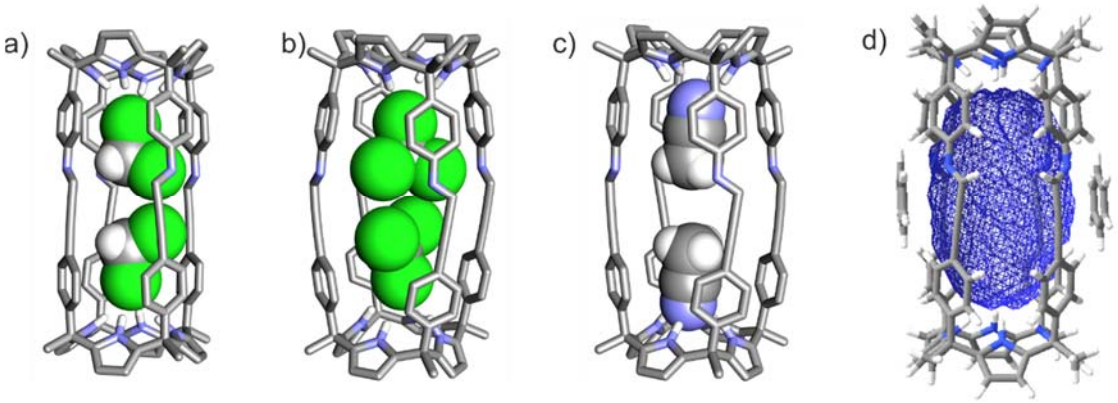
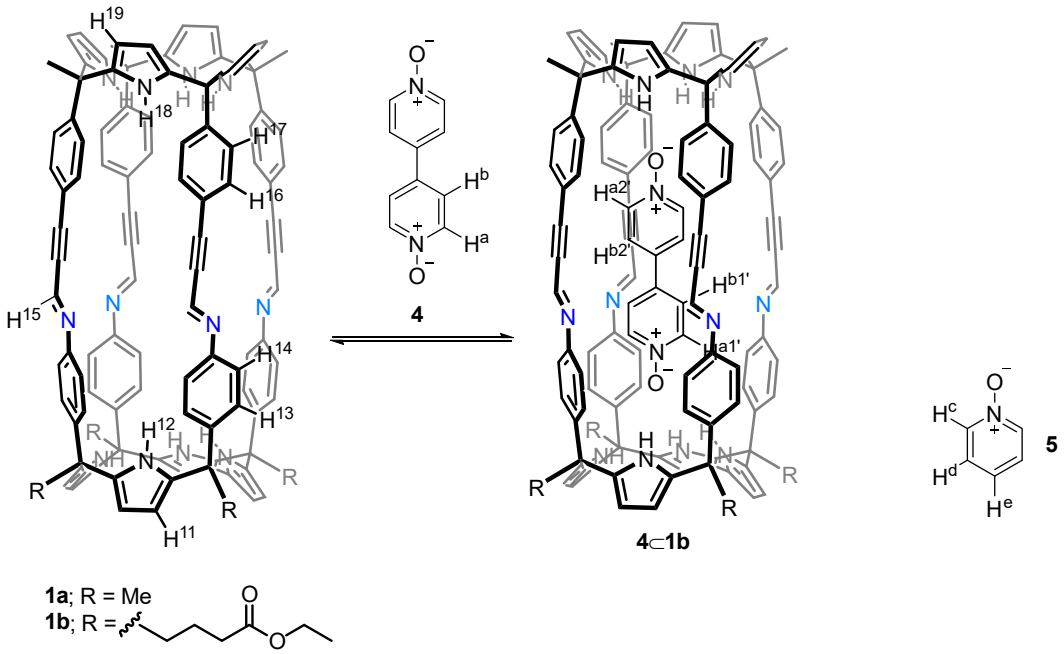


Figure S 29. MM3 energy minimized structures of $(CD_2Cl_2)_2\subset$**1b** (a), $(CDCl_3)_2\subset$**1b** (b) and $(CD_3CN)_2\subset$**1b** (c). (d) Rendering of the MM3 minimized structure of the $(CDCl_3)_2\subset$**1b** complex used to calculate the inner volume (in blue) using Swiss-PDB Viewer version 4.10 (~254 A$^{\circ 3}$) after guest deletion. Two benzene molecules were needed to cover the big-sized portal (distance between N_{imine} atom and ortho proton of the benzene was 2.4 Å).

Table S 1. Calculated cavity volumes, solvent molecules volumes and packing coefficient for the series of complexes of **1b** with solvent guests ($CDCl_3$, CD_2Cl_2 and CD_3CN) using Swiss-PDB software Version 4.10 and MM3-level energy minimized structures. Volumes are given in Å^3. Two benzene molecules were needed to cover the big-sized portal (distance between N_{imine} atom and ortho proton of the benzene was 2.4 Å). The packing coefficient values were calculated as PC % = ($V_{guest}/V_{inner\ cavity}$) × 100). Analogous calculations were performed using energy minimized structures from DFT calculations at the BP86[4,5]/def2SVP level of theory using GAUSSIAN 09.[6] The calculated packing coefficients using these structures very large (~80 %) most likely due to dispersion

	$V_{inner\ cavity}$ **host (Å^3)**	V_{guest} **(Å^3)**	**PC%**
$(CD_2Cl_2)_2\subset$**1b**	266	2 × 57	43
$(CDCl_3)_2\subset$**1b**	254	2 × 73	57
$(CD_3CN)_2\subset$**1b**	247	2 × 43	35

3. *Binding studies in $CDCl_3$*



Scheme S 2. Binding equilibrium of tetra-imine cage **1b** with bis-pyridine bis-N-oxide **4** with the corresponding proton assignment. Line drawing structure of pyridine N-oxide **5** with its proton assignment is also shown.

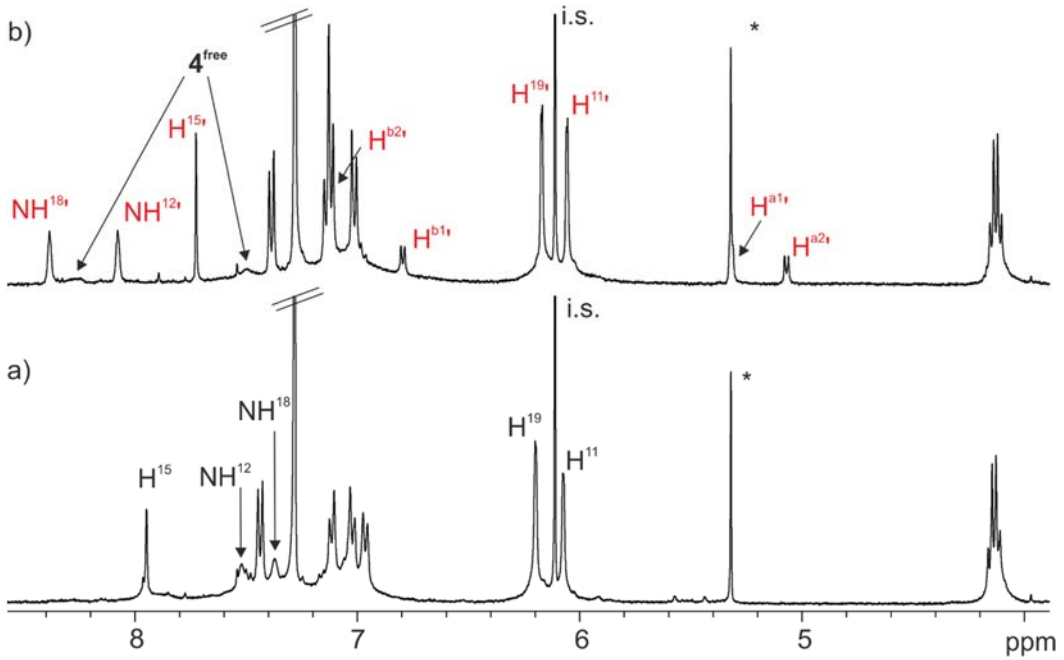


Figure S 30. Selected ^{1}H NMR region of spectra (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage $(CDCl_3)_2$⊂**1b**, before (a) and immediately after addition of **4** (2 equiv.) (b). Primed red letters indicate the bound host and guest. See **Scheme S 2** for protons assignment. (*) Indicates residual solvents. i.s. internal standard.

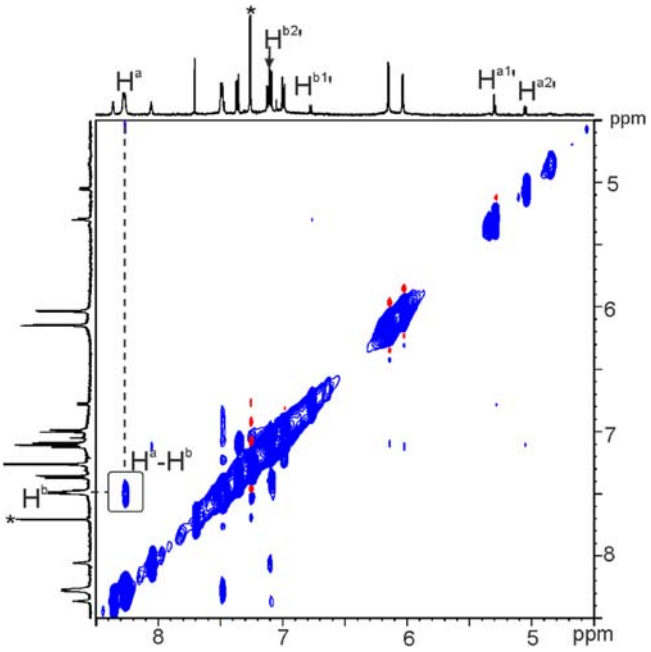


Figure S 31. Selected region of the ^{1}H-^{1}H- EXSY NMR (400 MHz, $CDCl_3$, 298 K, mixing time = 0.3 s) of a solution containing tetra-imine cage compex **4**⊂**1b** in the presence of an excess of **4** (2 equiv.). The spectrum does not show cross-peaks between free and bound guest. This is indicative of a slow chemical exchange process between free and bound guest on the EXSY NMR timescale. See **Scheme S 2** for protons assignment. (*) Indicates residual solvents.

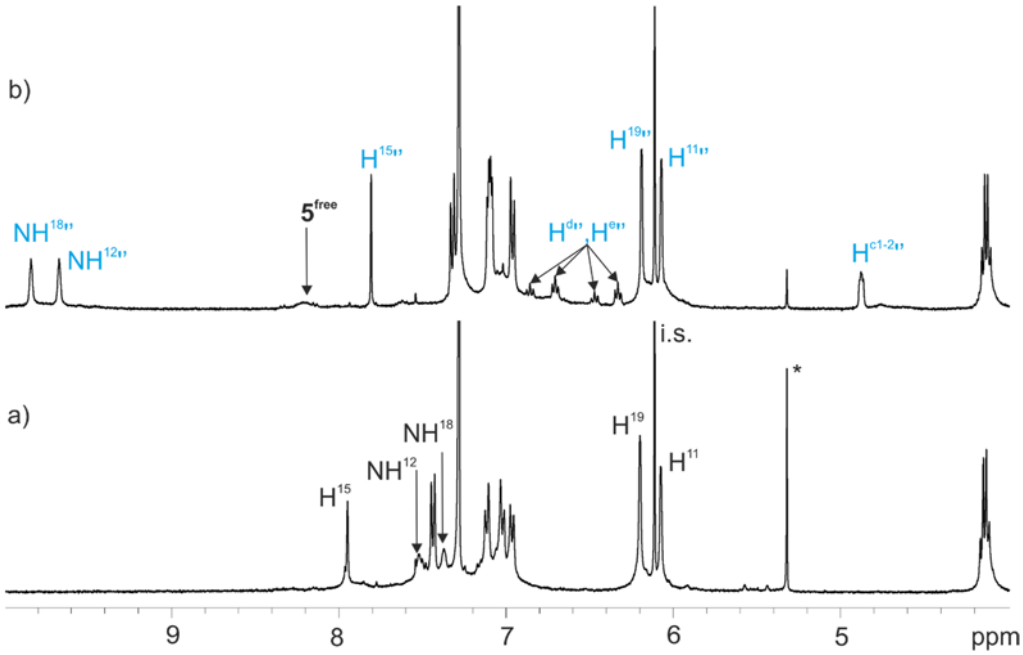


Figure S 32. Selected ^{1}H NMR region of spectra (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage solvate $(CDCl_3)_2$⊂**1b**, before (a) and immediately after addition of **5** (3 equiv.) (b). Primed and blue letters indicate the bound host and guest in a 2:1 stoichiometry. See **Scheme S 2** for protons assignment. (*) Indicates residual solvents. i.s. internal standard.

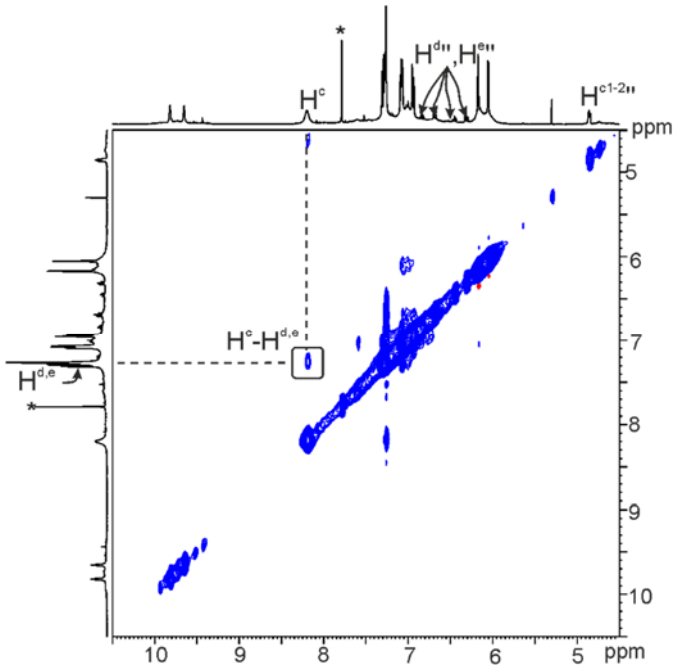


Figure S 33. Selected region of the ^{1}H-^{1}H- EXSY NMR (400 MHz, $CDCl_3$, 298 K, mixing time = 0.3 s) solution containing tetra-imine cage complex (**5**)$_2$⊂**1b** in presence an excess of **5** (3.5 equiv.). The spectrum does not show cross-peaks between free and bound guest. This is indicative of a slow chemical exchange process between free and bound components on the EXSY NMR timescale. See **Scheme S 2** for protons assignment. (*) indicates residual solvents.

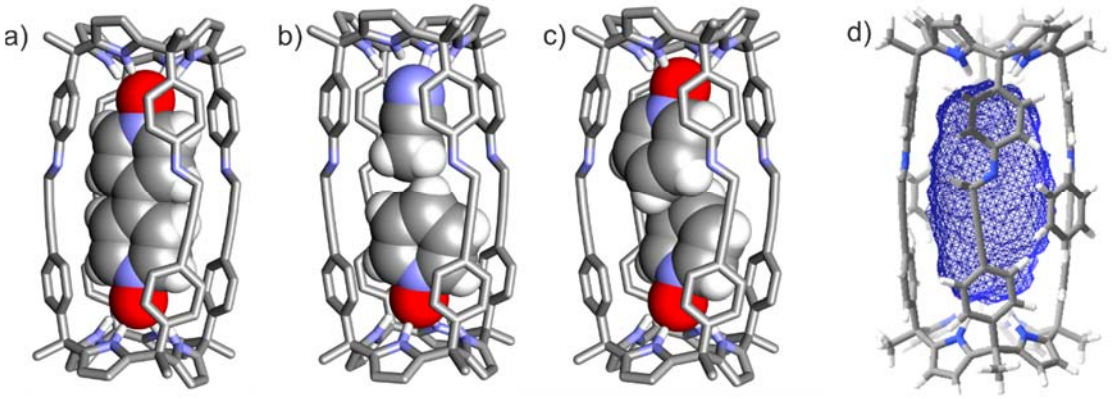


Figure S 34. MM3 Energy minimized structures (MM3) of a) **4**⊂**1b**, b) (**5**•CD_3CN)⊂**1b**, c) (**5**)$_2$⊂**1b**. d) Rendering of the MM3 minimized structure of the **4**⊂**1b** complex used to calculate the inner volume (in blue) using Swiss-PDB Viewer version 4.10 (~269 $Å^3$) after guest deletion. Two benzene molecules were needed to cover the big-sized portal (distance between N_{imine} atom and ortho proton of the benzene was 2.4 Å)

Table S 2. Calculated cavity volumes, guest volumes and packing coefficient for the series of complexes of **1b** with guests **4** and **5** using Swiss-PDB software version 4.10 and MM3-level energy minimized structures. Volumes are given in Å^3. Two benzene molecules were needed to cover the big-sized portal (distance between N_{imine} atom and ortho proton of the benzene was 2.4 Å). The packing coefficient values were calculated as PC %= ($V_{guest}/V_{inner\ cavity}$)× 100). Analogous calculations were performed using energy minimized structures from DFT calculations at the BP86[4,5]/def2SVP level of theory using GAUSSIAN 09.[6] The calculated packing coefficients using these structures very large (~80 %) most likely due to dispersion.

	$V_{inner\ cavity}$ (Å^3)	V_{guest} (Å^3)	PC(%)
4⊂1b	269	161	60
(5•CD_3CN)⊂1b	242	85 + 43	53
$(5)_2$⊂1b	297	85 × 2	57

4. *Guest exchange experiments in $CDCl_3$ solution*

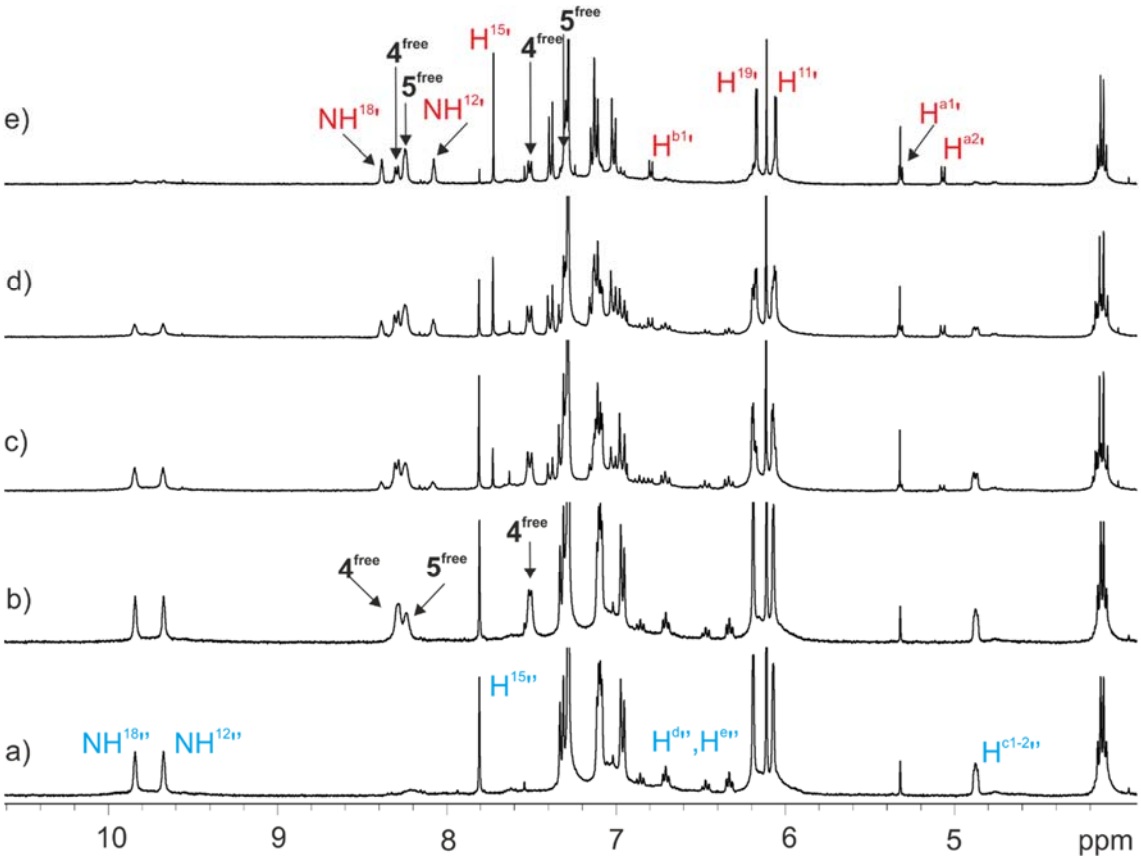


Figure S 35. Selected ^{1}H NMR region of spectra (400 MHz, at 298 K, $CDCl_3$) of a solution containing tetra-imine cage complex $(5)_2$⊂**1b** and free **5**, before (a) and after addition of **4** (2 equiv.) at t= 0 min (b), 48h (c) 8 days (d) and 1 month (e). Primed and blue letters indicate complex $(5)_2$⊂**1b** and red and primer letters complex **4**⊂**1b**. See **Scheme S 2** for protons assignment. (*) Indicates residual solvents. i.s. internal standard.

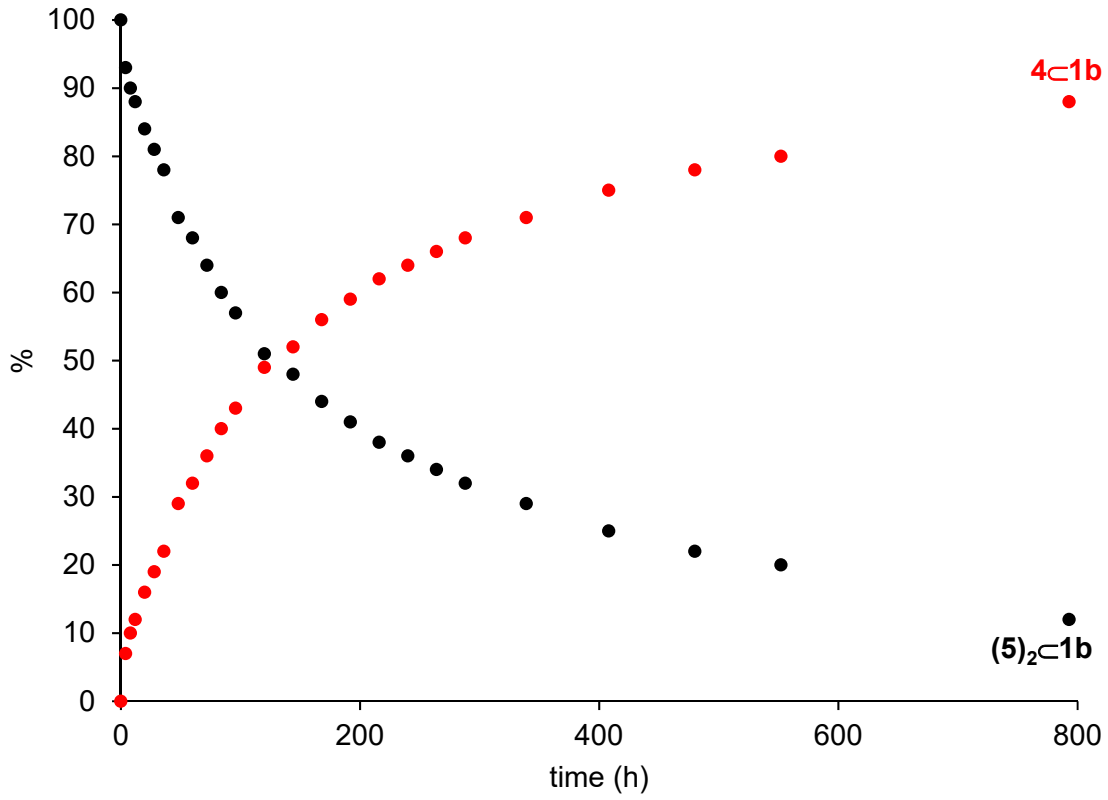


Figure S 36. Experimental changes in the concentration of **5**$_2$**⊂1b** (red) and **4⊂1b** (black) versus time (h) following the addition of 2 equiv. of bis-*N*-oxide **4** to a mixture of **1b** and **5** in $CDCl_3$ (initial concentrations: [**1b**] = 1 mM, [**5**] = 2 mM)).

5. *Binding studies of pyridine N-oxide **5** in $CDCl_3$ solution*

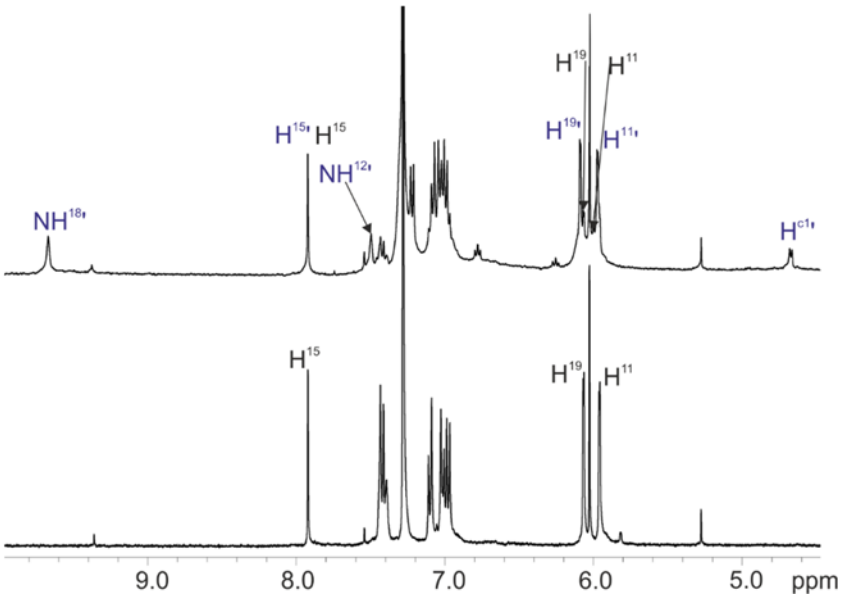


Figure S 37. Selected regions of the ^{1}H NMR spectra (500 MHz, at 298 K) of 1 mM solution of tetra-imine cage solvate $(CD_3CN)_2$**⊂1b** in $CDCl_3$:CD_3CN 9:1 mixture (bottom) and after (top) the addition of pyridyl *N*-oxide **5** (0.8 mM).

6. *Characterization in gas phase*

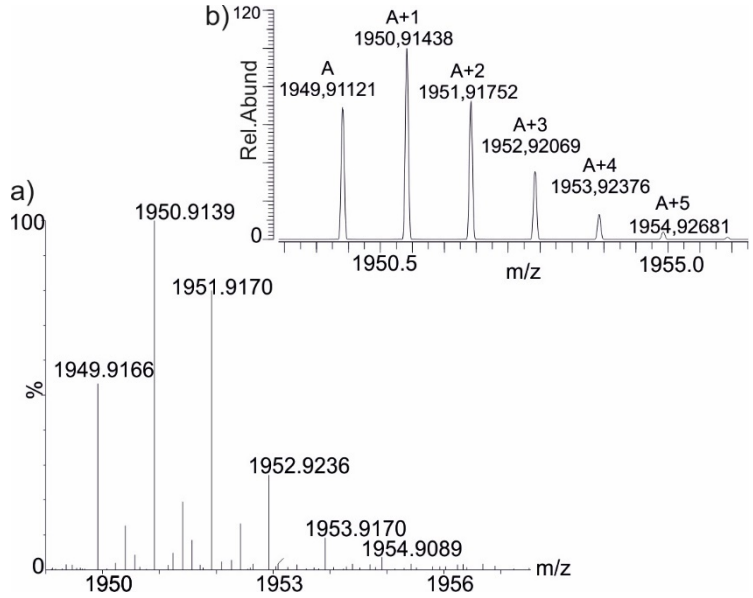


Figure S 38. Experimental (a) and calculated (b) isotopic distributions of cage [**1b**+H]$^+$. The exact mass for the monoisotopic peak is indicated as A in (b).

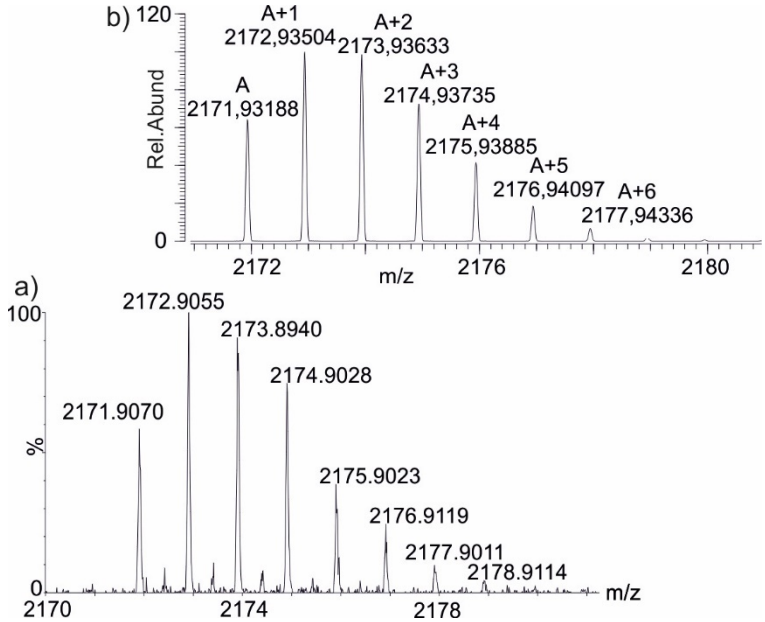


Figure S 39. Experimental (a) and calculated (b) isotopic distributions of cage complex [**4⊂1b** + Cl]$^-$. The exact mass for the monoisotopic peak is indicated as A in (b).

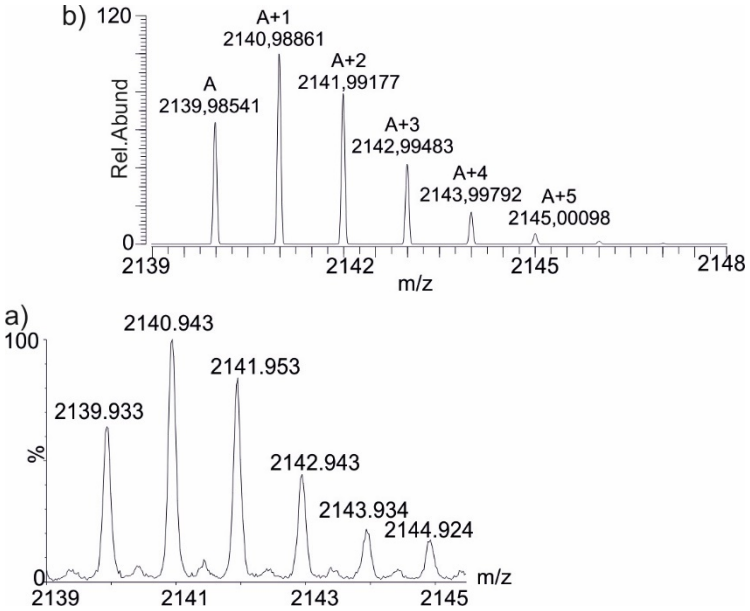


Figure S 40. Experimental (a) and calculated (b) isotopic distributions of cage complex [**(5)$_2$⊂1b** + H]$^+$. The exact mass for the monoisotopic peak is indicated as A in (b).

7. *References*

1 P. Ballester and G. Gil-Ramírez, *Proc. Natl. Acad. Sci. U.S.A.*, 2009, **106**, 10455-10459.
2 L. Escobar, F. A. Arroyave and P. Ballester, Eur. J. Org. Chem., 2018, 2018, 1097-1106.
3 A. Galán, E. C. Escudero-Adán and P. Ballester, Chem. Sci., 2017, 8, 7746-7750.
4 J. P. Perdew, *Phys. Rev. B*, 1986, **33**, 8822-8824.
5 A. D. Becke, Phys. Rev. A, 1988, 38, 3098-3100.
6 Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.