Supplementary Material (ESI) for Chemical Communications

Electronic Supporting information

Restricted rotation due to lack of free space within a capsule translates into product selectivity: Photochemistry of cyclohexyl phenyl ketones within a water-soluble organic capsule

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Contents

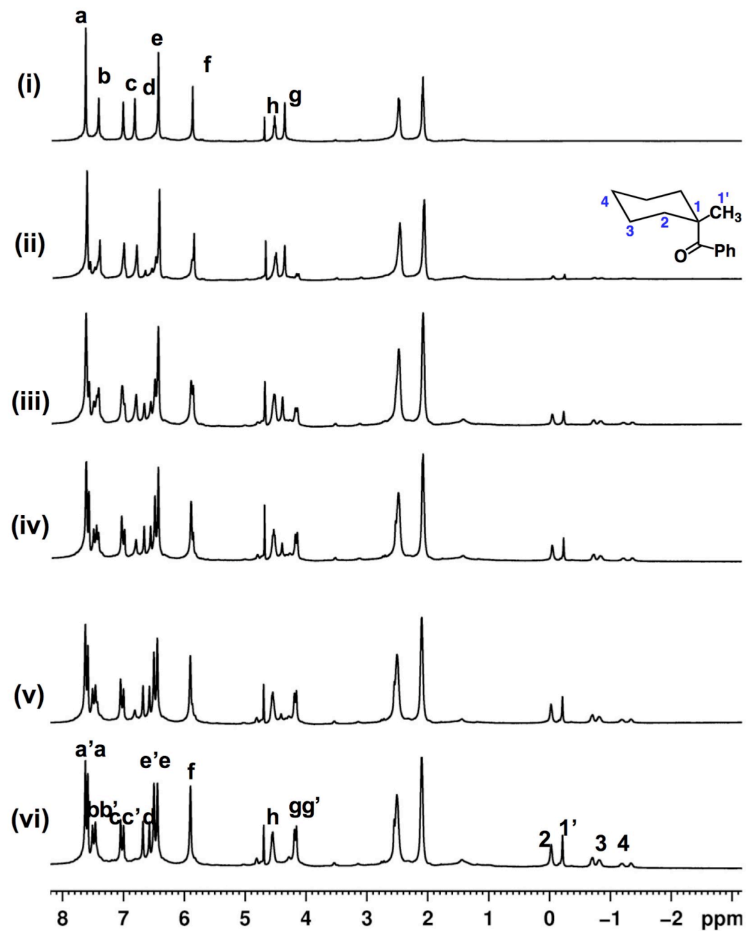


Figure S1. [1]H NMR (500 MHz, D_2O) spectra (i) **A** (1mM in 10mM borate buffer), (ii) **A**:**B** (1:0.1), (iii) **A**:**B** (1:0.2), (iv) **A**:**B** (1:0.3), (v) **A**:**B** (1:0.4), and (vi) **A**:**B** (1:0.5). Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4.

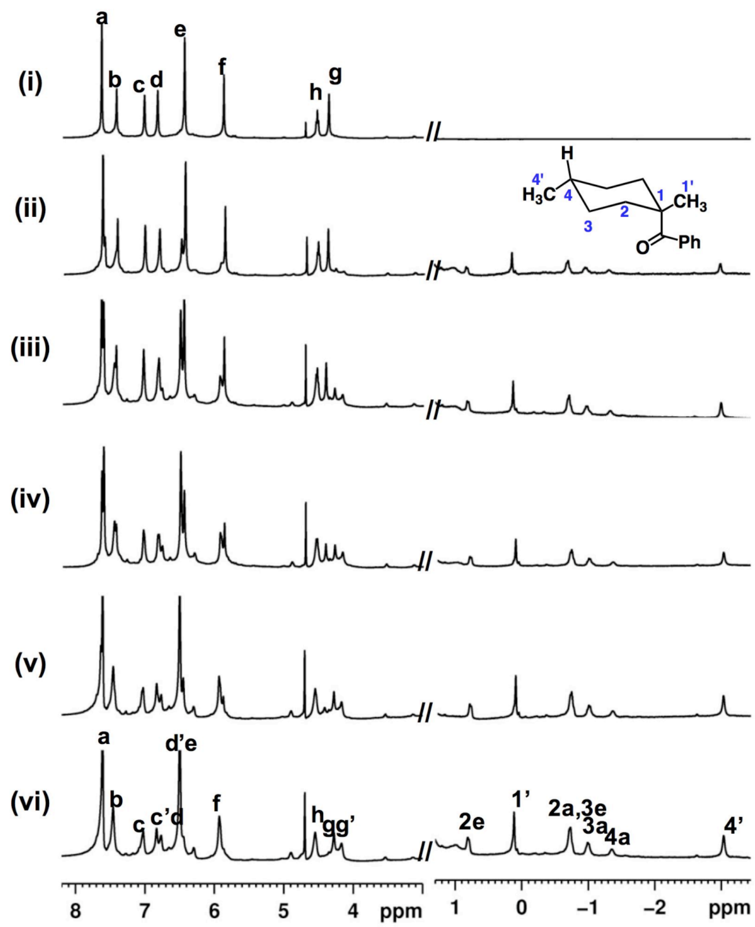


Figure S2. [1]H NMR (500 MHz, D_2O) spectra (i) **A** (1mM in 10mM borate buffer), (ii) **A**:**C** (1:0.1), (iii) **A**:**C** (1:0.2), (iv) **A**:**C** (1:0.3), (v) **A**:**C** (1:0.4), and (vi) **A**:**C** (1:0.5)**.** Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4.

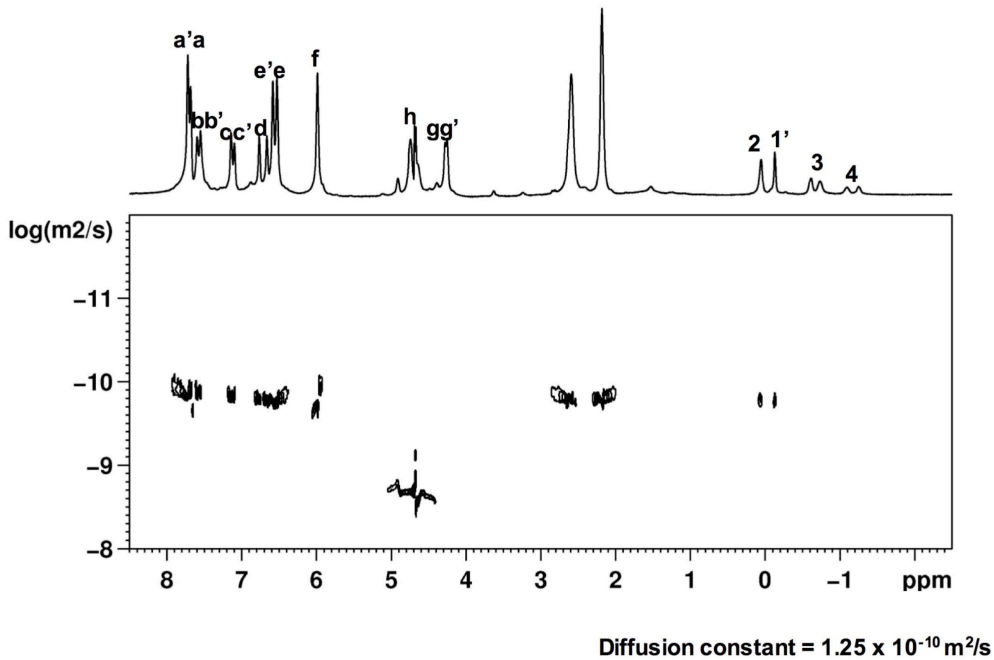
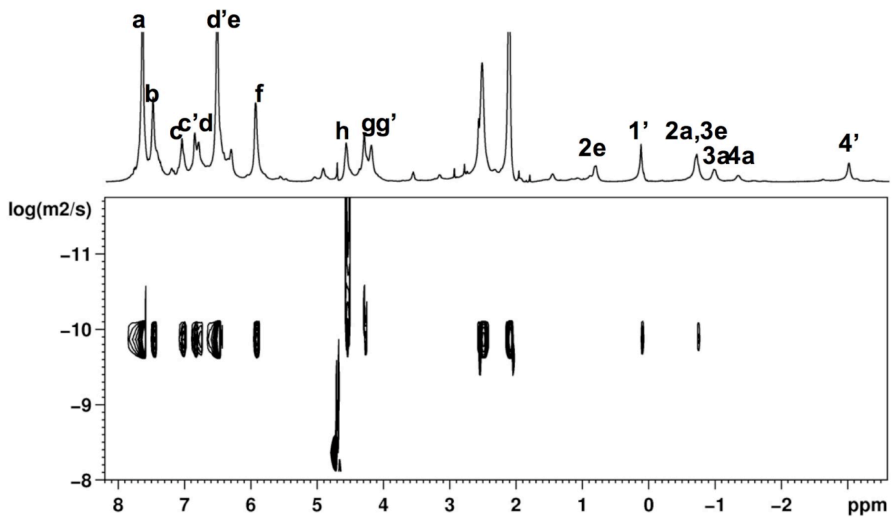


Figure S3. DOSY NMR of **B**@**A**$_2$ (500 MHz, D_2O) spectrum.



Diffusion constant = 1.17 x 10^{-10} m^2/s

Figure S4. DOSY NMR of **C@$\mathbf{A_2}$** (500 MHz, D_2O) spectrum.

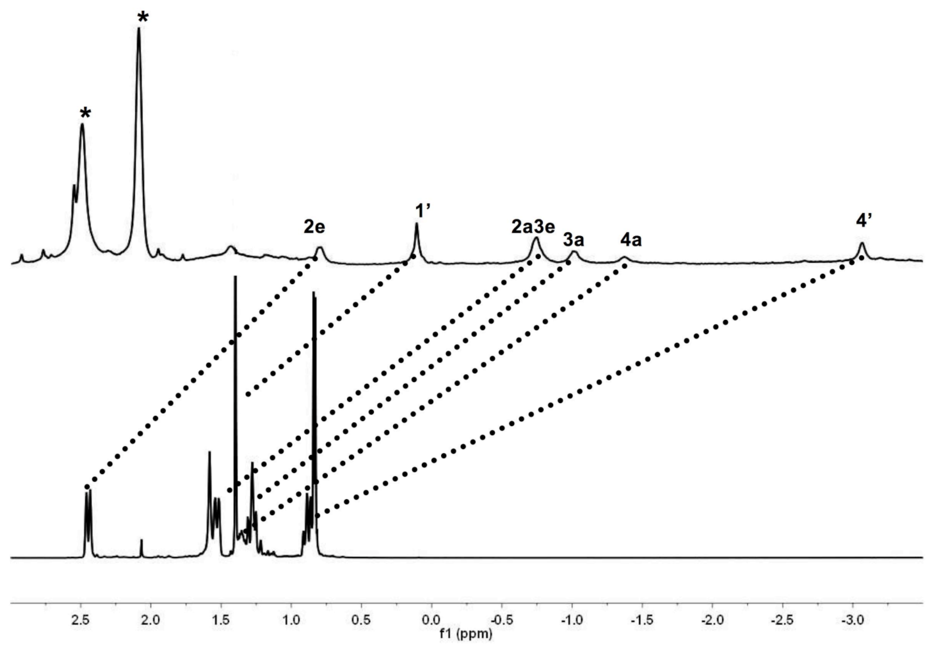


Figure S5. Upfield shift of guest **C** protons within the capsuleplex of **A.** ^{1}H NMR (500 MHz, D_2O) spectra (i) **C**@$\mathbf{A}_2$ and (ii) **C** in $CDCl_3$. (* labeled signals are host resonances).

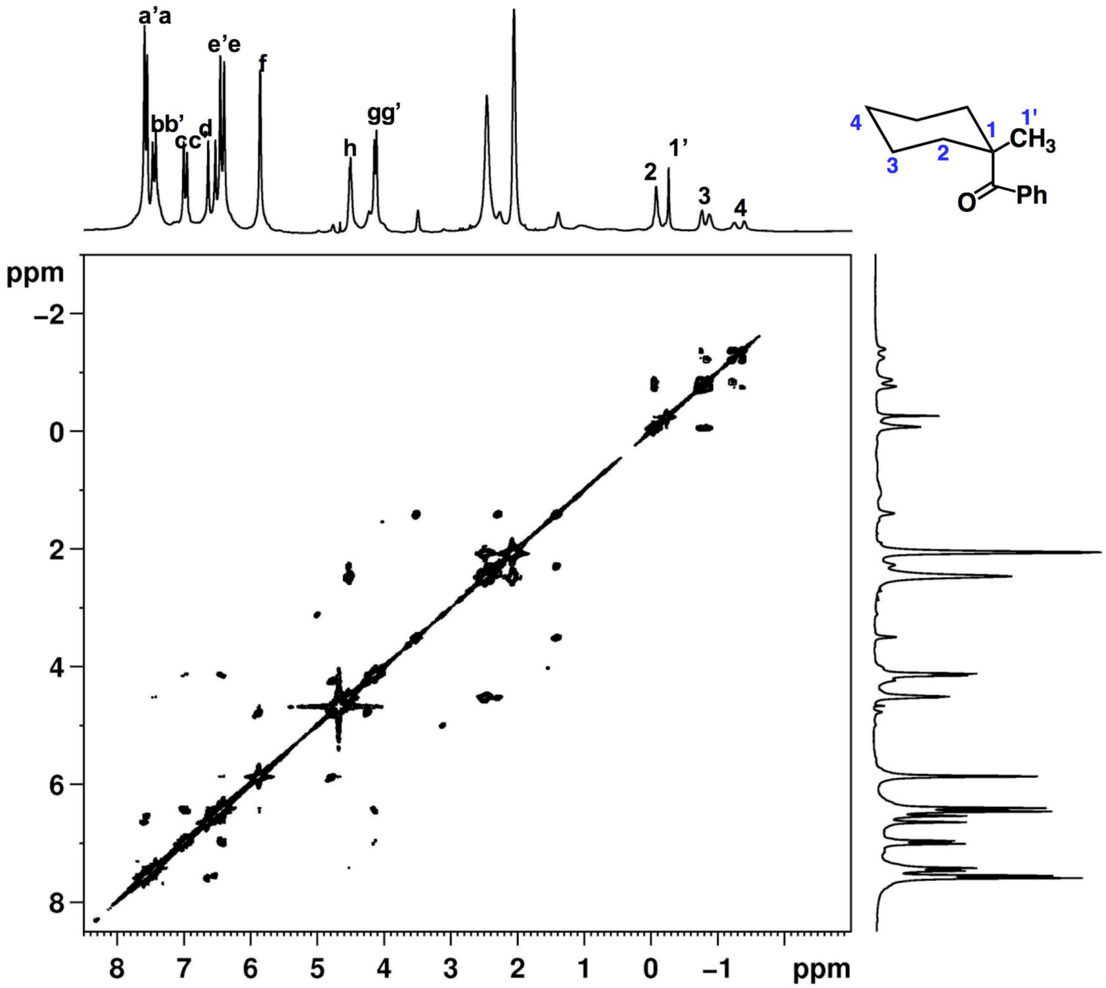


Figure S6. 2D-COSY NMR spectrum of **B**@**A**$_2$ (500 MHz, D_2O). ([**A**] = 5 mM in 50 mM sodium tetraborate buffer, [**B**] = 2.5 mM. Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4.

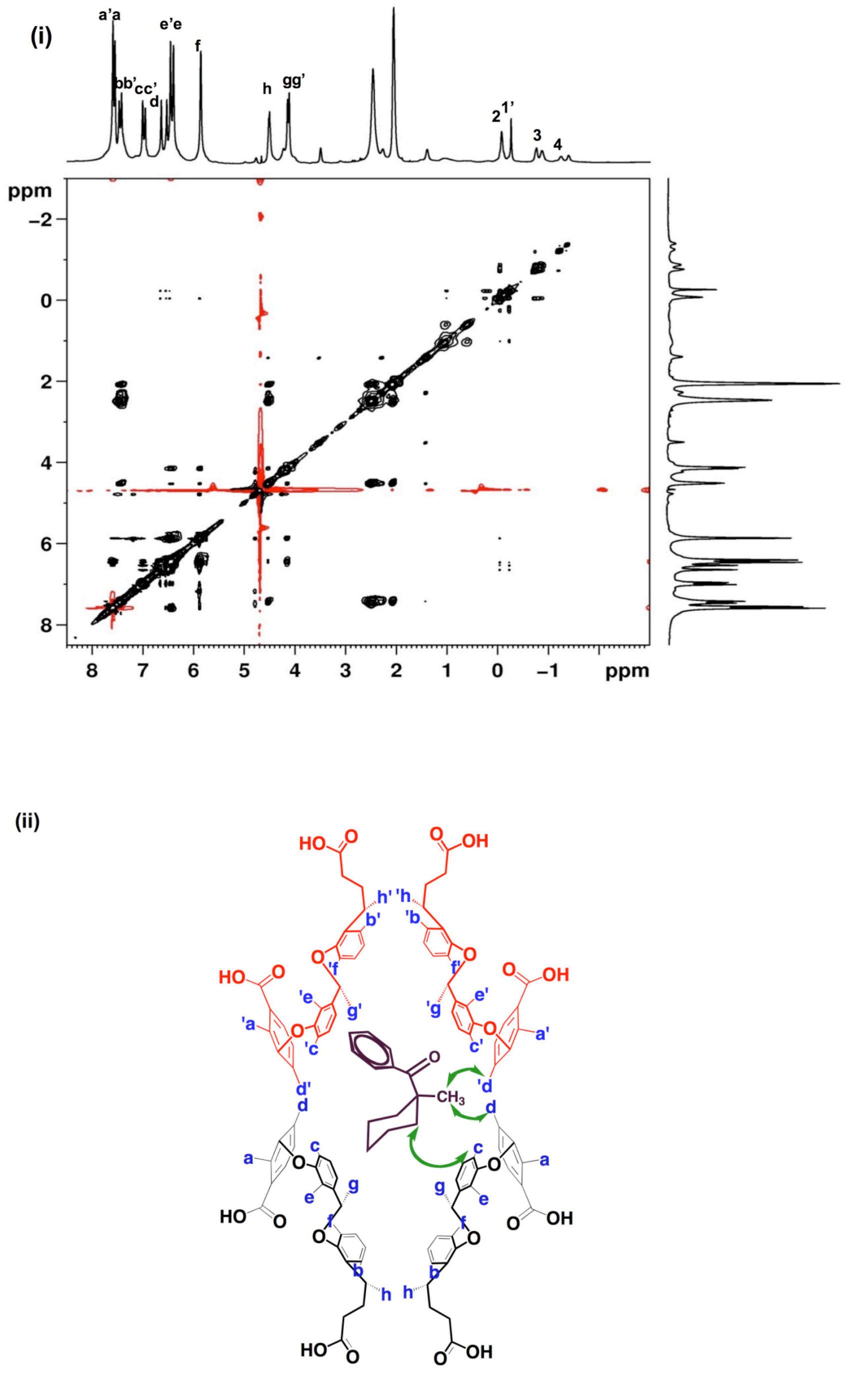


Figure S7. 2D NOESY NMR spectrum of (i) **B@A**$_2$ (500 MHz, D_2O). ([**A**] = 5 mM in 50 mM sodium tetraborate buffer, [**B**] = 2.5 mM. Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4. (ii) Orientation of **B** within Capsuleplex of **A**.

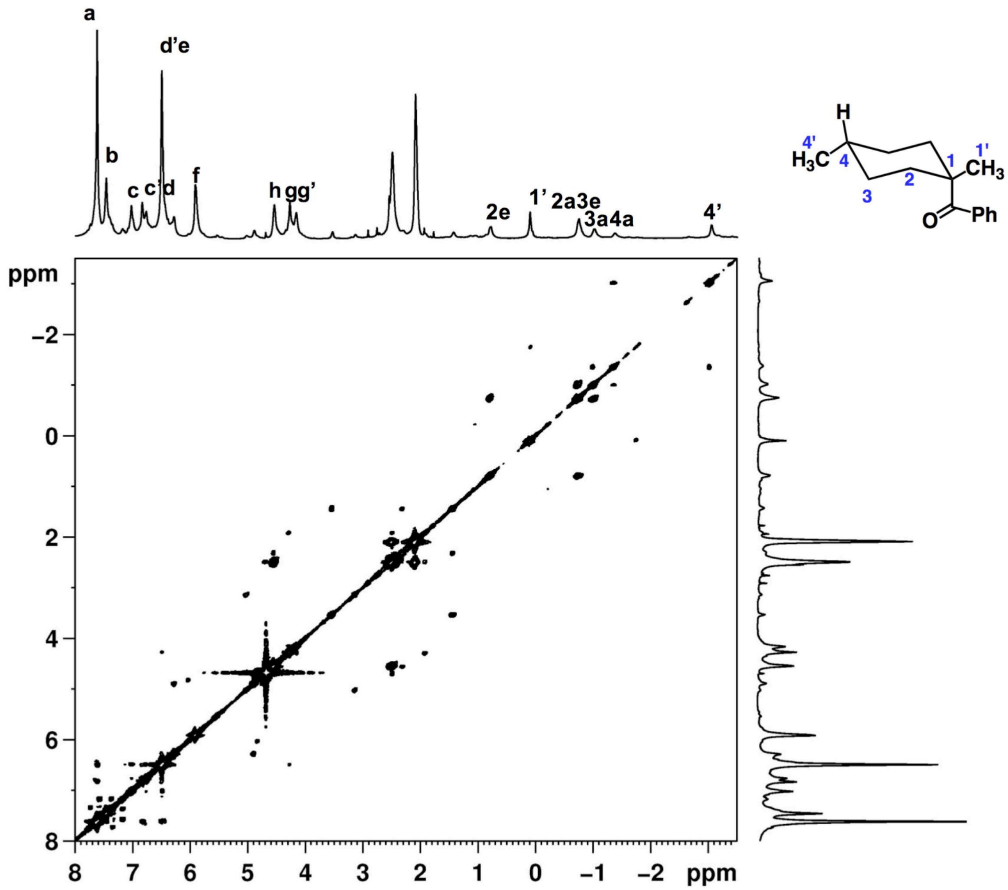


Figure S8. 2D-COSY NMR (500 MHz, D_2O) spectrum of **C**@**A**$_2$. ([**A**] = 5 mM in 50 mM sodium tetraborate buffer, [**C**] = 2.5 mM Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4.

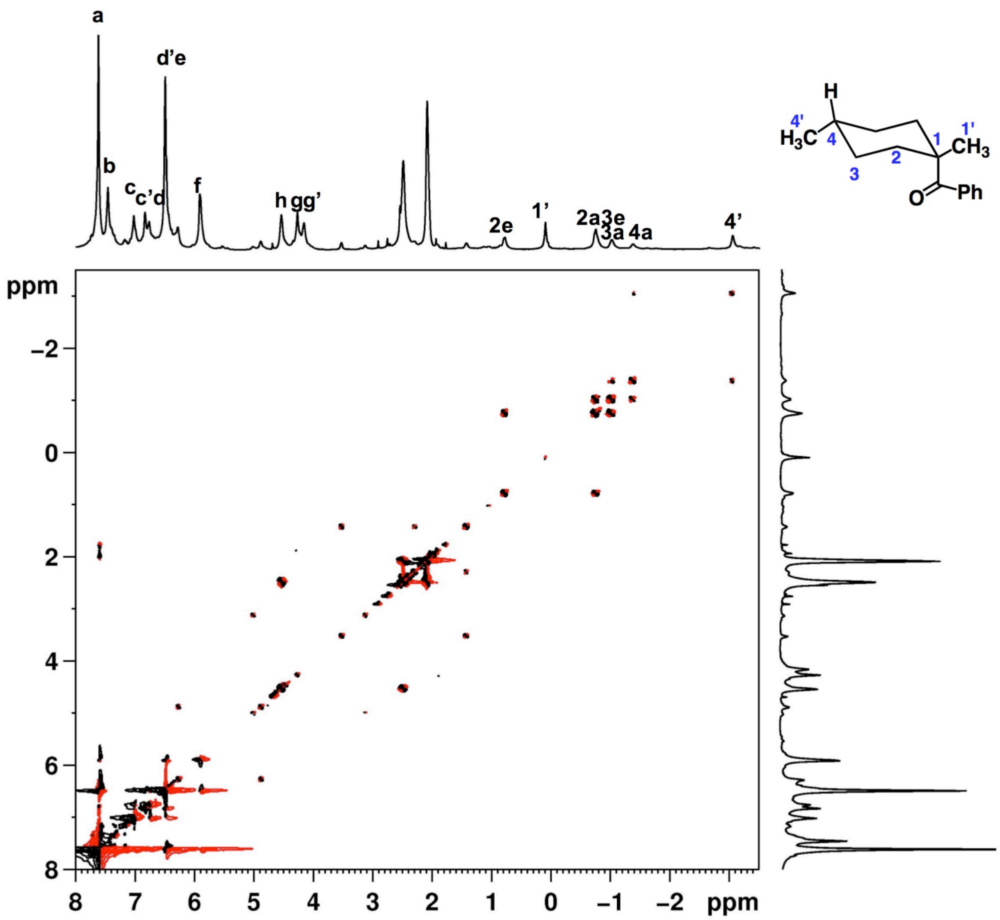


Figure S9. [1]H DQF COSY NMR (500 MHz, D_2O) spectrum of **C@A$_2$.** ([**A**] = 5 mM in 50 mM sodium tetraborate buffer, [**C**] = 2.5 mM. Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4.

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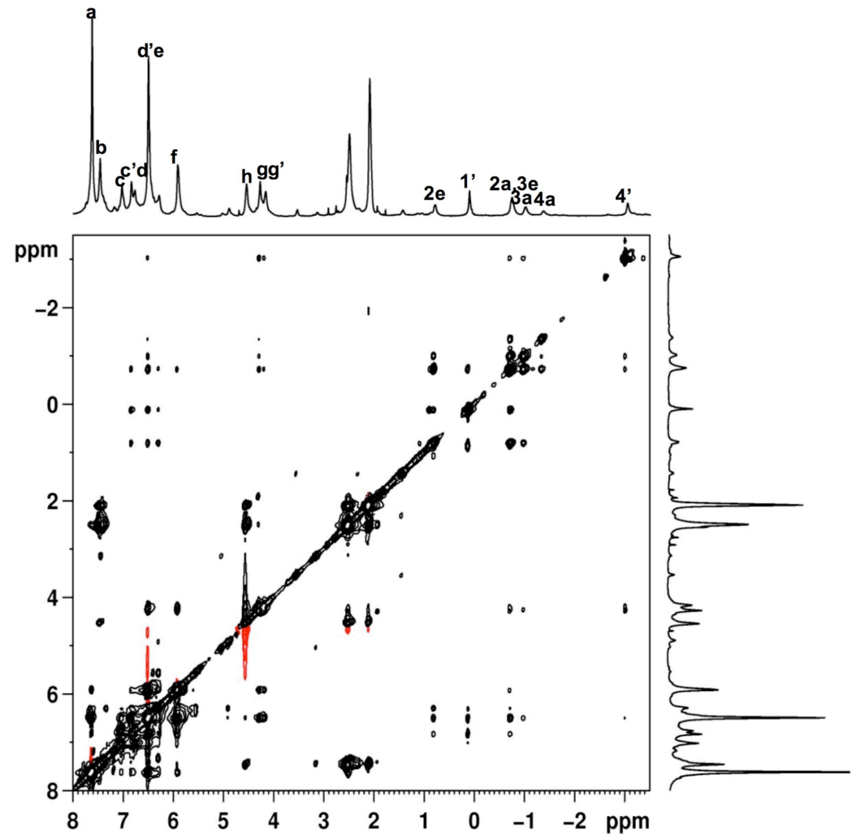
(i)



(ii)

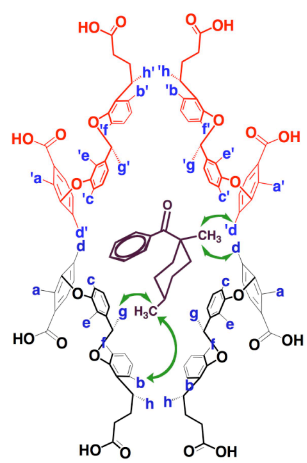


Figure S10. 2D NOESY NMR spectrum of (i) **C@A$_2$** (500 MHz, D_2O**).** ([**A**] = 5 mM in 50 mM sodium tetraborate buffer, [**C**] = 2.5 mM. Aromatic resonances of the host **A** are represented by labels a-h, and bound guest resonances are labeled 1-4. (ii) Orientation of **C** within Capsuleplex of **A**.

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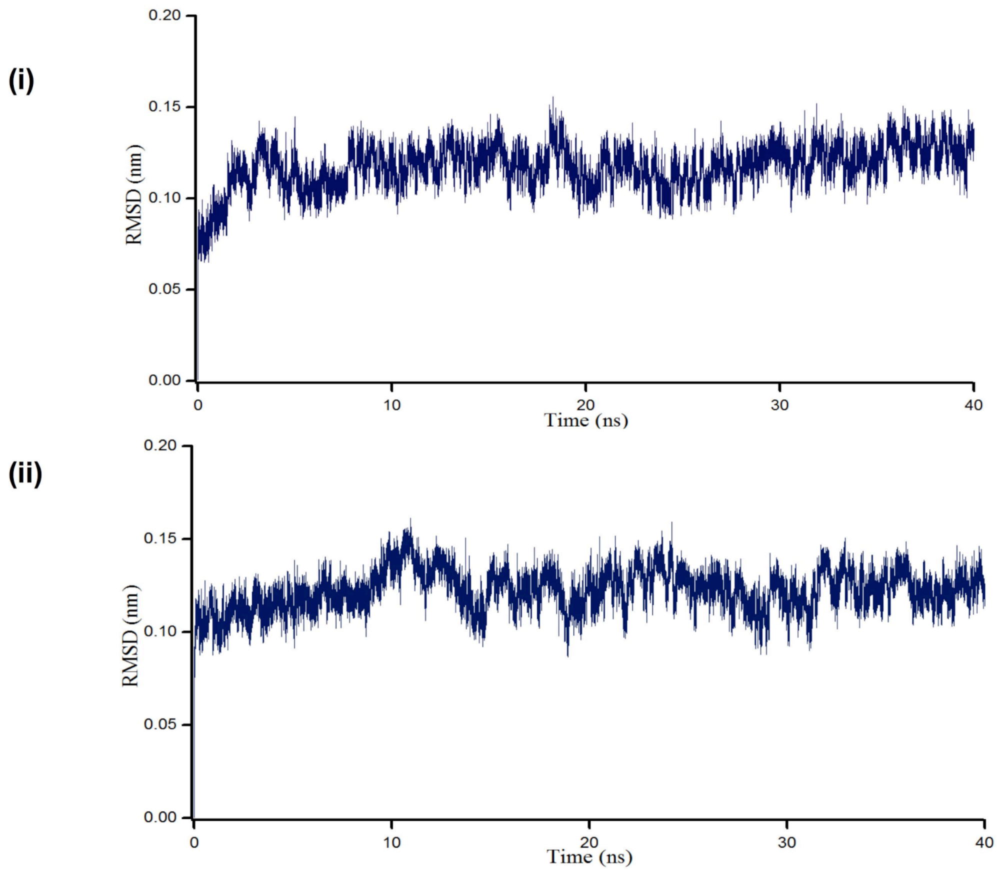


Figure S11. RMSD plot of MD trajectories plotted against time showing equilibrated structure for the 40 ns MD simulation. (i) **B@A$_2$** and (ii) **C@A**$_2$.

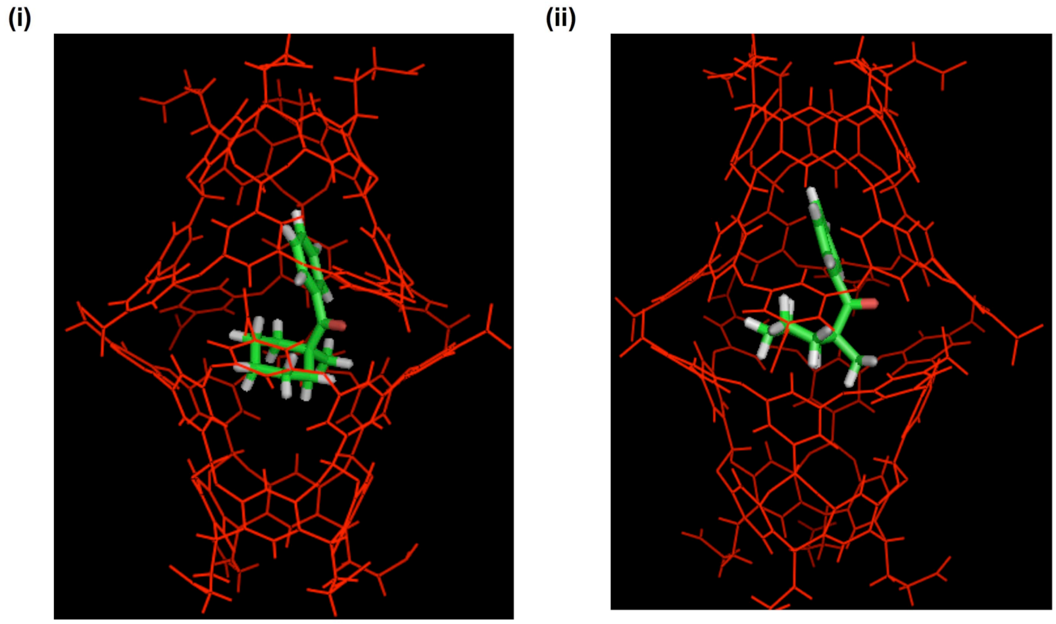


Figure S12. Calculated structure of **B**@**A**$_2$ (i) initial structure obtained from docking analysis and (ii) most representative structure obtained from clustering 4000 structures taken from entire 40 ns trajectory.

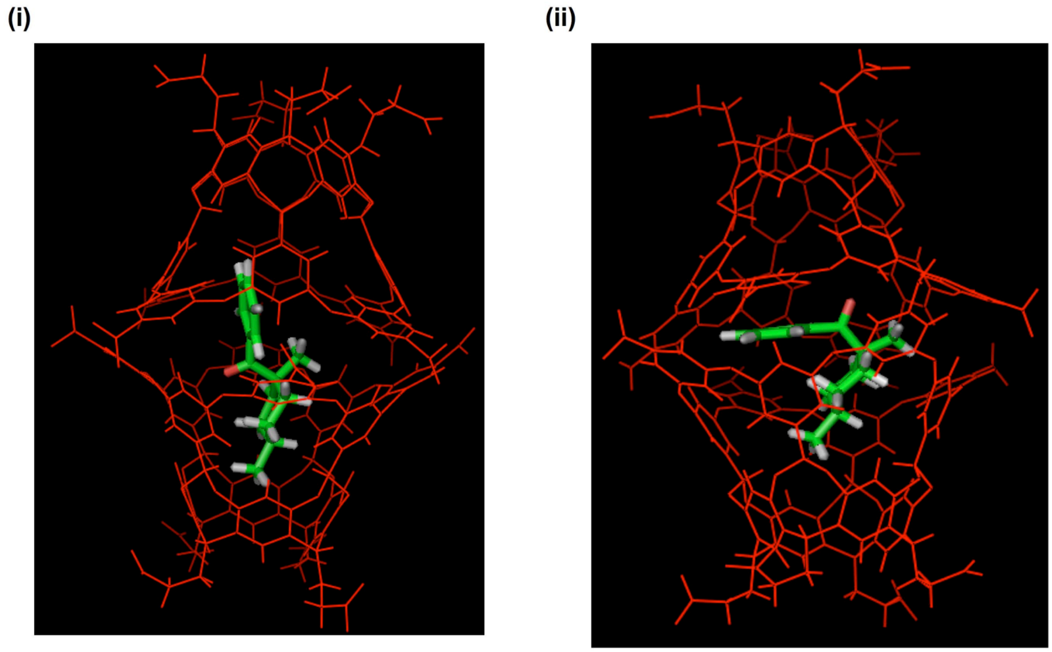


Figure S13. Calculated structure of **C**@**A**$_2$ (i) initial structure obtained from docking analysis and (ii) most representative structure obtained from clustering 4000 structures taken from entire 40 ns trajectory.

Experimental section:

Molecular Dynamics (MD) simulation

The MD simulations were performed by using GROMACS software package[1, 2] utilizing the OPLS-AA force field.[3, 4] The preliminary 3D structure of the octa acid (OA) was constructed by using available templates of SPARTAN program followed by geometry optimization using MMFF force field. The initial structure of the host-guest complex was obtained by docking the guest molecules on the host **A** utilizing the Auto Dock Vina program.[5] The docking procedure yielded different possible poses. Among these poses, the structure with the highest binding energy was chosen for the MD simulation. The topology of the guest molecules were created by using the MKTOP program.[6] The partial charges for the molecules were generated at the B3LYP/6-31G* level[7, 8] level using ChelpG method[9] as implemented in the Gaussian 98 program.[10] A cubic box of dimensions 40 × 40× 40 Å^3 was constructed around the capsular complex. The box was filled with explicit water molecules and sixteen Na+ ions were added to neutralize the system. The starting structures were energy minimized with a steepest descent method for 1000 steps. The periodic boundary conditions (PBC) were applied and the equation of motion was integrated at time step of 2 fs using the LEAP-FROG algorithm using the NPT ensemble at 300 K and pressure of 1 bar. Initial velocities were assigned according to a Maxwell distribution at 300 K. A non-bond pair list cutoff of 12 Å was used. The bond lengths were constrained using the LINCS algorithm.[11] The long–range electrostatic interactions were calculated by the particle-mesh Ewald method.[12] The VMD[13] and Pymol programs[14] were used for trajectory analysis and preparation of figures.

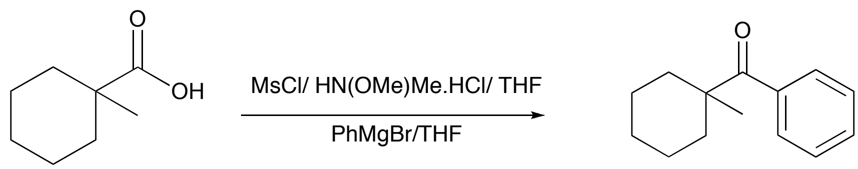
Materials and Methods: Octa acid (OA) was synthesized following a literature procedure.[15] All ^{1}H NMR spectra and 2D NMR studies were carried out on a Bruker 500 MHz NMR spectrometer at 25 °C.

General Protocol for NMR Study:

^{1}H NMR of studies on capsular assemblies: Six hundred microliter of a D_2O solution of host OA (1 mM OA in 10 mM $Na_2B_4O_7$) was taken in a NMR tube and to this 0.25

equivalent increment of guests (2.5 µL of a 60 mM solution in DMSO-d_6) was added. The ^{1}H NMR experiments were carried out after shaking the NMR tube for 5 min after each addition or the NMR tube was sonicated with heating for 1h. For all the 2D-NMR studies 5 mM of OA in 50 mM borate buffer was utilized.

Synthesis of **B**



To the solution of 1-methylcyclohexylcarboxylic acid (1 g, 7.04 mmol) in THF added triethylamine (3 mL, 21mmol) and methanesulphonyl chloride (0.65 mL, 8.4 mmol) at 0 °C allowed stirring for 15 min. Charged N, O-dimethylhydroxylamine to the reaction mixture and stirred for 1h. The reaction mixture was quenched with 30 mL of water and extracted with ether. The obtained Weinreb amide was reacted with corresponding Grignard reagent and refluxed in THF for 2 h. The reaction was quenched with 5 % HCl in ethanol and separated between brine and chloroform: ether (1:1) mixture. The obtained yellow liquid was purified through column in hexane system.

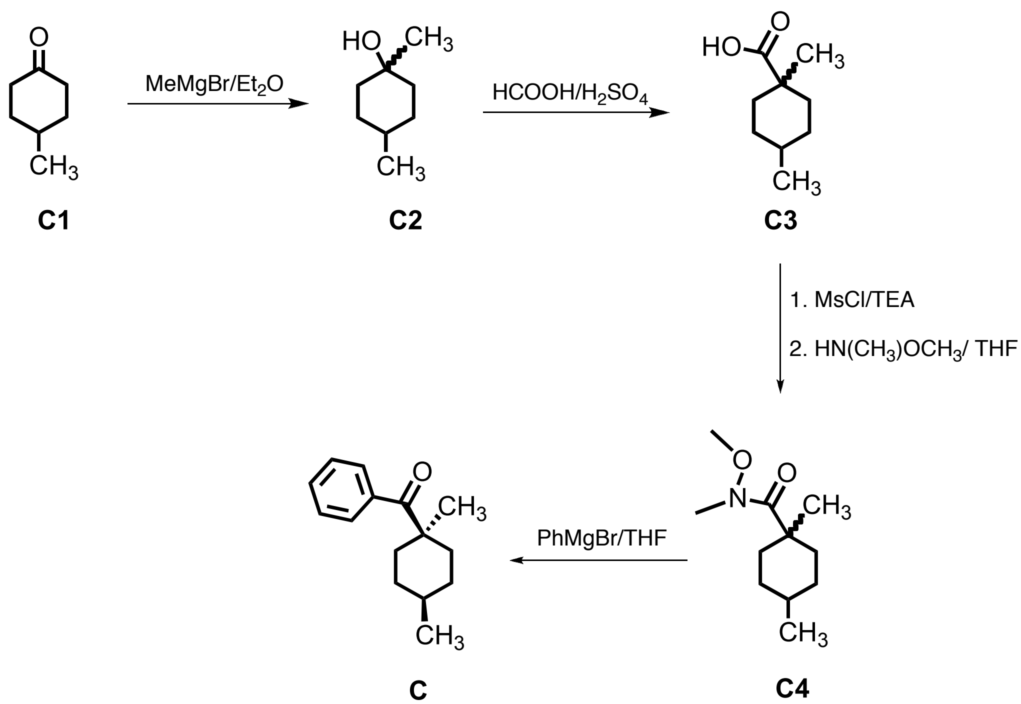
B

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36-1.39 (m, 8H), 1.405 (s, 3H), 1.54 (q, 2H, J = 7.5 Hz), 7.40 (t, 3H, 8 Hz), 7.64 (d, 2H, J = 3Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 23.5, 37.0, 49.5, 127.3, 127.8, 132.2 139.8 and 210.1.

GC-MS (m/z, %): 203 (M+H, 3.8%), 202 (M, 31%), 105 (M-97, 100%), 97 (M-105, 81%)

Synthesis of **C** (*cis*- 1,4- Dimethylcyclohexyl phenylketone)



Synthesis of C2

To a solution of 4-Methyl cyclohexanone (C1) (5 g, 4.5 mmol) in THF added methyl magnesium iodide (32 mL, 9 mmol) at 0 °C. Reaction mixture was allowed for 2h stirring at 20 °C. Then the reaction mixture was quenched with 5% HCl in ethanol and extracted with diethyl ether. The solvent was dried and evaporated without heat to yield transparent oily liquid. Formation of *cis* and *trans* in 1:1 ratio[16] was evident in GC analysis.

Synthesis of C3

Mixture of *cis* and *trans* dimethyl cyclohexanol (C2) (4 g, 0.031 mol) in formic acid (99%, 0.38 mol) was added to fast stirring con. H_2SO_4 (98%, 0.75 mol) at 10 °C. Stirring was allowed for 2 h. Then the reaction mixture was kept at refrigeration for an additional

27 h. The reaction mixture was poured in ice and extracted with DCM. The organic layer was washed twice with 20% NaOH solution. The basic layer was acidified using conc. HCl and again extracted with DCM. The organic layer was washed with brine and dried over sodium sulphate. The organic layer was evaporated to yield oily liquid. The ratio of *cis*-to-*trans* isomer was found to be (9:1).[17]

Synthesis of C4

To a solution of 1,4- dimethyl cyclohexyl carboxylic acid (C3) (0.85g, 5.5 mmol) in THF (30 mL) added TEA (2.3 mL, 16.5 mmol) and methane sulphonyl chloride (0.52 mL, 6.6 mmol) and stirred at 0 °C. To this solution added freshly prepared N, O dimethyl hydroxylamine (3.3 mmol) and stirred for 3 h at RT. The reaction mixture was quenched with water and separated between brine and ether. The ratio of *cis*-to-*trans* isomer was found to be (9:1) in GC. The *cis* product was purified by column chromatography in hexane system.

Synthesis of **C**

To the solution of Weinreb amide(C3) (0.52 g 1mmol) in diethyl ether 30 mL added phenyl magnesium bromide (2mL, 6 mmol) and stirred at RT for overnight. The reaction mixture was quenched 5% HCl in ethanol and separated between chloroform: ether (1:1) mixture. The organic layer was dried over sodium sulphate and evaporated. The product was purified in hexane system to remove biphenyl impurities to yield transparent oily liquid.

C

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85-0.90 (d, 3H), 1.25-1.3(m, 2H), 1.33-1.38 (m, 2H), 1.393 (s, 3H), 1.508-1.53 (m, 2H), 2.42-2.45 (m, 2H), 7.39-7.41 (m, 2H) 7.45-7.48 (m, 1H) and 7.66-7.68 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 28.4, 32.2, 32.3, 36.5, 48.6, 127.5, 128.0, 136.6, 139.59 and 209.74.

GC-MS (m/z, %): 217 (M+H, 4.7%), 216 (M, 28.3%), 110 (M-106, 79.2%), 105 (M-111, 100%), 95 (M-121, 38%).

References

1. E. Lindahl, B. Hess and D. V. D. Spoel, *J. Mol. Model.*, 2001, **7**, 306-317.
2. D. V. D. Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark and H. J. C. Berendsen, *J. Comput. Chem.*, 2005, **26**, 1701-1718.
3. G. A. Kaminski, R. A. Friesner, J. Tirado-Rives and W. L. Jorgensen, *J. Phys.Chem. B*, 2001, **105**, 6474-6487.
4. W. L. Jorgensen and J. Tirado-Rives, *J. Am. Chem. Soc.*, 1988, **110**, 1657-1666.
5. O. Trott and A. J. Olson, *J. Comput. Chem.*, 2009, **31**, 455-461.
6. A. A. S. T. Ribeiro, B. A. C. Horta and R. B. d. Alencastro, *J. Braz. Chem. Soc.*, 2008, **19**, 1433-1435.
7. C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.
8. A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098-4000.
9. C. M. Breneman and K. B. Wiberg, *J. Comput. Chem.*, 1990, **11**, 361-373.
10. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Camm, B. Mennucci, C. Pomell, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
11. B. Hess, H. Bekker, H. J. C. Berendsen and J. G. E. M. Fraaije, *J. Comput. Chem.*, 1997, **18**, 1463-1472.
12. T. Darden, D. York and L. Pederson, *J. Chem. Phys.*, 1993, **98**, 10089-10092.
13. W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graphics.*, 1996, **14**, 33-38.
14. W. L. Delano, Delano Scientific, San Carlos, CA, USA, 2002.
15. C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2004, **126**, 11408-11409.
16. C. Cianetti, G. D. Maio, V. Pignatelli, P. Tagliatesta, E. Vecchi and E. Zeuli, *Tetrahedran*, 1983, **39**, 657-666.
17. W. C. Agosta and S. Wolff, *J. Org. Chem.*, 1975, **40**, 1027-1030.