Supporting Information

for

Isotope Effects as Probe of *Constrictive* and *Intrinsic* Binding in Hemicarceplexes

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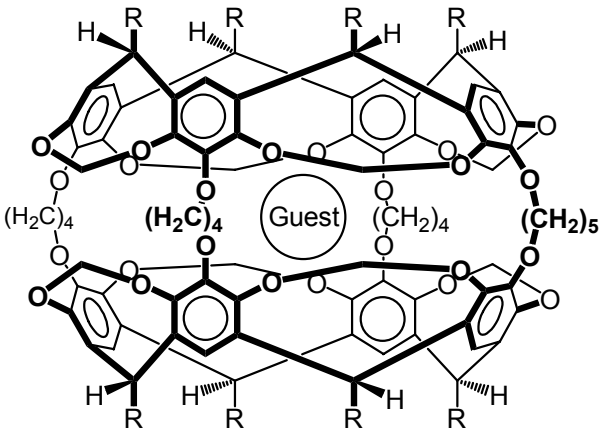
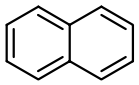
Experimental Section

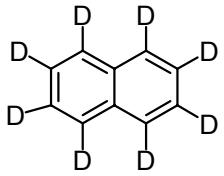
1. General. Nitrobenzene was distilled before use. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm and $CDCl_3$ at 77.0 ppm. MALDI-TOF mass spectra were recorded on an Applied Biosystems Voyager DE-Pro mass spectrometer in the reflector mode. 2, 4, 6-Trihydroxylacetophenone (THAP) containing silver trifluoroacetate was used as matrix.

2. Synthesis of isotopomeric hemicarceplexes 1⊙naphthalene



Guests:





1⊙Guest: R = $(CH_2)_2C_6H_5$

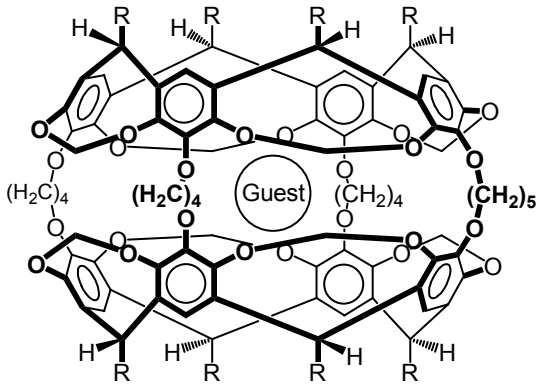
Hemicarceplexes **1**⊙naphthalene and **1**⊙naphthalene-d_8 were synthesized according to a literature procedure [1].

Hemicarceplex **1**⊙naphthalene (61 % yield): ^{1}H NMR (400 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.30-7.21 (m, 24H); 7.15-7.21 (m, 20H); 7.13 (s, 2H); 7.11 (s, 2H); 6.95 (s, 4H); 5.60 (d, 4H, J = 7.0 Hz); 5.59 (d, 4H, J = 7.0 Hz); 4.88 (t, 4H, J = 7.8 Hz); 4.88 (t, 4H, J = 7.8 Hz); 4.32 (d, 4H, J = 7.0 Hz); 4.30 (d, 4H, J = 7.0 Hz); 4.22-4.16 (m, 4H); 3.35 (m, 4H Guest); 3.26-3.11 (m, 8H); 2.78-2.66 (m, 16H), 2.64-2.52 (m, 16H), 2.2 (sb, 4H); 2.12-

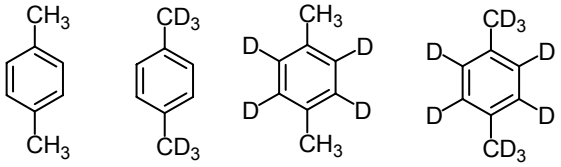
2.02 (m, 2H); 1.99-1.88 (m, 4H); 1.42-1.26 (m, 8H). MALDI-MS *m/z* 2497.94 ($[M+Ag]^+$ calc. 2497.92).

Hemicarceplex **1**⊙naphthalene-d_8 (60 % yield): ^{1}H NMR (400 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.30-7.21 (m, 24H); 7.15-7.21 (m, 16H); 7.13 (s, 2H); 7.11 (s, 2H); 6.95 (s, 4H); 5.60 (d, 4H, *J* = 7.0 Hz); 5.59 (d, 4H, *J* = 7.0 Hz); 4.88 (t, 4H, *J* = 7.8 Hz); 4.88 (t, 4H, *J* = 7.8 Hz); 4.32 (d, 4H, *J* = 7.0 Hz); 4.30 (d, 4H, *J* = 7.0 Hz); 4.22-4.16 (m, 4H);.26-3.11 (m, 8H); 2.78-2.66 (m, 16H), 2.64-2.52 (m, 16H), 2.2 (sb, 4H); 2.12-2.02 (m, 2H); 1.99-1.88 (m, 4H); 1.42-1.26 (m, 8H). MALDI-MS *m/z* 2506.01 ($[M+Ag]^+$ calc. 2505.98).

3. Synthesis of isotopomeric hemicarceplexes 1⊙*p*-xylene



Guests:



1⊙Guest: R = $(CH_2)_2C_6H_5$

Hemicarcerand **1** (39 mg, 0.017 mmol) [1] and *p*-xylene (0.5 mL) were sealed in a glass ampoule and heated to 150 ^{o}C for 18 hrs. The ampoule was opened and the solvent removed at a rotavaporator. The crude product was purified by preparative TLC (silica gel; $CHCl_3$/ethyl acetate (200:1)), which gave the product as a white powder.

Hemicarceplex **1**⊙*p*-xylene (77 % yield): ^{1}H NMR (300 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.15-7.25 (m, 40H); 6.91 (s, 6H); 6.88 (s, 2H); 5.94 (s, 4H, Guest); 5.71 (d, 4H, *J* = 7.1 Hz); 5.70 (d, 4H, *J* = 7.1 Hz); 4.88 (t, 8H, *J* = 7.8 Hz); 4.14 (d, 4H, *J* = 7.1 Hz); 4.13 (d,

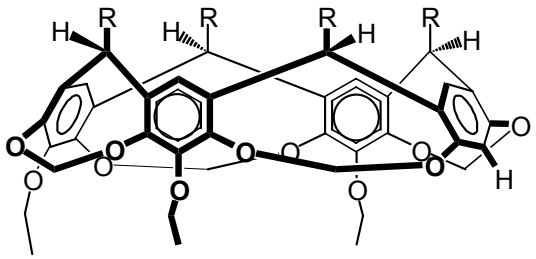
4H, J = 7.1 Hz); 3.75-3.95 (m, 16H); 2.45-2.78 (m, 32H), 1.7-2.0 (m, 18H); -1.94 (s, 6H, Guest). ^{13}C NMR (100 MHz, $CDCl_3$; 22 ^{o}C) δ_C 149.19; 148.98; 148.96; 148.95; 145.56; 144.46; 144.43; 141.83; 138.78; 138.77; 138.71; 138.65; 132.99 (Guest); 128.58; 128.43; 127.49 (Guest); 126.01; 114.28; 114.23; 114.18; 98.98; 98.96; 72.84; 72.10; 71.77; 27.14; 34.54; 32.32; 29.95; 27.47; 27.36; 22.3; 13.52 (Guest). MALDI-MS *m/z* 2475.94 ($[M+Ag]^+$ calc. 2475.94).

Hemicarceplex **1**⊙*p*-xylene-d_4 (71 % yield): ^{1}H NMR (300 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.15-7.25 (m, 40H); 6.91 (s, 6H); 6.87 (s, 2H); 5.70 (d, 4H, J = 7.0 Hz); 5.69 (d, 4H, J = 7.0 Hz); 4.88 (t, 8H, J = 7.8 Hz); 4.13 (d, 4H, J = 7.0 Hz); 4.12 (d, 4H, J = 7.0 Hz); 3.75-3.95 (m, 16H); 2.43-2.78 (m, 32H), 1.7-2.0 (m, 18H); -2.03 (s, 6H, Guest). MALDI-MS *m/z* 2479.98 ($[M+Ag]^+$ calc. 2479.97).

Hemicarceplex **1**⊙*p*-xylene-d_6 (67 % yield): ^{1}H NMR (300 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.15-7.25 (m, 40H); 6.90 (s, 6H); 6.87 (s, 2H); 5.95 (s, 4H, Guest); 5.70 (d, 4H, J = 7.1 Hz); 5.69 (d, 4H, J = 7.1 Hz); 4.87 (t, 8H, J = 7.8 Hz); 4.14 (d, 4H, J = 7.1 Hz); 4.13 (d, 4H, J = 7.1 Hz); 3.75-3.95 (m, 16H); 2.43-2.78 (m, 32H), 1.7-2.0 (m, 18H). MALDI-MS *m/z* 2481.97 ($[M+Ag]^+$ calc. 2481.98).

Hemicarceplex **1**⊙*p*-xylene-d_{10} (73 % yield): ^{1}H NMR (300 MHz, $CDCl_3$; 22 ^{o}C) δ_H 7.15-7.25 (m, 40H); 6.90 (s, 6H); 6.88 (s, 2H); 5.71 (d, 4H, J = 7.1 Hz); 5.70 (d, 4H, J = 7.1 Hz); 4.87 (t, 8H, J = 7.8 Hz); 4.13 (d, 4H, J = 7.1 Hz); 3.75-3.95 (m, 16H); 2.43-2.78 (m, 32H), 1.7-2.0 (m, 18H). MALDI-MS *m/z* 2486.02 ($[M+Ag]^+$ calc. 2486.00).

4. Synthesis of standard 3



R = $(CH_2)_2C_6H_5$

3

Trihydroxycavitand [2] (400 mg, 0.4 mmol) was dissolved in degassed DMF (25 mL) under argon. After addition of anhydrous K_2CO_3 (2 g) and iodoethane (6 mL, 75 mmol), the reaction mixture was stirred 20 hrs at 80 ^oC. The reaction mixture was filtered and poured into water (200 mL). The precipitated product was filtered off and dried at high vacuum. Column chromatography on silica gel ($CHCl_3$; EtOAc 0 – 5%) gave triethoxy cavitand **3** as white solid (300 mg, 70% yield)

^1H NMR (360 MHz, $CDCl_3$; 22 ^oC) δ_H 7.15-7.25 (m, 40H); 7.10 (s, 1H); 6.84 (s, 3H); 6.56 (s, 1H); 5.86 (d, 2H, J = 7.2 Hz); 5.81 (d, 2H, J = 7.2 Hz); 4.83 (t, 4H, J = 7.9 Hz); 4.46 (d, 2H, J = 7.2 Hz); 4.39 (d, 2H, J = 7.2 Hz); 3.97-4.04 (m, 6H); 2.45-2.70 (m, 16H), 1.25-1.33 (m, 9H); MALDI-MS *m/z* 1191.31 ($[M+Ag]^+$ calc. 1191.38).

5. Decomplexation of hemicarceplexes

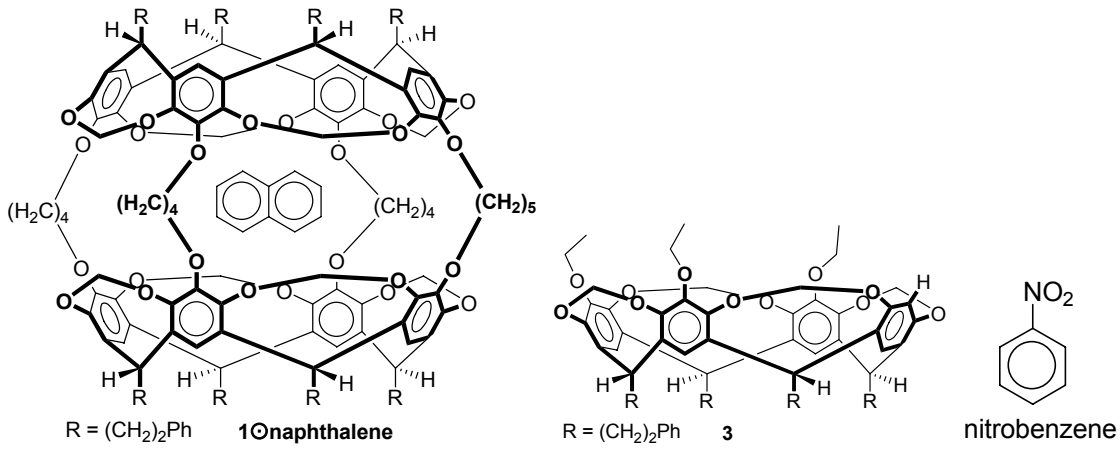
All decomplexation reactions were conducted in a thermostated silicon oil bath. The temperature variation were less than 0.1 °C. Approximately 1 mg of hemicarceplex and 0.5 mg of standard **3** were added to 0.8 ml of nitrobenzene in a 1 mL sample vial with teflon coated septum cap. The sample was sonicated until the solution was clear. To eliminate temperature difference between samples, decomplexation experiments involving isotopomeric hemicarceplexes were run in parallel. All sample vials were held

tightly together in a basket, which was fixed to a small stand inside the oil bath such that the silicon oil surface was just below the top of the septum cap. The sample vials were placed in the oil bath for 30 minutes to reach temperature equilibrium. 25 μl of samples were taken at 10 min time interval, diluted with 100 μl dichloromethane and subjected for HPLC analysis.

6. HPLC analysis

Two HPLC methods were developed For hemicarceplex **1**⊙naphthalene decomplexation reaction mixtures, the method conditions were as follows: column, Phenomenax Luna Si, 15.0 cm x 4.6 mm, 5 μm; flow rate, 1 mL/min; temperature, 40 °C; mobile phase, A, CH_2Cl_2, B, 20% ether in CH_2Cl_2; gradient, A/B, 90/10 to A/B, 75/25 in 8 min, hold for 2 min then to 100% B in 2 min and hold for 10 min; UV detection, 227 nm; injection volume 20 μl, post time 15 minutes (Figure S1). For hemicarceplex **1**⊙*p*-xylene decomplexation reaction mixtures the method conditions are as follows: column, Phenomenax Luna Si, 15.0 cm x 4.6 mm, 5 μm; flow rate, 1 mL/min; temperature, 40 °C; mobile phase, A, CH_2Cl_2, B, 20% ether in CH_2Cl_2; gradient, A/B, 95/5 for 5 min then to A/B, 90/10 in 8 min, hold for 2 min then to 100% B in 2 min and hold for 10 min; UV detection, 227 nm; injection volume 20 μl, post time 15 minutes (Figure S2). Three injections were made for each sample concentration measurement. The rsd% of concentration measurement among the three injections for all the samples was within 1.0%.

7. HPLC Traces



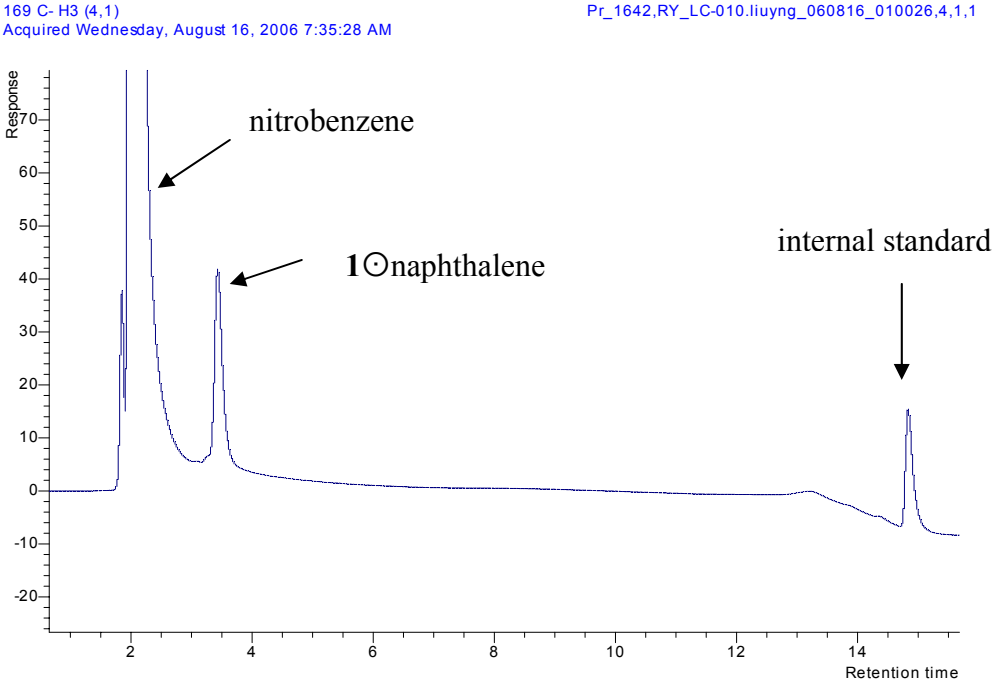
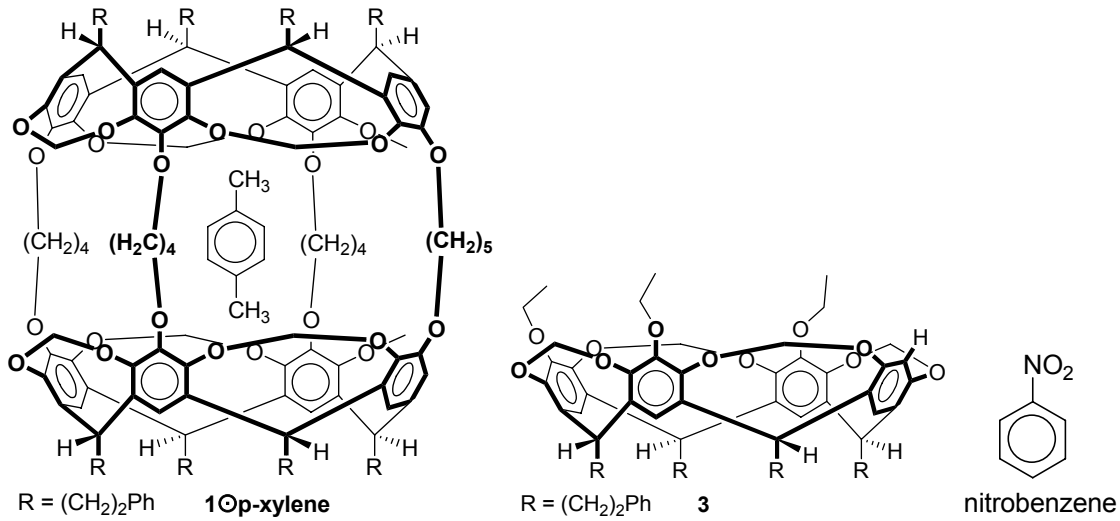


Figure S 1. NPLC separation of **1**⊙naphthalene, cavitand **3** (internal standard) and nitrobenzene.



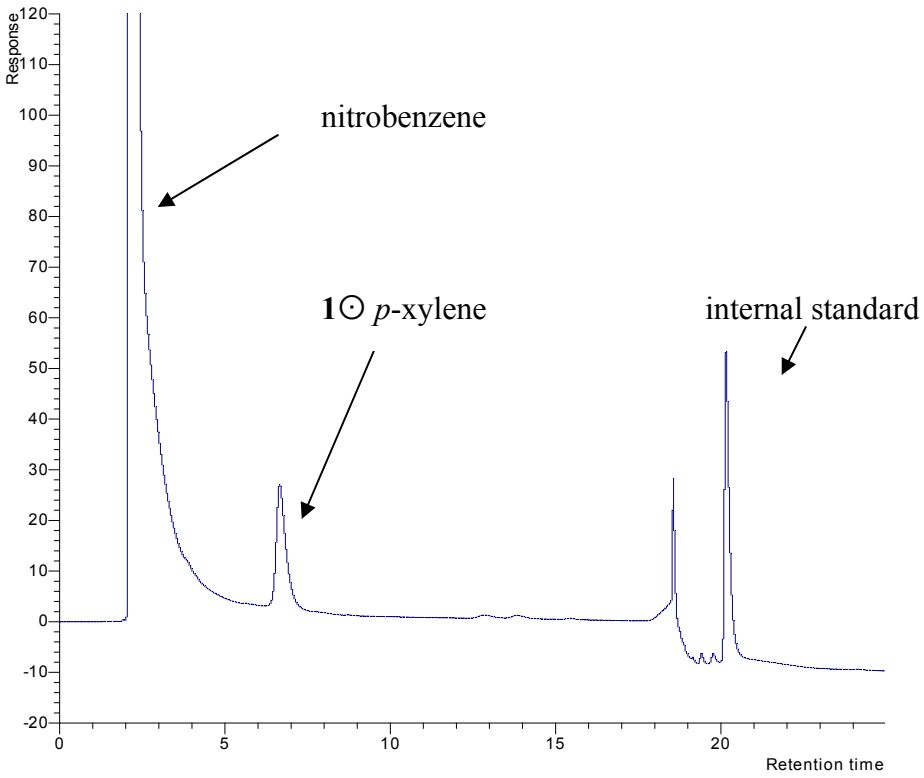


Figure S 2. NPLC separation of **1**⊙ *p*-xylene, cavitand **3**(internal standard) and nitrobenzene.

8. Spectra

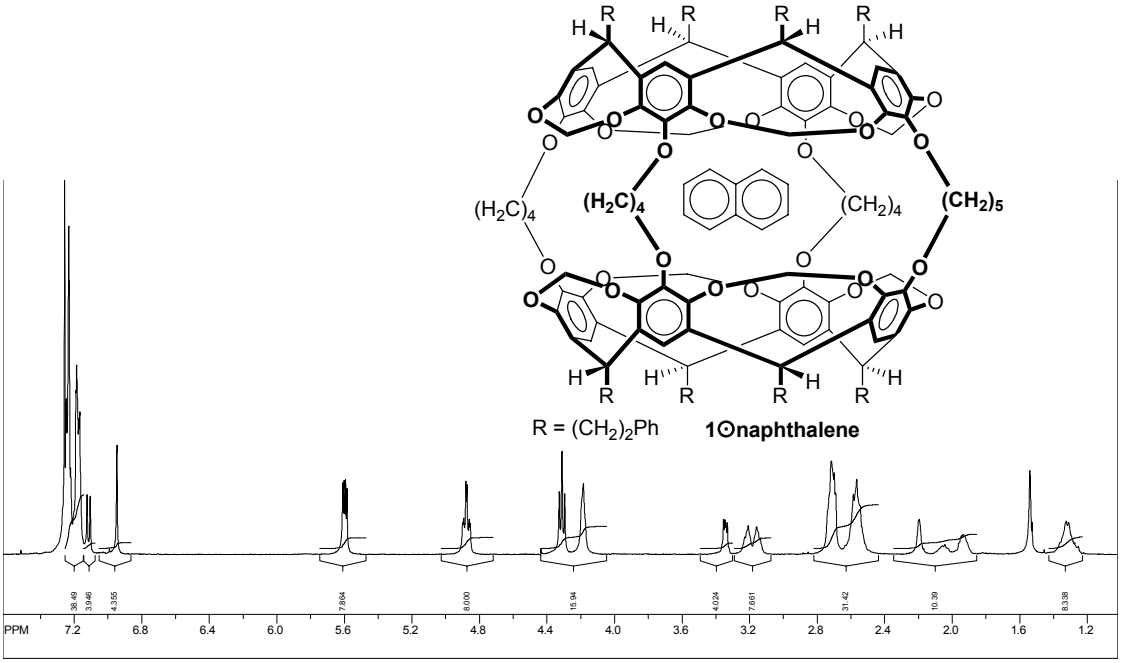


Figure S 3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙naphthalene

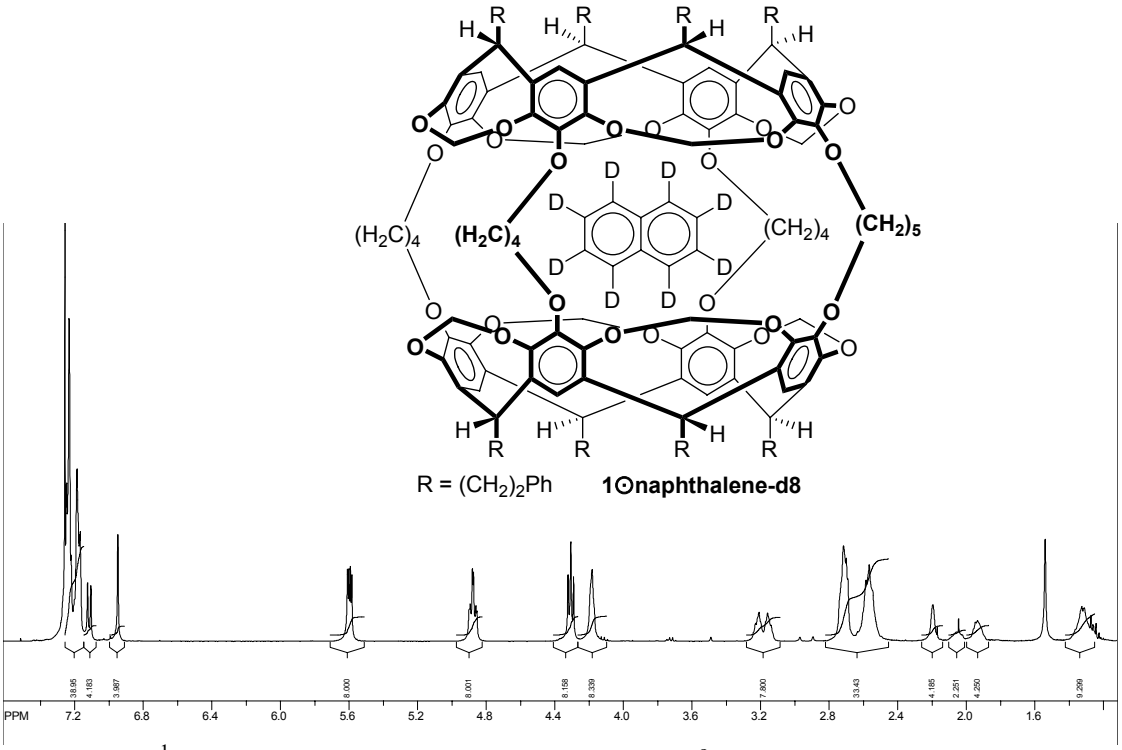


Figure S 4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙naphthalene-d_8

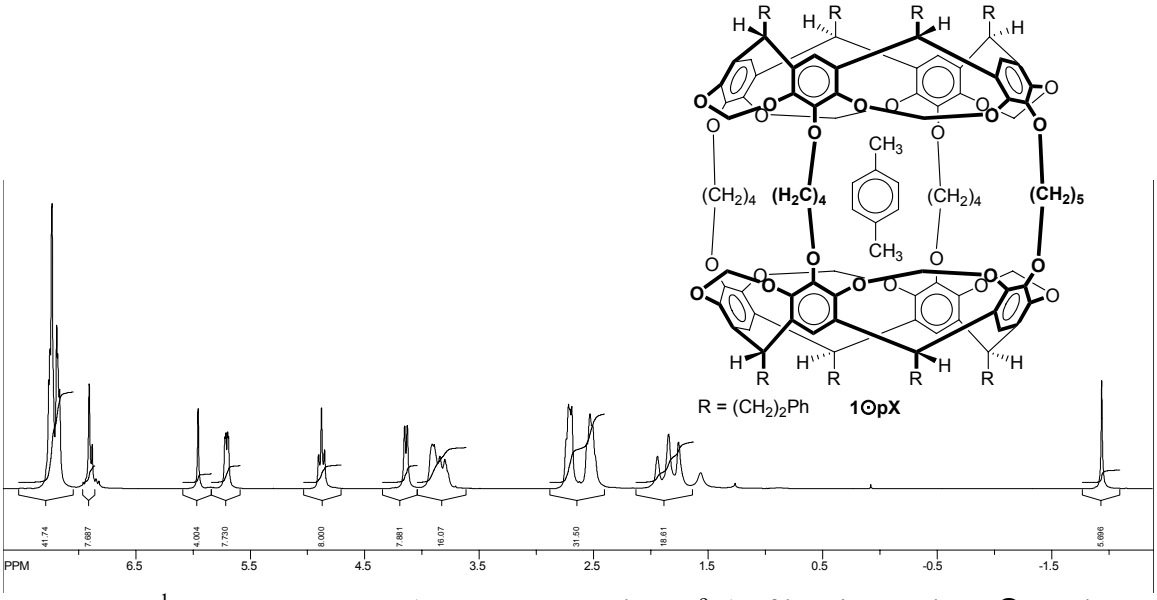


Figure S 5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙*p*-xylene

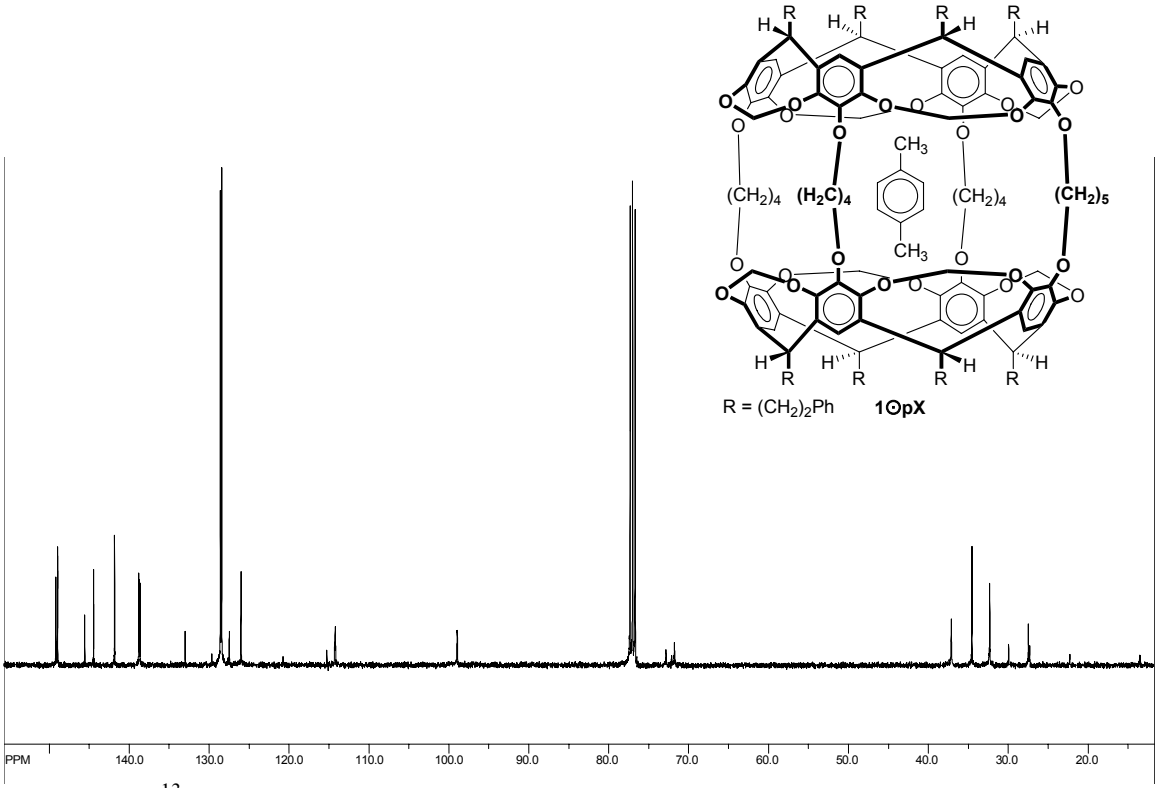


Figure S 6. ^{13}C NMR spectrum (100 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙*p*-xylene

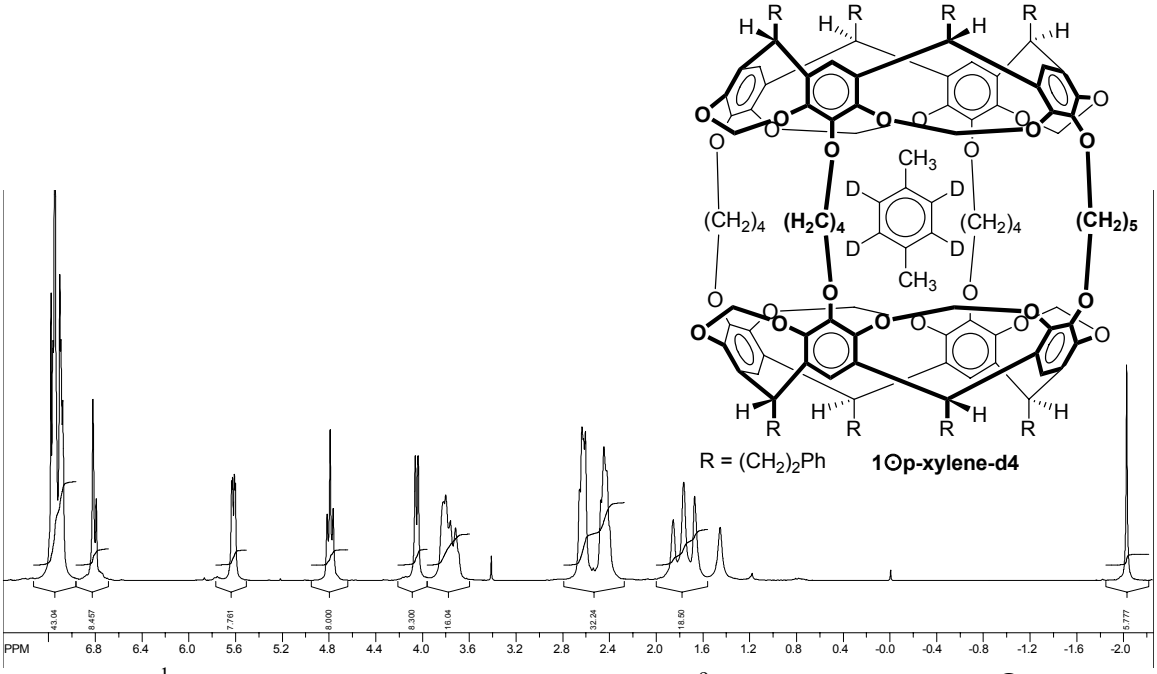


Figure S 7. ^{1}H NMR spectrum (300 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙*p*-xylene-d_4

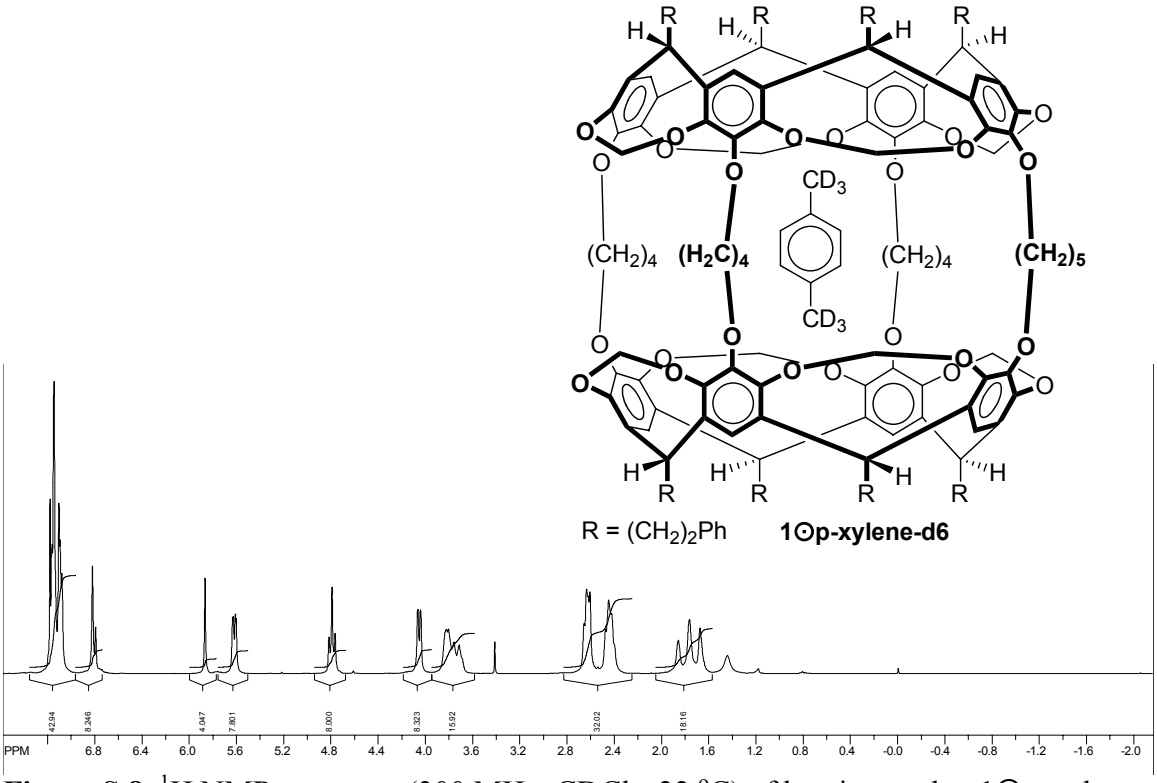


Figure S 8. ^{1}H NMR spectrum (300 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙*p*-xylene-d_6

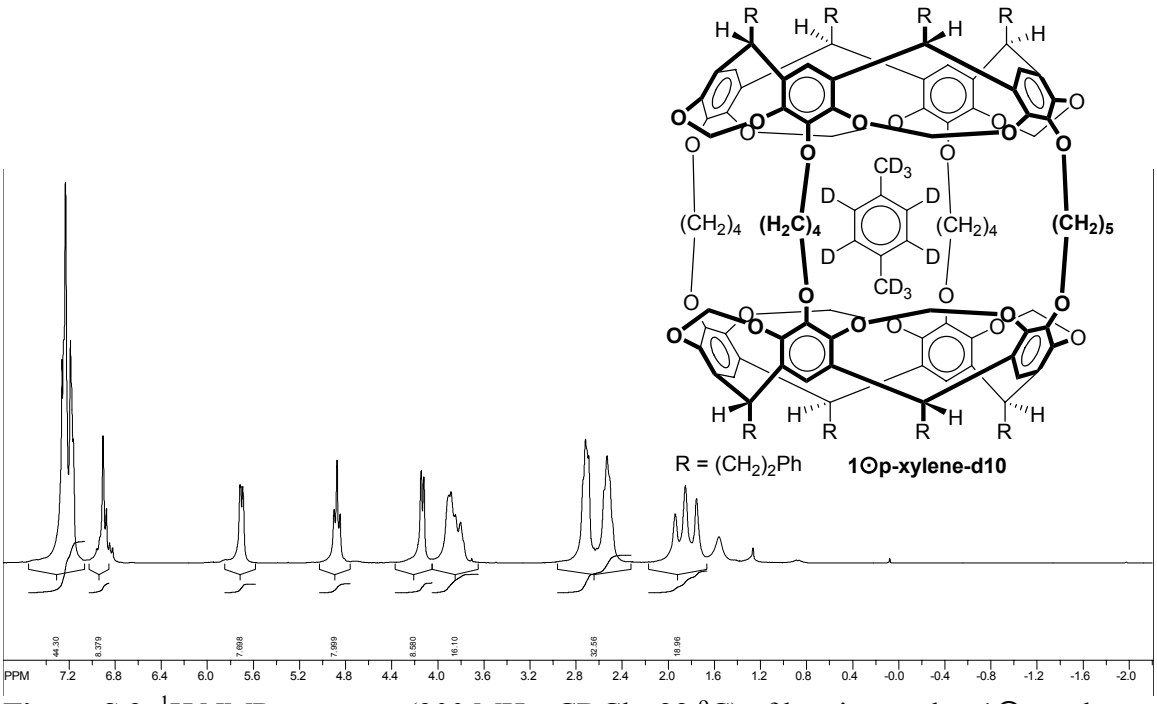


Figure S 9. ^{1}H NMR spectrum (300 MHz, $CDCl_3$; 22 ^{o}C) of hemicarceplex **1**⊙*p*-xylene-d_{10}

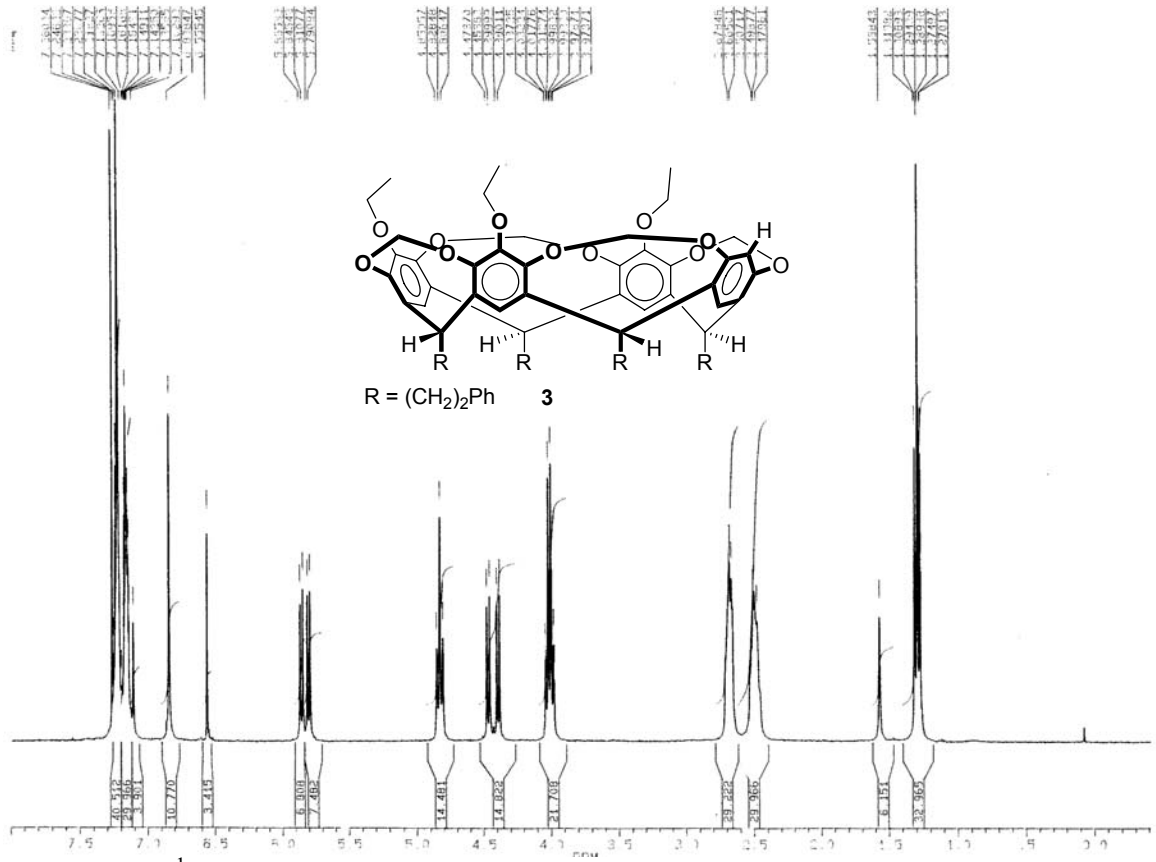
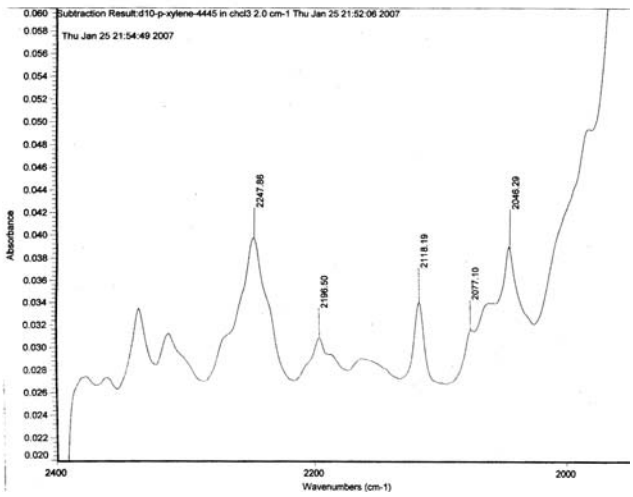
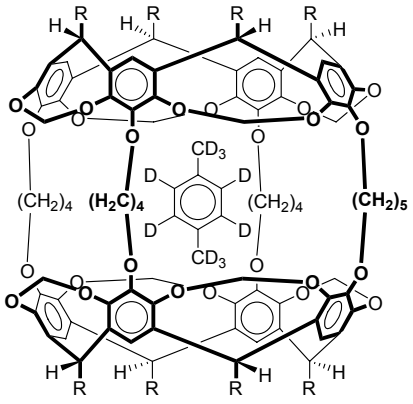


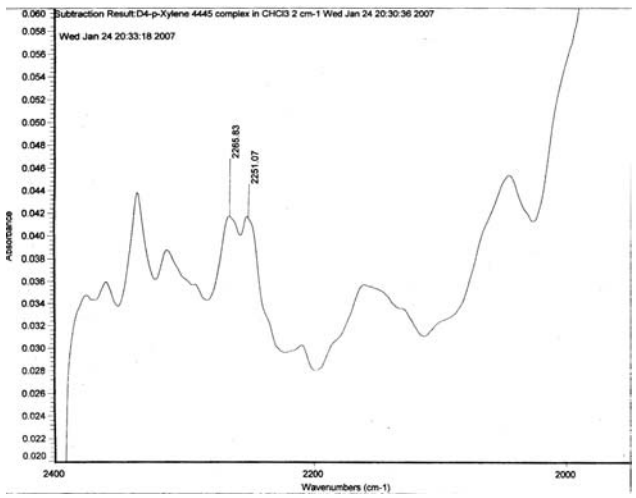
Figure S 10. ^{1}H NMR spectrum (360 MHz, $CDCl_3$; 22 ^{o}C) of **3**.

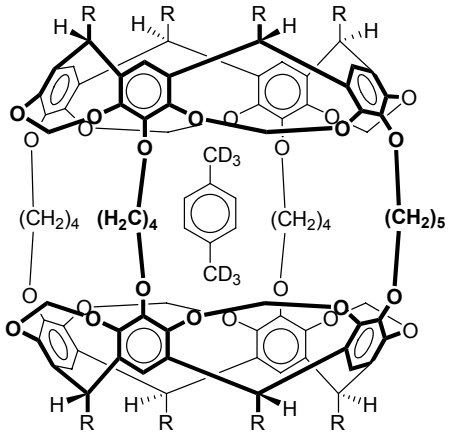
(A)





(B)





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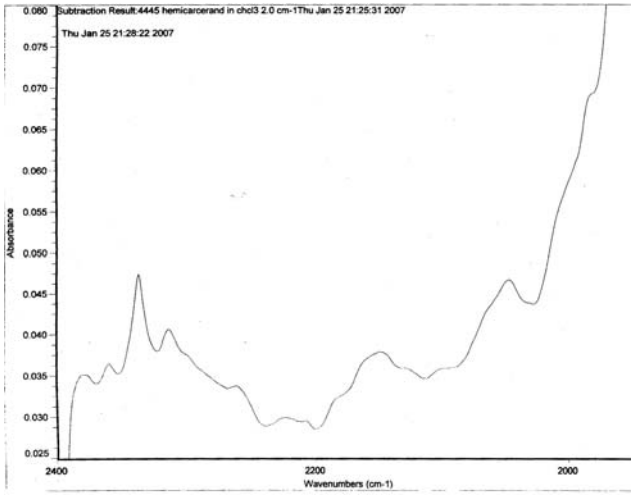

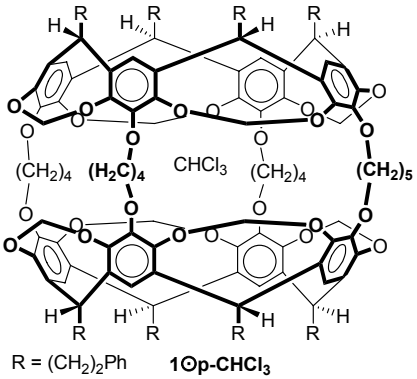

Figure S 11. Partial FT IR spectra of **1**⊙*p*-xylene-d_{10} (A), **1**⊙*p*-xylene-d_6 (B) and **1**⊙$CHCl_3$ (C) in $CHCl_3$

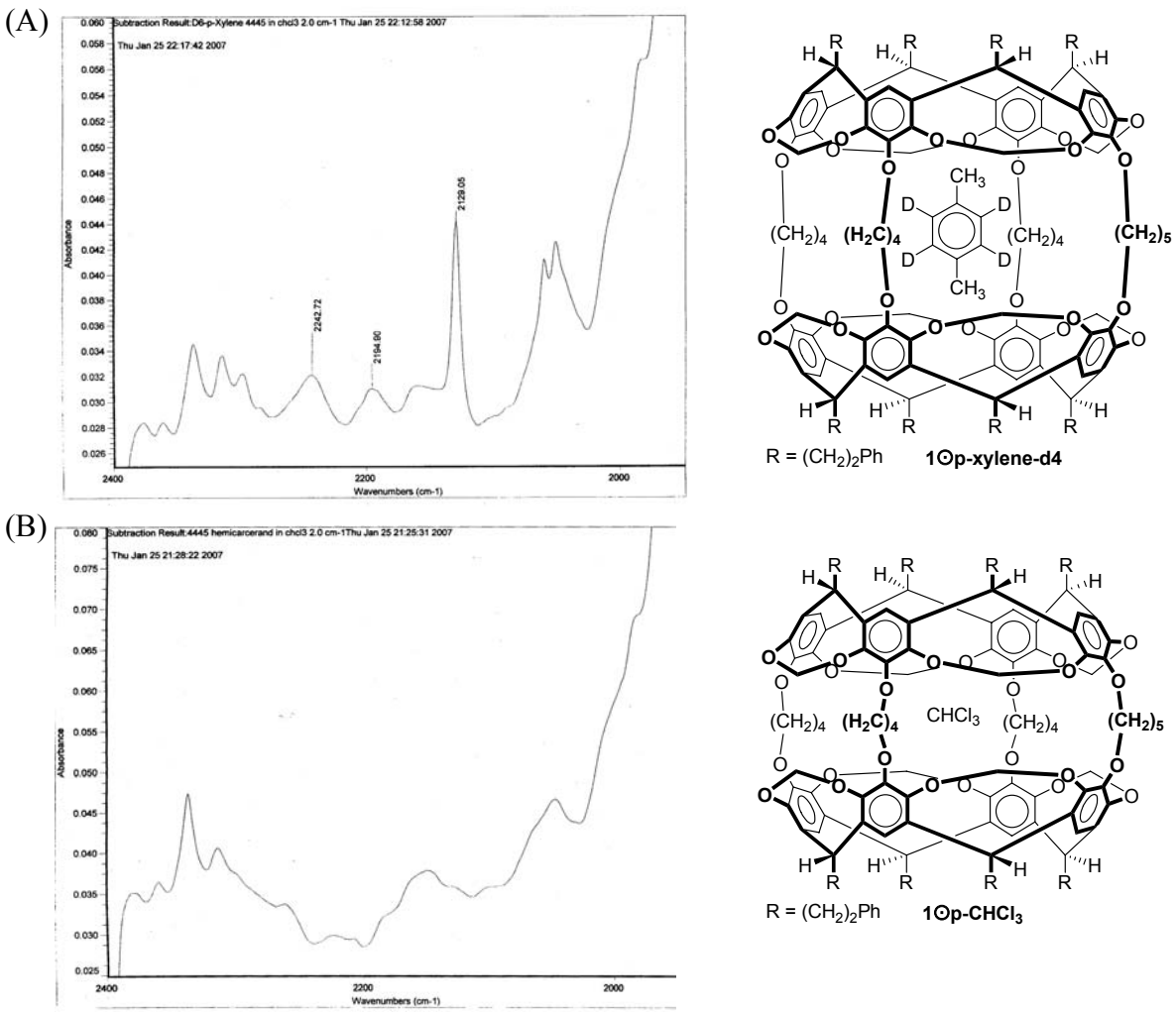

Figure S 12. Partial FT IR spectra of **1**⊙*p*-xylene-d_4 (A), and **1**⊙$CHCl_3$ (B) in $CHCl_3$

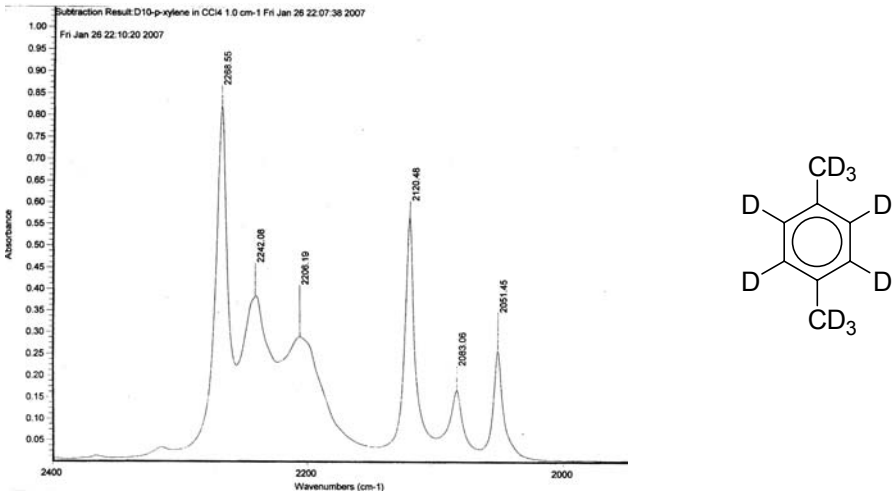

Figure S 13. Partial FT IR spectrum of *p*-xyelen-d_{10} in CCl_4

9. Kinetic Plots

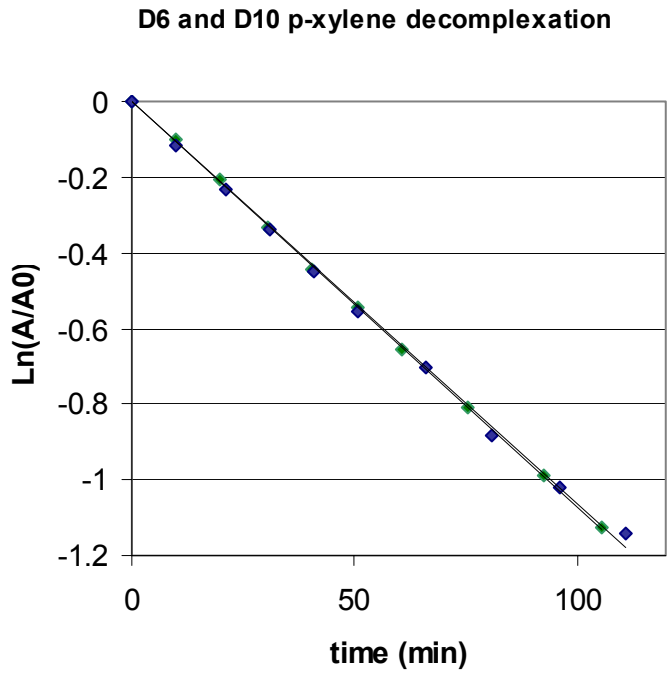

Figure S 14. Kinetic plots ($\ln(A/A_o)$ vers time) for the decomplexation of **1**⊙*p*-xylene-d_{10} (dark blue squares) and **1**⊙*p*-xylene-d_6 (green squares) at 120 °C in nitrobenzene.

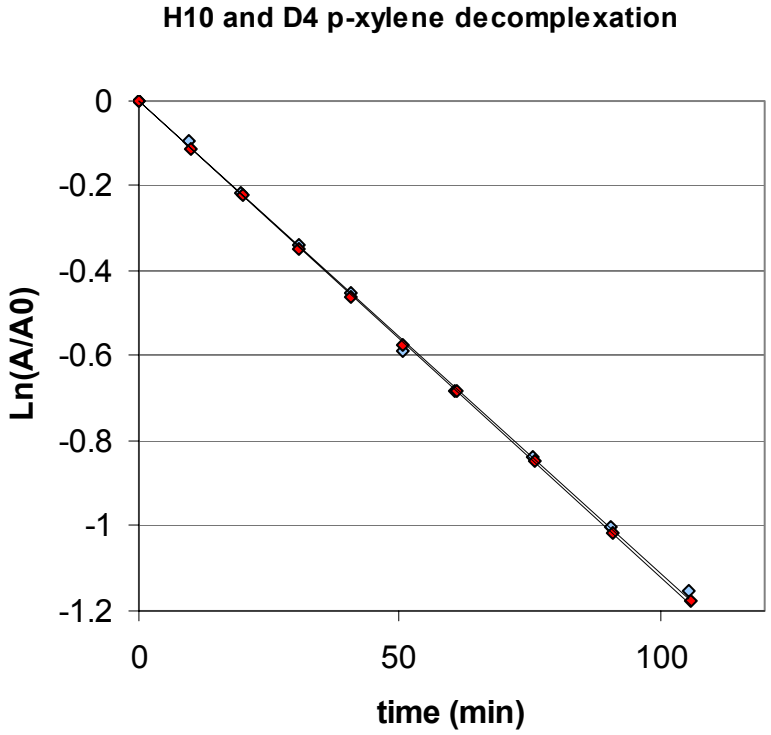

Figure S 15. Kinetic plots ($\ln(A/A_o)$ vers time) for the decomplexation of **1**⊙*p*-xylene (red squares) and **1**⊙*p*-xylene-d_4 (light blue squares) at 120 °C in nitrobenzene.

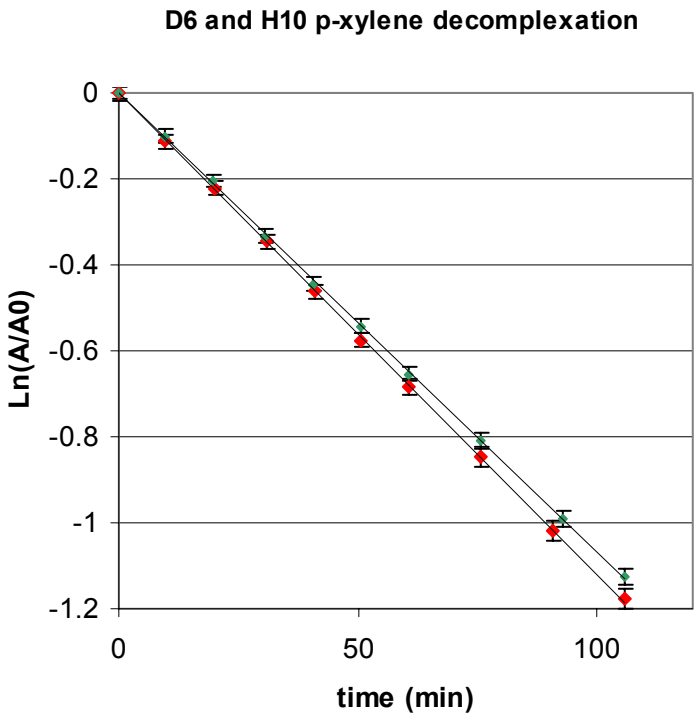

Figure S 16. Kinetic plots ($\ln(A/A_o)$ vers time) for the decomplexation of **1**⊙*p*-xylene (red squares) and **1**⊙*p*-xylene-d_6 (green squares) at 120 °C in nitrobenzene.

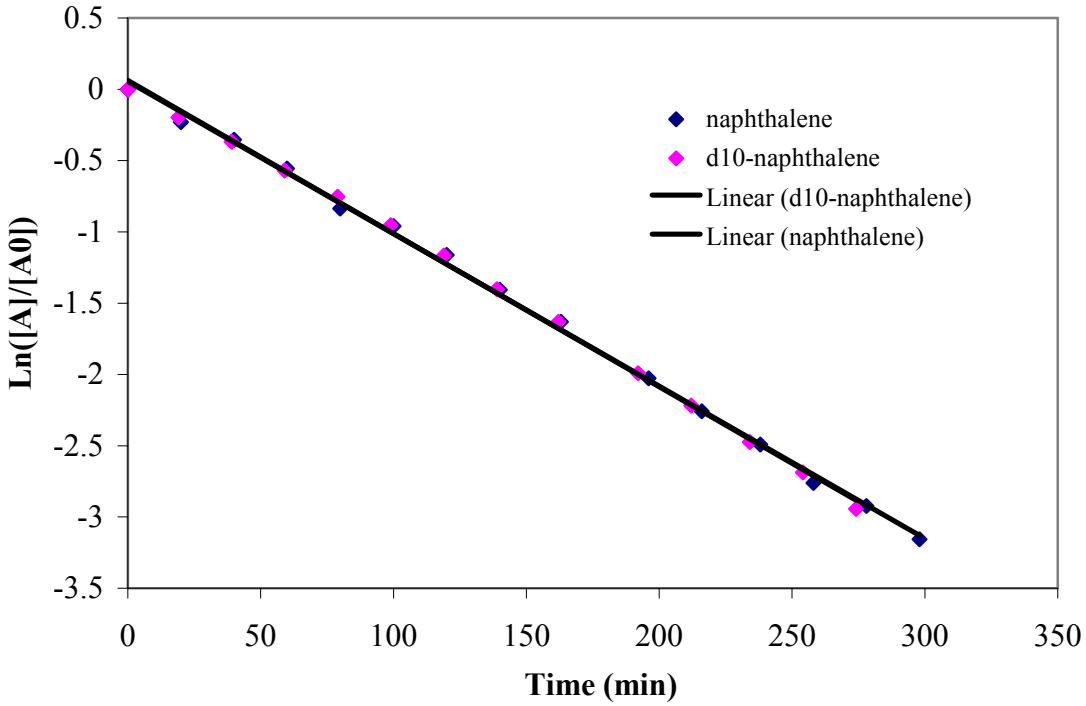

Figure S 17. Kinetic plots ($\ln(A/A_o)$ vers time) for the decomplexation of **1**⊙**Naph** (blue) and **1**⊙**Naph**-d_8 (pink) at 169 °C in nitrobenzene.

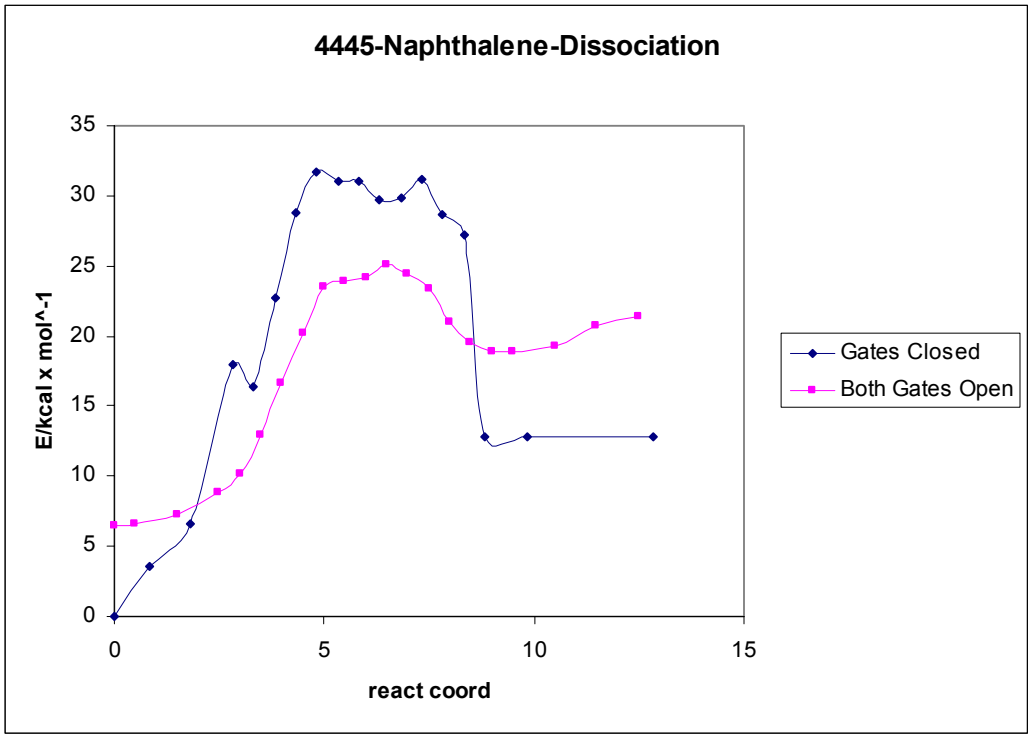

Figure S 18. Computed Energy surface (MM3) for decomplexation of **1⊙Naph** with (pink) and without (blue) *French door gating*. Computations were performed as described in reference [3]. No correction for bulk phase solvation was performed.

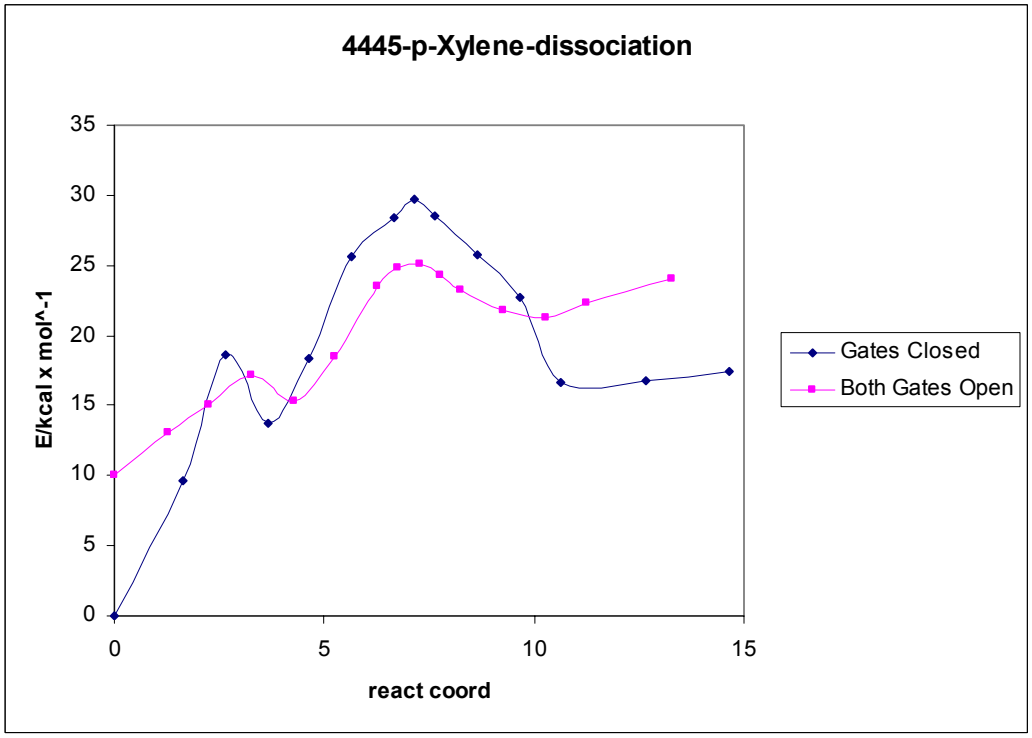

Figure S 19. Computed Energy surface (MM3) for decomplexation of **1⊙pX** with (pink) and without (blue) *French door gating*. Computations were performed as described in reference [3]. No correction for bulk phase solvation was performed.

References

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