Reversible switching between self-assembled homomeric and hybrid capsules†

Jacques Lux and Julius Rebek Jr.*

The Skaggs Institute for Chemical Biology and Department of Chemistry,
The Scripps Research Institute, 10550 North Torrey Pines Rd,
La Jolla, California, 92037, USA.

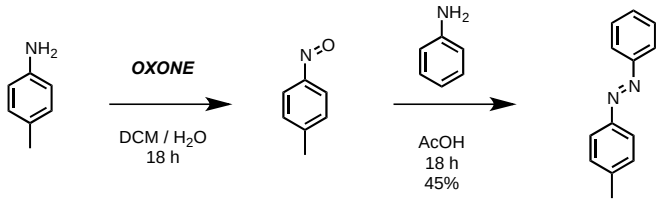
Supporting Information

I. General methods

All reactions were carried out under an atmosphere of argon unless otherwise indicated. All reagents were purchased from Aldrich and were used as received without further purification. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Analytical thin-layer chromatography (TLC) was performed on Silicycle 60 F254 glass-backed plates. Column chromatography was performed using Silicycle R10030B 60 Å 230-400 mesh silica gel. ^{1}H NMR spectra were recorded at 600 MHz, using a Bruker DRX-600 spectrometer equipped with a 5 mm QNP probe. Chemical shifts of ^{1}H NMR of characterized compounds are given in ppm by using $CHCl_3$ as reference (7.26 ppm for ^{1}H spectrum and 77.16 ppm for ^{13}C spectrum). Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), sex (sextet) and m (multiplet). High-resolution mass spectra (HRMS) were recorded on an Applied Biosystems Voyager STR (2) apparatus.

II. Synthetic procedures

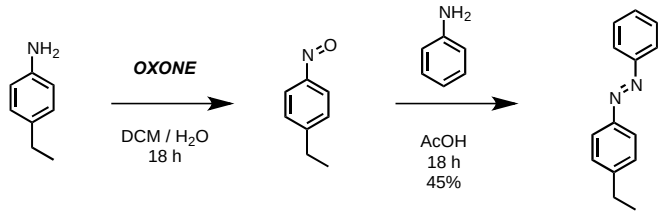
Synthesis of 4-methyl-azobenzene 3



To a solution of *p*-toluidine (1.405 g, 13.1 mmol) in DCM (15 mL), a solution of *OXONE* (15.74 g, 25.6 mmol) in water (70 mL) was added making the organic phase become green and the reaction mixture was stirred vigorously for 40 minutes. After this time, the product was extracted with DCM and the organic layer was evaporated to dryness to give the nitrosotoluene as a green solid. The product was used in the second step without any further purification. ES-MS: M^{+} = 122.06 g.mol^{-1} (calculated 122.05 g.mol^{-1} for $C_7H_7NOH^{+}$).

The nitroso compound (283 mg, 2.4 mmol) and aniline (219 mg, 2.4 mmol) were dissolved in acetic acid and the reaction mixture was stirred overnight until completion of the reaction. After this time, the product was extracted with hexane and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organic phases were dried over Na_2SO_4, filtered and concentrated and the crude product was purified with a flash chromatography over SiO_2 with hexane as eluent. The title compound **3** was obtained as an orange crystalline solid (280 mg, 45%). ^1H NMR ($CDCl_3$, 600 MHz, 298 K): δ (ppm) = 7.948 (d, 2H, *J*=7.9Hz), 7.88 (d, 2H, *J*=7.9 Hz), 7.550 (t, 2H, *J*=7.9 Hz, 7.5 Hz), 7.493 (t, 1H, *J*=7.5 Hz), 7.35 (d, 2H, *J*=8.1 Hz), 2.476 (s, 3H).

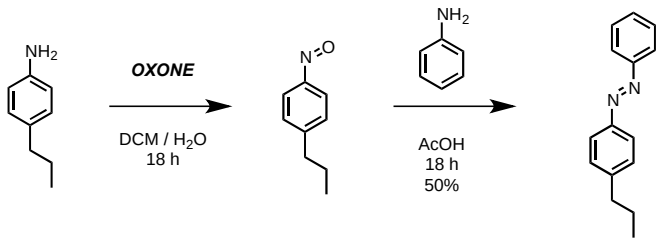
Synthesis of 4-ethyl-azobenzene 4



To a solution of 4-ethylaniline (1.517 g, 12.5 mmol) in DCM (15 mL), a solution of *OXONE* (15.4 g, 25 mmol) in water (70 mL) was added making the organic phase become green and the reaction mixture was stirred vigorously for 30 minutes. After this time, the product was extracted with DCM and the organic layer was evaporated to dryness to give the 4-ethyl-nitrosophenyl as a green solid. The product was used in the second step without any further purification. ES-MS: M^+ = 136.07 $g.mol^{-1}$ (calculated 136.07 $g.mol^{-1}$ for $C_8H_9NOH^+$).

All the raw nitroso compound (12.5 mmol) and aniline (1.16 mg, 12.5 mmol) was dissolved in acetic acid and the reaction mixture was stirred overnight completion of the reaction. After this time, the product was extracted with hexane and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organic phases were dried over Na_2SO_4, filtered and concentrated and the crude product was purified with a flash chromatography over SiO_2 with hexane as eluent. The title compound **4** was obtained as an orange oil (1.1 g, 45%). ^1H NMR ($CDCl_3$, 600 MHz, 298 K): δ (ppm) = 7.93 (d, 2H, *J*=7.5Hz), 7.88 (d, 2H, *J*=8.3 Hz), 7.54 (t, 2H, *J*=7.5 Hz), 7.49 (t, 1H, *J*=7.5 Hz), 7.37 (d, 2H, *J*=8.3 Hz), 2.76 (q, 2H, *J*=7.7 Hz), 1.31 (t, 3H, *J*=7.7 Hz). ES-MS: M^+ = 211.1236 $g.mol^{-1}$ (calculated 211.123 $g.mol^{-1}$ for $C_{14}H_{14}N_2H^+$).

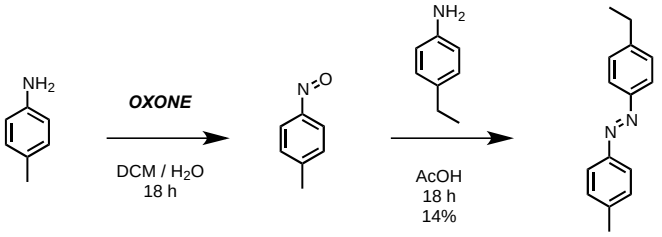
Synthesis of 4-propyl-azobenzene 5



To a solution of 4-propylaniline (1.567 g, 11.5 mmol) in DCM (15 mL), a solution of *OXONE* (14.3 g, 23.2 mmol) in water (70 mL) was added making the organic phase become green and the reaction mixture was stirred vigorously for 30 minutes. After this time, the product was extracted with DCM and the organic layer was evaporated to dryness to give the 4-propyl-nitrosophenyl as green solid. The product was used in the second step without any further purification. ES-MS: M^+ = 150.09 g.mol^{-1} (calculated 150.08 g.mol^{-1} for $C_9H_{11}NOH^+$).

All the raw nitroso compound (11.5 mmol) and aniline (1.07 mg, 11.5 mmol) were dissolved in acetic acid and the reaction mixture was stirred overnight completion of the reaction. After this time, the product was extracted with hexane and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organic phases were dried over Na_2SO_4, filtered and concentrated and the crude product was purified with a flash chromatography over SiO_2 with hexane as eluent. The title compound **5** was obtained as an orange oil (1.38 g, 50%). ^{1}H NMR ($CDCl_3$, 600 MHz, 298 K): δ (ppm) = 7.93 (d, 2H, *J*=7.5Hz), 7.87 (d, 2H, *J*=8.1 Hz), 7.55 (t, 2H, *J*=7.5 Hz), 7.48 (t, 1H, *J*=7.5 Hz), 7.34 (d, 2H, *J*=8.1 Hz), 2.7 (t, 2H, *J*=7.5 Hz), 1.73 (sex, 2H, *J*=7.5 Hz), 1.001 (t, 3H, *J*=7.5 Hz). ES-MS: M^+ = 225.1396 g.mol^{-1} (calculated 225.1386 g.mol^{-1} for $C_{15}H_{16}N_2H^+$).

Synthesis of 4-ethyl-4'-methyl-azobenzene 7

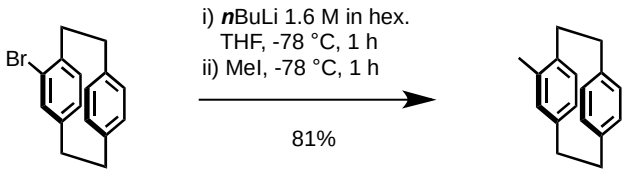


To a solution of *p*-toluidine (1.405 g, 13.1 mmol) in DCM (15 mL), a solution of *OXONE* (15.74 g, 25.6 mmol) in water (70 mL) was added making the organic phase become green and the reaction mixture is stirred vigorously for 40 minutes. After this time, the product was extracted with DCM and the organic layer was evaporated to dryness to give the nitrosotoluene as a green solid. The product was used in the second step without any further purification. ES-MS: M^+ = 122.06 g.mol^{-1} (calculated 122.05 g.mol^{-1} for $C_7H_7NOH^+$).

The nitroso compound (285 mg, 2.4 mmol) and 4-ethylaniline (285 mg, 2.4 mmol) were dissolved in acetic acid (20 mL) and the reaction mixture was stirred overnight completion of

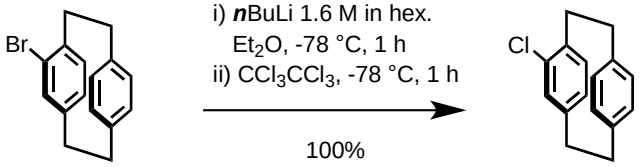
the reaction. After this time, the product was extracted with hexane and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organic phases were dried over Na_2SO_4, filtered and concentrated and the crude product was purified with a flash chromatography over SiO_2 with hexane as eluent. The title compound **7** was obtained as an orange crystalline solid (280 mg, 45%). ^{1}H NMR ($CDCl_3$, 600 MHz, 298 K): δ (ppm) = 7.89 (d, 2H, *J*=8.3Hz), 7.87 (d, 2H, *J*=8.3 Hz), 7.37 (d, 2H, *J*=8.3 Hz), 7.34 (d, 2H, *J*=8.3 Hz), 2.77 (q, 2H, *J*=7.5 Hz), 2.47 (s, 3H), 1.33 (t, 3H, *J*=7.5 Hz). ES-MS: M^+ = 225.1396 g.mol^{-1} (calculated 225.1386 g.mol^{-1} for $C_{15}H_{16}N_2H^+$).

Synthesis of 4-methyl-[2.2]paracyclophane



To a solution of 4-bromo-[2.2]-*p*-cyclophane (150 mg, 0.52 mmol) in dry THF (5 mL), a solution of 1.6 M *n*-BuLi in hexane (0.33 mL, 0.52 mmol) was added under argon at -78 °C. The resulting mixture was stirred one hour at this temperature. After this time, MeI (33 µL, 0.52 mmol) was added dropwise at -78 °C and the solution was stirred one more hour at this temperature. The reaction mixture was then poured in cold water and extracted with diethyl ether. The organic layers were dried over Na_2SO_4, filtered and concentrated to give the product as a white solide (94 mg, 81%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) = 6.82 (dd, 1H), 6.57 (dd, 1H), 6.51 (bs, 1H), 6.485 (dd, 1H), 6.45 (dd, 1H), 6.416 (bs, 1H), 6.407 (dd, 1H), 3.324 (m, 1H), 3.134 (m, 1H), 3.1-3.0 (m, 4H), 2.96 (m, 1H), 2.81 (m, 1H), 2.119 (s, 3H). ES-MS: M^+ = 223.1480 g.mol^{-1} (calculated 223.1481 g.mol^{-1} for $C_{17}H_{18}H^+$).

Synthesis of 4-chloro-[2.2]paracyclophane



To a solution of 4-bromo-[2.2]-*p*-cyclophane (150 mg, 0.52 mmol) in dry diethyl ether (5 mL), a solution of 1.6 M *n*-BuLi in hexane (0.36 mL, 0.57 mmol) was added under argon at -78 °C. The resulting mixture was stirred 50 minutes at this temperature. After this time, a solution of hexachloroethane (123.7 mg, 0.52 mmol) in diethyl ether (5 mL) was added dropwise at -78 °C and the solution was stirred 50 additional minutes at this temperature. The reaction mixture was then poured in cold water and extracted with ethyl acetate. The organic phases were dried over Na_2SO_4, filtered and concentrated to give the product as a white solide (126 mg, 100%). ^{1}H NMR ($CDCl_3$, 600 MHz, 298 K): δ (ppm) = 7.19 (dd, 1H), 6.59 (dd, 1H), 6.55 (dd, 1H), 6.541 (bs, 1H), 6.509 (dd, 1H), 6.484 (bs, 1H), 6.48 (dd, 1H), 3.491 (m, 1H), 3.225 (m, 1H), 3.16-3.05 (m, 4H), 2.945 (m, 1H), 2.853 (m, 1H).

III. Additional encapsulation experiments

Encapsulation study of paracyclophane derivatives

Encapsulation experiments were carried out in presence of the resorcinarene **1**, the cavitand **2** and four different bulky paracyclophane derivatives as guests (Figure S1). The chloro and bromo derivatives are too bulky and no significant signal is visible in the upfield regions of the spectra. In the case of the methyl derivative, some encapsulation is detected. However many signals, assigned to undesired hexameric assemblies, appear in the aromatic region. Thus, the hydroxy derivative was selected for the future encapsulation experiments.

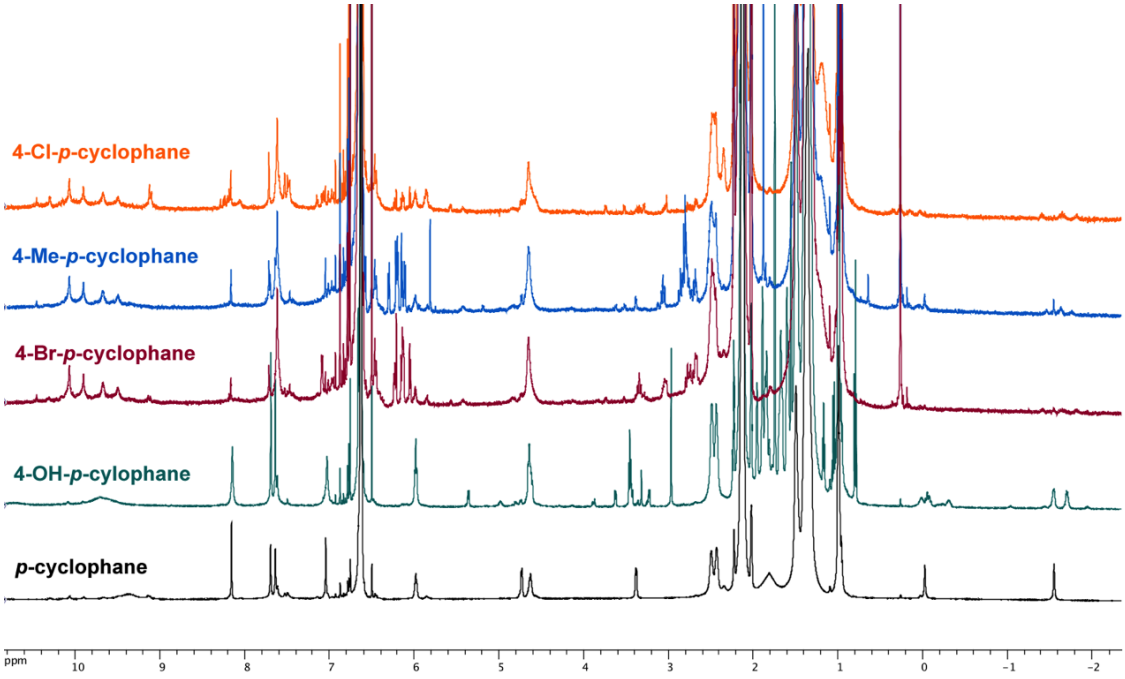


Figure S1. Encapsulation experiments with paracyclophane derivatives.

Evaluation of the homomeric capsule formation with increasing amounts of guest

For the NMR study of the switching process in presence of the resorcinarene **1**, the cavitand **2**, 4,4'-dimethyl-azobenzene **6** and 4-hydroxy[2.2]paracyclophane **10**, increasing amounts of the azobenzene **6** were added, however no significant improvement was seen with more than 10 eq. (15, 25 and 30 eq., Figure S2).

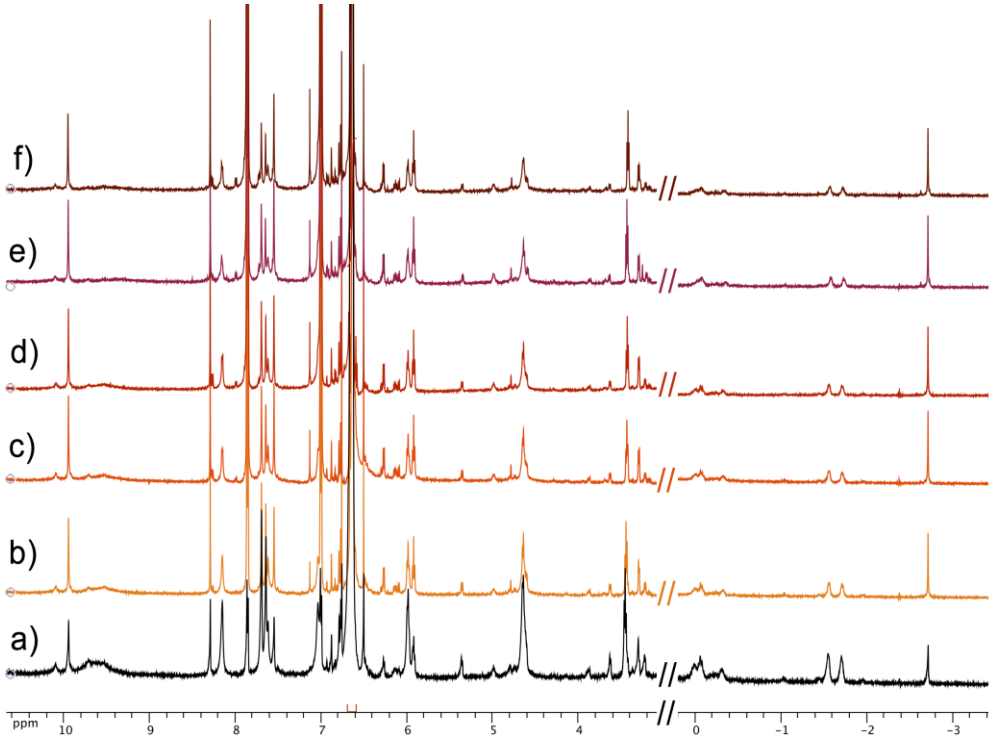


Figure S2. Sample heated 5 minutes at 150 °C and containing **1**, **2**, **10** and increasing quantities of **6** : a) 1 eq., b) 5 eq., c) 10 eq., d) 15 eq., e) 20 eq. f) 35 eq.