Supplementary Information for

Extended covalent containers: Synthesis and guest encapsulation

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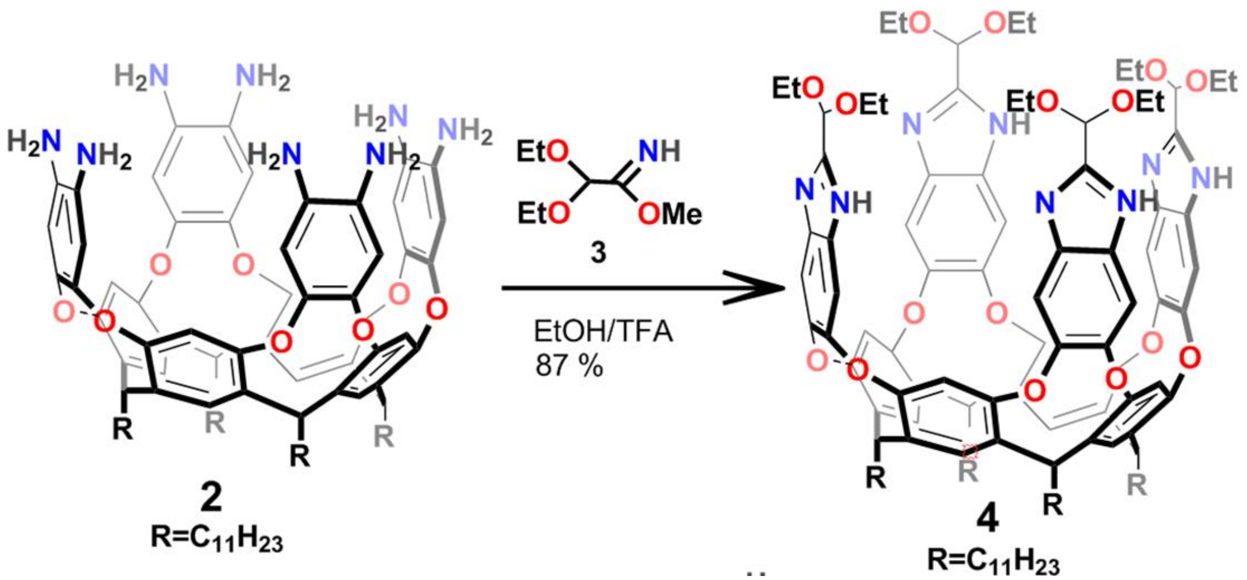
General Information

All reactions were carried out under an atmosphere of argon unless otherwise indicated. ^1H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz respectively, using a Bruker DRX-600 spectrometer equipped with a 5 mm QNP probe. Chemical shifts of ^1H NMR and ^{13}C NMR are given in ppm by using $CHCl_3$, Benzene, 1,3,5-Trimethylbenzene or DMF as references.

Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), m (multiplet). MALDI-TOF spectra and high-resolution mass spectra (HRMS) were recorded on an Applied Biosystems Voyager STR (2) apparatus and an Agilent ESI-TOF mass spectrometer respectively. Anhydrous CH2Cl2, NEt3 and Et2O were taken from a solvent drying system (SG Water USA).

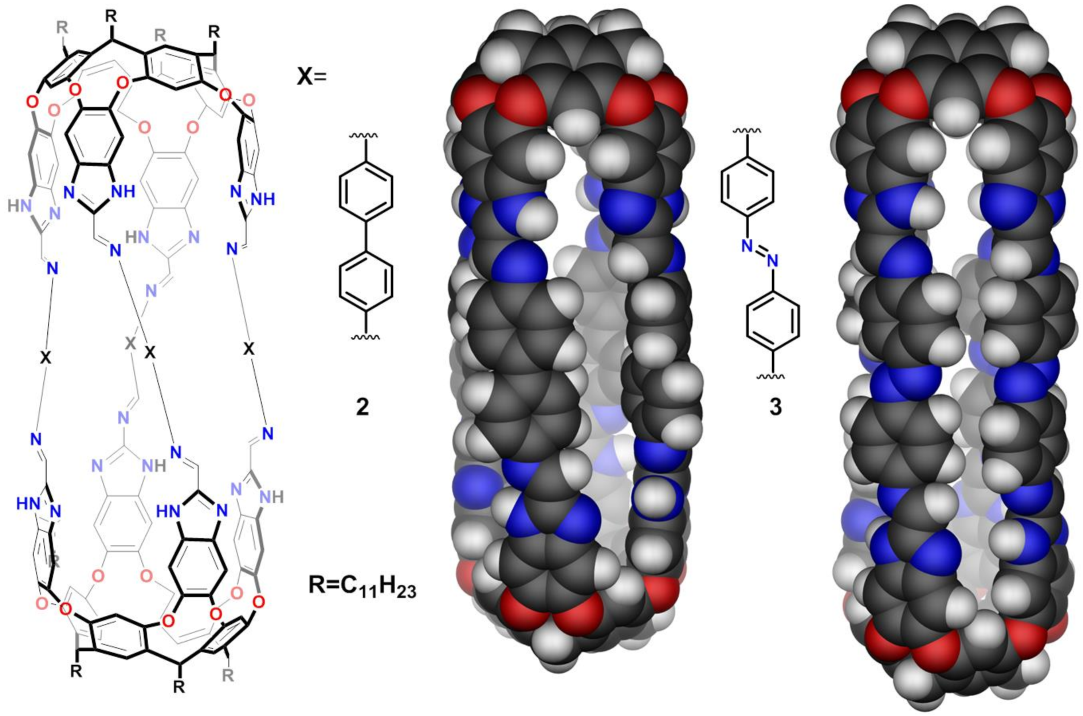
All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. All chemicals and reagents were obtained from commercial suppliers and used without further purification.

Materials and Methods



Synthesis of Tetra 2-(Diethoxymethyl)-1H-Benzo-[d] Imidazole Cavitand (4)

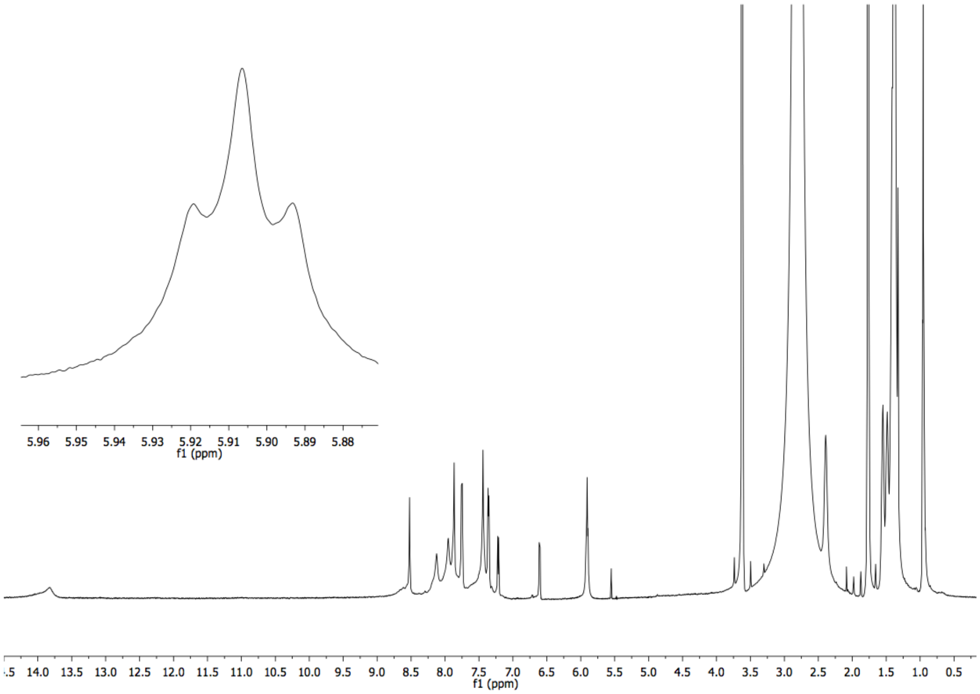
To a stirred solution of octaamine cavitand **2**[i] (2 gr, 1.2 mmol) in dry ethanol (100 mL) was added dropwise 2 mL (12 mmol) of **3**[ii]. After the addition, the reaction mixture was stirred at room temperature overnight (~16 hours). Then 2 ml of TFA was added and the solution was heated under reflux for six hours. The resulting solution was cooled overnight in the refrigerator and tan crystalline tetra 2-(diethoxymethyl)-1H-benzo[d]imidazole was collected by filtration (Yield= 87 %). ^1H NMR (600 MHz, DMSO-*d6*)δ (ppm): 0.88 (12H, t, J=7 Hz), 1.2-1.4 (72H, m), 5.7 (t, 8H, J=7 Hz), 7.3 (s, 8H), 7.8 (s, 4H), 8.2 (s, 4H), 11 (s, 4NH). MS (MALDI-TOF, m/z) (Found: $[M + H]^+$, 1971 $C_{120}H_{160}N_8O_{16}$ required, 1970.59.



Synthesis of Expanded Covalent Capsule 2

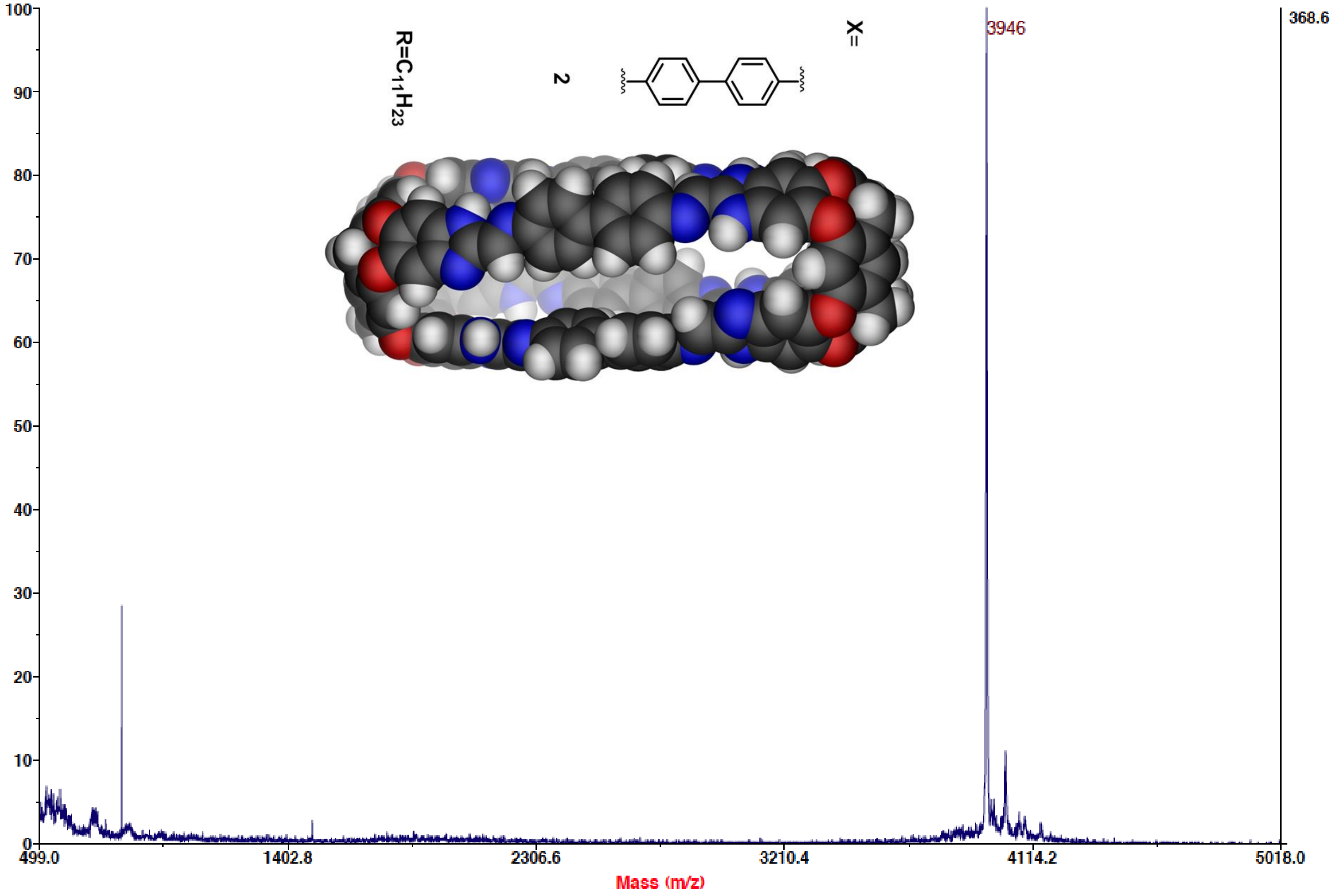
Cavitand **4** (0.985 gr, 0.5 mmol, 1eq) was added to a solution of benzidine (1.11 gr, 6 mmol, 12 eq) and trifluoroacetic acid (TFA) (2 mL) in 100 mL of degassed and dry chloroform. The mixture was placed inside a sealed tube under nitrogen atmosphere then heated to 110 °C for 24 hours. After cooling to room temperature, 5 mL of triethylamine was added to the mixture to neutralize the TFA while cooling the solution at 0 °C using an ice bath. The solvent was then removed under reduced pressure by rotary evaporation and the yellow powder obtained was suspended in 100 mL of warm methanol (40° C) under constant stirring in order to remove the excess benzidine and the side products formed. The resulting precipitate was re-suspended in 100 mL of dry methanol and was sonicated for 20 min at 40° C. The resulting mixture was filtered and the cake was washed with 20 mL water and 100 mL of methanol consecutively. The resulting bright yellow powder was dried under high vacuum. (Yield = 90 %). The solid was used for encapsulation studies with no further purification (HPLC chromatogram confirmed the purity of the expanded covalent capsule **2**). ^{1}H NMR (600 MHz, THF-*d8*) δ (ppm): 0.88 (24H, t, J=7 Hz), 1.2-1.4 (144H, m), 5.8 (t, 8H, J=7 Hz), 6.75 (s, 4H), 7.3 (s, 8H), 7.8 (s, 4H), 7.9 (s, 16H), 8.1 (s, 8H), 8.3 (s, 16H), 14 (s, NH). ^{13}C NMR (600 MHz, THF-*d8*) δ (ppm): 154.7, 149.8, 148.6, 138.9, 134, 133.6, 130.5, 121.6, 115.4, 112.4, 105.2, 31.9, 30.8, 28.4, 28.3, 28, 26.7, 23.3, 21.2, 15.1, 12.1. MS (MALDI-TOF, m/z) (Found: $[M + H]^+$, 3946 $C_{256}H_{272}N_{24}O_{16}$ Calculated 3941

^{1}H NMR of expanded capsule 2 in THF-d_8 in the presence of D_2O

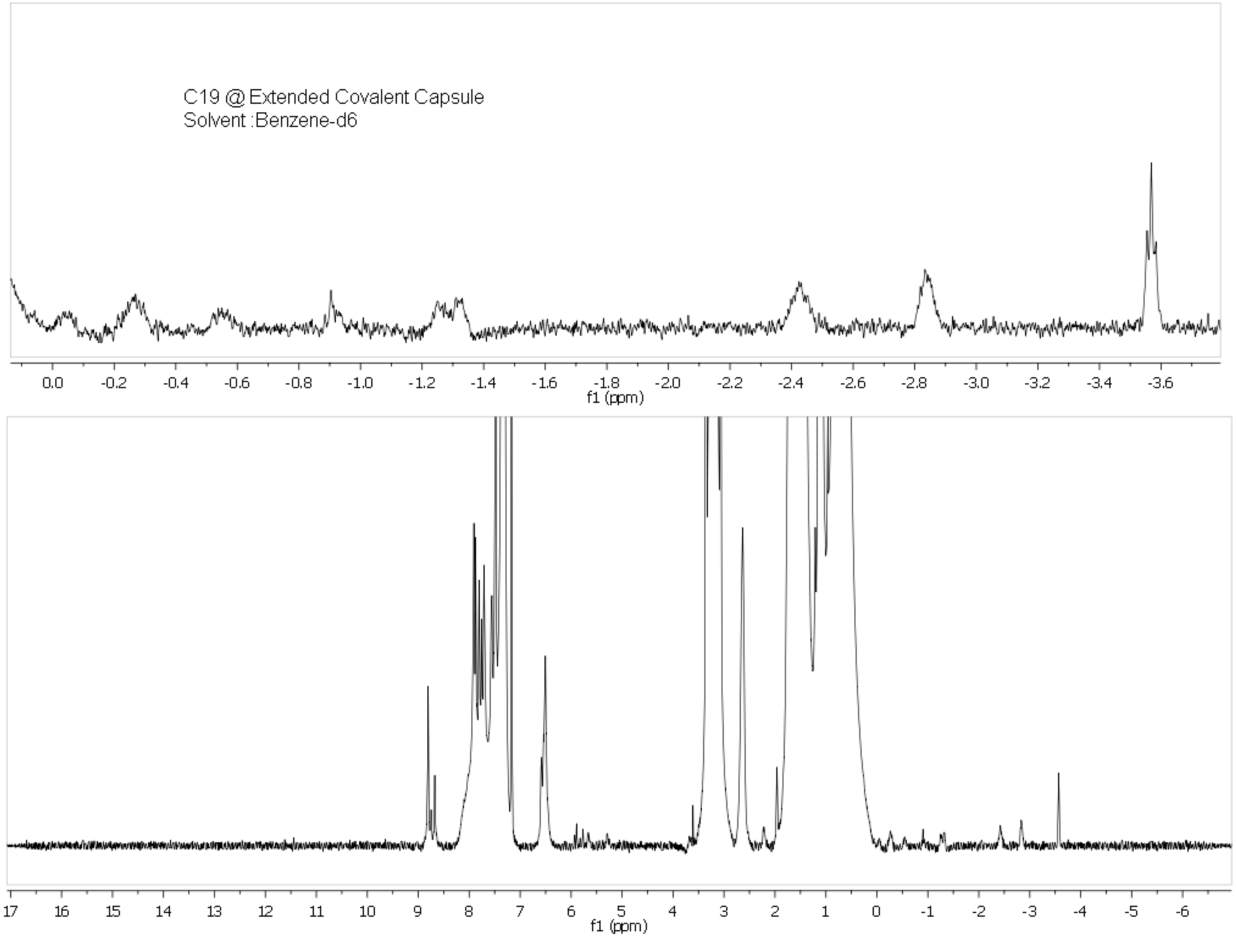


MALDI-TOF Mass Spectrum of the expanded covalent capsule 2

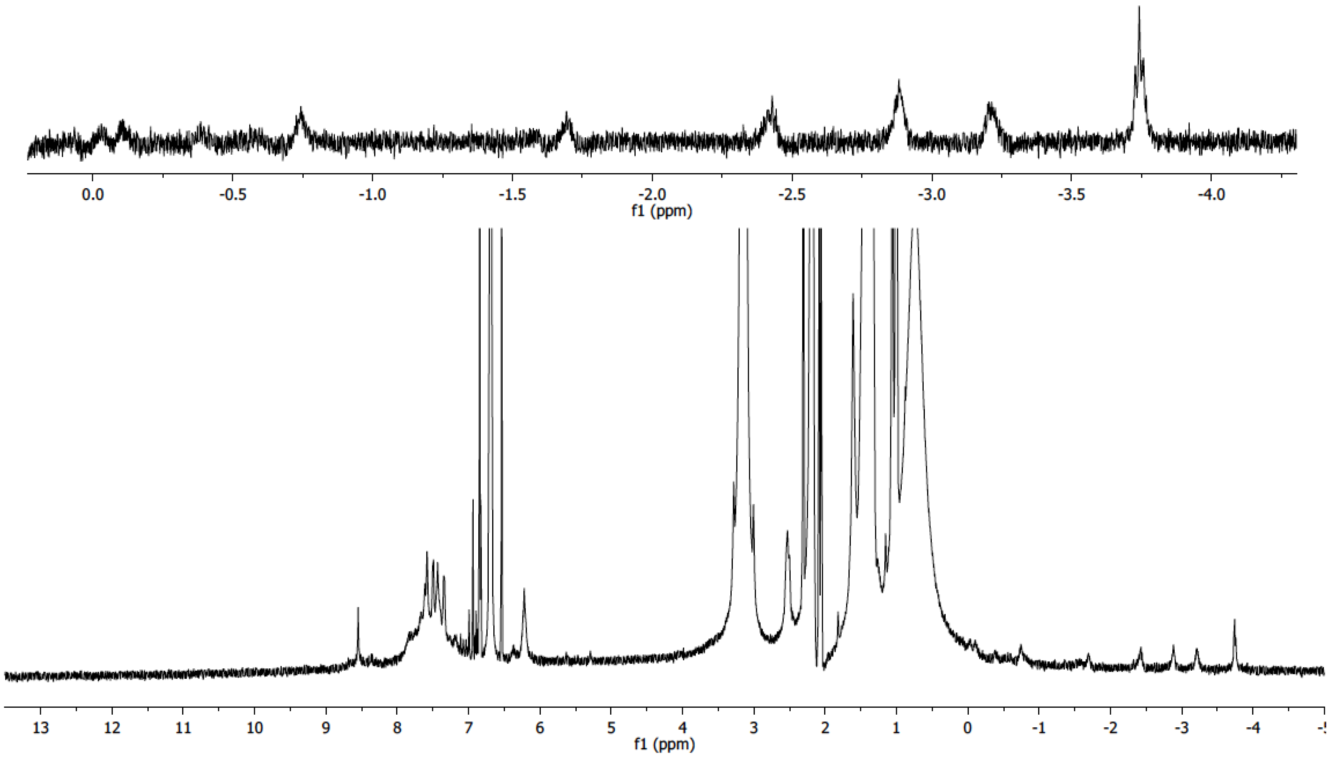
Chemical Formula: $C_{256}H_{272}N_{24}O_{16}$



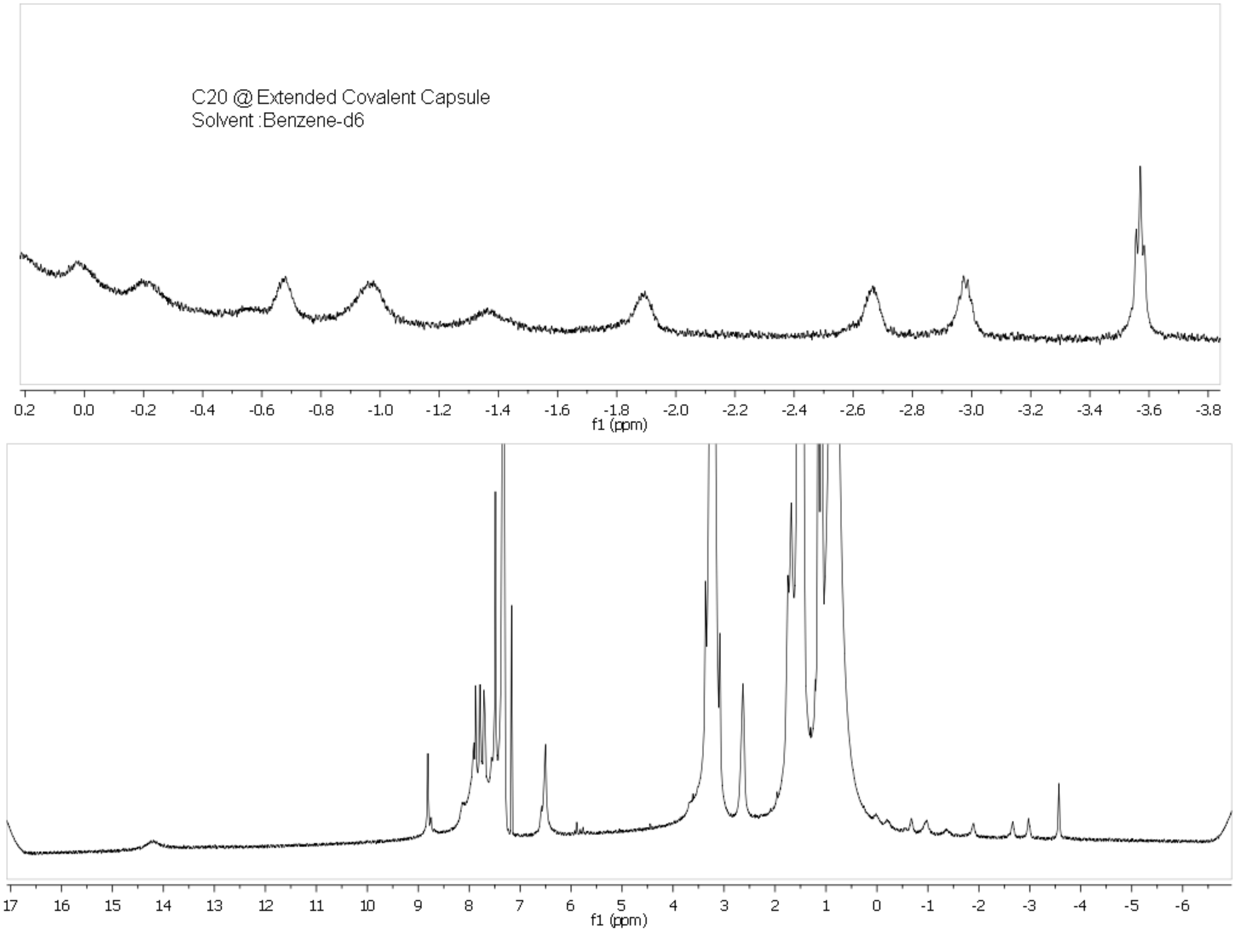
^{1}H NMR of Nonadecane (C19) encapsulated in expanded covalent capsule 2 using benzene-d_6 with added MeOH as solvent at ambient temp



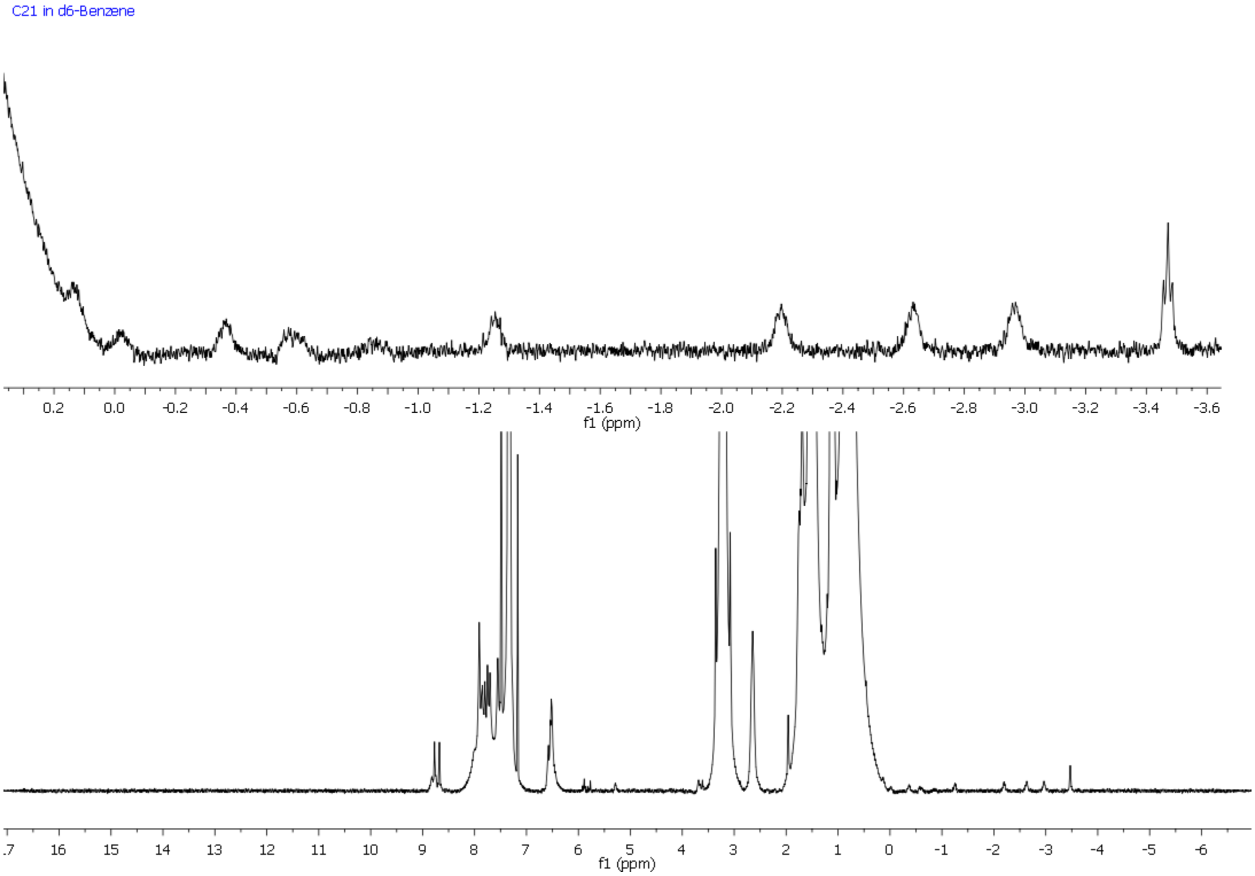
^{1}H NMR of n-Tricosane (C23) encapsulated in expanded covalent capsule 2 using benzene-d_6 with added MeOH as solvent at ambient temp



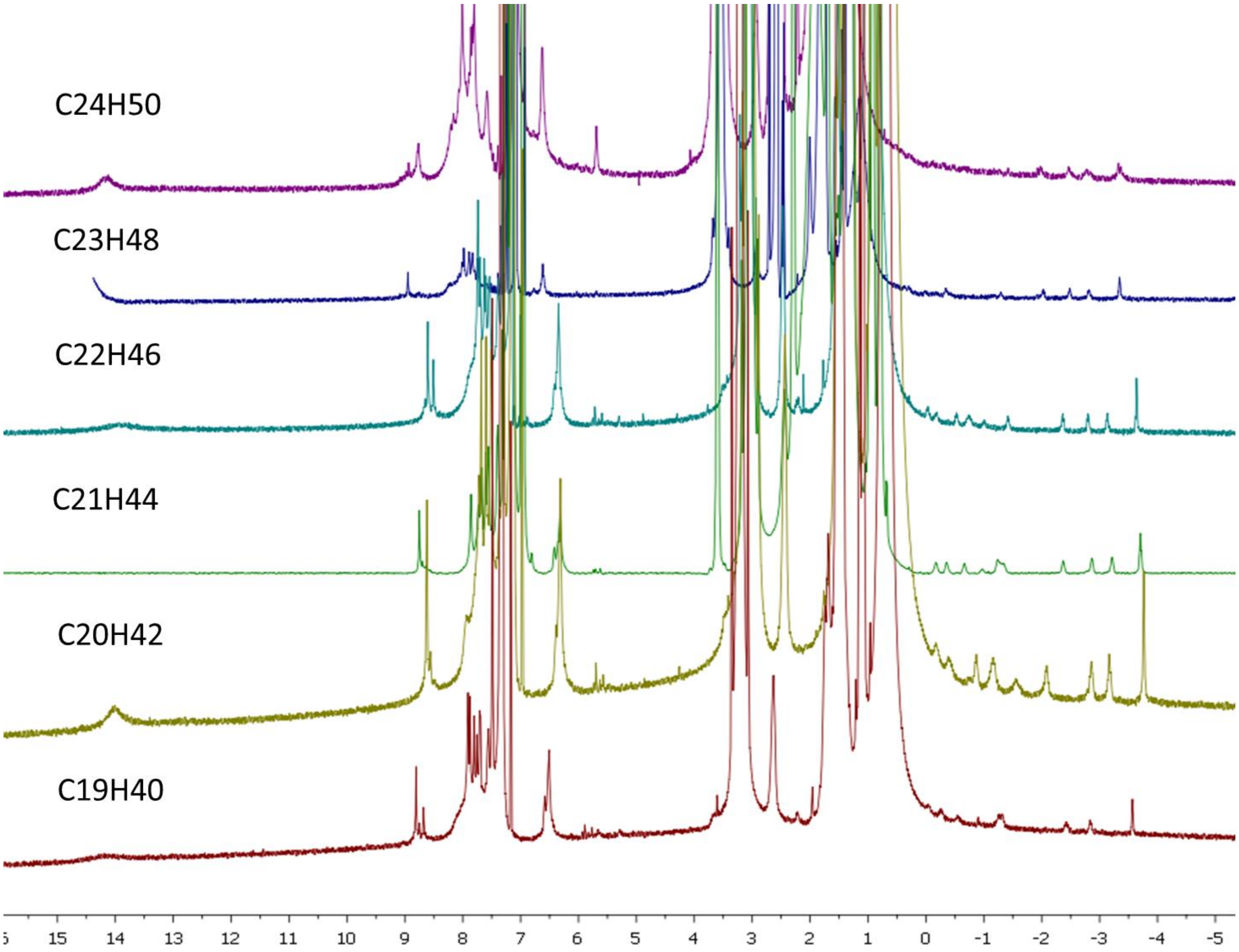
^{1}H NMR of n-Icosane (C20) encapsulated in expanded covalent capsule 2 using benzene-d_6 with added MeOH as solvent at ambient temp



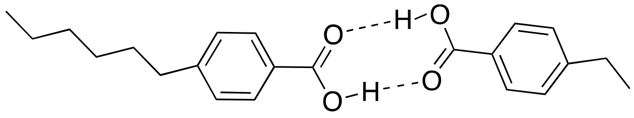
^{1}H NMR of n-Heneicosane (C21) encapsulated in expanded covalent capsule 2 using benzene-d_6 with added MeOH as solvent at ambient temp

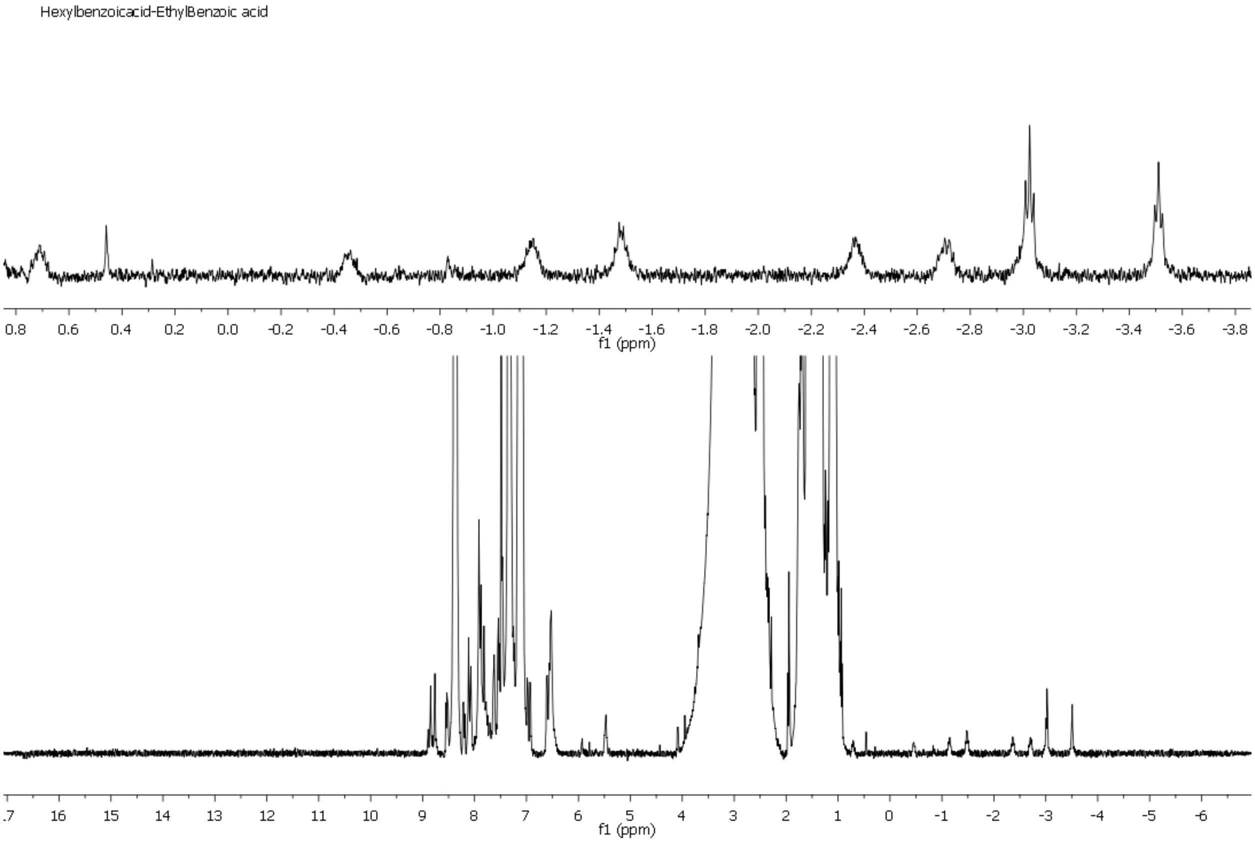


^{1}H NMR of normal alkanes (C19-C24) encapsulated in expanded covalent capsule 2 using benzene-d$_6$ with added MeOH as solvent at ambient temp

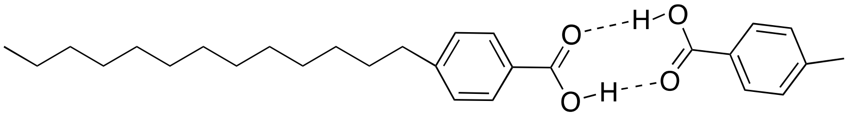


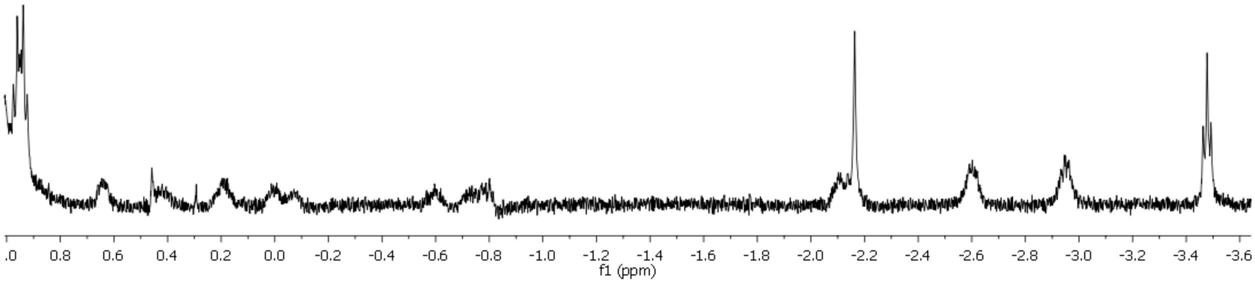
^{1}H NMR of acid-dimer: p-hexyl benzoic acid and p-ethyl benzoic acid encapsulated in expanded covalent capsule 2 using mesitylene-d_{12} with added MeOH as solvent at ambient temp

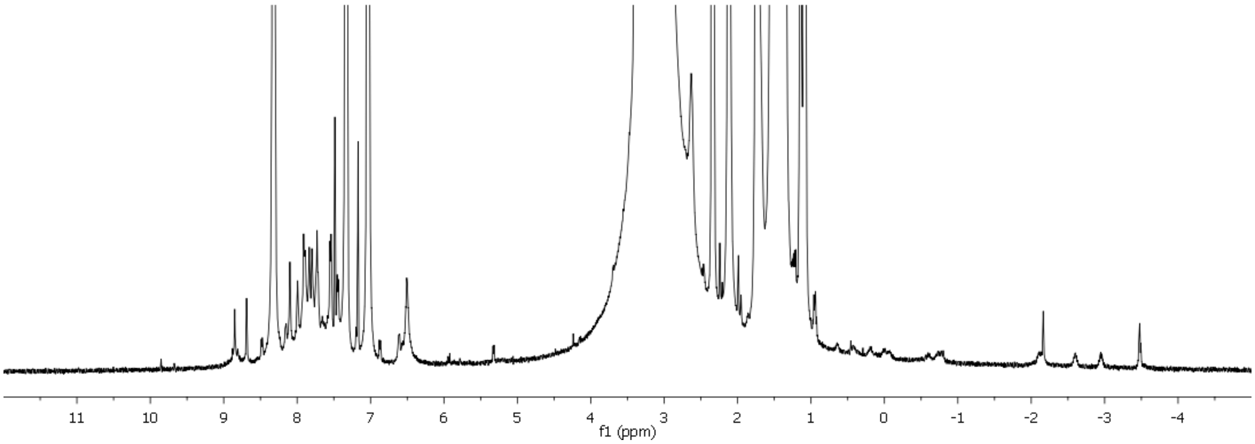




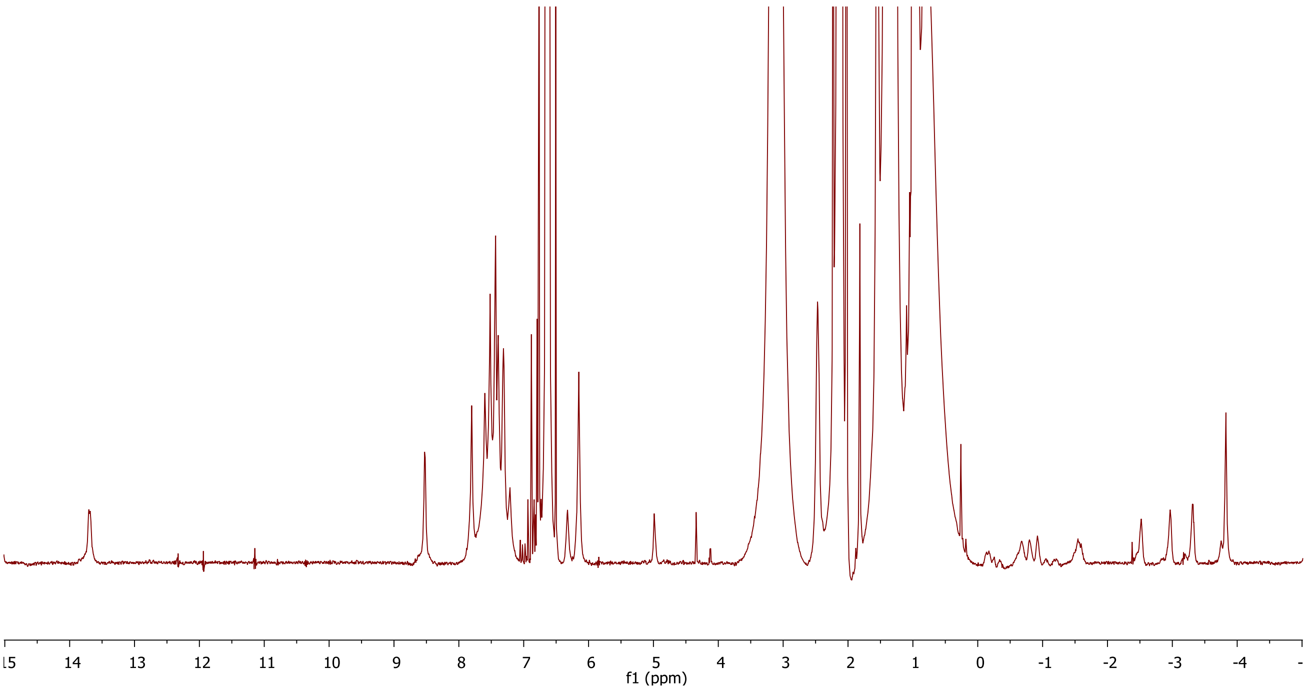
^{1}H NMR of acid-dimer: p-hexyl benzoic acid and p-ethyl benzoic acid encapsulated in expanded covalent capsule 2 using mesitylene-d_{12} with added MeOH as solvent at ambient temp



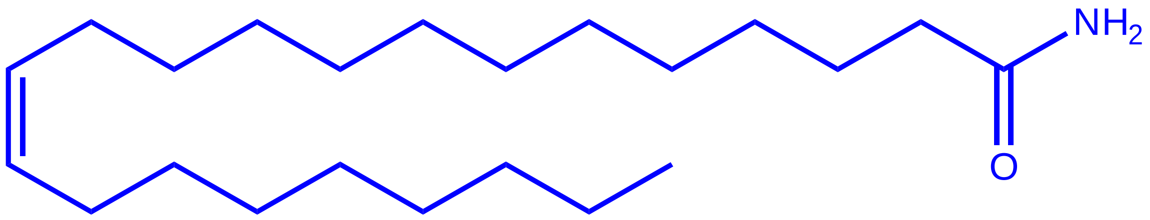


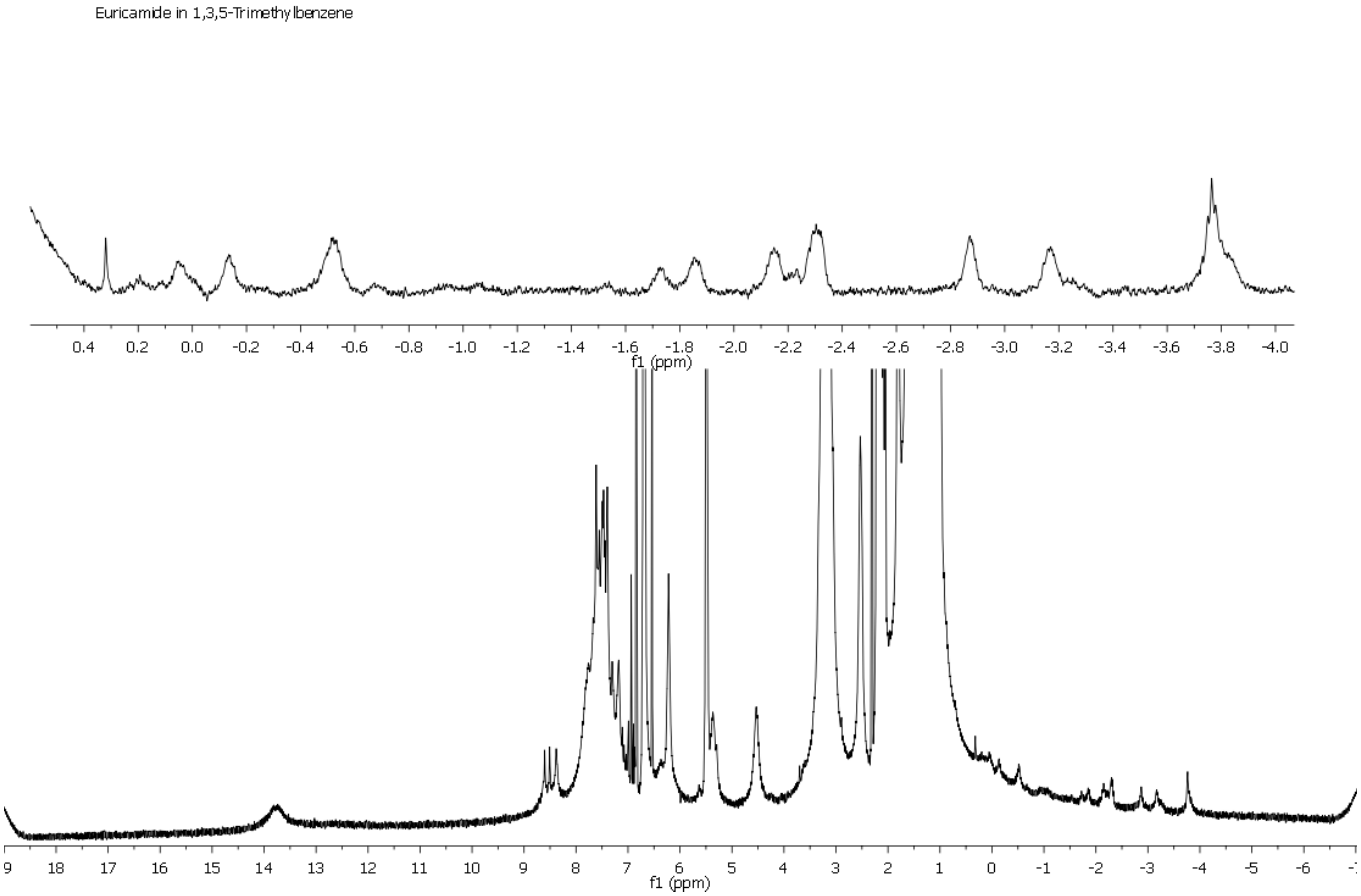


^{1}H NMR of n-Docosane, C22 encapsulated in expanded covalent capsule 2 using mesitylene-d$_{12}$ with added MeOH as solvent at ambient temp



^{1}H NMR of Erucamide (*cis*-13-Docosenamide) encapsulated in expanded covalent capsule 2 using mesitylene-d_{12} with added MeOH as solvent at ambient temp

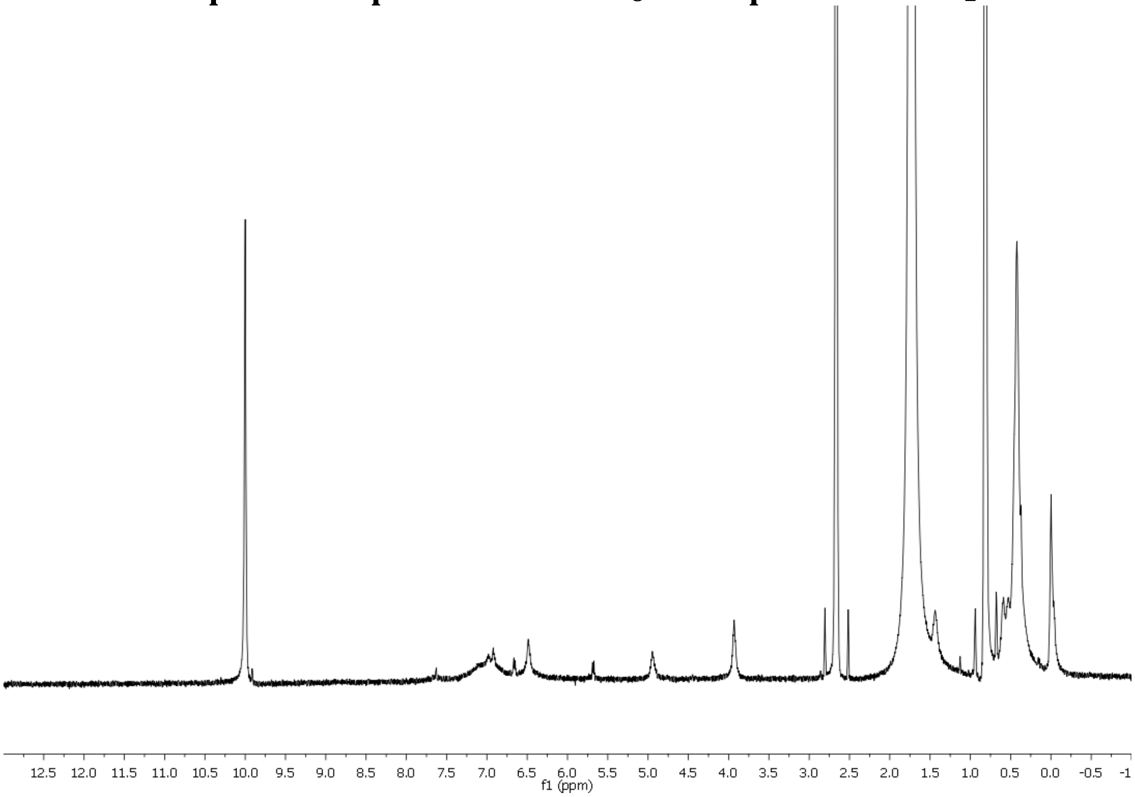




Synthesis of Expanded Covalent Capsule 3

Cavitand **4** (0.985 gr, 0.5 mmol, 1eq) was added to a solution of (*E*)-4,4'-(diazene-1,2-diyl)dianiline (1.28 gr, 6 mmol, 12 eq) and trifluoroacetic acid (TFA) (2 mL) in 100 mL of degassed and dry chloroform. The mixture was placed inside a sealed tube under nitrogen atmosphere, then was heated to 110 °C for 24 hours. After cooling to room temperature, 5 mL of triethylamine was added to the mixture to neutralize the TFA while cooling the solution at 0 °C using an ice bath. The solvent was then removed under reduced pressure by rotary evaporation and the obtained yellow powder was suspended in 100 mL of warm methanol (40° C) under constant stirring in order to remove the excess benzidine and the side products formed. The resulting precipitate was re-suspended in 100 mL of dry methanol and was sonicated for 20 min at 40° C. The resulting mixture was filtered and the cake was washed with 20 mL water and 100 mL of methanol consecutively. The resulting bright magenta powder was dried under high vacuum. (Yield = 85 %). The solid was used for encapsulation studies without further purification (HPLC chromatogram confirmed the purity of the expanded covalent capsule **3**). ^{1}H NMR (600 MHz, THF-*d8*) δ (ppm): 0.88 (24H, t, J=7 Hz), 1.2-1.4 (144H, m), 5.8 (t, 8H, J=7 Hz), 6.75 (s, 4H), 7.3 (s, 8H), 7.8 (s, 4H), 7.9 (s, 16H), 8.1 (s, 8H), 8.3 (s, 16H), 14 (s, NH). ^{13}C NMR (600 MHz, THF-*d8*) δ (ppm): 154.7, 149.8, 148.6, 138.9, 134, 133.6, 130.5, 121.6, 115.4, 112.4, 105.2, 31.9, 30.8, 28.4, 28.3, 28, 26.7, 23.3, 21.2, 15.1, 12.1.

^{1}H NMR of expanded capsule 3 in THF-d$_8$ in the presence of D$_2$O



References:

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[i] Rudkevich, Dmitry M.; Hilmersson, Goeran; Rebek, Julius Jr. **Self-Folding Cavitands,** *Journal of the American Chemical Society* (1998), 120(47), 12216-12225.

[ii] Lei Zhang, Bruce N. Rogers, Allen J. Duplantier, Stanley F. McHardy, Ivan Efremov, Helen Berke,Weimin Qian, Andy Q. Zhang, Noha Maklad, John Candler, Angela C. Doran, John T. Lazzaro Jr., Alan H. Ganong. **3-(Imidazolylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl)methyl ethers: A novel series of mGluR2 positive allosteric modulators.** *Bioorganic&Medicinal Chemistry Letters* (2008), 18, (20), 5493-5496.