Supplementary Information for

Covalent Capsules: Reversible Binding in a Chiral Space

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General Information

All reactions were carried out under an atmosphere of argon unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz respectively, using a Bruker DRX-600 spectrometer equipped with a 5 mm QNP probe. Chemical shifts of ^{1}H 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 were used as received. All reagents were obtained from commercial suppliers and used without further purification. NMR spectra were recorded on a Bruker DRX-600 spectrometer. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc and used without further purification.

Materials and Methods

Synthesis of Tetra 2-(Diethoxymethyl)-1H-Benzo-[d] Imidazole Cavitand (5)

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 %). ^{1}H 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 Covalent Capsule 1

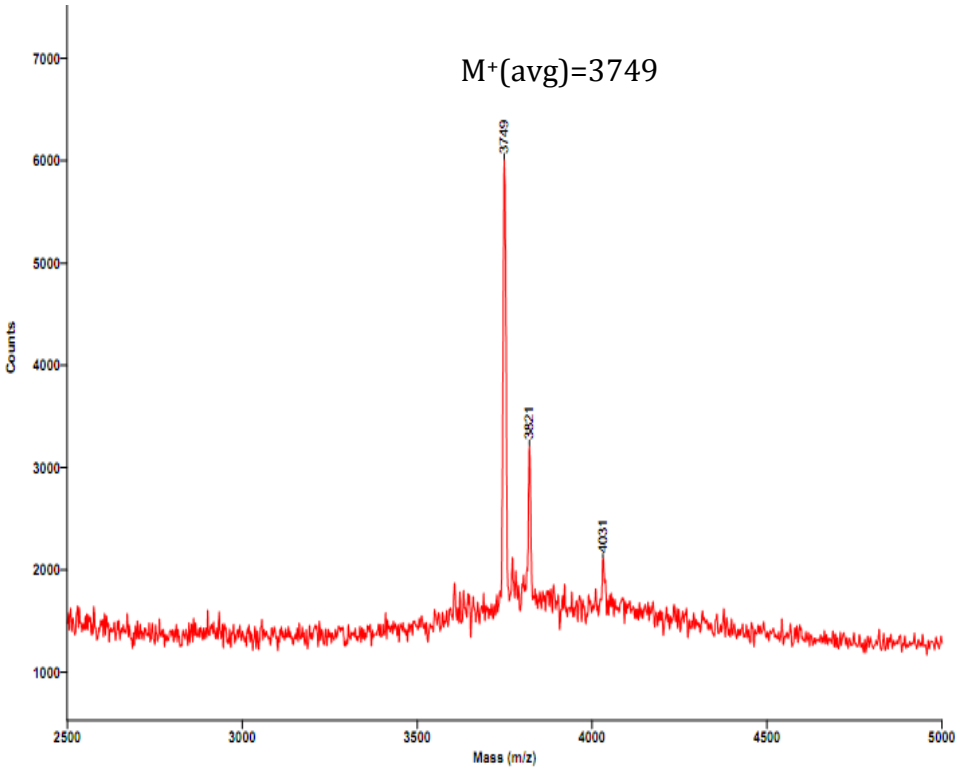
Cavitand **4** (0.985 gr, 0.5 mmol, 1eq) was added to a solution of 2,5-dimethyl-1,4-phenylenediamine (0.816 gr, 6 mmol, 12 eq) and trifluoroacetic acid (TFA) (2 mL) in 100 mL of degassed and dry chloroform. The mixture was placed inside a sealed tube under nitrogen atmosphere. The mixture then was heated to 110 °C for 24 hours. After cooling to room temperature, 3 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 2,5-dimethyl-1,4-phenylenediamine and the formed side products. 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 = 92 %). The solid was used for encapsulation studies with no further purification (HPLC chromatogram confirmed the purity of the covalent capsule **1**). ^{1}H NMR (600 MHz, THF-*d8*)δ (ppm): 0.88 (24H, t, J=7 Hz), 1.2-1.4 (144H, m), 3.4 (s, 24H), 5.7 (t, 8H, J=7 Hz), 6.75 (s, 4H), 7.3 (s, 8H), 7.8 (s, 4H), 7.9 (s, 8H), 8.1 (s, 8H), 8.3 (s, 8H). ^{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: $[M + H]^+$, 3749 $C_{240}H_{272}N_{24}O_{16}$ required 3748.87.

General procedure for the encapsulation studies

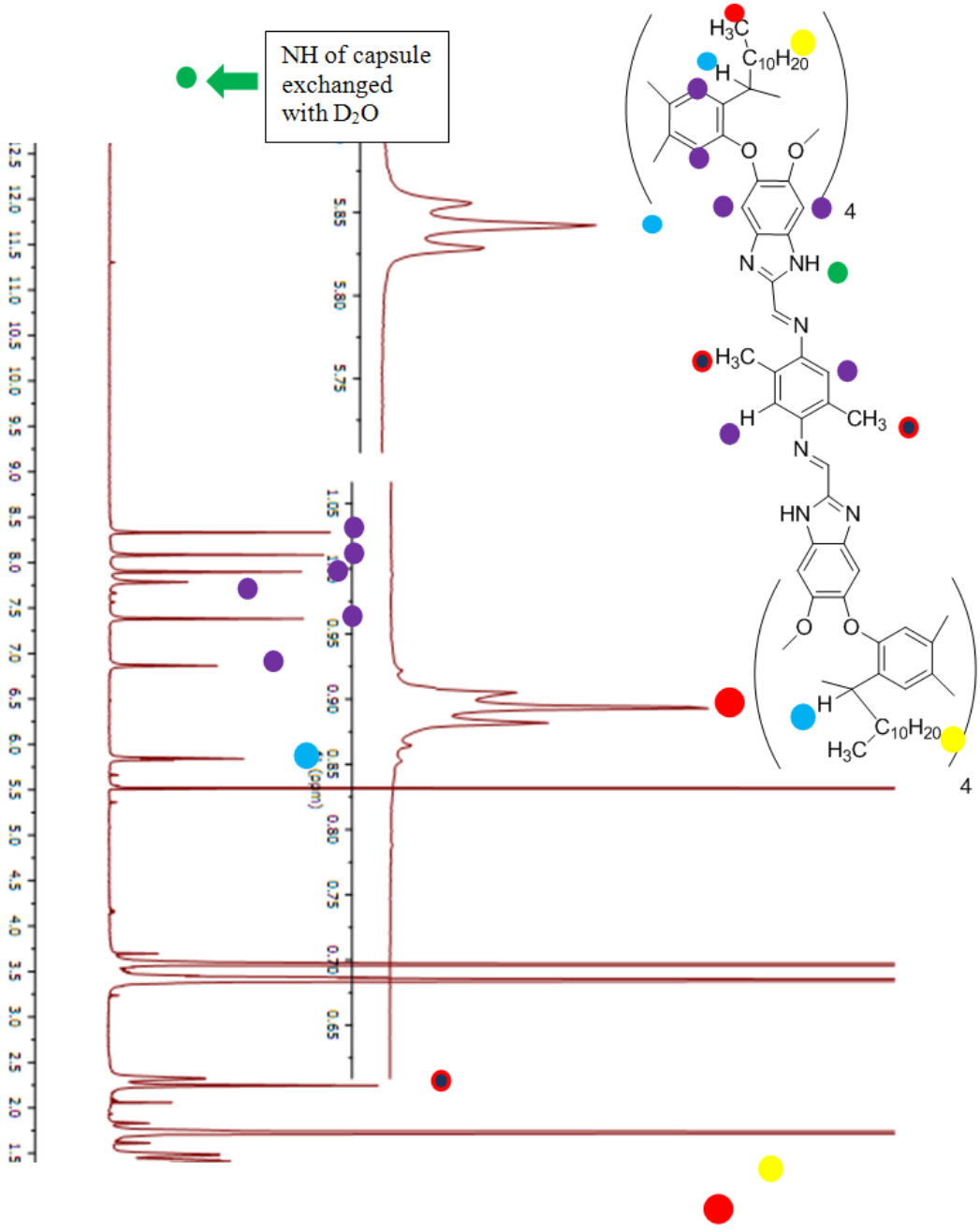
To a mixture of covalent capsule **1** (3.0 mg, 0.0008 mmol), and the corresponding guest (4 to 8 eq.) in a NMR-tube was added 0.40 mL of CS_2 (In the case of NMR studies using CS_2, an internal coaxial capillary tube containing deuterated chloroform was used as an internal standard) , 1,3,5-trimethylbenzene-d_{12}, DMF-d_7 or benzene-d_6 . To the sample was added up to 20 microliters of MeOH (in the case of CS_2, 1,3,5-trimethylbenzene-d_{12}, and benzene-d_6) or 5 microliters of H_2O or D_2O in the case of DMF-d_7 . The spectra were recorded 25 °C instantly.

MALDI-TOF Mass Spectrum of the Schiff based Assembled covalent capsule 1

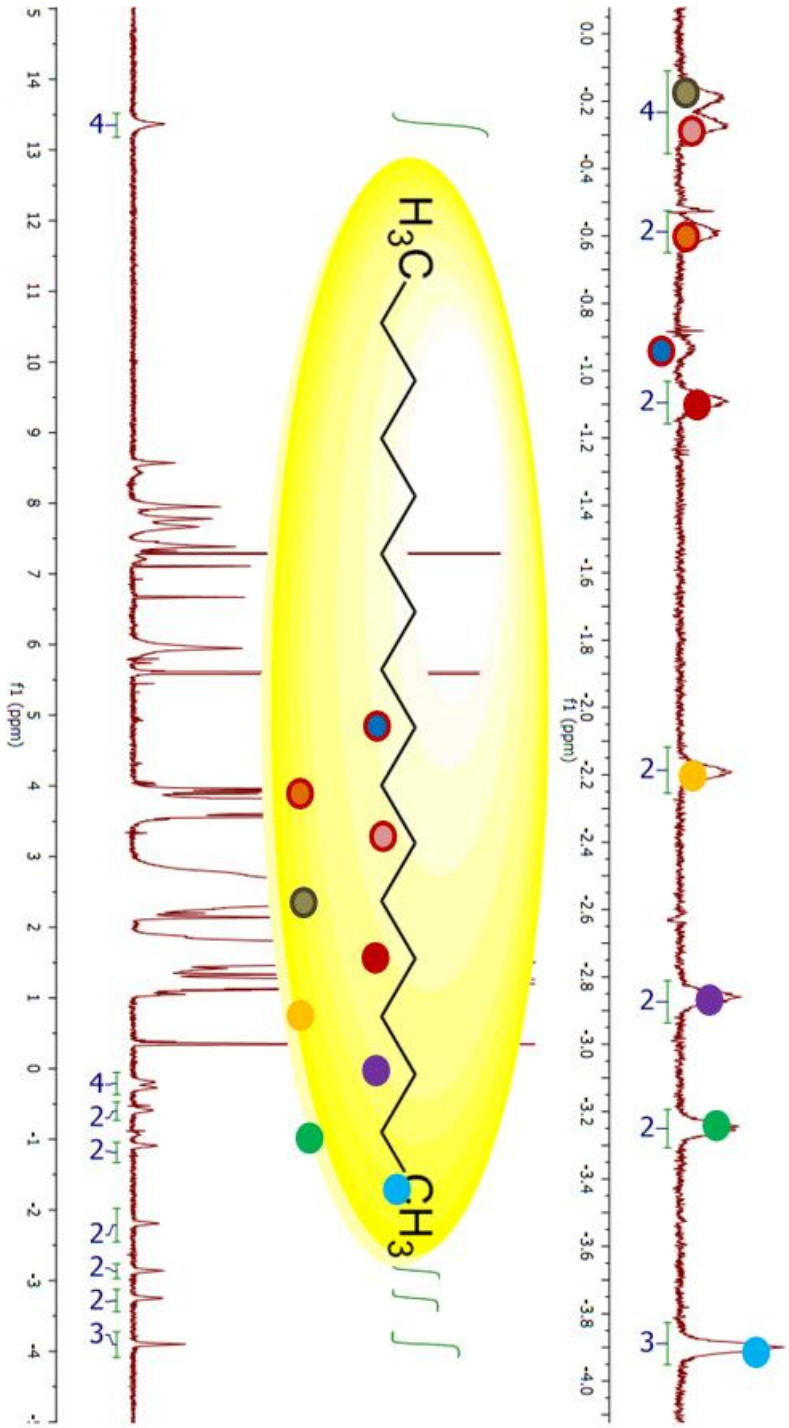
Chemical Formula:
$C_{240}H_{272}N_{24}O_{16}$



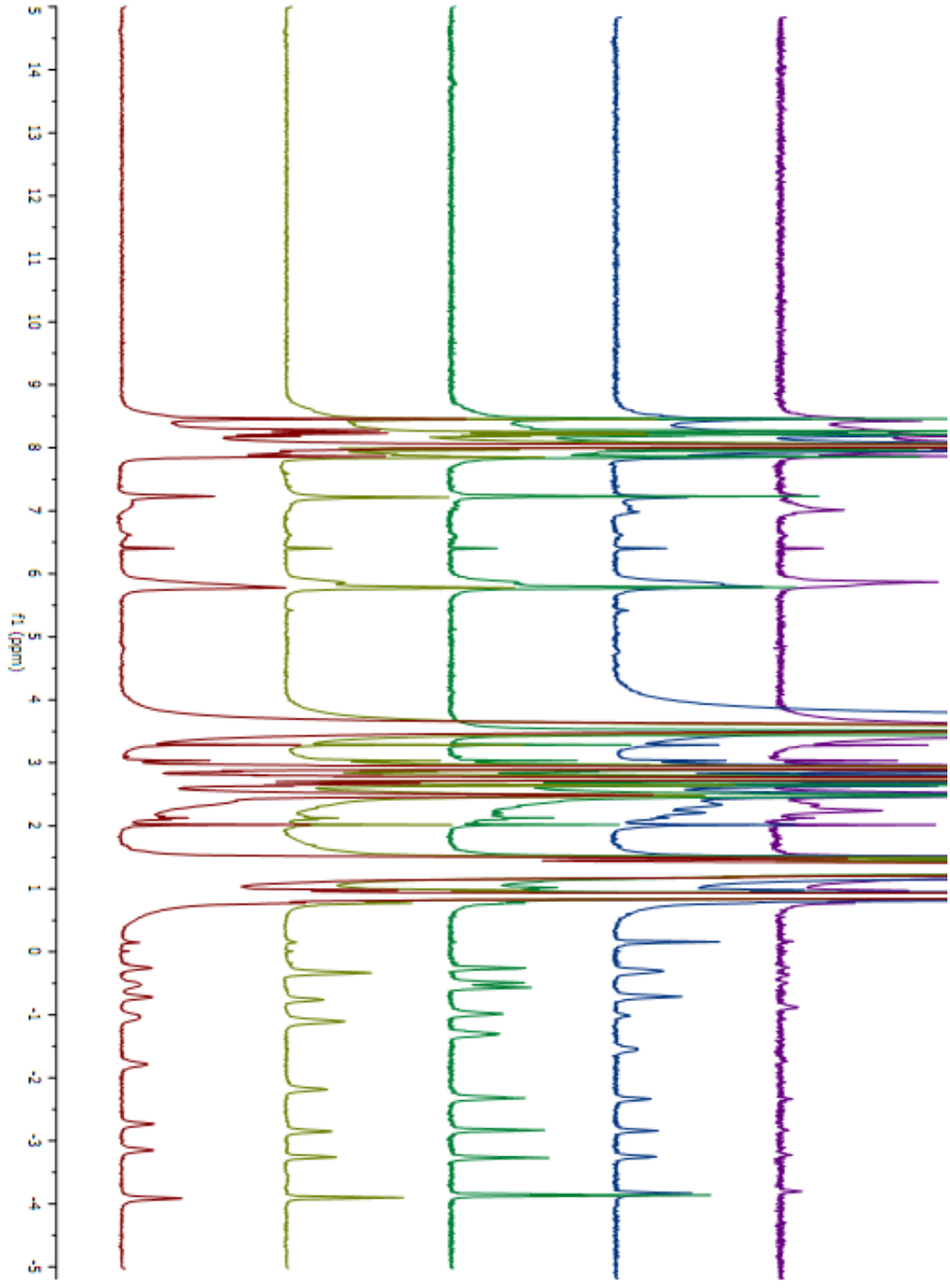
^{1}H NMR Spectra (600 MHz, 300K) of covalent capsule 1 in THF-d_8 in the presence of 2 uL of D_2O



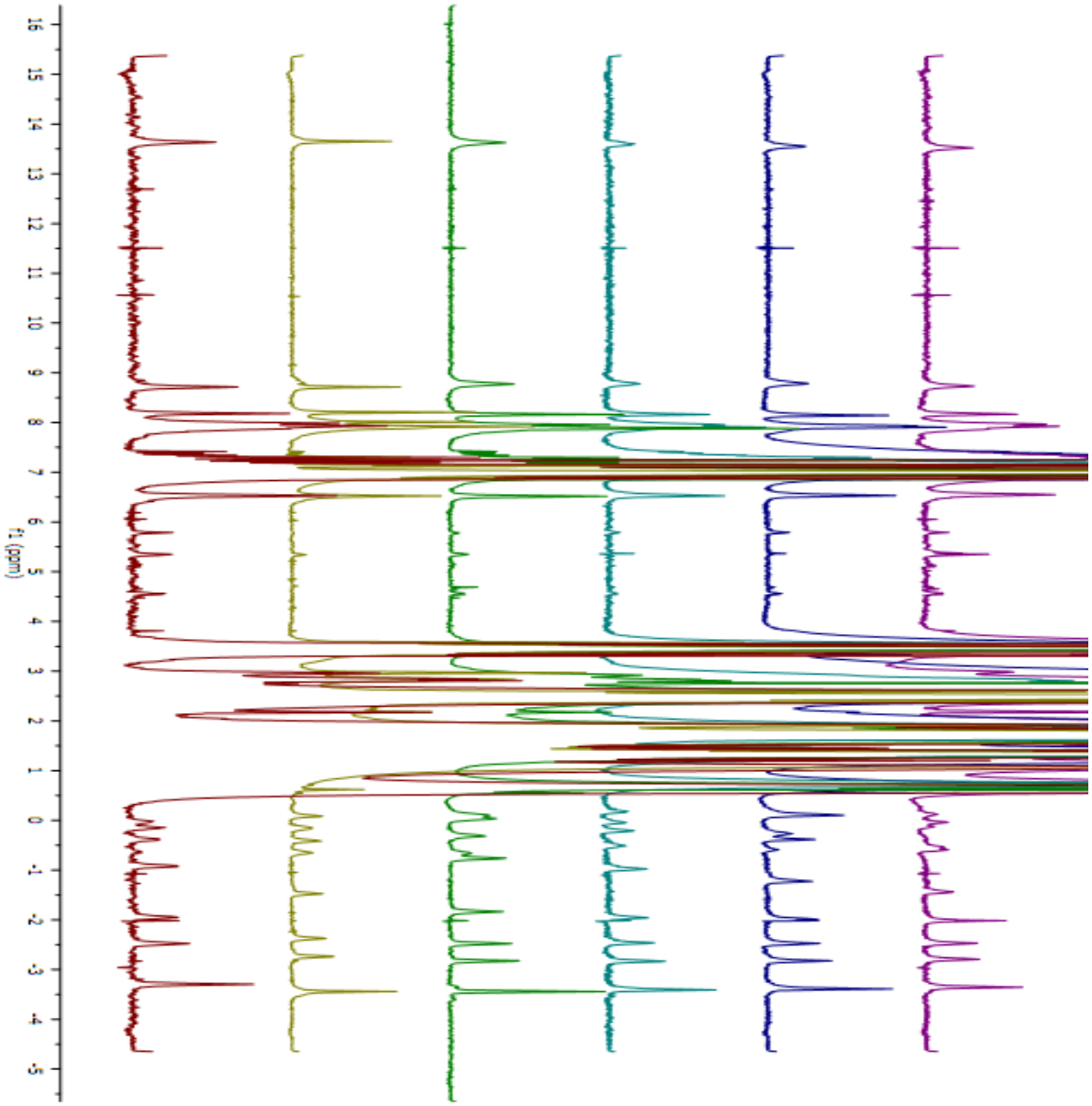
^{1}H NMR Spectra (600 MHz, 300K) of heptadecane encapsulated in covalent capsule 1 in CS_2, in the presence of 5% v/v of D_2O



^{1}H NMR Spectra (600 MHz, 300K) of normal alkanes in 1, using $(CD_3)_2NCO$ D with added 5% v/v D_2O as solvent at ambient temperature

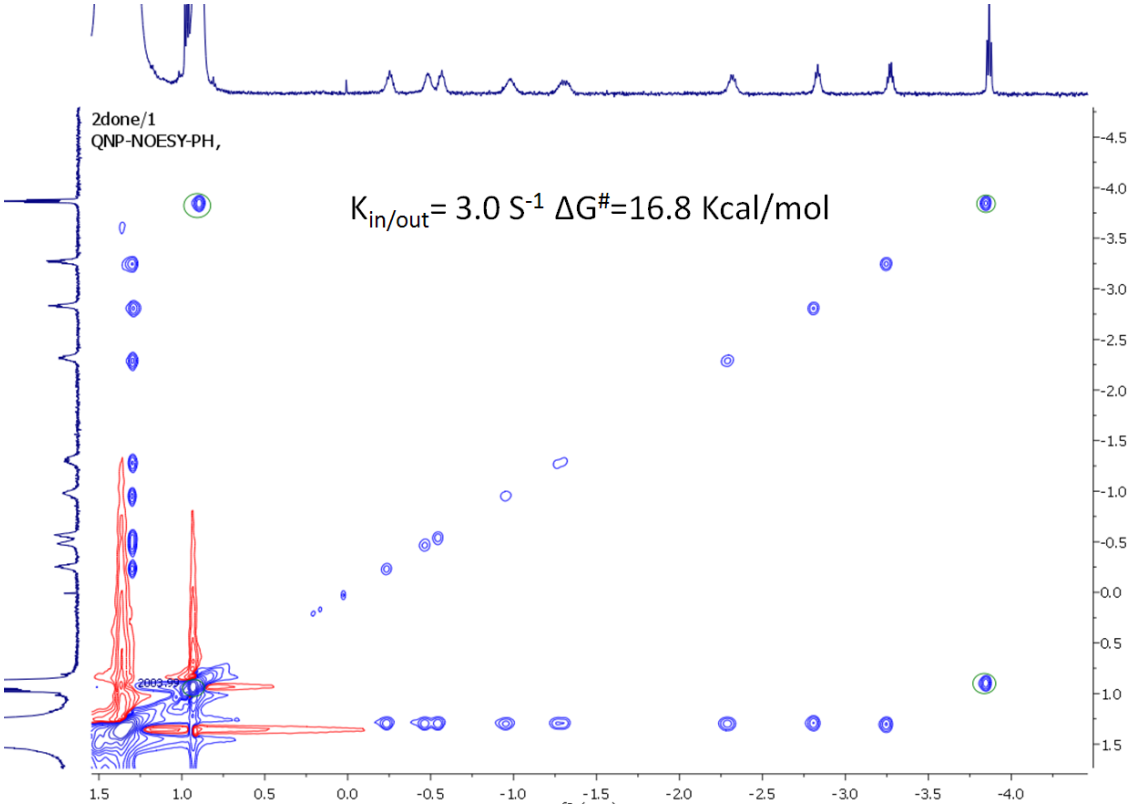


^{1}H NMR Spectra (600 MHz, 300K) of normal alkanes in 1, using mesitylene-d$_{12}$ with added 5% (v/v) MeOH-*d4* as solvent at ambient temp

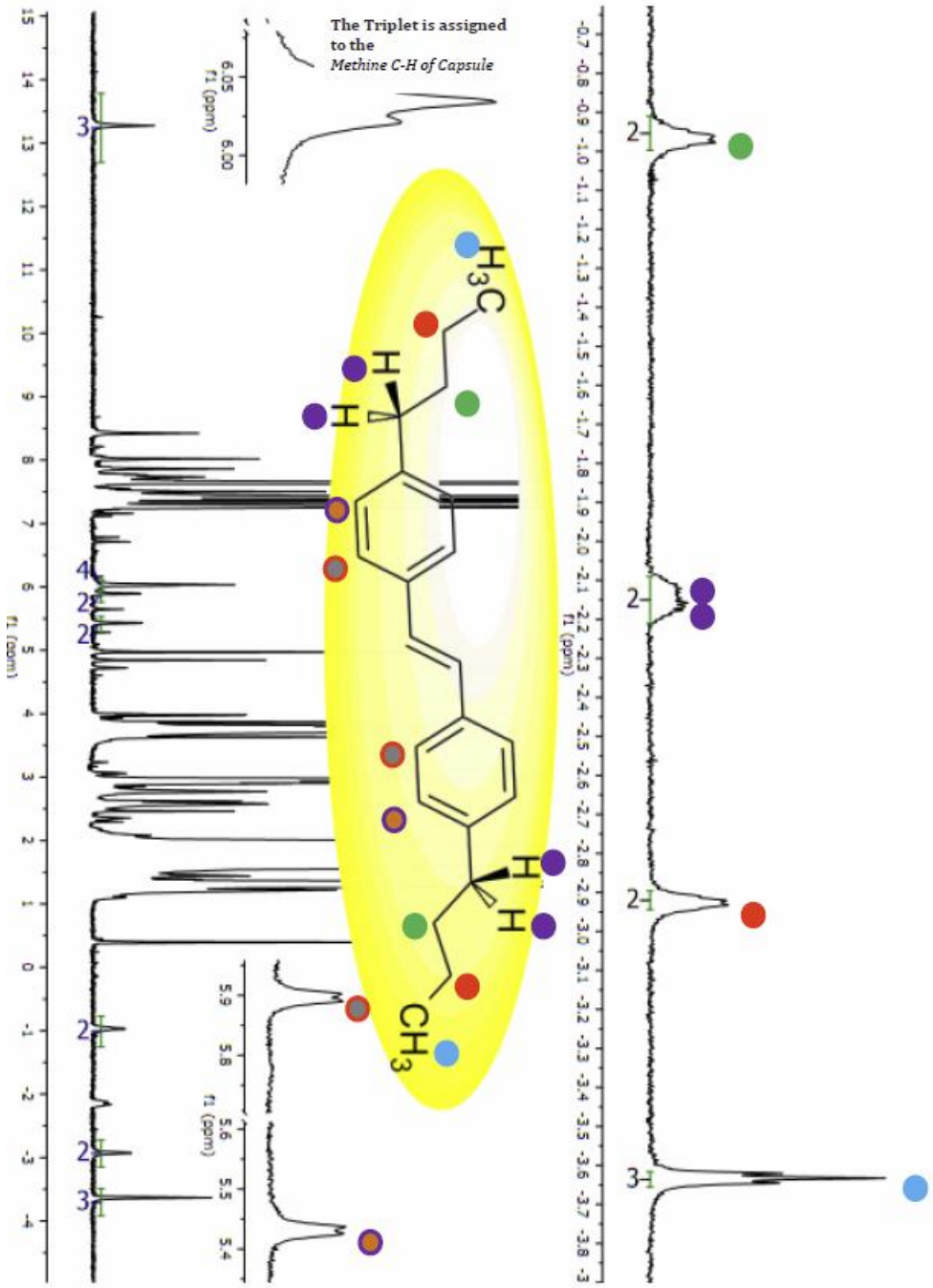


***n*-$C_{15}H_{32}$** ***n*-$C_{16}H_{34}$** ***n*-$C_{17}H_{36}$** ***n*-$C_{18}H_{38}$** ***n*-$C_{19}H_{40}$** ***n*-$C_{20}H_{42}$**

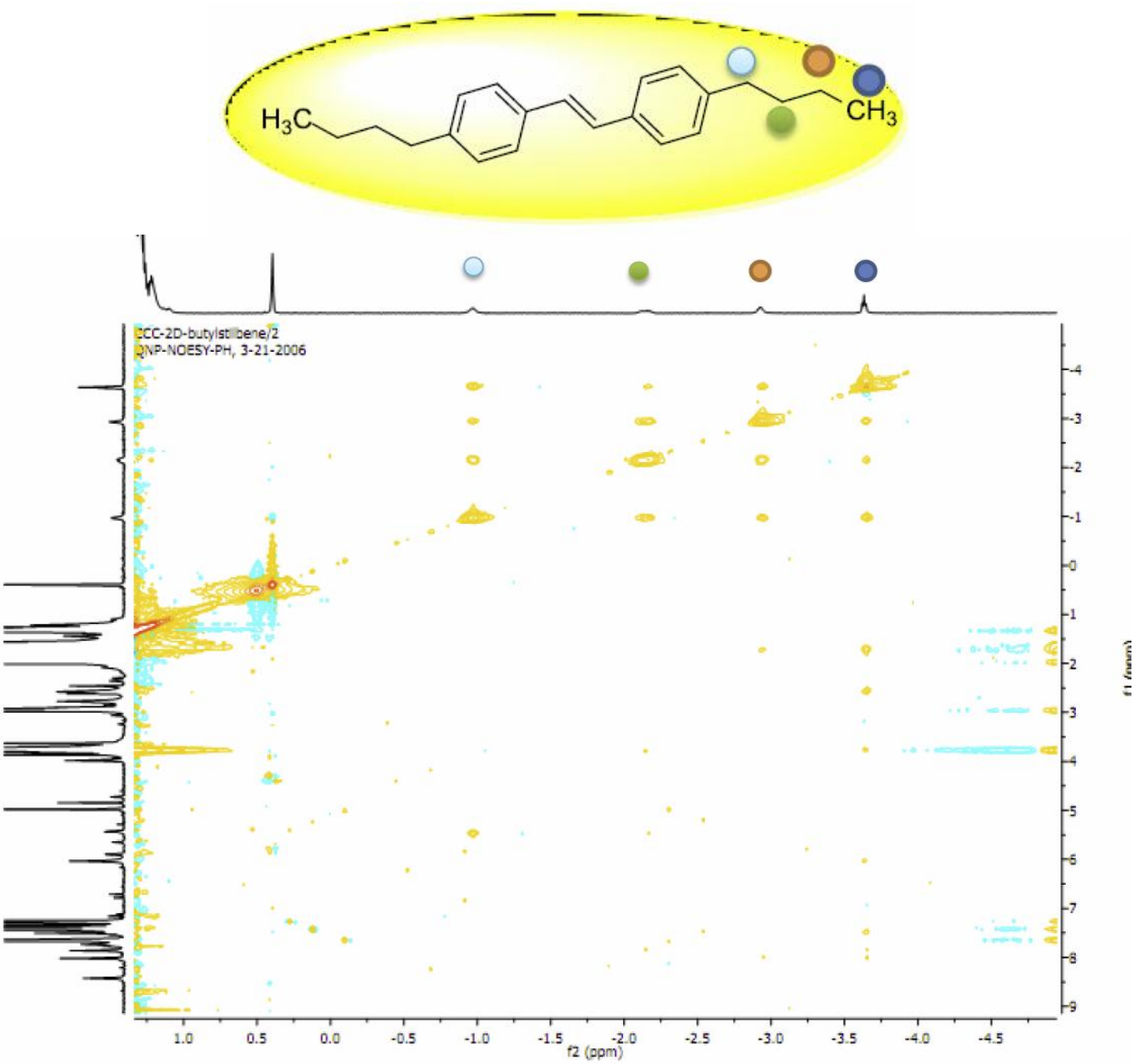
2D EXSY spectrum of encapsulated Octadecane n-$C_{18}H_{38}$ in Covalent Capsule 1 (600 MHz, CS2,300 K in the presence of 5% (v/v) of MeOH-*d4*)



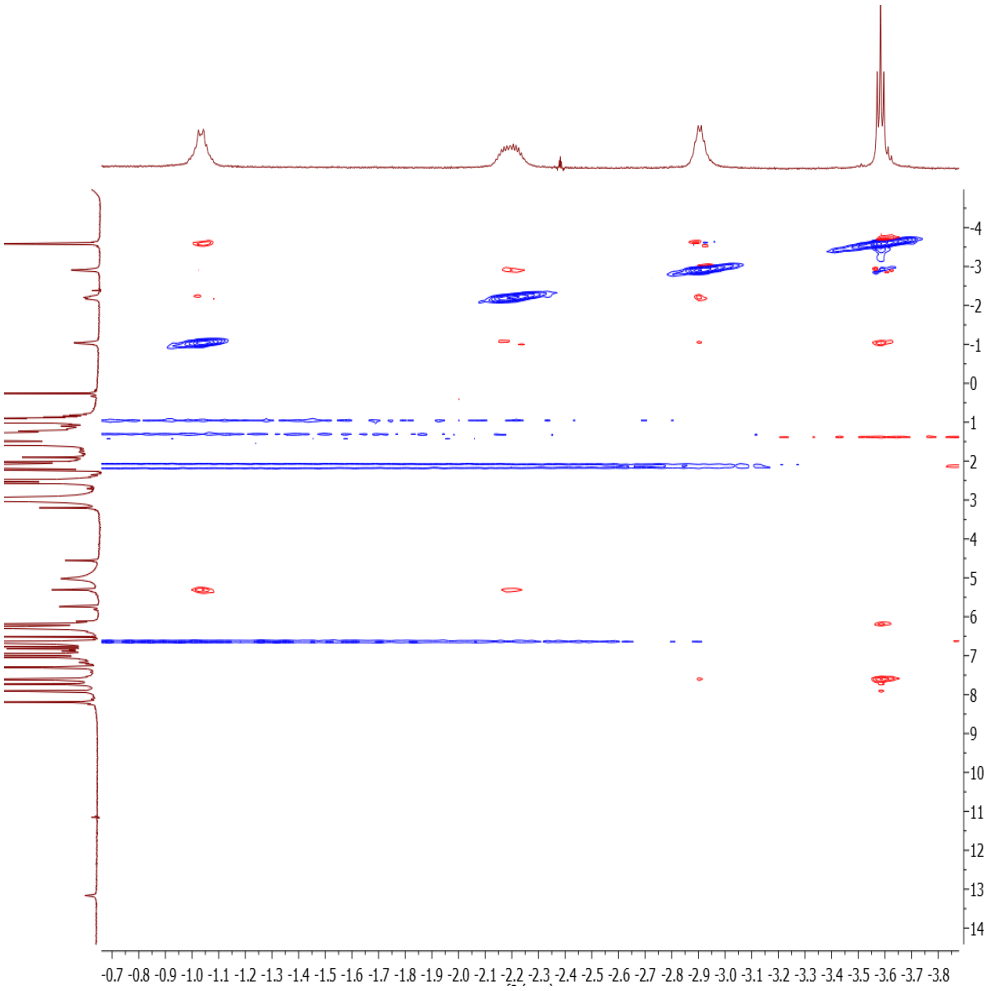
^{1}H NMR Spectra (600 MHz, 300K) (E)-1,2-bis(4-butylphenyl)ethene Encapsulation in Covalent Capsule 1 (CS_2, in the presence of 5% (v/v) of MeOH-*d4*)



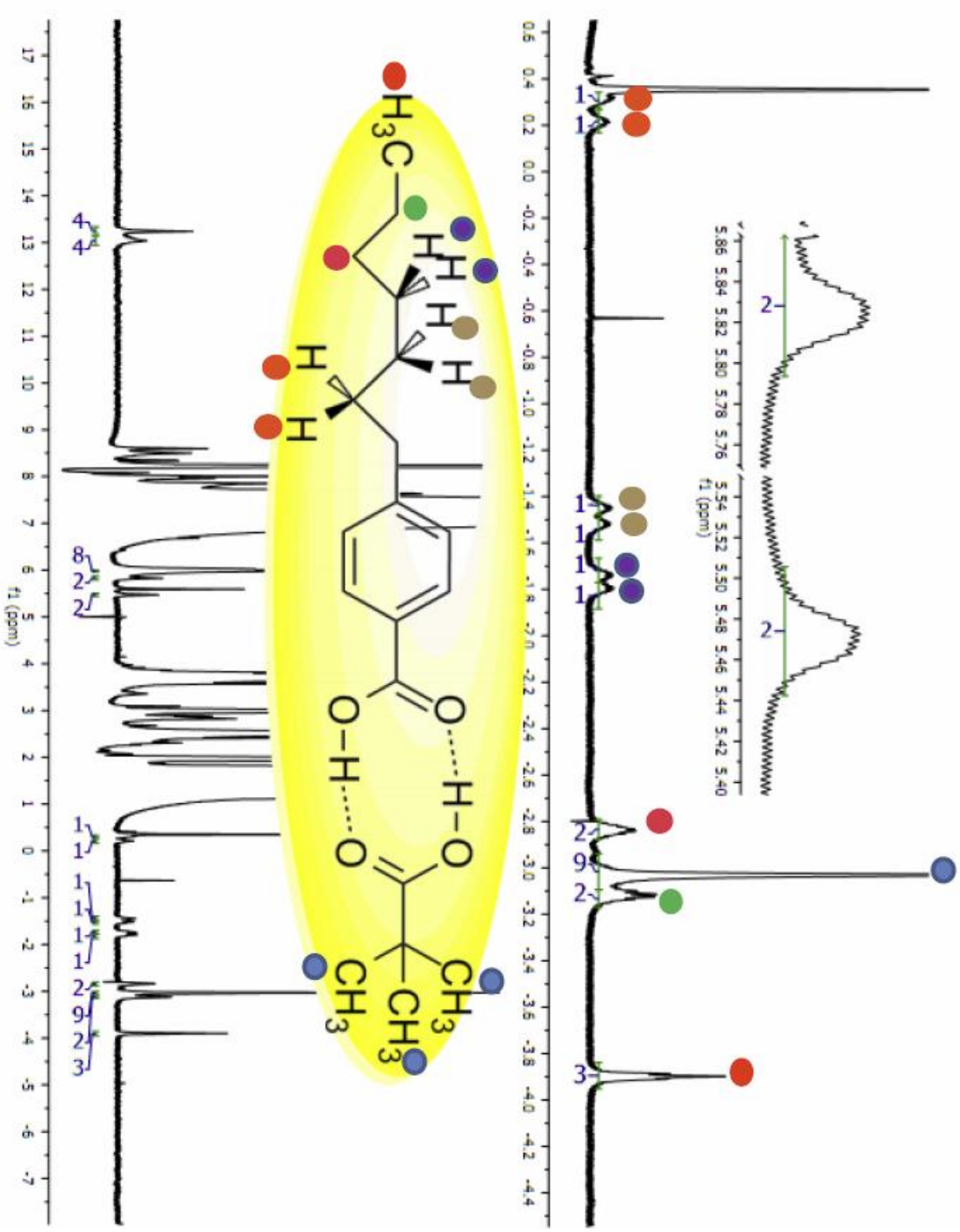
2D-NOESY Spectrum of Encapsulated p,p'-Dibutyl stilbene in Covalent Capsule, (600 MHz, CS2, 300K in the presence of 5% (v/v) of MeOH-*d4*)



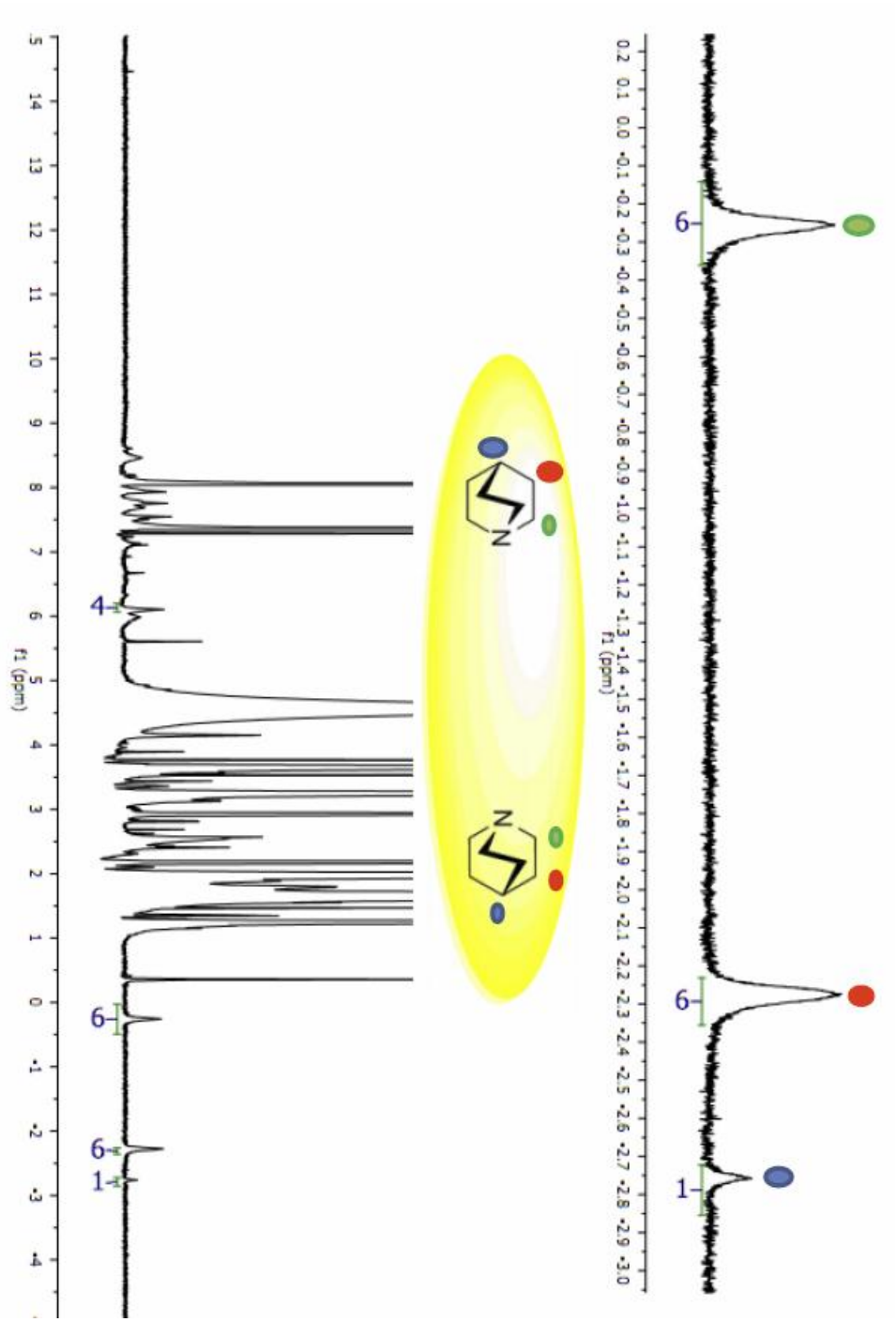
2D-ROESY Spectrum of Encapsulated p,p'-Dibutyl stilbene in Covalent Capsule, (600 MHz, Mesitylene-*d12*, 300K in the presence of 5% v/v of MeOH-*d4*)



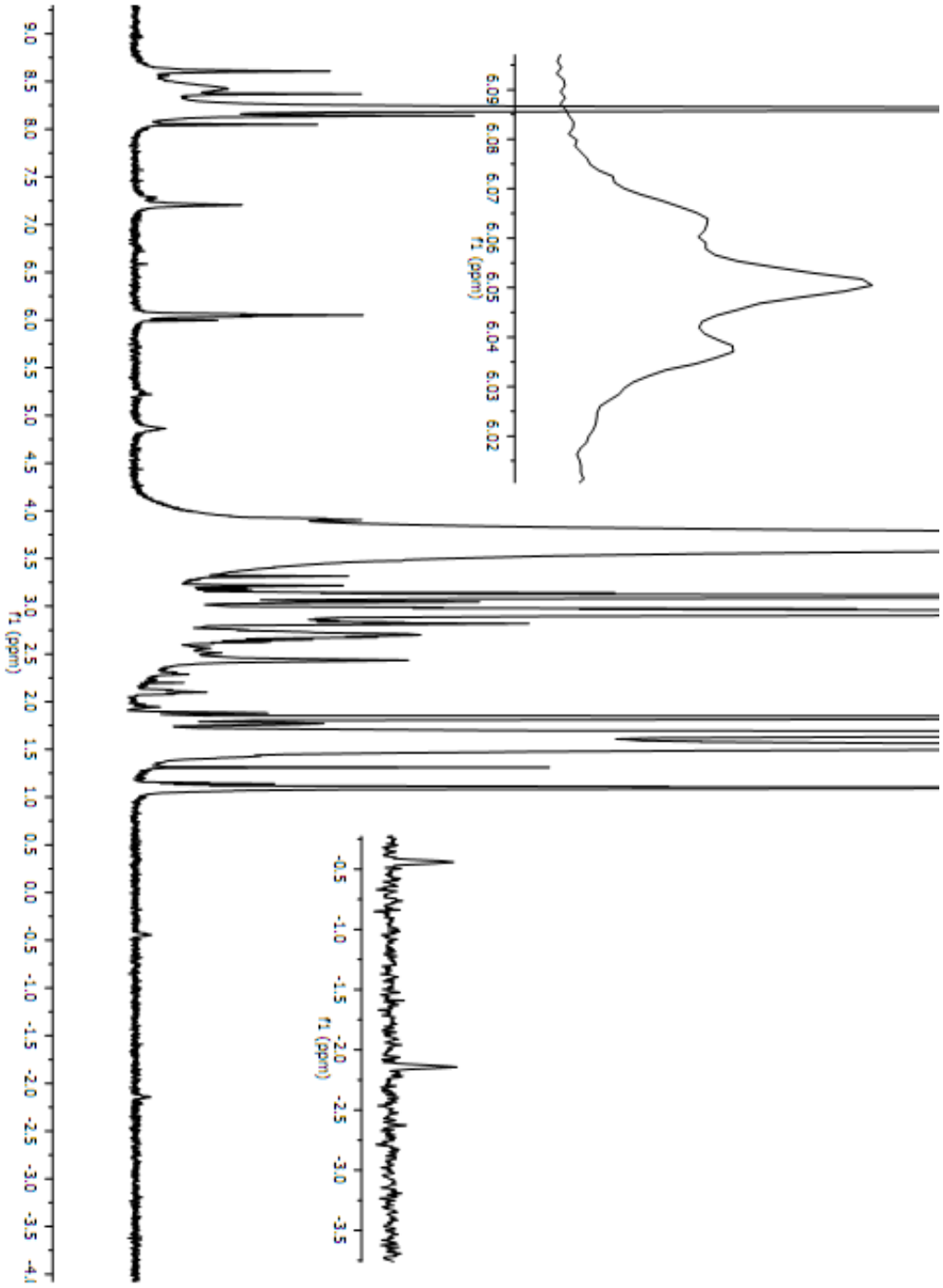
Heteromolecular H-Bonding; p-Heptyl Benzoic acid and Trimethyacetic acid Dimer in Covalent Capsule 1 (^{1}H NMR 600 MHz 300K, , CS_2, in the presence of 5% v/v of MeOH-*d4*)



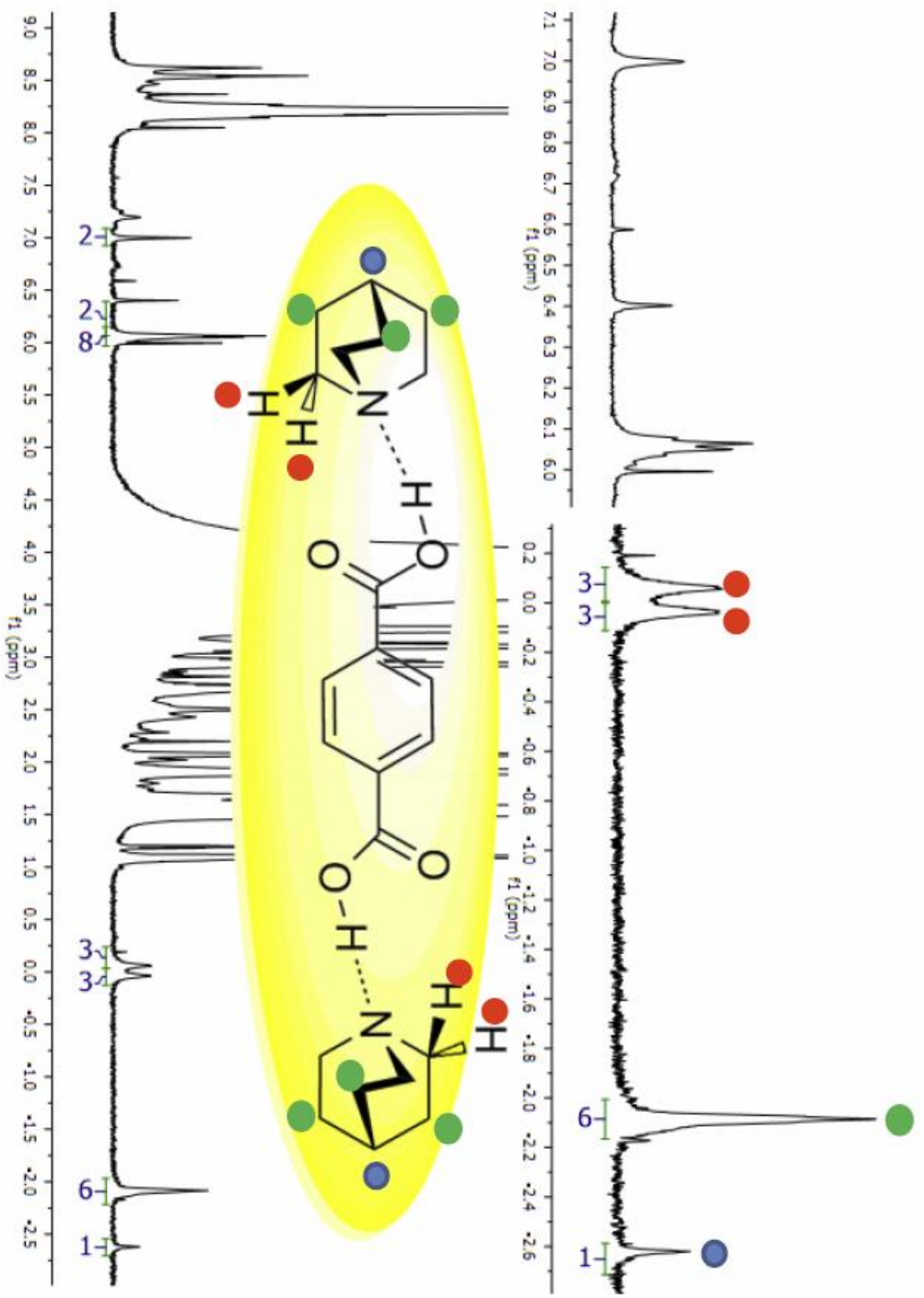
Quinuclidine Encapsulation in 1 (^{1}H NMR 600 MHz 300K, CS_2, in the presence of 5% v/v of MeOH-*d4*)



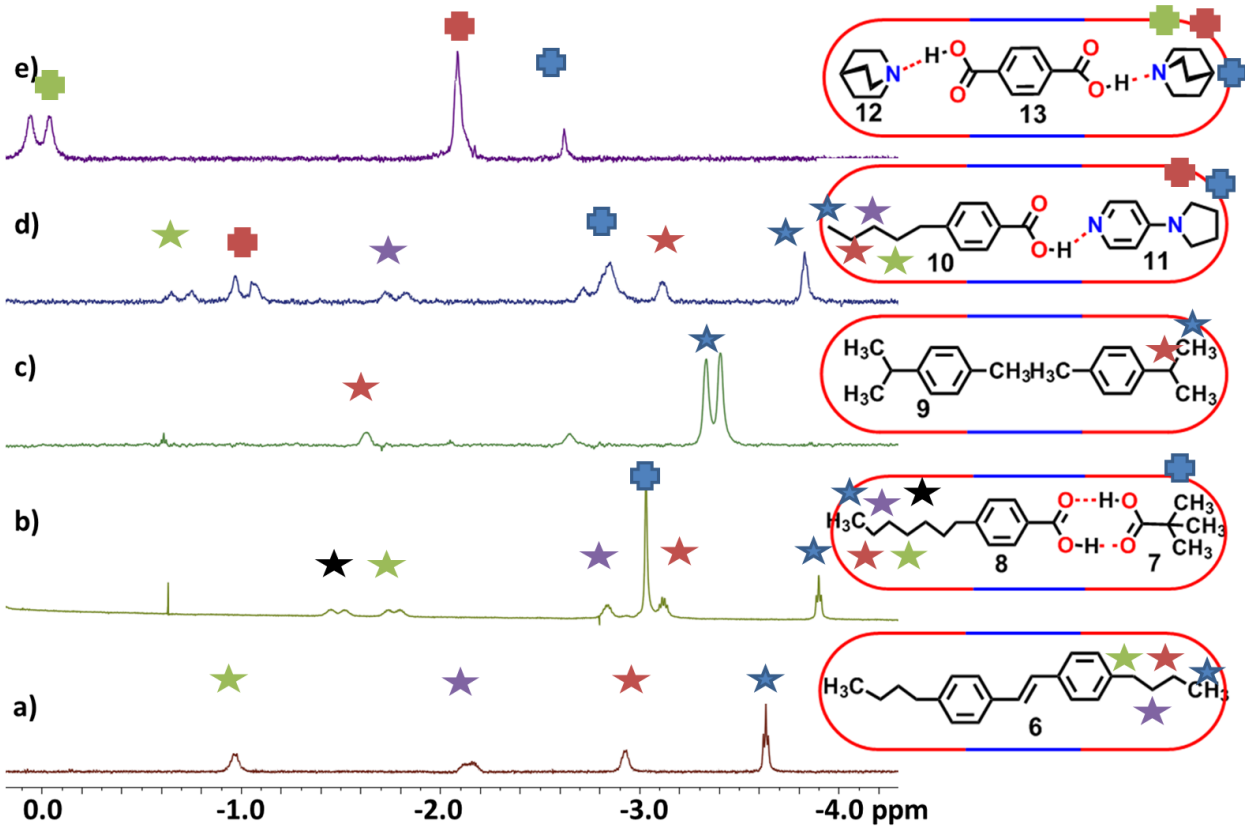
Termolecular Encapsulation; Very weak Encapsulation of Quinuclidine before addition of Terephthalic acid in Covalent Capsule 1 (^{1}H NMR 600 MHz 300K, DMF-d_7, in the presence of 5% v/v of MeOH-*d4*)



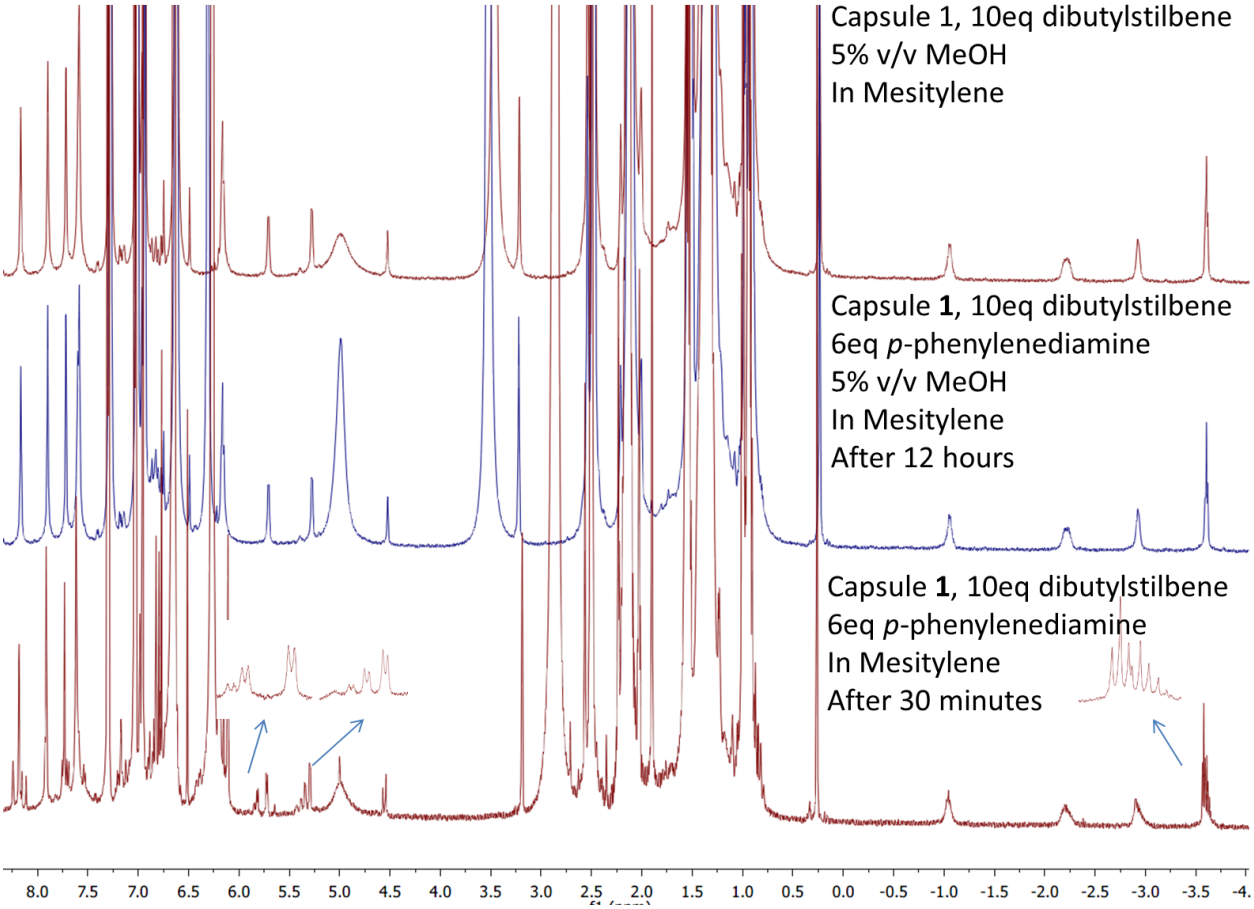
Termolecular Encapsulation; Quinuclidine and Terephthalic acid complex in Covalent Capsule 1 (^{1}H NMR 600 MHz 300K, DMF-d_7, in the presence of 5% v/v of MeOH-*d4*)



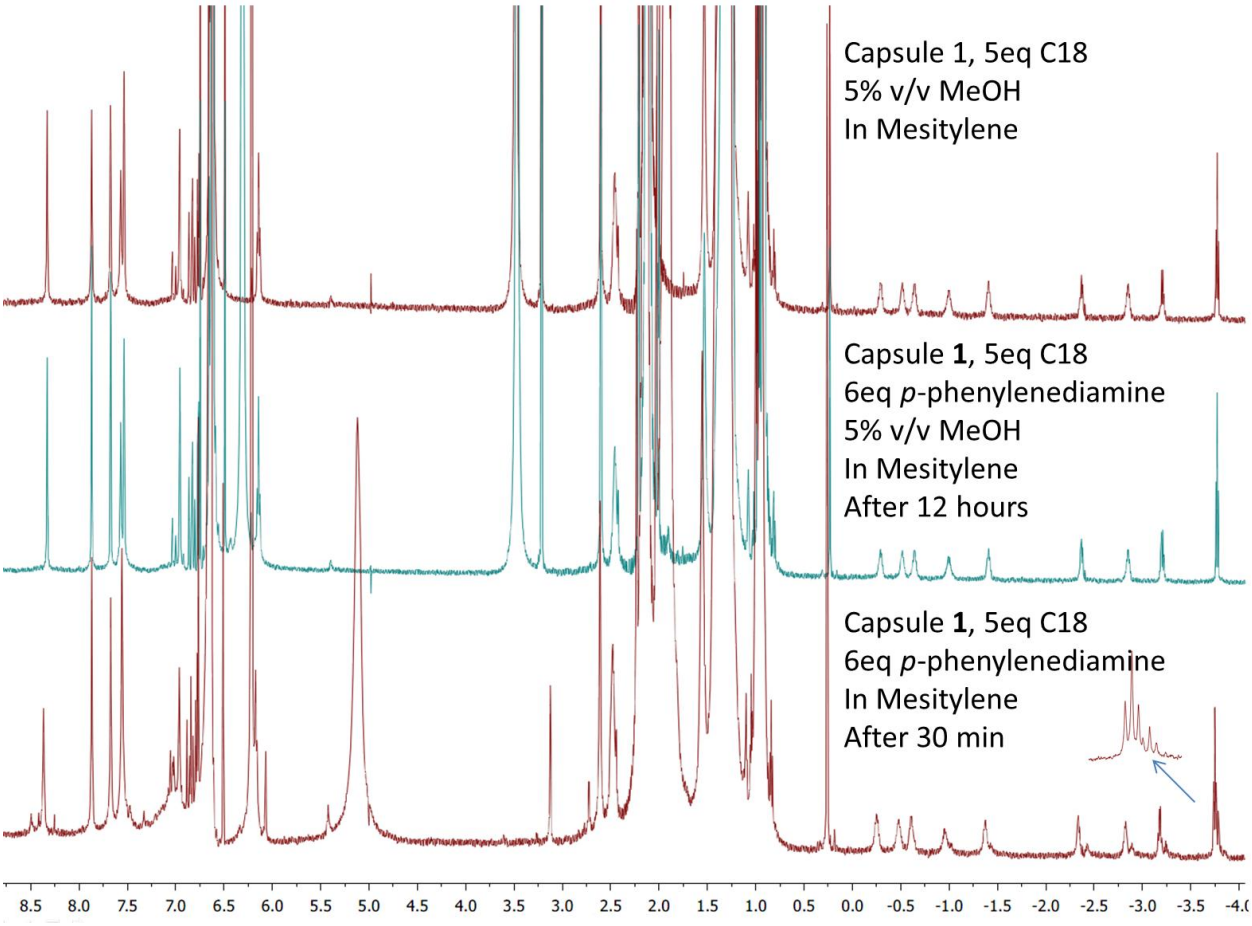
Proton signals assignments of Figure 4.



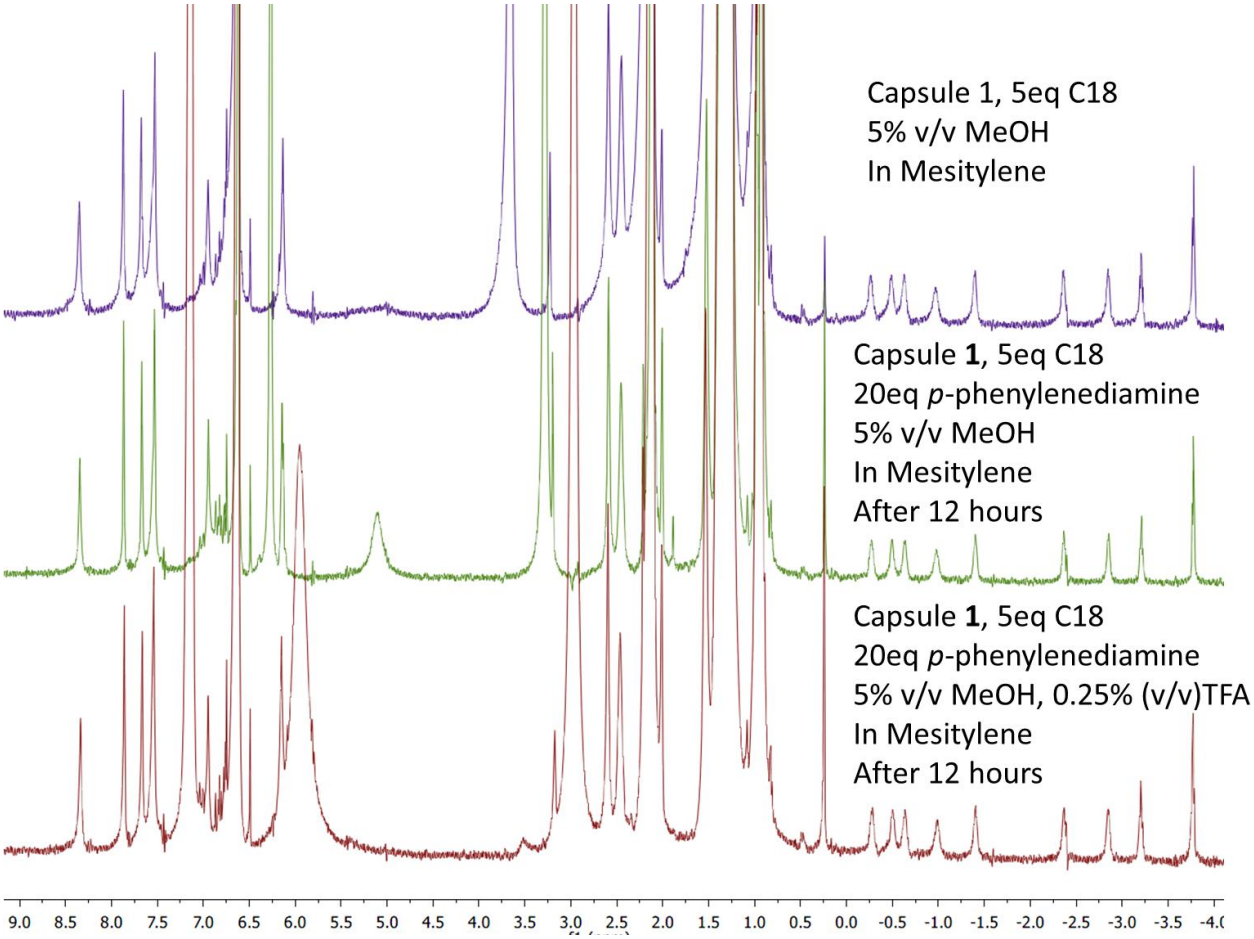
^{1}H NMR Spectra (600 MHz, 300K) p,p'-Dibutyl stilbene encapsulation in covalent Capsule 1 in Mesitylene-*d12* in presence or abscense of MeOH-*d4* or p-phenylenediamine.



^{1}H NMR Spectra (600 MHz, 300K) of *n*-Octadecane (C18) encapsulated in covalent Capsule 1 in Mesitylene-*d12* in presence or abscense of MeOH-*d4* or p-phenylenediamine.



^{1}H NMR Spectra (600 MHz, 300K) of *n*-Octadecane (C18) encapsulated in covalent Capsule 1 in Mesitylene-*d12* in presence of 5% v/v MeOH-*d4* with added *p*-phenylenediamine and TFA 1%(v/v).



References:

[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.