SUPPORTING INFORMATION

A pH-Switch in Supramolecular Polymeric Capsules

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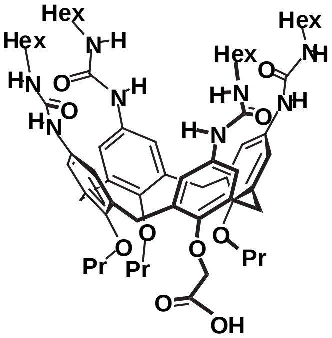
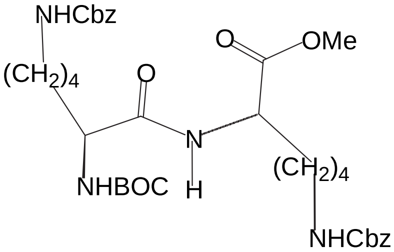
General. ^1H and ^{13}C NMR spectra were recorded at 295 ± 1 ^{O}C on JEOL Eclipse 500 MHz spectrometer. Chemical shifts were measured relative to residual non-deuterated solvent resonances. FTIR spectra were recorded on a Bruker Vector 22 FTIR spectrometer. ESI-MS spectra were obtained on a Finnigan LCQ Ion Trap apparatus. HRMS MALDI spectra were obtained on an IonSpec Ultima FTMS. Elemental analysis was performed on a Perkin-Elmer 2400 CHN analyzer. All experiments with moisture- and/or air-sensitive compounds were run under a dried nitrogen atmosphere. For column chromatography, Silica Gel 60 Å (Sorbent Technologies, Inc.; 200–425 mesh) was used. Parent tetrahydroxycalix[4]arene, other calixarene precursors, and model calix[4]arene tetraurea **4** were prepared according to the published procedures.[1-3] Molecular modeling was performed using commercial MacroModel 7.1 with MM2 Force Field.



Calix[4]arene Tetraurea Acid: A mixture of tetraurea ester (1.5g, 1.2 mmol), THF-H_2O, 5:1 (60 mL) and KOH (0.67g, 12.0mmol) was refluxed overnight, after which H_2O (60 mL) was added, and the pH was adjusted to 2 with aq 1 M HCl. The product was extracted with $CHCl_3$ (3 x 60 mL), the organic layer was dried over Na_2SO_4, evaporated and recrystallized from MeOH to give the tetraurea acid as a yellow powder (1.13 g, 80%). ^{1}H NMR (DMSO-d_6): δ 8.07 (s, 1 H), 8.03 (s, 1 H), 7.83 (s, 2 H), 6.87 (s, 4 H), 6.59 (s, 4 H), 5.88 (q, *J* =5.3 Hz, 2 H), 5.72 (t, *J* = 5.0 Hz, 2 H), 4.56 (s, 2 H), 4.43 (d, *J* = 12.6 Hz, 2 H), 4.27 (d, *J* = 12.6 Hz, 2 H), 3.76 (t, *J* = 7.8 Hz, 2 H), 3.69 (t, *J* = 7.8 Hz, 2 H), 3.67 (t, *J* = 7.8 Hz, 2 H), 3.01 (m, 8 H), 2.95 (m, 4 H), 1.95-1,75(m, 6 H), 1.5-1.1 (m, 32 H), 1.0-0.8 (m, 21 H); ^{13}C NMR (DMSO-d_6): δ 171.5, 155.8, 151.1, 150.4, 150.2, 135.6, 135.3, 135.1, 134.8, 134.3, 134.1, 118.7, 77.5, 77.2, 71.2, 31.7, 30.4, 30.3, 26.7, 23.1, 23.0, 22.7, 14.4, 10.8, 10.5; IR (KBr): ν 3376, 3333, 2961, 2931, 2858, 1761, 1654, 1558, 1478, 1213.



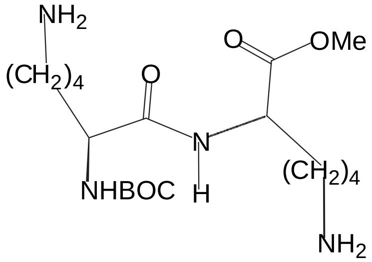
Dilysine, bis-ε-Cbz. To a stirred and ice cooled solution of *N*-ε-Cbz-*l*-lysine TFA salt (1.0 g, 2.45 mmol) in DMF (30 mL) was added Et_3N (0.34 mL, 2.45 mmol), and then after 15 min, successively acid *N*-α-BOC-*N*-ε-Cbz-*l*-lysine (0.93 g, 2.45 mmol), HOBT (0.66 g, 4.90 mmol), and DCC (1.01 g, 4.90 mmol). The mixture was allowed to stir for 30 min at 0°C and for 24 h at rt, then filtered, concentrated under reduced pressure, diluted with EtOAc (200 mL), and washed successively with 1N $NaHSO_4$ (4 x

50 mL), water (3 x 50 mL), 1N $NaHCO_3$ (4 x 50 mL), and again water (3 x 50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with THF-hexanes, 2:3 to afford the desired dipeptide (1.14 g, 71%). ^1H NMR (DMSO-d_6): δ 8.10 (d, *J* = 7.3 Hz, 1 H), 7.34 (m, 10 H), 7.22 (t, *J* = 5.5 Hz, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 4.99 (s, 4 H), 4.20 (m, 1 H), 3.90 (m, 1 H), 3.59 (s, 3 H), 2.96 (m,4 H), 1.32 (s, 9 H), 1.8-1.1 (4 m, 12 H);

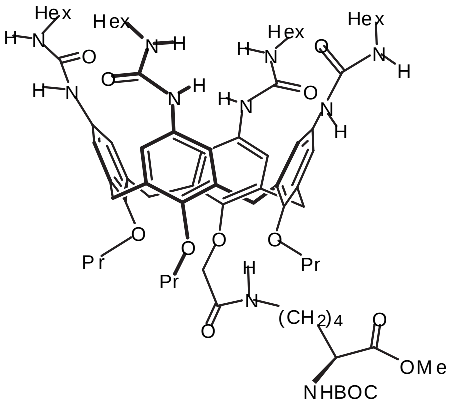
^{13}C NMR

($CDCl_3$):δ 172.8, 172.7, 156.8, 156.7, 156.0, 136.7, 136.6, 128.6, 128.57, 128.3, 128.2, 128.2, 80.1, 66.8, 66.7, 54.1, 52.4, 52.1, 40.5, 32.2, 31.6, . 29.4, 29.2, 28.4, 22.6, 22.3;

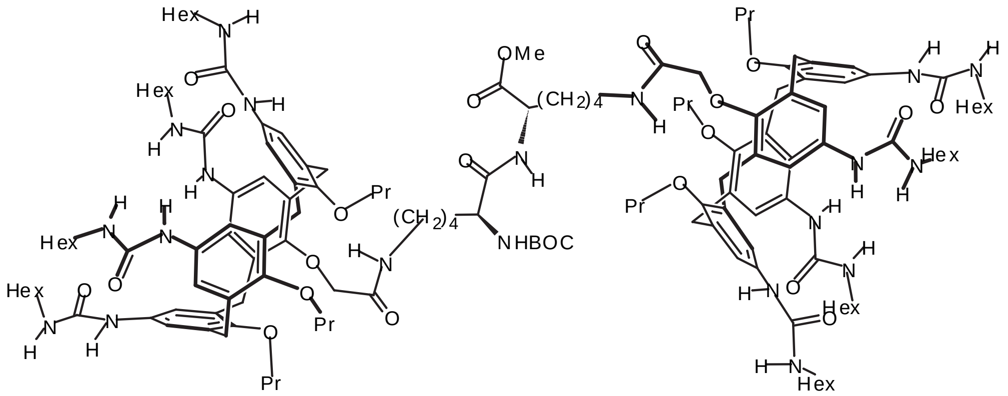
IR (KBr): ν 3359, 3036, 2948, 1699, 1544, 1259.



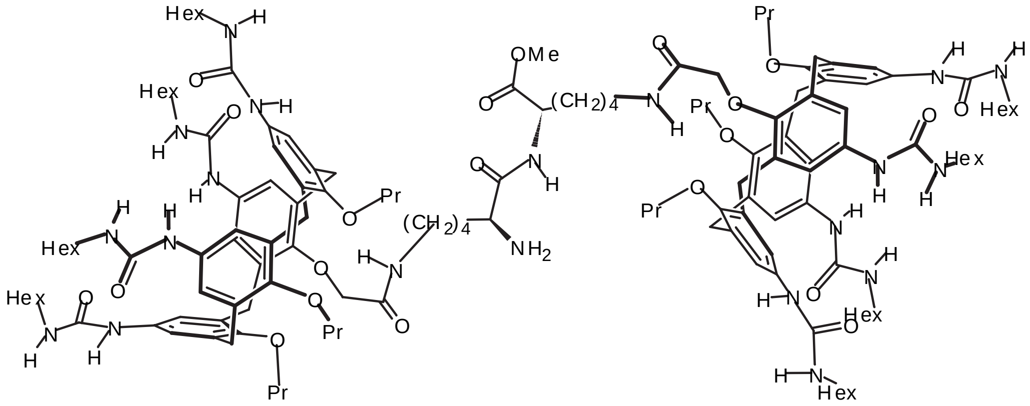
Dilysine. A solution of the Cbz-protected dipeptide (0.2 g, 0.30 mmol) in CH_3OH (10 mL) was treated with 10% Pd/C (20 mg) and stirred under a hydrogen atmosphere for 6 h. The mixture was filtered through Celite and concentrated under reduced pressure to give the product (0.11 g, 94%) as an oil: ^1H NMR (DMSO-d_6): δ 8.28 (d, *J* = 7.3 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 4.22 (m, 1 H), 3.93 (m, 1 H), 3.62 (s, 3 H), 2.72 (t, *J* = 7.1 Hz, 4 H), 1.36 (s, 9 H), 2.0-1.0 (m, 12 H); MALDI-TOF MS, *m/z* 388.8 (M^+, calcd for $C_{18}H_{36}N_4O_5$ 388.5).



N-α-BOC-N-ε-(Calix[4]arenetetraurea)-l-lysine, Methyl Ester (5). To an ice-cooled solution of *N*-α-BOC-*l*-lysine methyl ester (0.26 g, 1.0 mmol) in DMF (30 mL) was added calixtetraurea acid (1.19 g, 1.0 mmol), DCC (0.41 g, 2.0 mmol), and HOBt (0.27 g, 2.0 mmol). The mixture was allowed to stir for 30 min at 0°C and for 24 h at rt, filtered, concentrated, diluted with $CHCl_3$, and washed successively with 1N $NaHSO_4$(4 x 100 mL), water (3 x 100 mL), 1N $NaHCO_3$(4 x 100 mL) and again water (3 x 100 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$-CH_3OH, 95:5 to afford the calix[4]arene amino acid (1.0 g, 70%). ^{1}H NMR (DMSO-d_6): δ 8.21(t, *J* = 5.7 Hz, 1 H), 8.03 (s, 1 H), 7.99 (s, 1 H), 7.83 (s, 2 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 6.82 (s, 2 H), 6.81 (s, 2 H), 6.61 (s, 4 H), 5.85 (m, 2 H), 5.77 (t, *J* = 5.0 Hz, 2 H), 4.37 (d, *J* = 8.0 Hz, 2 H), 4.32 (d, *J* = 12.8 Hz, 2 H), 4.26 (d, *J* = 12.8 Hz, 2 H), 3.96 (m, 1 H), 3.76 (t, *J* = 7.3 Hz, 4 H), 3.71 (t, *J* = 7.3 Hz, 2 H), 3.61(s, 3 H), 3.23 (m, 2 H), 3.00 (m, 12 H), 1.37 (s, 9 H), 1.9-0.8 (6 m, 65 H); FTIR (KBr): ν 3332, 2930, 2859, 1654, 1559, 1474, 1219; MALDI-FTMS, *m/z* : 1419.9255 [$(M+H)^+$, calcd. for $C_{79}H_{123}N_{10}O_{13}$ 1419.9265]. Anal. Calcd. for $C_{79}H_{123}N_{10}O_{13}$: C, 66.83; H, 8.66; N, 9.86. Found: C, 66.44, H, 8.76, N, 9.67.

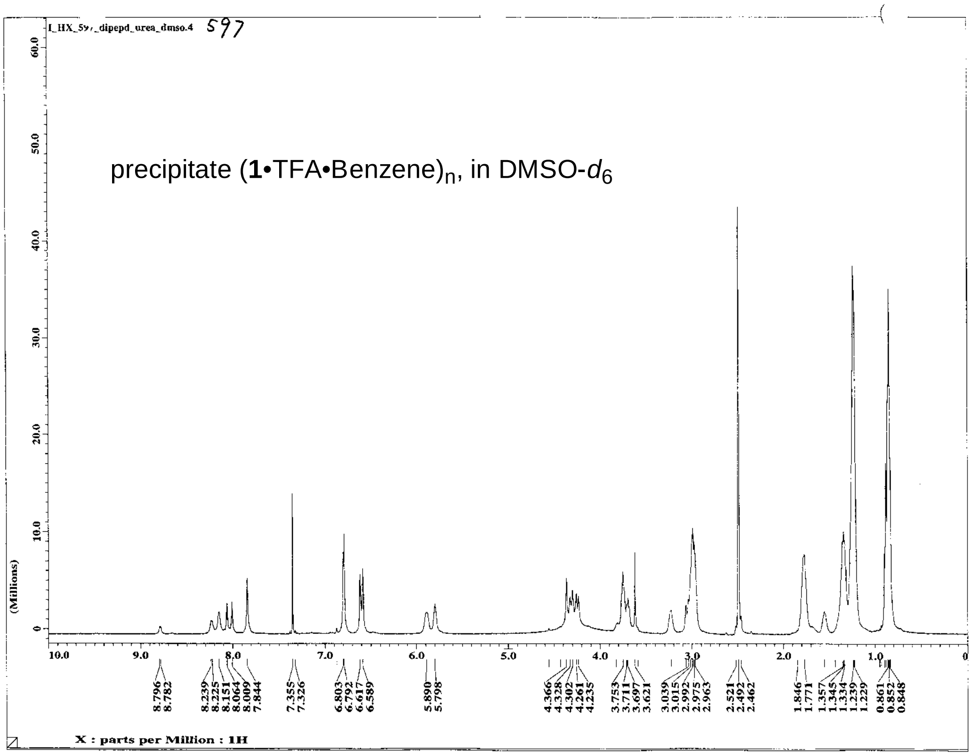


Dipeptide (1), *N*-α-BOC-protected. To an ice cooled solution of dilysine (0.16 g, 0.42 mmol) in DMF (30 mL) was added calixtetraurea acid (1.0 g, 0.84 mmol), EDCI (0.32 g, 1.68 mmol), and HOBt (0.23 g, 1.68 mmol). The mixture was stirred for 30 min at 0°C and for 24 h at rt, filtered, concentrated, diluted with $CHCl_3$, and washed with water (3 x 100 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$-CH_3OH, 95:5 to afford the product (0.64 g, 56 %). ^{1}H NMR (DMSO-d_6): δ 8.19 (m, 2 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 8.02 (s, 1 H), 8.01 (s, 1 H), 7.97 (s, 1 H), 7.96 (s, 1 H), 7.81 (s, 2 H), 7.80 (s, 2 H), 6.79 (s, 2 H), 6.78 (s, 4 H), 6.77 (s, 2 H), 6.59 (s, 4 H), 6.58 (s, 4 H), 5.84 (m, 4 H), 5.76 (m, 4 H), 4.33 (br s, 4 H), 4.30 (d, *J* = 12.4 Hz, 4 H), 4.23 (d, *J* = 12.4 Hz, 4 H), 3.91 (m, 1 H), 3.72 (t, *J* = 6.9 Hz, 8 H), 3.68 (t, *J* = 6.9 Hz, 4 H), 3.58 (s, 3 H), 3.20 (m, 4 H), 3.1-2.9 (m, 24 H), 1.34 (s, 9 H), 1.9-0.8 (6 x m, 130 H); ^{13}C NMR (DMSO-d_6): δ 173.0, 172.9, 169.3, 155.74, 155.7, 151.25, 151.2, 150.7, 150.3, 135.3, 135.16, 135.1, 135.0, 134.5, 134.46, 134.2, 134.1, 134.0, 118.8, 118.72, 118.5, 118.4, 79.8, 78.5, 77.3, 76.5, 74.8, 54.5, 52.3, 32.3, 31.6, 31.4, 31.2, 30.4, 30.1, 29.9, 28.7, 26.7, 23.6, 23.4, 23.0, 22.9, 22.7, 14.5, 10.6; FTIR (KBr): ν 3333, 2931, 2858, 1653, 1559, 1213, 1042, 965; MALDI-FTMS, *m/z:* 2728.7671 [$(M+Na)^+$, calcd for $C_{152}H_{232}N_{20}O_{23}Na$ 2728.7491); ESI-MS, *m/z*: 2743 ($[M+Cl]^-$, calcd for $C_{152}H_{232}N_{20}O_{23}Cl$ 2741).

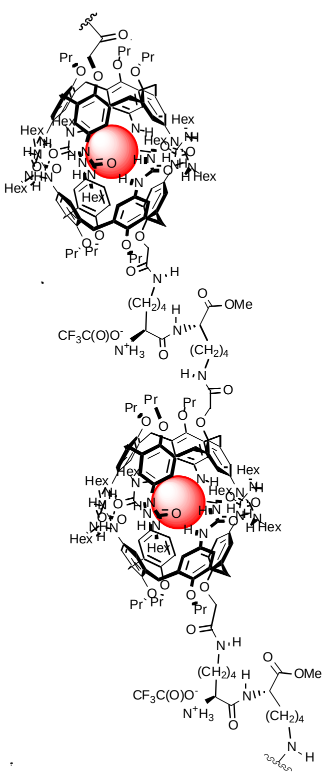


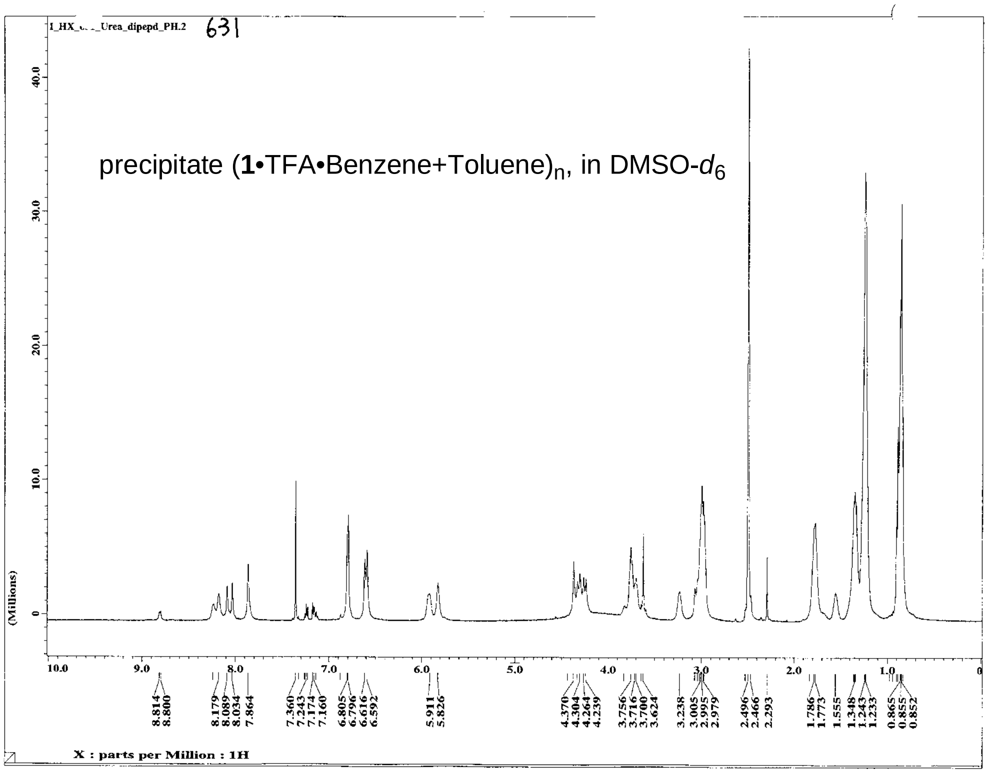
Dipeptide (1). A solution of the BOC-protected dipeptide (0.5g, 0.18 mmol) in THF (15 mL) was treated with TFA (10 mL) and then stirred at rt for 4 h. The reaction mixture was concentrated in vacuo to afford pure **1** as a TFA salt. ^{1}H NMR (DMSO-d_6): δ 8.24 (br s, 2 H), 8.15 (br s, 1 H), 8.06 (s, 2 H), 8.01 (s, 2 H), 7.84 (s, 4 H), 6.80 (s, 4 H), 6.79 (s, 4 H), 6.62 (s, 4 H), 6.59 (s, 4 H), 5.89 (m, 4 H), 5.80 (m, 4 H), 4.40 (s, 4 H), 4.33 (d, *J* = 12.3 Hz, 4 H), 4.24 (d, *J* = 12.3Hz, 4 H), 3.80 (m, 1 H), 3.75 (t, *J* = 7.0 Hz, 8 H), 3.69 (t, *J* = 7.0 Hz, 4 H), 3.62 (s, 3 H), 3.22 (m, 4 H), 3.00 (m, 24 H), 1.9-0.8 (6 x m, 130 H); FTIR (KBr): ν 3347, 3082, 2932, 2860, 1670, 1599, 1474, 1205. ESI-MS, *m/z*: 2719 (M$^+$, calcd for $C_{149}H_{224}N_{20}O_{23}F_3$ 2719).

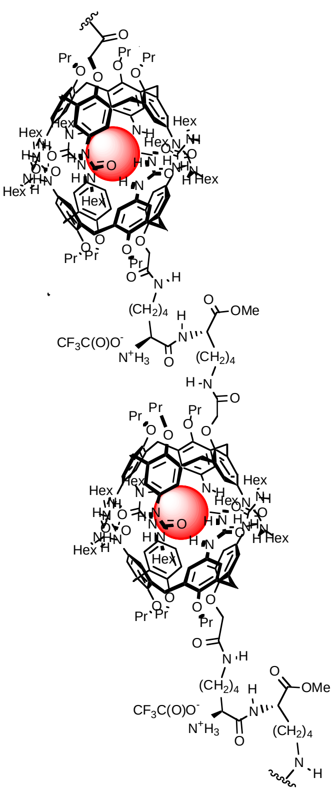
The salt was then dissolved in $CHCl_3$ (60 mL) and washed with 10% NaOH (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give free amine **1** (0.44g, 92%): ^{1}H NMR (DMSO-d_6): δ 8.34 (d, *J* = 6.8 Hz, 1 H), 8.18 (br s, 2 H), 8.04 (s, 2 H), 7.99 (s, 2 H), 7.83 (s, 4 H), 6.82 (s, 4 H), 6.81 (s, 4 H), 6.62 (s, 8 H), 5.86 (m, 4 H), 5.78 (t, *J* = 5.0 Hz, 4 H), 4.38 (s, 4 H), 4.34 (d, *J* = 12.3 Hz, 4 H), 4.25 (d, *J* = 12.3 Hz, 4 H), 3.76 (t, *J* = 7.0 Hz, 8 H), 3.71 (t, *J* = 7.0 Hz, 4 H), 3.62 (s, 3 H), 3.22 (m, 4 H), 3.00 (m, 24 H), 1.9-0.8 (6 x m, 130 H); ^{13}C NMR (DMSO-d_6): δ 175.9, 173.1, 169.3, 155.7, 151.2, 150.7, 150.3, 135.3, 135.1, 134.9, 134.4, 134.1, 133.9, 118.7, 118.5, 79.6, 77.2, 76.5, 74.7, 54.9, 52.2, 52.0, 35.5, 31.6, 31.4, 30.3, 29.8, 26.6, 23.4, 22.8, 22.6, 14.4, 10.5; ESI-MS, *m/z*: 2608 ([M+H]$^+$, calcd for $C_{147}H_{225}N_{20}O_{21}$ 2607).

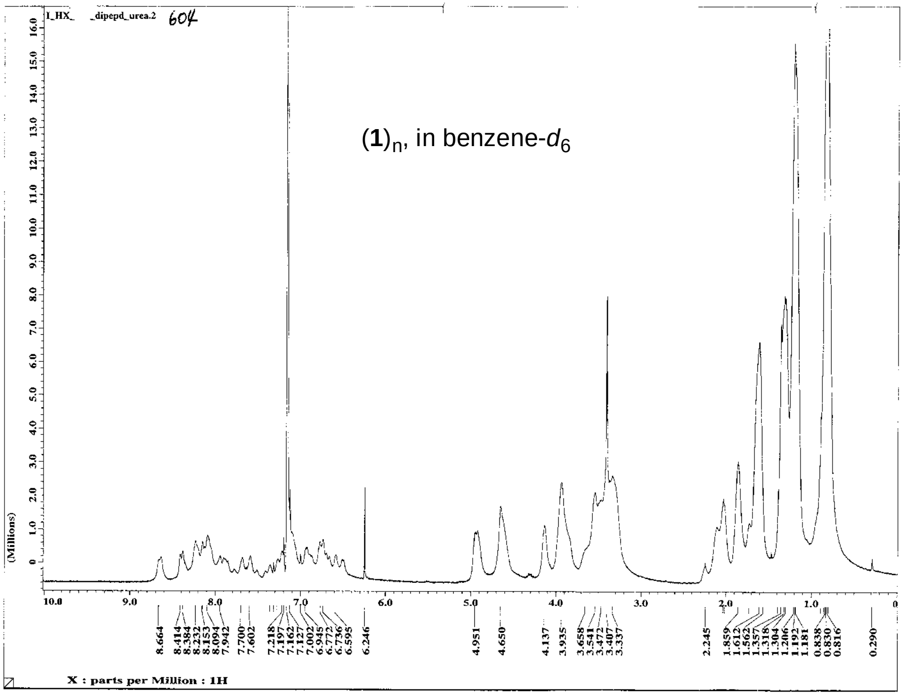


precipitate (**1**•TFA•Benzene)$_n$, in DMSO-d_6




precipitate ($(\mathbf{1}\cdot\text{TFA}\cdot\text{Benzene+Toluene})_n$), in DMSO-$d_6$




I_HX_ _dipepd_urea.2 604
(**1**)$_n$, in benzene-d_6
(Millions)
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
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8.232
8.153
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7.700
7.602
7.218
7.197
7.162
7.127
7.002
6.945
6.772
6.736
6.595
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4.650
4.137
3.935
3.658
3.541
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1.562
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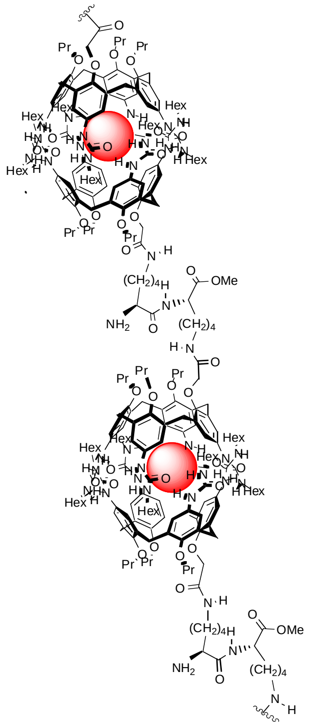
0.290
X : parts per Million : 1H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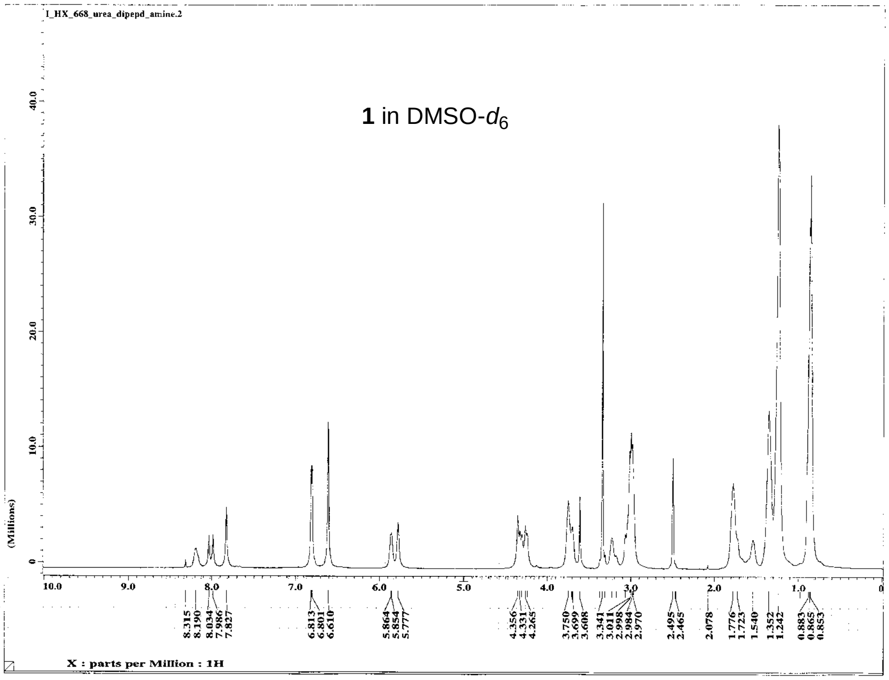
Pr
Pr
O
Hex
Hex
OMe
NH$_2$
(CH$_2$)$_4$
H
N
O


I_HX_668_urea_dipepd_amine.2
1 in DMSO-d_6
(Millions)
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30.0
20.0
10.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.315
8.190
8.034
7.986
7.827
6.813
6.801
6.610
5.864
5.854
5.777
4.356
4.331
4.265
3.750
3.699
3.608
3.341
3.011
2.998
2.984
2.970
2.495
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1.723
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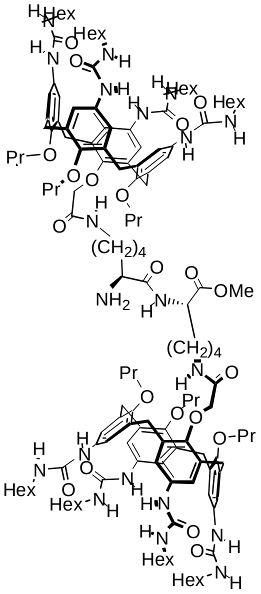
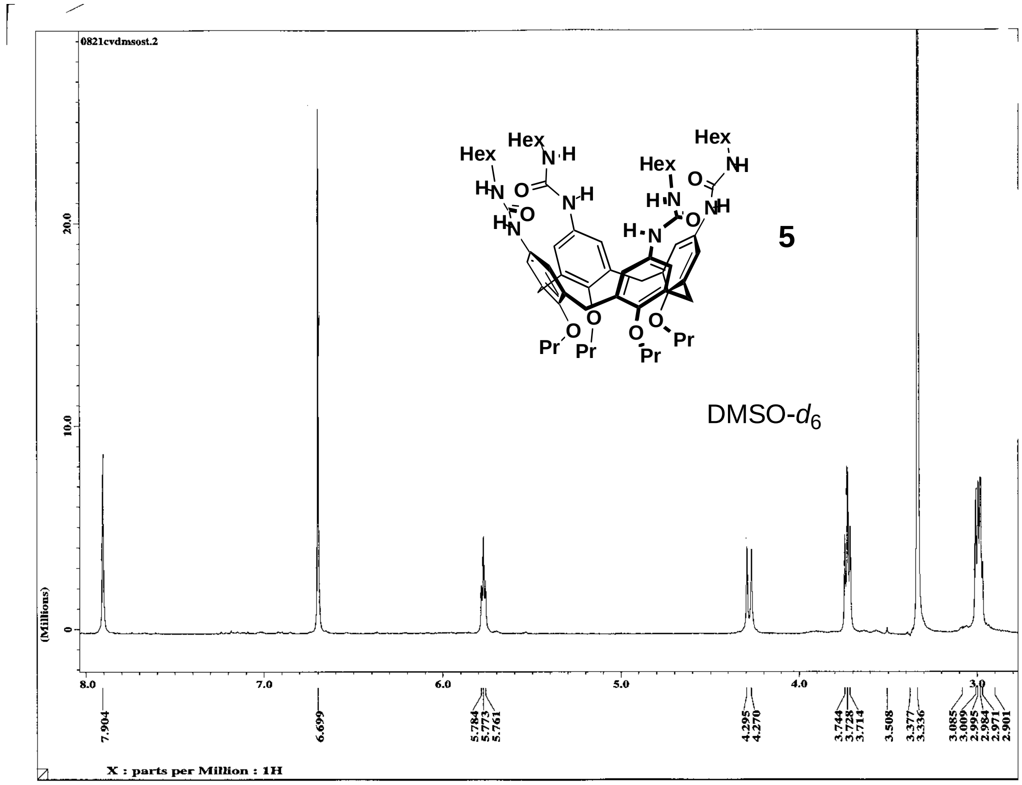
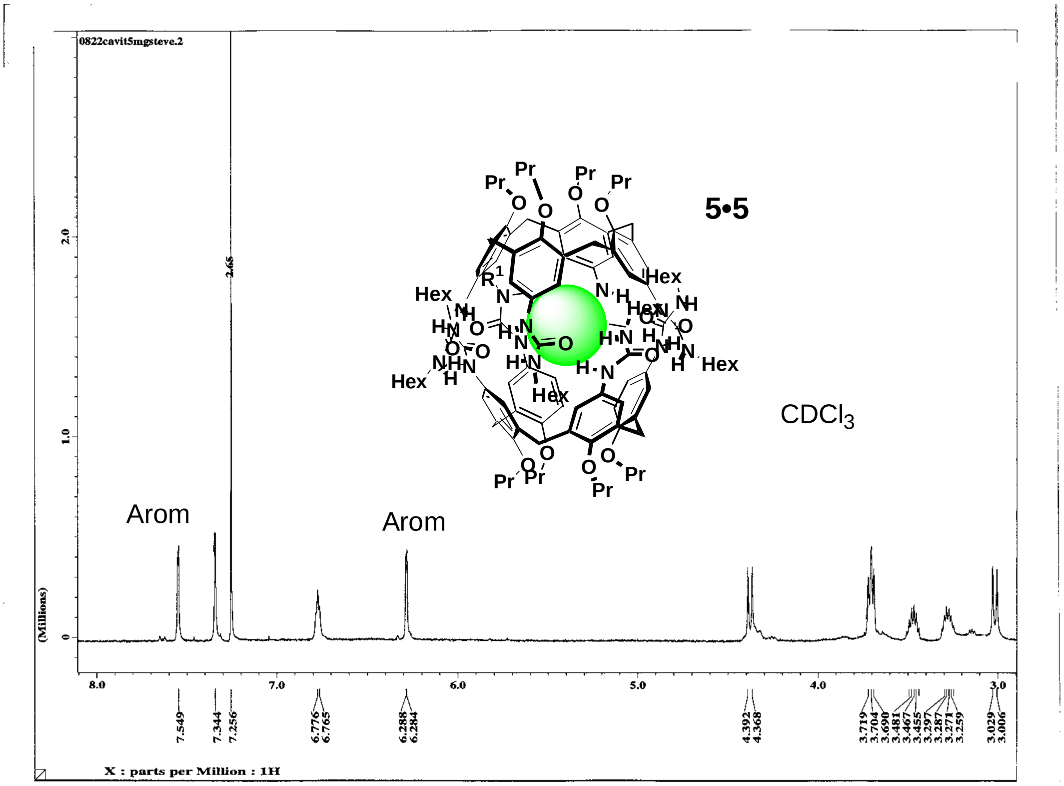
0.853
X : parts per Million : 1H

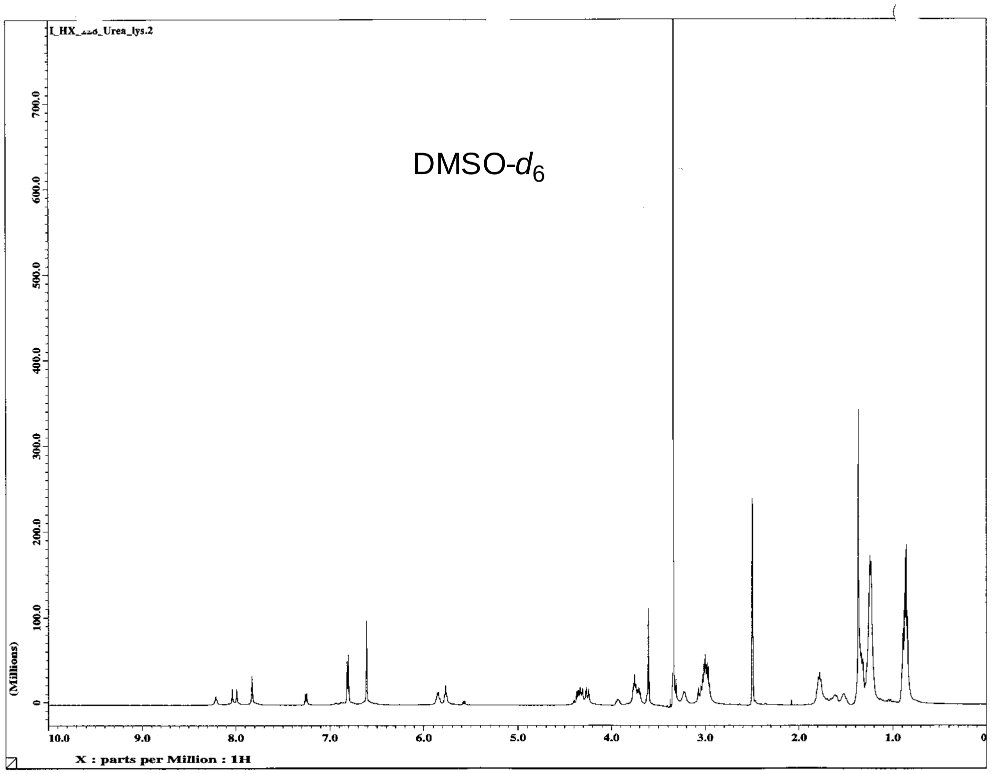

Hex
Pr
Pr–O
O–Pr
OMe
NH$_2$
(CH$_2$)$_4$
H
N
O

^{1}H NMR Experiments with Self-Assembling Capsules and Polymers. ^{1}H NMR spectra were recorded at 295 ± 1 ^{O}C in $CDCl_3$, benzene-d_6, and DMSO-d_6. Self-assembly takes place in apolar solution ($CDCl_3$, benzene-d_6) with the formation of hydrogen bonding capsules. It is now well established that dimerization of calixarene tetraureas in apolar solution results in significant downfield shifts ($\Delta\delta \sim 2$-3 ppm) of the urea NH protons, compared to model, monomeric ureas.[3] Furthermore, self-assembly of calixarene tetraureas causes significant differences in the ^{1}H NMR spectra symmetry, when taken in $CDCl_3$ (or benzene-d_6) and DMSO-d_6.[4,5] For example, while the calixarene tetraurea monomers **5** in competitive DMSO-d_6 possess apparent C_{4V} symmetry, the corresponding dimers **5•5** are S_8 symmetrical and composed of two calixarene moieties of C_4 symmetry each (in $CDCl_3$).





Calix[4]arene tetraurea **6**, substituted at the lower rim with one lysine fragment, was prepared for spectroscopic comparison with more complex bis-calixarene dilysine **1**. Both calix[4]arene tetraureas **6** and **1** (and its *N*-BOC protected precursor) lack the symmetry. The result is a multiple set of NH urea signals in the ^{1}H NMR spectra. In apolar solvents, these were characteristically shifted down field, compared to the model ureas,[3] showing the key features of the capsule formation. Both a proximal and distal regioisomers of **1•1** and **6•6** form, with respect to the orientation of the acetamide OCH$_2$C(O)NH-substituents at the lower rims of each calixarene **1** and **6**.[2] Moreover, the circular array of hydrogen bonds can be arranged either clockwise or counterclockwise. Capsules **6•6** and **4** dissociate to monomeric species **6** and **1**, respectively, in more competitive DMSO-d_6. This results in a simpler ^{1}H NMR picture, reflecting the presence of a vertical symmetry plane in **6** and **1**. Below, a set of ^{1}H NMR spectra is presented both in polar and apolar solutions, reflecting the above self-assembling processes and formation of capsules **6•6** and **4.**


DMSO-d_6
(Millions)
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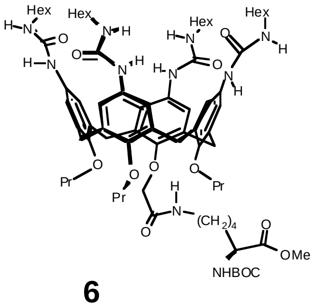
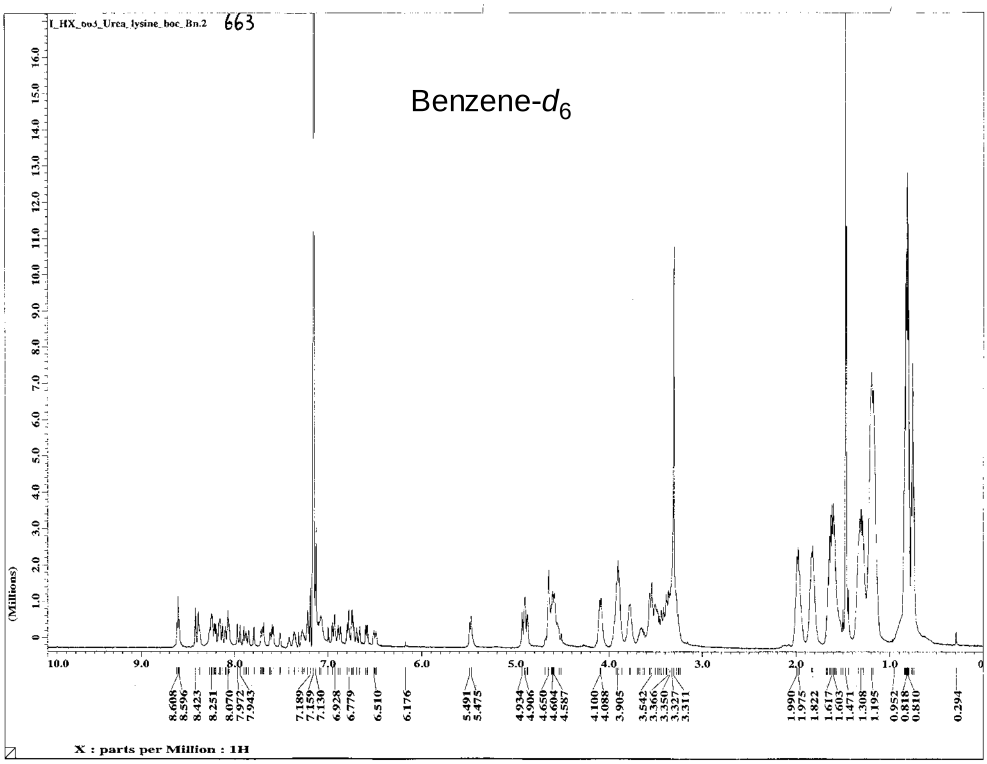
200.0
300.0
400.0
500.0
600.0
700.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H


Hex
Hex
Hex
Hex
H
N
O
O
Pr
Pr
Pr
(CH2)4
OMe
NHBOC

6


I_HX_oo3_Urea_lysine_boc_Bn.2
663
Benzene-d_6
(Millions)
0
1.0
2.0
3.0
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6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
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15.0
16.0
10.0
9.0
8.0
7.0
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5.0
4.0
3.0
2.0
1.0
0
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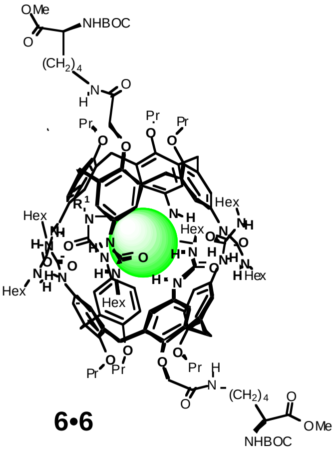
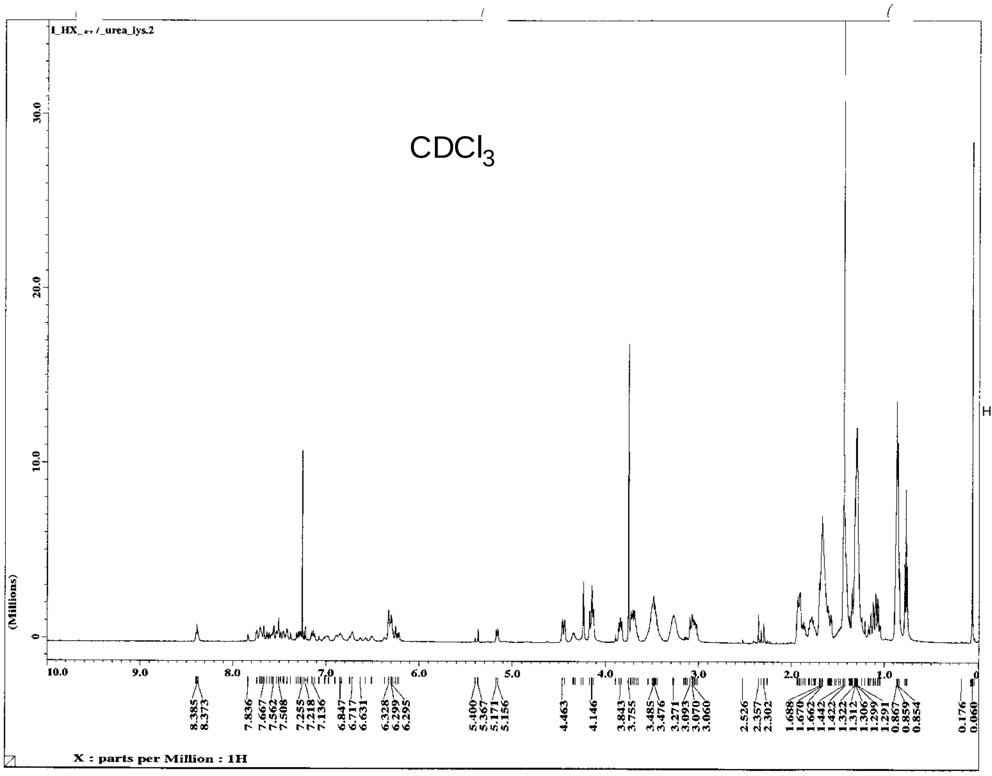
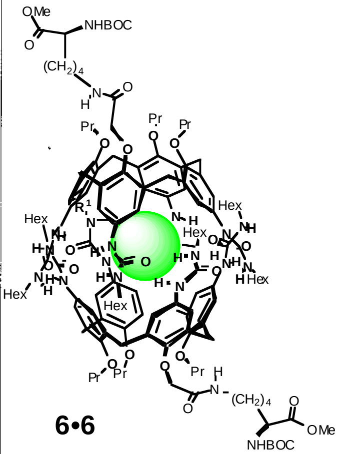
8.596
8.423
8.251
8.070
7.972
7.943
7.189
7.159
7.130
6.928
6.779
6.510
6.176
5.491
5.475
4.934
4.906
4.650
4.604
4.587
4.100
4.088
3.905
3.542
3.366
3.350
3.327
3.311
1.990
1.975
1.822
1.617
1.603
1.471
1.308
1.195
0.952
0.818
0.810
0.294
X : parts per Million : 1H

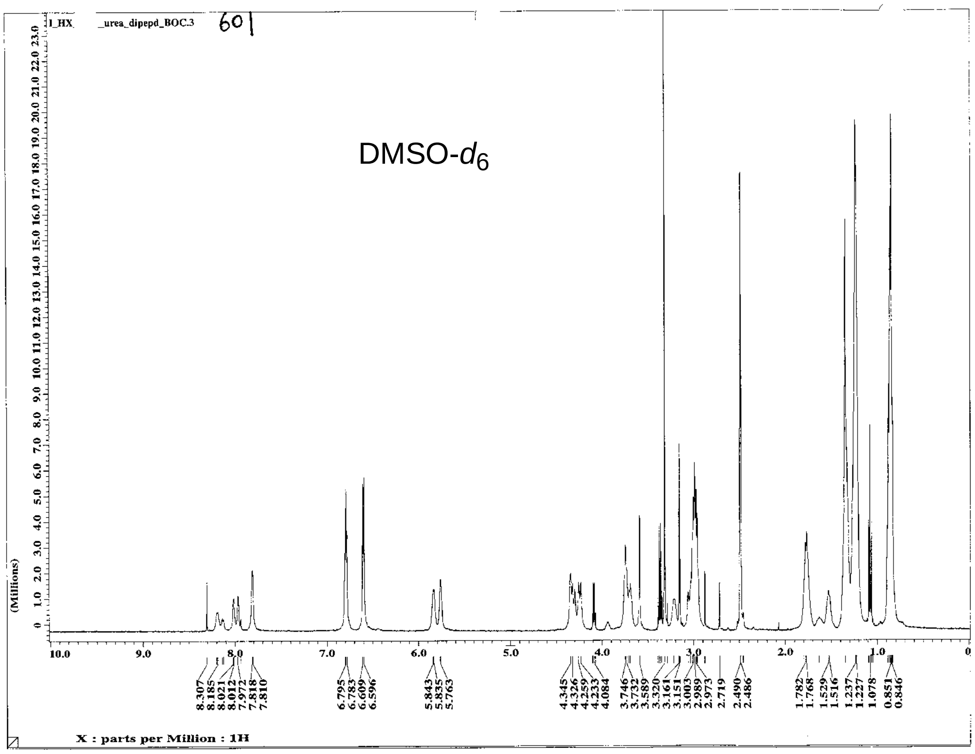

OMe
O
NHBOC
(CH2)4
N
H
O
Pr
Pr
Pr
O
O
O
R1
N
H
Hex
Hex
Hex
Hex
Hex
Hex
N
H
O
O
O
O
O
Pr
Pr
Pr
H
N
(CH2)4
O
OMe
NHBOC

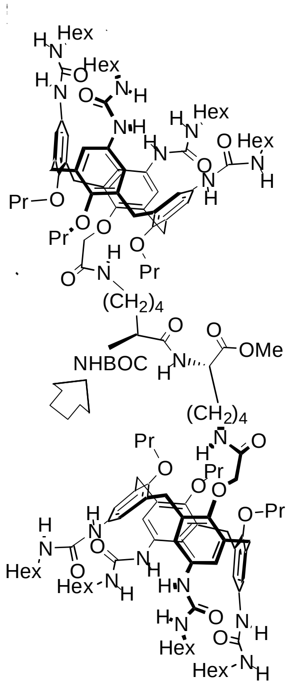
6•6

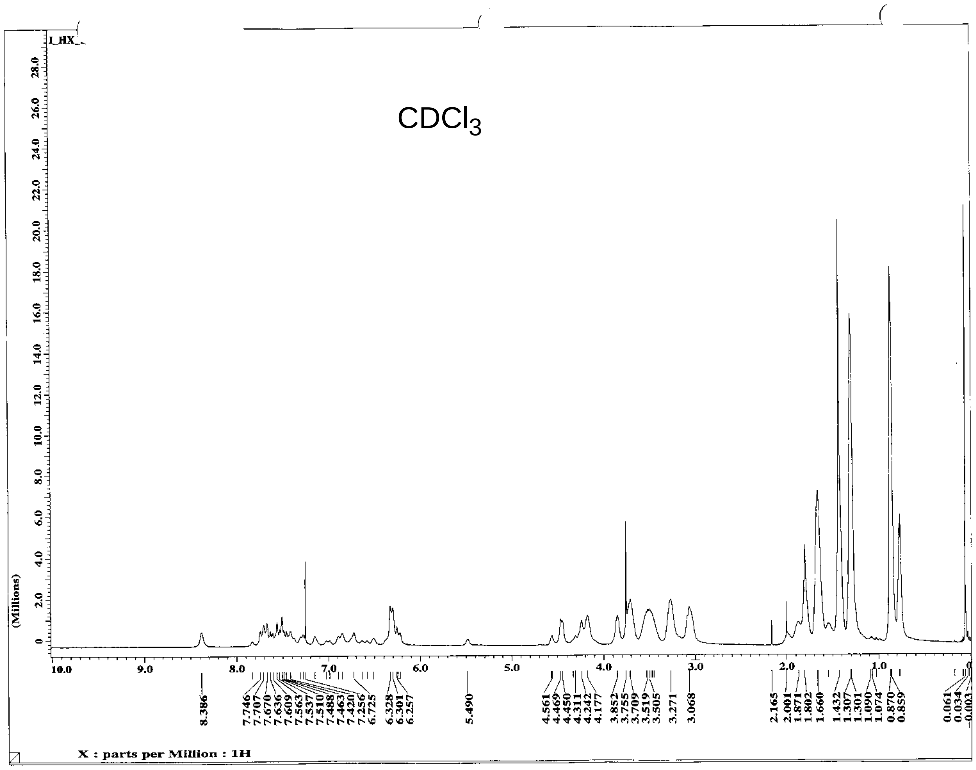

1_HX_... /_urea_lys.2
CDCl$_3$
(Millions)
30.0
20.0
10.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.385
8.373
7.836
7.667
7.562
7.508
7.255
7.218
7.136
6.847
6.717
6.631
6.328
6.299
6.295
5.400
5.367
5.171
5.156
4.463
4.146
3.843
3.755
3.485
3.476
3.271
3.093
3.070
3.060
2.526
2.357
2.302
1.688
1.670
1.662
1.442
1.422
1.322
1.312
1.306
1.299
1.291
0.867
0.859
0.854
0.176
0.060
X : parts per Million : 1H

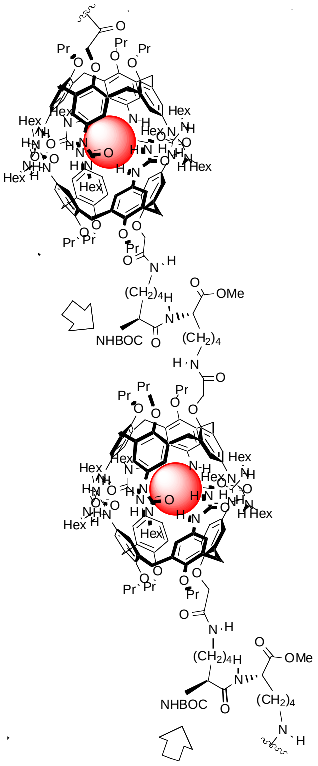

OMe
NHBOC
O
(CH$_2$)$_4$
N
H
O
Pr
Pr
Pr
O
O
O
Hex
Hex
Hex
Hex
Hex
Hex
R^1
N
H
O
Pr
Pr
Pr
H
N
(CH$_2$)$_4$
O
OMe
NHBOC

6•6


1_HX _urea_dipepd_BOC.3
60|
DMSO-d_6
(Millions)
0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0 19.0 20.0 21.0 22.0 23.0
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
8.307 8.185 8.021 8.012 7.972 7.818 7.810
6.795 6.783 6.609 6.596
5.843 5.835 5.763
4.345 4.326 4.259 4.233 4.084
3.746 3.732 3.589 3.320 3.161 3.151 3.003 2.989 2.973 2.719 2.490 2.486
1.782 1.768 1.529 1.516 1.237 1.227 1.078 0.851 0.846
X : parts per Million : 1H


Hex
Pr—O
Pr
O
H
N
(CH2)4
NHBOC
OMe
(CH2)4
O-Pr


1_HX
CDCl3
(Millions)
0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
26.0
28.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.386
7.746
7.707
7.670
7.636
7.609
7.563
7.537
7.510
7.488
7.463
7.420
7.256
6.725
6.328
6.301
6.257
5.490
4.561
4.469
4.450
4.311
4.242
4.177
3.852
3.755
3.709
3.519
3.505
3.271
3.068
2.165
2.001
1.871
1.802
1.660
1.432
1.307
1.301
1.090
1.074
0.870
0.859
0.061
0.034
-0.003
X : parts per Million : 1H


Pr
Pr
Pr
O
Hex
N-H
NHBOC
(CH2)4H
OMe
(CH2)4
H·N
O
Pr
Hex
NHBOC
(CH2)4H
OMe
(CH2)4
N·H

Addition of TFA to benzene solution of polymeric capsules **4** resulted in instant precipitation of material **4**•nTFA. To estimate the TFA concentration limits, at which capsules dissociate to monomers, model experiments with calixarene tetraurea **5** and its capsules **5•5** were performed.

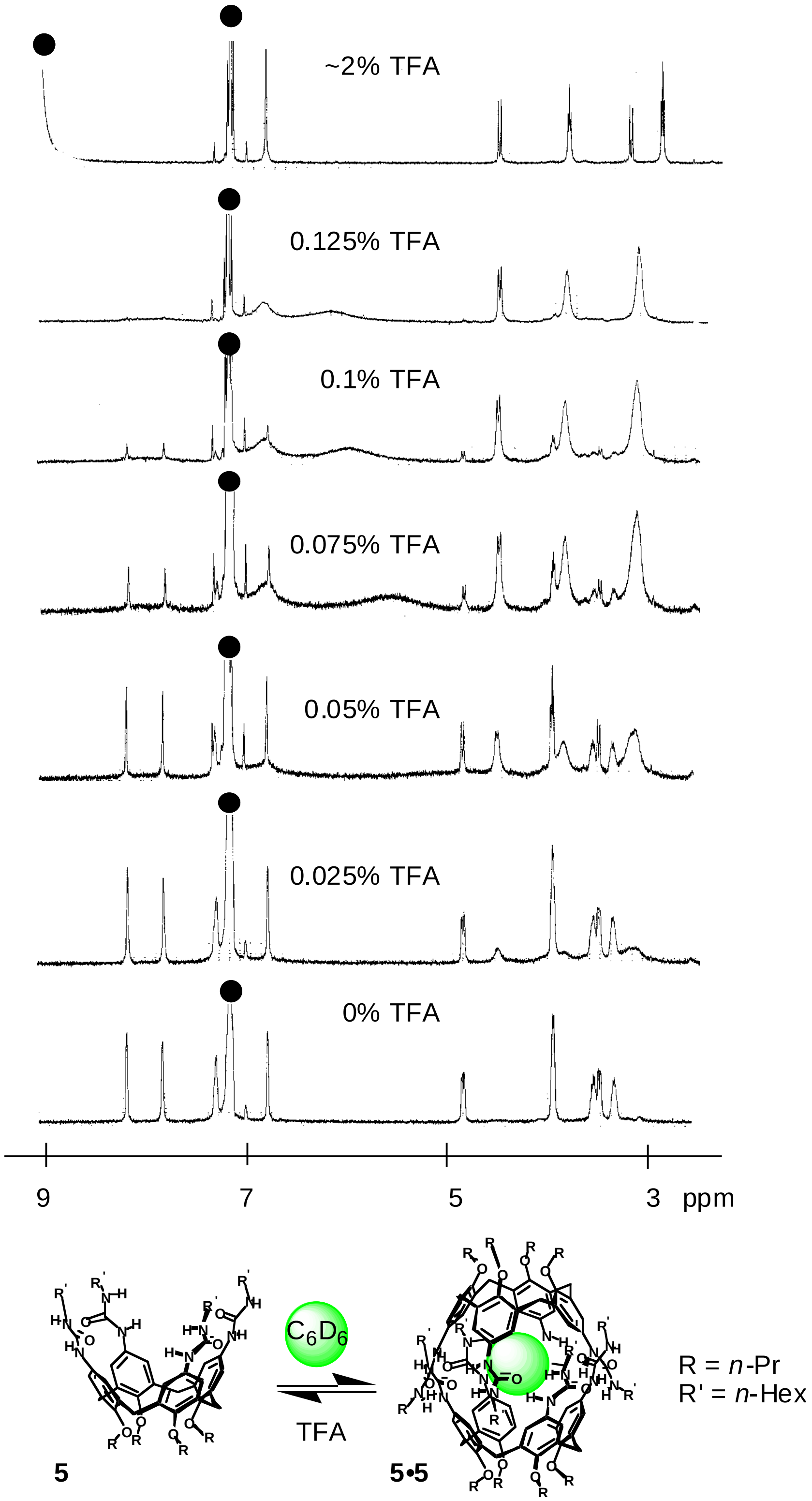


Figure. Titration of capsule **5•5** with TFA in benzene-d_6 at 295 K.

Stock solution of TFA in benzene-d_6 was gradually added to the benzene-d_6 solution of **5** (~0.1 mM) and the ^{1}H NMR spectral changes were recorded. In the absence of TFA, only dimers **5•5** were seen. At >1% v/v TFA, exclusively monomers **5** were detected. At <0.025% v/v of TFA in benzene (~10 eq TFA to 1 eq **5**), more than 70% of calixarene exists as dimer **5•5**. At >0.125% v/v of TFA, **5•5** cannot be detected. Accordingly, for precipitation of **4**•nTFA, only <0.02% v/v of TFA were used to prevent the dissociation processes.

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