Organic LETTERS

Allosteric Regulation of the Conformational Dynamics of a Cavitand Receptor

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Supporting Information

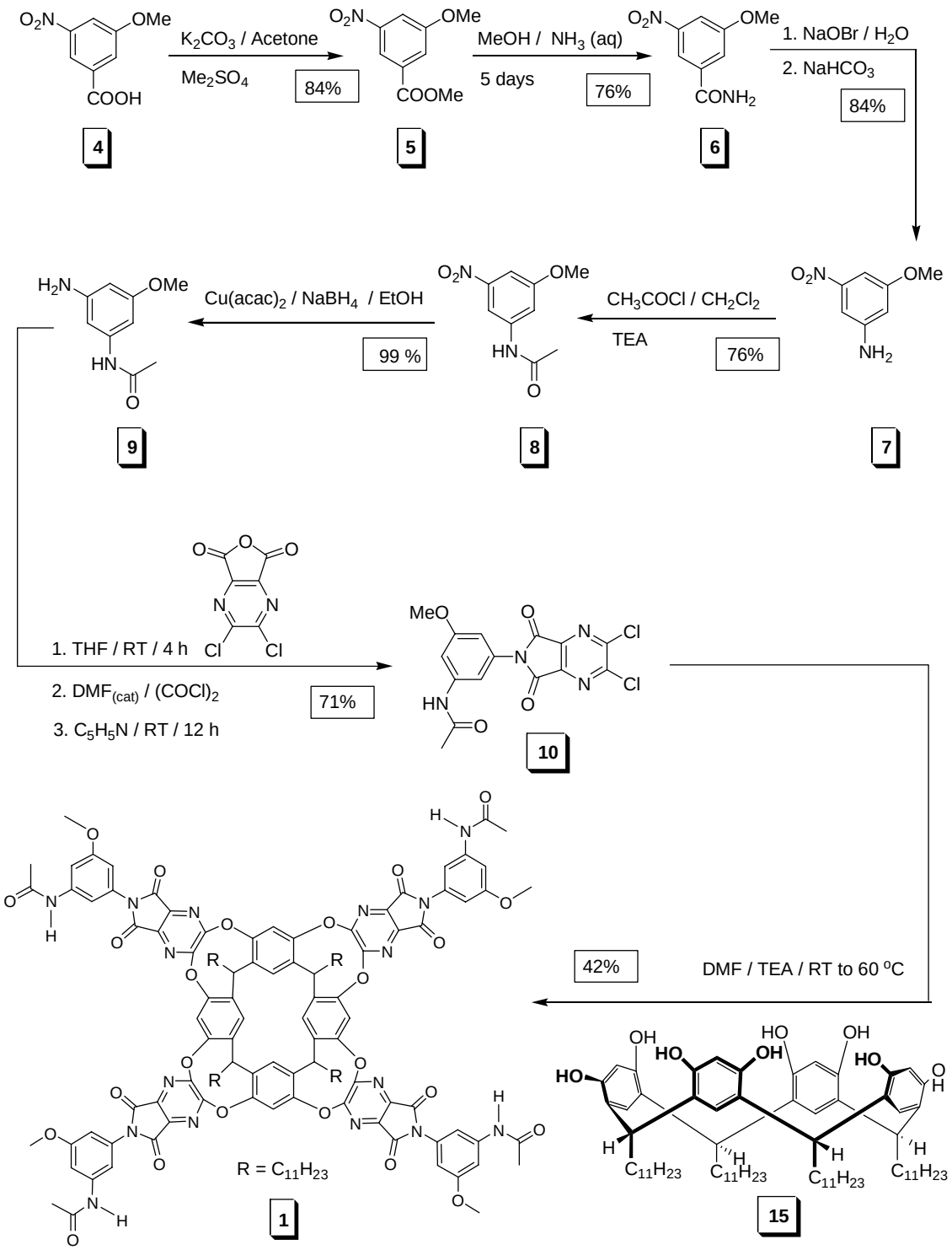
General. All chemicals were purchased from commercial sources, and used as received unless stated otherwise. All solvents were dried prior to use according to standard literature protocols. Chromatography purifications were performed using silica gel 60 (Sorbent technologies 40-75 μm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed on silica-gel plate w/UV254 (200 μm). Chromatograms were visualized by UV-light, and also stained using 20% phosphomolybdic acid in ethanol. Melting points were determined on an Electrothermal melting point apparatus in open capillaries and reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using 500 MHz and 125 MHz a Bruker DRX-500 spectrometer, unless stated otherwise. They were referenced using the solvent residual signal as internal standard. Samples were prepared using $CDCl_3$ and CD_3SOCD_3 purchased from Cambridge Isotope Laboratories. The chemical shift values are expressed as δ values and the coupling constants values (J) are in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. High resolution electron-ionization (HRMS-EI) spectra were recorded on a Micromass Q-TOF2 instrument.

Preparation of the Starting Materials. The syntheses of **1**-**3** are outlined in Schemes S1, S2, and S3. 3-methoxy-5-nitrobenzoic acid was prepared from commercially available 3,5-dinitrobenzoic acid **4** , in a nucleophilic aromatic substitution reaction with $LiOCH_3$.[1] 2,3-dichloroquinoxaline was oxidized with $KMnO_4$ to yield 5,6-dichloropyrazine-2,3-dicarboxy acid anhydride following a reported procedure.[2] Resorcinarene **15** was obtained in a condensation reaction of resorcinol and dodecanal.[3]

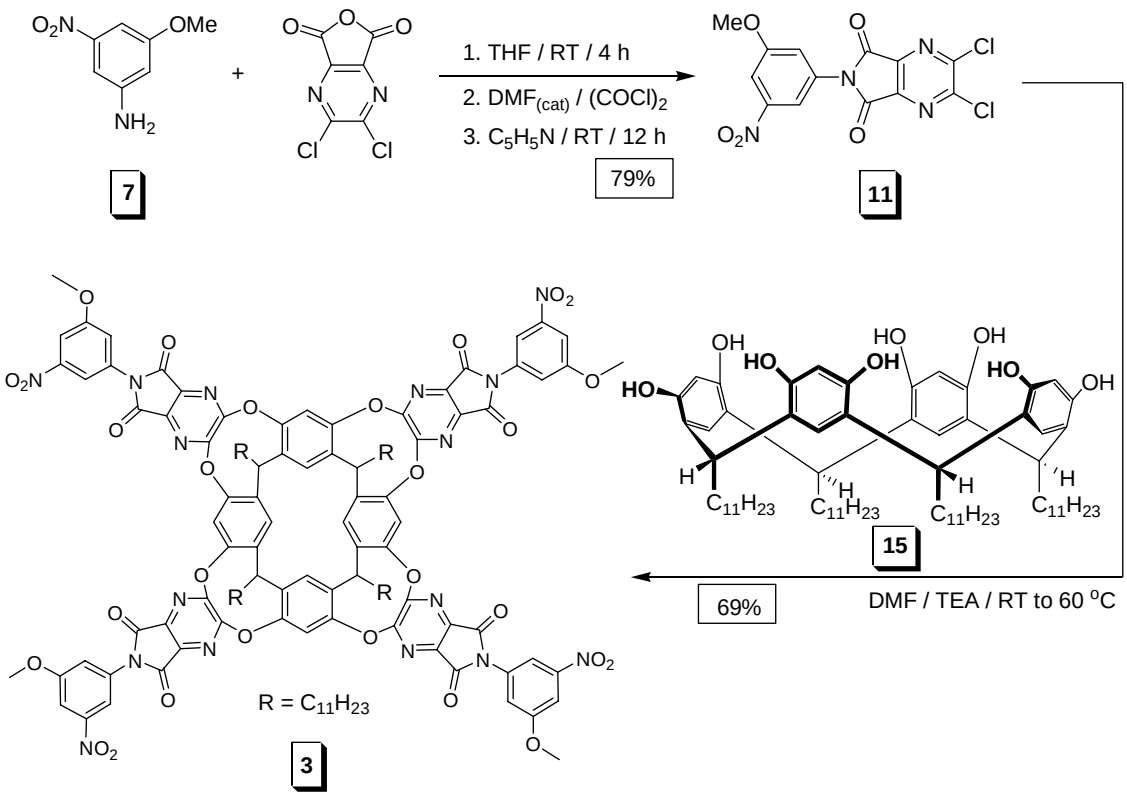
Compound 5. To a refluxing solution of 3-methoxy-5-nitrobenzoic acid (2.12 g, 10.7 mmol) and K_2CO_3 (1.68 g, 12.2 mmol) in anhydrous acetone (20 mL), dimethyl sulfate (2 mL) was added dropwise over a period of 15 minutes. The reaction mixture was refluxed for an additional 12 h, cooled to room temperature, and the solvent was removed in vacuo. The resulting solid residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 5:1) to afford **1** as a white solid (1.92 g, 84 %). M.p. = 89.4–91.2 ^{o}C; ^{1}H NMR (250 MHz, $CDCl_3$, 27 ^{o}C): δ = 8.45 (dd, 1H, J_1 = 2.0 Hz, J_2 = 1.5 Hz), 7.91 (dd, 1H, J_1 = 2.5 Hz, J_2 = 2.0 Hz), 7.88 (dd, 1H, J_1 = 1.5 Hz, J_2 = 2.5 Hz), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 164.9, 160.2, 149.2, 132.6, 121.1, 116.6, 112.9, 56.2, 52.8; HRMS (ESI): *m/z* calcd. for $C_9H_9NO_5Na$ 234.0378 $[M+Na]^+$ found 234.0383.

Compound 6. To a methanol (19 mL) solution of **5** (1.79 g, 8.5 mmol), aqueous ammonium hydroxide (14.8 M, 13 mL) was added at room temperature. The mixture was kept in a closed vial for 5 days without any stirring. Needle-like crystals of pure **6** were collected by filtration (1.2 g, 73 %). The mother liquid was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 5:2) to afford additional quantities of **6** (0.05 g). M.p. = 190.8–192.0 ^{o}C; ^{1}H NMR (250 MHz, CD_3SOCD_3, 27 ^{o}C): δ = 8.20 (1H, Ar-H), 8.06 (br, 1H, N-H), 7.72 (1H, Ar-H), 7.63 (1H, Ar-H), 7.08 (br, 1H, N-H), 3.77 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 165.9, 160.3, 149.3, 137.2, 120.3, 114.9, 111.3, 56.8; HRMS (ESI): *m/z* calcd. for $C_8H_8N_2O_4Na$: 219.0382 $[M+Na]^+$, found: 219.0391.

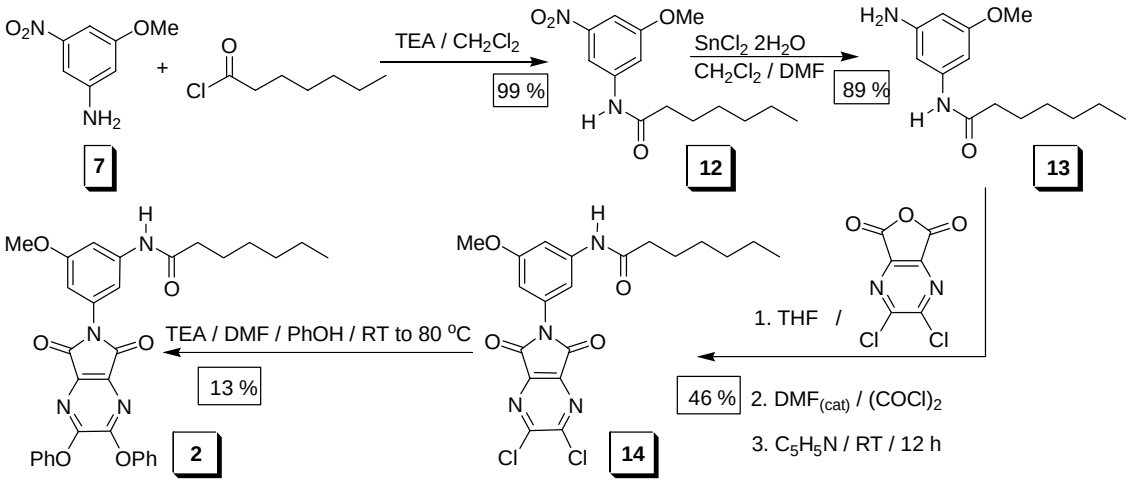
Scheme S1. Synthesis of cavitand **1**.



Scheme S2. Synthesis of model cavitand **3**.



Scheme S3. Synthesis of model compound **2**.



Compound 7. To a solution of NaOH (6 g, 150 mmol) in water (50 mL) at 4 °C, neat bromine (4.8 g, 30 mmol) was added dropwise. A portion of thus prepared aqueous NaOBr (7 mL) was slowly transferred to a solution of **6** (0.7 g, 3.6 mmol) in methanol (44 mL), and stirred for 1.5 h at room temperature. The solvent was removed under reduced pressure so that the external

temperature did not exceed 30 °C. The solid residue was redissolved in a solution of $NaHCO_3$ (0.45 g) in water (60 mL), heated to 80 °C, and stirred for 2 hours. Orange precipitate was collected by filtration to yield **7** (0.5 g, 84 %). M.p. = 119.6–121.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 7.13 (d, 2H, J = 2.0 Hz), 6.47 (t, 1H, J = 2.0 Hz), 3.94 (br, 1H, N-H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 161.0, 150.1, 148.0, 106.6, 102.7, 98.6, 55.7; HRMS (ESI): *m/z* calcd. for $C_7H_8N_2O_3Na$ 191.0433 $[M+Na]^+$ found 191.0429.

Compound 8. To a solution of **7** (0.1 g, 0.595 mmol) in dry dichloromethane (15 mL), freshly distilled acetyl chloride (0.07 g, 0.892 mmol) was added dropwise under an argon atmosphere. The mixture was stirred for 1 h, upon which triethylamine (0.24 g, 2.4 mmol) was added dropwise, and the resulting solution stirred for additional 12 h. The solvent was removed in vacuo, and the solid residue purified by column chromatography (SiO_2, hexanes/EtOAc, 2:1) to yield **8** as a white solid (0.1 g, 76%). M.p. = 196.8–197.8 °C (decomposition); ^{1}H NMR (250 MHz, CD_3SOCD_3, 27 °C): δ = 10.37 (s, 1H, N-H), 8.14 (dd, 1H, J_1 = 1.8 Hz, J_2 = 2.0 Hz), 7.56 (dd, 1H, J_1 = 2.2 Hz, J_2 = 1.8 Hz), 7.40 (dd, 1H, J_1 = 2.2 Hz, J_2 = 2.0 Hz), 3.83 (s, 3H, OCH_3), 2.07 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6, 27 °C): δ = 169.0, 159.9, 148.8, 141.0, 110.7, 105.9, 102.6, 55.9, 24.0; HRMS (ESI) *m/z* calcd. for $C_9H_{10}N_2O_4Na$ 233.0541 $[M+Na]^+$ found 233.0538.

Compound 9. To a suspension of copper acetylacetonate (0.005 g, 0.017 mmol) in ethanol (4 mL), sodium borohydride (0.016 g, 0.418 mmol) was added portionwise, so that a dark fawn colored granular precipitate appeared shortly thereafter. To this mixture, a solution of **8** (0.09 g, 0.428 mmol) in methanol (4 mL), was added slowly followed by an additional quantity of sodium borohydride (0.033 g, 0.862 mmol). After 12 h of stirring at room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/acetone, 1:1) to yield **9** as a brown oil (0.077 g, 99 %). ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.00 (br, 1H, CON-H), 6.66 (s, 1H), 6.40 (s, 1H), 6.01 (s, 1H), 3.74 (s, 3H, OCH_3), 2.63 (s, 2H, NH_2), 2.14 (s, 3H, COCH3); ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 168.7, 161.0, 148.1, 139.8, 99.5, 97.0, 96.0, 68.9, 55.1; HRMS (ESI) *m/z* calcd. for $C_9H_{11}N_2O_2$ 181.0977 $[M+H]^+$ found 181.0975.

Compound 10. A solution of 5,6-dichloropyrazine-2,3-dicarboxy acid anhydride (0.103 g, 0.471 mmol) and **9** (0.077 g, 0.428 mmol) in THF (11 mL) was stirred under an atmosphere of argon for 4 h. A catalytic amount of DMF (10 μL) followed by oxalyl chloride (0.108 g, 0.848 mmol) was added to this solution, which turned turbid. After 2 hours, pyridine (0.143 g, 1.8 mmol) was added, and the reaction mixture was allowed to stir at room temperature for additional 12 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO_2, benzene/acetone, 5:1) to yield **10** as a pale yellow solid (0.107 g, 71 %). M.p. = 189.0–190.2 °C (decomposition); ^{1}H NMR (500 MHz, CD_3SOCD_3, 27 °C): δ = 10.16 (s, 1H, N-H), 7.34 (s, 1H), 7.33 (s, 1H), 6.68 (s, 1H), 3.76 (s, 3H, OCH_3), 2.05 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, CD_3SOCD_3, 27 °C): δ = 168.6, 161.7, 159.6, 151.0, 144.2, 140.8, 131.8, 110.1, 107.6, 104.7, 55.3, 24.0; HRMS (ESI): *m/z* calcd. for $C_{15}H_{10}Cl_2N_4O_4Na$ 402.9977 $[M+Na]^+$ found 402.9975.

Compound 1. To a solution of **10** (0.020 g, 0.052 mmol) and resorcinarene **15** (0.013 g, 0.012 mmol) in dry DMF (2 mL), triethylamine (0.011 g, 0.113 mmol) was added dropwise under an atmosphere of argon. The stirring was continued for 8 h at RT, followed by 12 h at 80 °C. The solvent was removed under reduced pressure, and the solid residue was purified by column chromatography (SiO_2, benzene/acetone, 1:3) to yield **1** as a waxy yellow solid (0.011 g, 42%). ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 8.10 (s, 4H), 7.38 (s, 4H), 7.35 (s, 4H), 7.02 (s, 4H), 6.38 (s, 4H), 5.65 (t, 4H, J = 8.0Hz), 5.66 (br, 1H, N-H), 3.68 (s, 12H, OCH_3), 2.29 (q, 8H, J = 7.0Hz), 2.00 (s, 12H, $COCH_3$) 1.26 – 1.50 (m, 72H), 0.92(t, 12H, J = 8.5Hz); ^{13}C NMR (75 MHz, CD_3SOCD_3, 27 °C): δ = 169.8, 169.4, 168.4, 162.2, 159.4, 153.6, 151.2, 140.5, 132.0, 129.5, 128.6, 110.1, 107.5, 104.4, 55.2, 45.7, 36.8, 31.1, 30.2, 28.6, 28.8, 28.5, 26.7, 26.4, 23.9, 21.9, 13.7, 8.5; HRMS (ESI) *m/z* calcd. for $C_{132}H_{145}N_{16}O_{24}$ 2338.0617 $[M+H]^+$ found 2338.0637.

Compound 11. A solution of 5,6-dichloropyrazine-2,3-dicarboxy acid anhydride (0.175 g, 0.799 mmol) and **7** (0.135 g, 0.805 mmol) in THF (11 mL) was stirred under an atmosphere argon for 4 h. A catalytic amount of DMF (10 μL) followed by oxalyl chloride (0.11 g, 0.871 mmol) was added to this solution, which turned turbid. After 2 hours, pyridine (0.143 g, 1.8 mmol) was added, and the reaction mixture was allowed to stir at 60 °C for additional 12 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO_2, benzene/acetone, 10:1) to yield **11** as a pale yellow solid (0.201 g, 79 %). M.p. = 244.0–245.2 °C (decomposition); ^{1}H NMR (500 MHz, CD_3SOCD_3, 27 °C): δ = 7.96 (dd, 1H, J_1 = 1.6 Hz, J_2 = 2.1 Hz), 7.87 (dd, 1H, J_1 = 2.1 Hz, J_2 = 2.4 Hz), 7.50 (dd, 1H, J_1 = 1.6 Hz, J_2 = 2.4 Hz), 4.92 (br, 1H, N-H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, CD_3SOCD_3, 27 °C): δ = 161.3, 160.0, 151.8, 148.8, 143.8, 132.4, 120.0, 114.1, 108.6, 56.5; HRMS (ESI): *m/z* calcd. for $C_{13}H_6Cl_2N_4O_5Na$ 390.9613 $[M+Na]^+$ found 390.9637.

Compound 3. To a solution of **11** (0.015 g, 0.041 mmol) and resorcinarene **15** (0.009 g, 0.008 mmol) in dry DMF (0.5 mL), triethylamine (0.007 g, 0.113 mmol) was added dropwise under an atmosphere of argon. The stirring was continued for 8 h at RT, followed by 12 h at 60 °C. The solvent was removed under reduced pressure, and the solid residue was purified by column chromatography (SiO_2, benzene/acetone, 95:5) to yield **3** as a waxy yellow solid (0.006 g, 69%). M.p. = 244.0–245.2 °C (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 7.83 (dd, 4H, J_1 = 1.6 Hz, J_2 = 2.0 Hz), 7.69 (dd, 4H, J_1 = 2.0 Hz, J_2 = 2.4 Hz), 7.62 (s, 4H), 7.22 (dd, 4H, J_1 = 1.6 Hz, J_2 = 2.4 Hz), 7.04 (s, 4H), 4.45 (br, 4H), 3.84 (s, 12H), 2.18 (q, 8H, J = 4.4Hz), 1.26~1.36 (m, 72H), 0.879(t, 12H, J = 6.8Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3, 45 °C) δ = 161.7, 159.8, 157.6, 154.3, 151.2, 148.7, 140.0, 133.0, 132.7, 129.4, 119.8, 113.8, 107.9, 56.2, 45.8, 36.9, 31.0, 28.9, 28.8, 28.7, 28.6, 28.4, 26.6, 21.8, 13.6, 8.4.

Compound 12. To a dichloromethane (3 mL) solution of **7** (0.05 g, 0.297 mmol), heptanoic chloride[4] (0.066 g, 0.446 mmol) was added dropwise. The mixture was stirred for 1 h, and triethylamine (0.012 g, 1.19 mmol) was added dropwise. After additional stirring for 6 h, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 5:2) to yield **12** as a yellow oil (0.083 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.80 (dd, 1H, J_1 = 1.8 Hz, J_2 = 2.0 Hz), 7.74 (dd, 1H, J_1 =

2.2 Hz, J_2 = 1.8 Hz), 7.47 (dd, 1H, J_1 = 2.0 Hz, J_2 = 2.2 Hz), 3.88 (s, 3H, OCH_3), 2.39 (t, 2H, J = 7.5 Hz), 1.73 (m, 2H), 1.39 ~ 1.23 (m, 6H), 0.893 (t, 3H, J = 4.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 171.7, 160.7, 149.3, 139.7, 111.5, 106.7, 104.3, 56.0, 31.5, 30.9, 28.9, 25.3, 22.5, 14.0; HRMS (ESI): *m/z* calcd. for $C_{14}H_{20}N_2O_4Na$ 303.1321 $[M+Na]^+$ found 303.1325.

Compound 13. To a dichloromethane (5 mL) solution of **12** (104 mg, 0.370 mmol), a solution of $SnCl_2{\cdot}2H_2O$ (5 g, 26.4 mmol) in dry DMF (2 mL) was added dropwise. The mixture was stirred for 7 h, the solvent was removed in vacuo, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 2:1) to afford **13** as a green oil (0.073 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, 27 ^{o}C): δ = 7.14 (br, 1H, CON-H), 6.66 (s, 1H), 6.46 (s, 1H), 5.99 (s, 1H), 3.73 (s, 3H, OCH_3), 2.31 (t, 2H, J = 7.5 Hz), 1.69 (m, 2H), 1.37 ~ 1.20 (m, 6H), 0.881 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 171.4, 161.1, 148.0, 139.9, 99.4, 97.1, 95.8, 55.2, 31.6, 30.9, 28.9, 25.6, 22.5, 14.0; HRMS (ESI): *m/z* calcd. for $C_{14}H_{22}N_2O_2Na$ 273.1579 $[M+Na]^+$ found 273.1577.

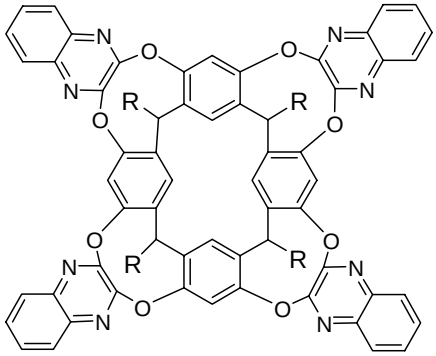
Compound 14. A solution of 5,6-dichloropyrazine-2,3-dicarboxy acid anhydride (0.07 g, 0.327 mmol) and **13** (0.073 g, 0.292 mmol) in THF (10 mL) was stirred under an atmosphere of argon for 2 h. A catalytic amount of DMF (10 μL) followed by oxalyl chloride (0.07 g, 0.584 mmol) was added to this solution, which turned turbid. After 3 hours, pyridine (0.089 g, 1.1 mmol) was added, and the reaction mixture was allowed to stir at RT for additional 12 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO_2, benzene/acetone, 15:1) to afford **14** as a red waxy solid (61 mg, 46 %). ^{1}H NMR (500 MHz, $CDCl_3$, 27 ^{o}C): δ = 7.39 (s, 1H), 7.22 (s, 1H, N-H), 7.14 (s, 1H), 6.71 (s, 1H), 3.84 (s, 3H, OCH_3), 2.36 (t, 2H, J = 7.5 Hz), 1.72 (m, 2H), 1.40 ~ 1.26 (m, 6H), 0.894 (t, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 172.0, 161.0, 160.5, 154.0, 143.0, 139.9, 131.2, 109.7, 108.2, 105.8, 55.6, 31.5, 30.9, 28.9, 25.3, 22.4, 14.0; HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}Cl_2N_4O_4Na$ 473.0759 $[M+Na]^+$ found 473.0755.

Compound 2. To a solution of **14** (0.018 g, 0.04 mmol) and phenol (0.009 g, 0.096 mmol) in dry DMF (2 mL) under an atmosphere of argon, triethylamine (0.036 g, 0.359 mmol) was added dropwise, and the mixture was stirred at 80 ^{o}C for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, benzene/acetone, 95:5) to afford **2** as a waxy yellow solid (0.029 g, 13%). ^{1}H NMR (250 MHz, $CDCl_3$, 27 ^{o}C): δ = 7.53 – 7.31 (m, 11H), 7.14 (s, 1H), 6.96 (s, 1H), 6.65 (s, 1H), 3.79 (s, 3H, OCH_3), 2.33 (t, 2H, J = 5.0 Hz), 1.69 ~ 1.20 (m, 8H), 0.882 (t, 3H, J = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 27 ^{o}C): δ = 171.3, 162.8, 160.5, 154.3, 151.9, 139.6, 137.1, 132.1, 129.0, 128.2, 126.5, 109.7, 108.4, 105.2, 55.6, 31.5, 29.7, 28.9, 25.4, 22.5, 14.0; HRMS (ESI): *m/z* calcd. for $C_{32}H_{30}N_4O_6Na$ 589.2063 $[M+Na]^+$ found 589.2063.

Vapor Pressure Osmometry (VPO). VPO measurements were made with a Knauer K-7000 apparatus operated at 310 K. HPLC-grade $CHCl_3$, distilled from CaH_2, was used in all sample preparation. Calibration curves were obtained with benzil, sucrose octaacetate, and triacetyl-β-cyclodextrine as standards. In assessing the behavior of the receptors used in our study, we have determined the molecular weight of cavitand **16** (Scheme S4) as this molecule

is: a) structurally close to the molecules of interest presented herein and b) does not have a tendency to associate *intermolecularly*.[5]

Scheme S4. Chemical structure of cavitand receptor **16** used in our VPO studies.



R = $C_{11}H_{23}$

16

Table S1. VPO data for benzil ($CHCl_3$, 310 K).

Entry	Concentration of benzil (mmol/kg)	VPO reading[a] (mV)
1	11.0008	13.0 ± 0.4
2	8.3632	8.9 ± 0.1
3	7.5912	8.6 ± 0.1
4	6.2724	7.7 ± 0.1
5	5.7256	5.9 ± 0.1
6	4.7606	5.6 ± 0.1
7	1.8013	2.5 ± 0.1
8	0.7720	1.0 ± 0.1

[a]Reported values are mean values obtained from six measurements; the errors are presented as standard deviations.

Figure S1. VPO standard curve obtained for benzil in $CHCl_3$ at 310 K.

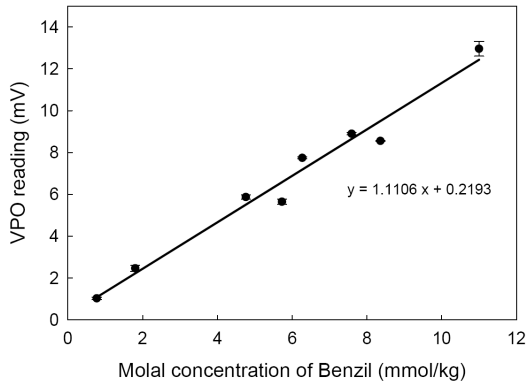


Figure S2. VPO standard curve obtained for benzil in $CHCl_3$ at 310 K.

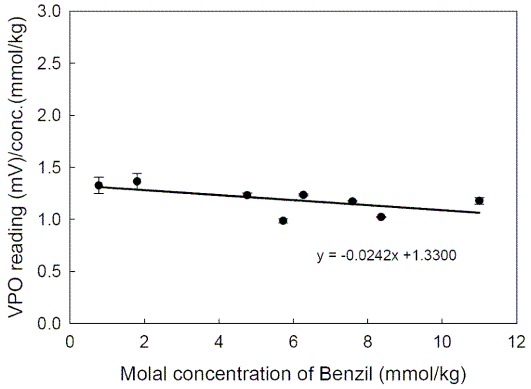


Table S2. VPO data for sucrose octaacetate ($CHCl_3$, 310 K):

Entry	Concentration of sucrose octaacetate (mmol/kg)	VPO reading[a] (mV)
1	13.2335	17.6 ± 0.1
2	8.9486	11.2 ± 0.1
3	7.8125	9.9 ± 0.1
4	6.0786	8.1 ± 0.2
5	4.5042	5.7 ± 0.1
6	3.4479	4.6 ± 0.2
7	2.3119	3.2 ± 0.2

[a]Reported values are mean values obtained from six measurements; the errors are presented as standard deviations.

Figure S3. VPO standard curve obtained for sucrose octaacetate in $CHCl_3$ at 310 K.

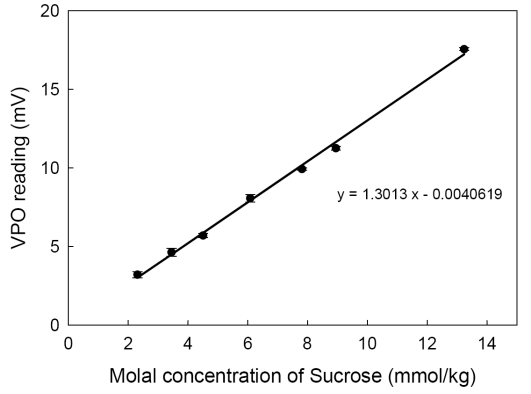


Figure S4. VPO standard curve obtained for sucrose octaacetate in $CHCl_3$ at 310 K.

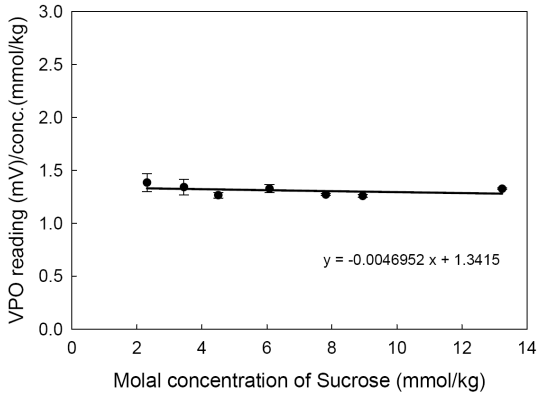


Table S3. VPO data for triacetyl-β-cyclodextrine ($CHCl_3$, 310 K).

Entry	Concentration of triacetyl-β-cyclodextrine (mmol/kg)	VPO reading[a] (mV)
1	12.8355	17.8 ± 0.1
2	9.1022	12.2 ± 0.1
3	7.0847	9.0 ± 0.6
4	5.6101	7.0 ± 0.2
5	4.3567	5.3 ± 0.1
6	2.9357	3.7 ± 0.1
7	2.0644	2.6 ± 0.1
8	0.4357	0.5 ± 0.1

[a]Reported values are mean values obtained from six measurements; the errors are presented as standard deviations.

Figure S5. VPO standard curve obtained for triacetyl-β-cyclodextrine in $CHCl_3$ at 310 K.

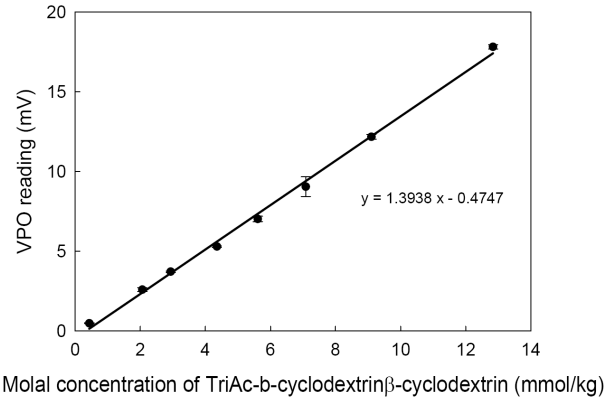


Figure S6. VPO standard curve obtained for triacetyl-β-cyclodextrine in $CHCl_3$ at 310 K.

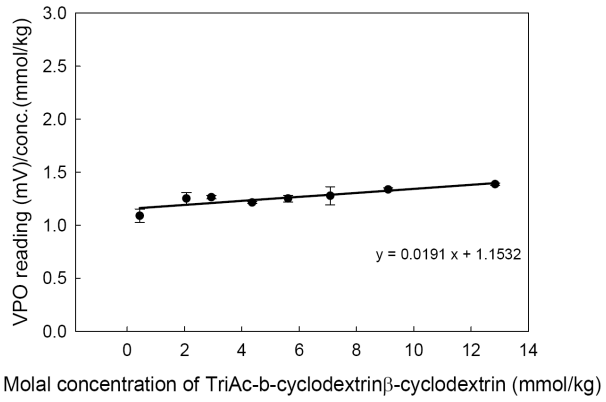


Table S4. VPO data for cavitand **1** ($CHCl_3$, 310 K).

Entry	Concentration of cavitand **9** (mmol/kg)	VPO reading[a] (mV)
1	14.1417	14.4 ± 0.4
2	11.4729	11.9 ± 0.6
3	9.8217	9.2 ± 0.1
4	6.9733	7.2 ± 0.2
5	4.8170	5.6 ± 0.2

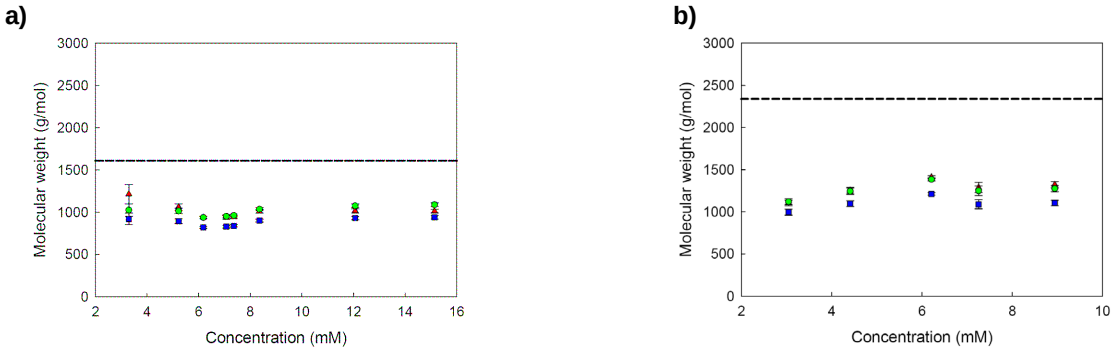
[a]Reported values are mean values obtained from six measurements; the errors are presented as standard deviations.

Table S5. VPO data for cavitand **16** ($CHCl_3$, 310 K).

Entry	Concentration of cavitand-Cram (mmol/kg)	VPO reading[a] (mV)
1	16.4894	19.7 ± 0.4
2	13.1387	15.9 ± 0.4
3	9.0952	11.4 ± 0.2
4	8.0136	10.8 ± 0.2
5	7.6981	10.5 ± 0.2
6	6.7266	9.3 ± 0.1
7	5.6853	7.3 ± 0.2
8	3.5849	4.5 ± 0.3

[a]Reported values are mean values obtained from six measurements; the errors are presented as standard deviations.

Figure S7. VPO determined molecular weights of a) model compound **16**, and b) cavitand **1**, in dry chloroform at 310 K, using sucrose octaacetate (●), triacetyl-β-cyclodextrine (▲), and benzyl (■) as standards. The error bars correspond to the standard deviations of the VPO measurements of the sample.



The results of the VPO measurements with **16** indicated a non-ideal behavior of this known receptor;[5] the experimental molecular weight (M_w^{obs} = 970 ± 90 g/mol) is about 40 % lower then the expected (M_w = 1610 g/mol). This justifies the deviation in the observed molecular weight of **1** (M_w^{obs} = 1210 ± 120 g/mol, 48 % lower than the expected M_w = 2339 g/mol), and to a first approximation implicates its monomeric state in solution.

^{1}H NMR Spectroscopic Measurements. Compounds **1**-**3**, used for the preparation of $CDCl_3$ solutions were dried in high vacuo at 50 ^oC using Kugelrorh distillation apparatus. The $CDCl_3$ was freshly distilled from CaH_2, and stored in a desiccator. Syringes and NMR tubes were dried on a vacuum line at room temperature overnight, and stored in a desiccator.
From the temperature dependence of the resonance line shape of $\mathbf{H_b}$ proton in **1**, Figure S11-S12, we obtained rate constants for $\mathbf{1_a/1_b}$ exchange using WinDNMR Software.[6] The software allowed for a direct automatic iterative matching of the calculated and experimental spectra which minimized the experimental error, so that the rate constants were determined precisely. From the Eyring equation (see below), we calculated the free energy of activation $\Delta G^{\ddagger}$ for the $\mathbf{1_a/1_b}$ interconversion using k_{app} at 300K.[7]

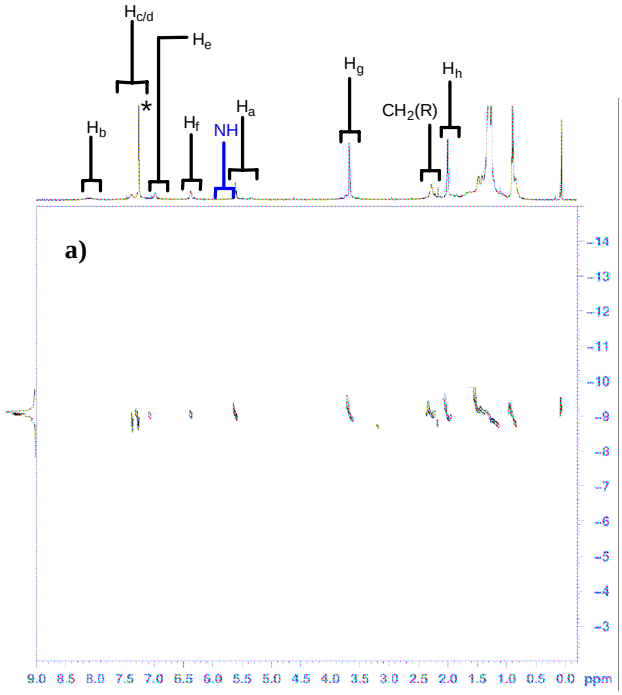
$$\Delta G^{\neq} = 19.14T(10.32 + \log(\frac{T}{k_{app}})$$

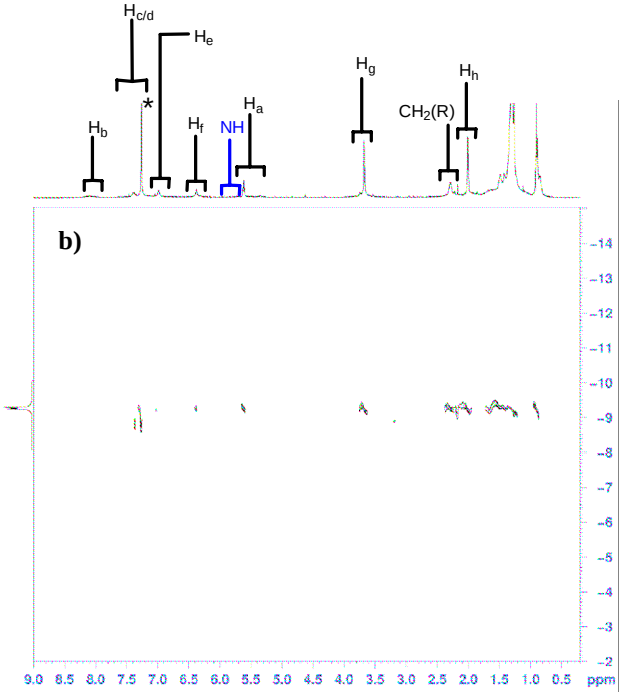
Double-reciprocal Eyring plots (Figure S) were constructed using the following expression:[7]

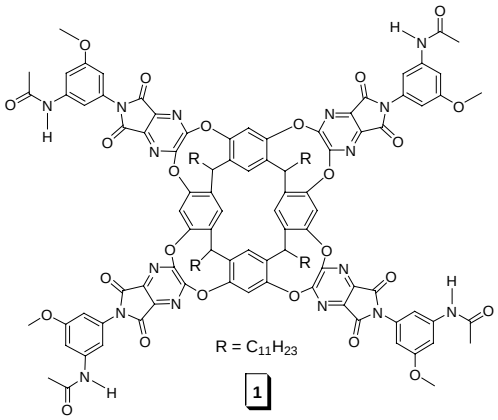
$$\log\frac{k_{app}}{T} = 10.32 - \frac{\Delta H^{\neq}}{19.14T} + \frac{\Delta S^{\neq}}{19.14}$$

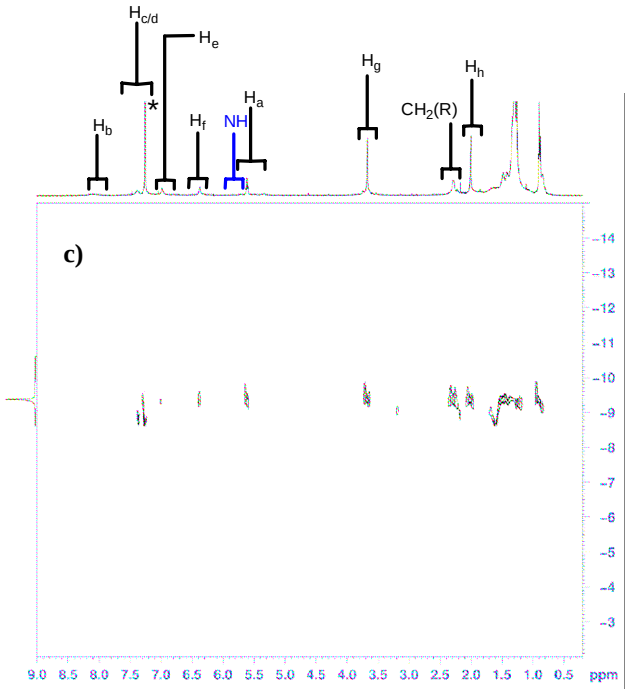
Plotting log(k_{app}/T) versus 1/T, over the temperature range of 258 to 328 K, yielded $\Delta H^{\ddagger}$ from the slope and $\Delta S^{\ddagger}$ from the intercept for the $\mathbf{1_a/1_b}$ interconversion.

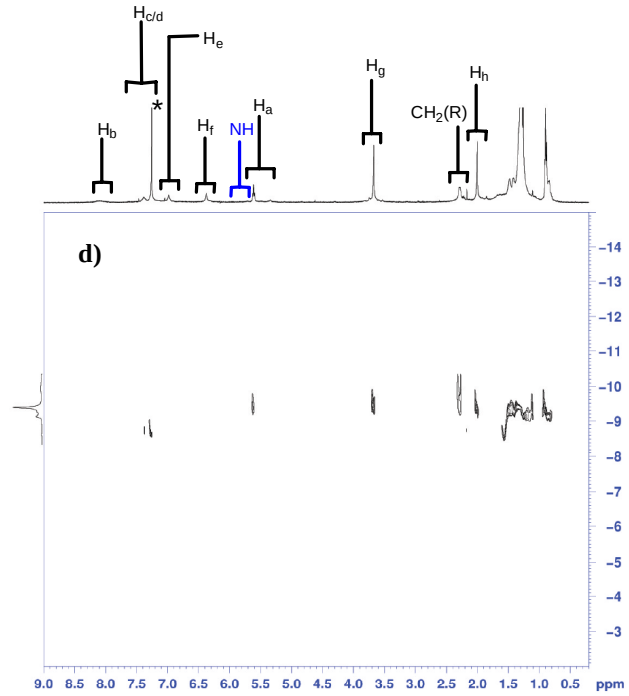
Figure S8. HR-DOSY spectra of a) 6.59 mM, b) 3.46 mM, c) 1.53 mM, and d) 0.66 mM solutions of **1** in $CDCl_3$ at 298 K (500 MHz).








Hc/d
He
Hb
Hf
NH
Ha
Hg
Hh
CH2(R)
c)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


Hc/d
He
Hb
Hf
NH
Ha
Hg
Hh
CH2(R)
d)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

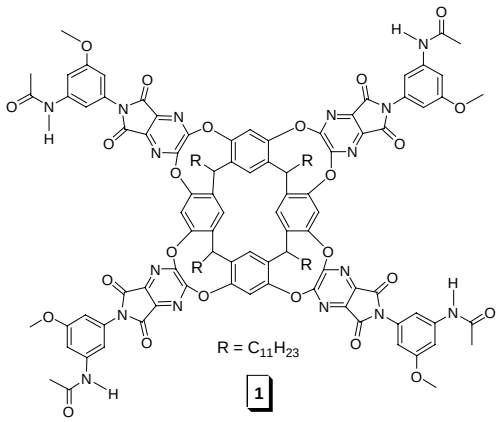
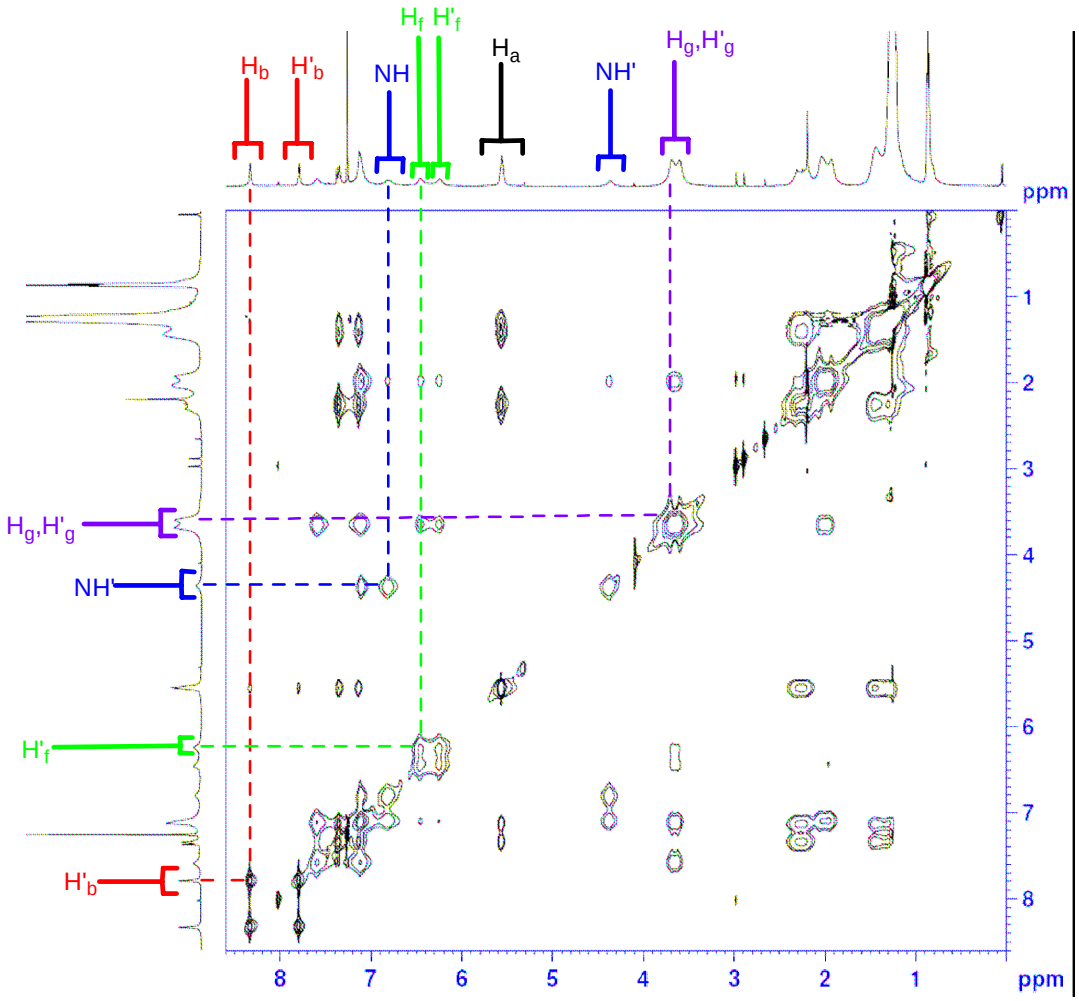

R = C11H23
1

Figure S9. 2D NOESY (EXSY) NMR spectrum of **1** (2.96 mM), $CDCl_3$, at 258 K (500 MHz).



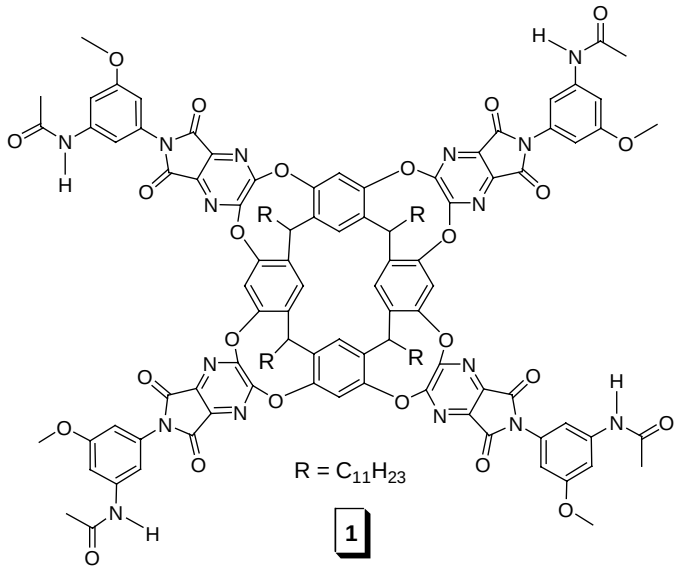
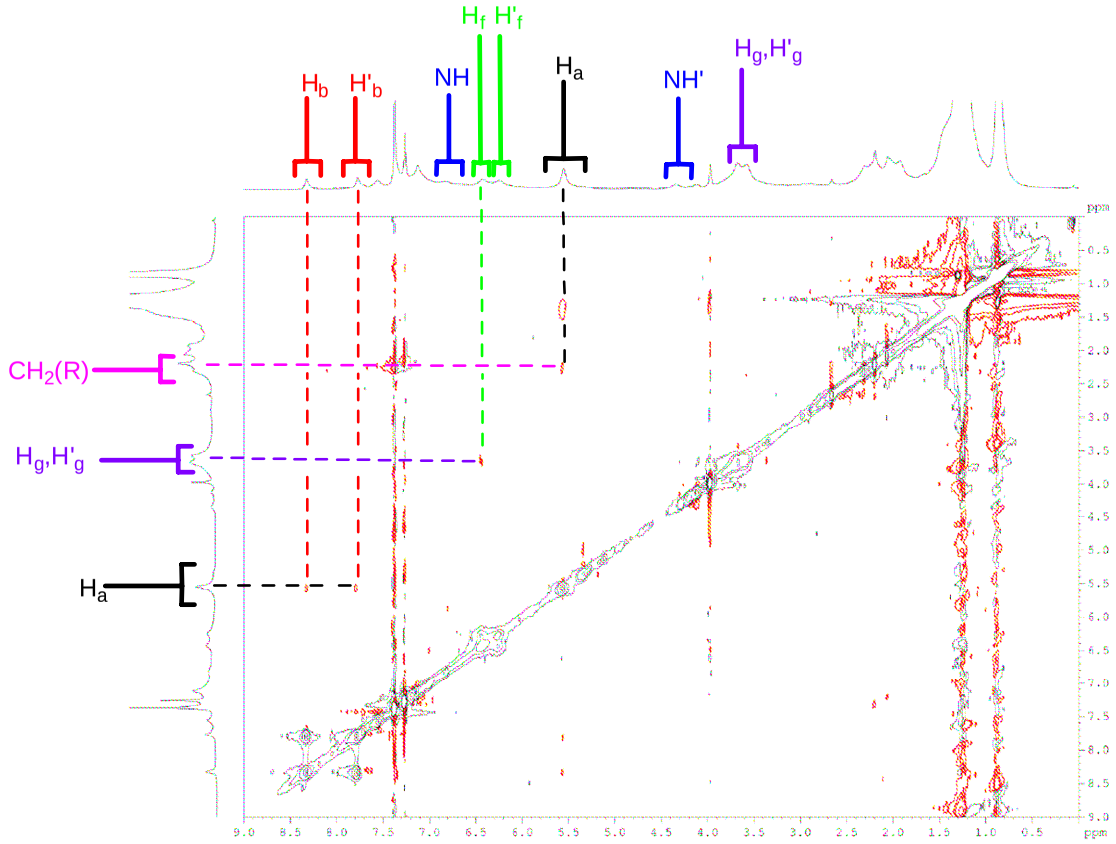


Figure S10. a) 2D ROESY NMR spectrum of **1** (2.49 mM), $CDCl_3$, at 258 K (500 MHz).



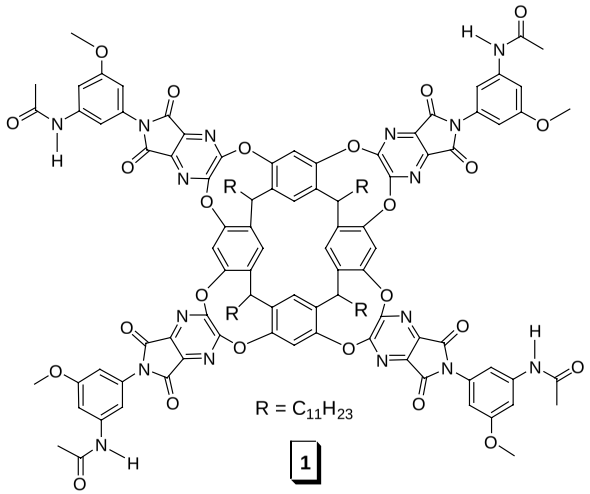
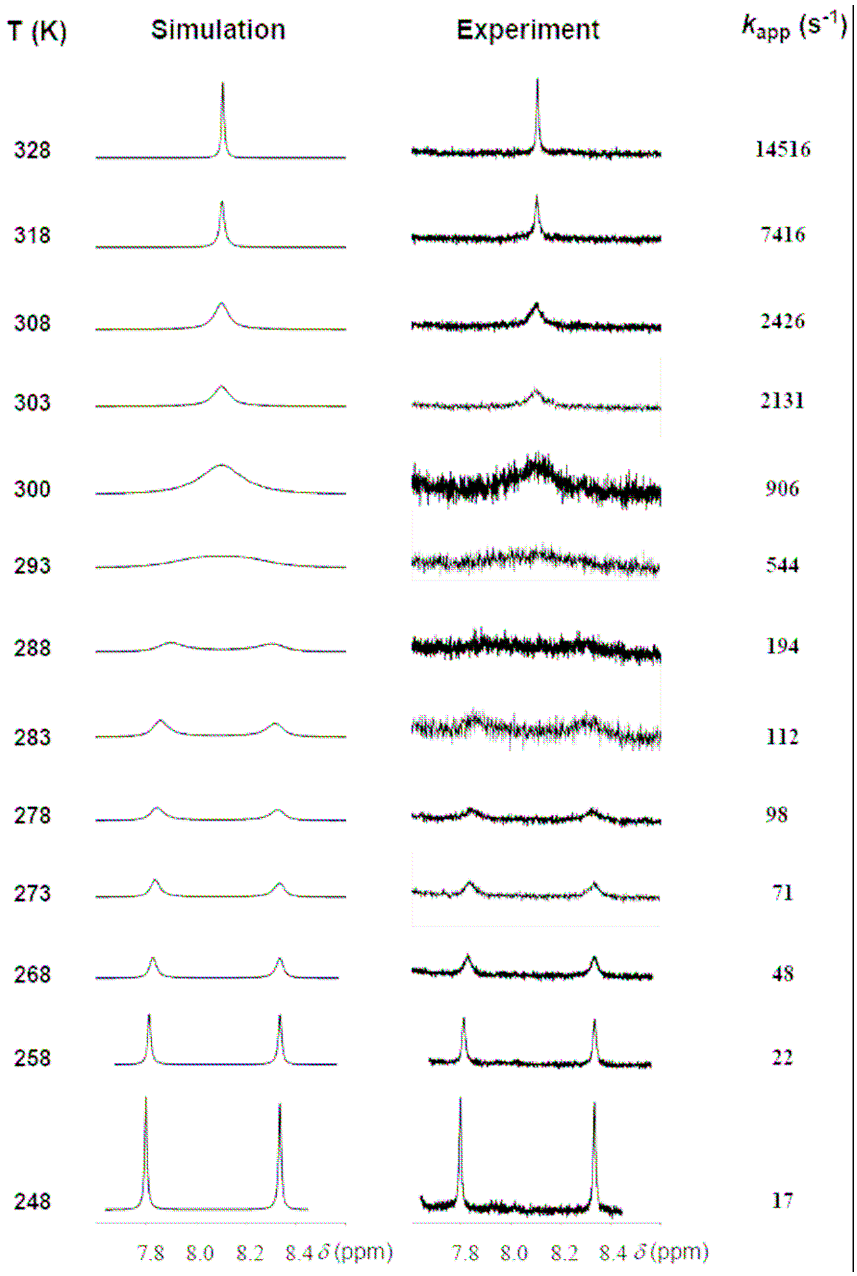


Figure S11. Experimental and simulated regions of ^{1}H NMR spectra of **1** (3.0 mM in $CDCl_3$; 500 MHz) showing H_b resonance at various temperatures.



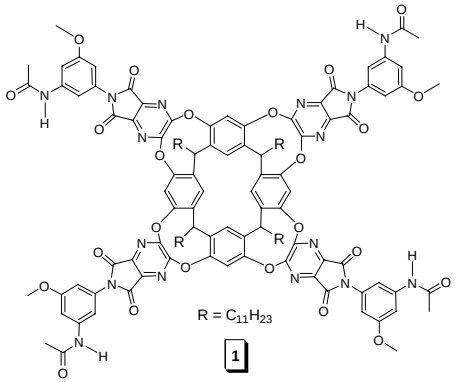
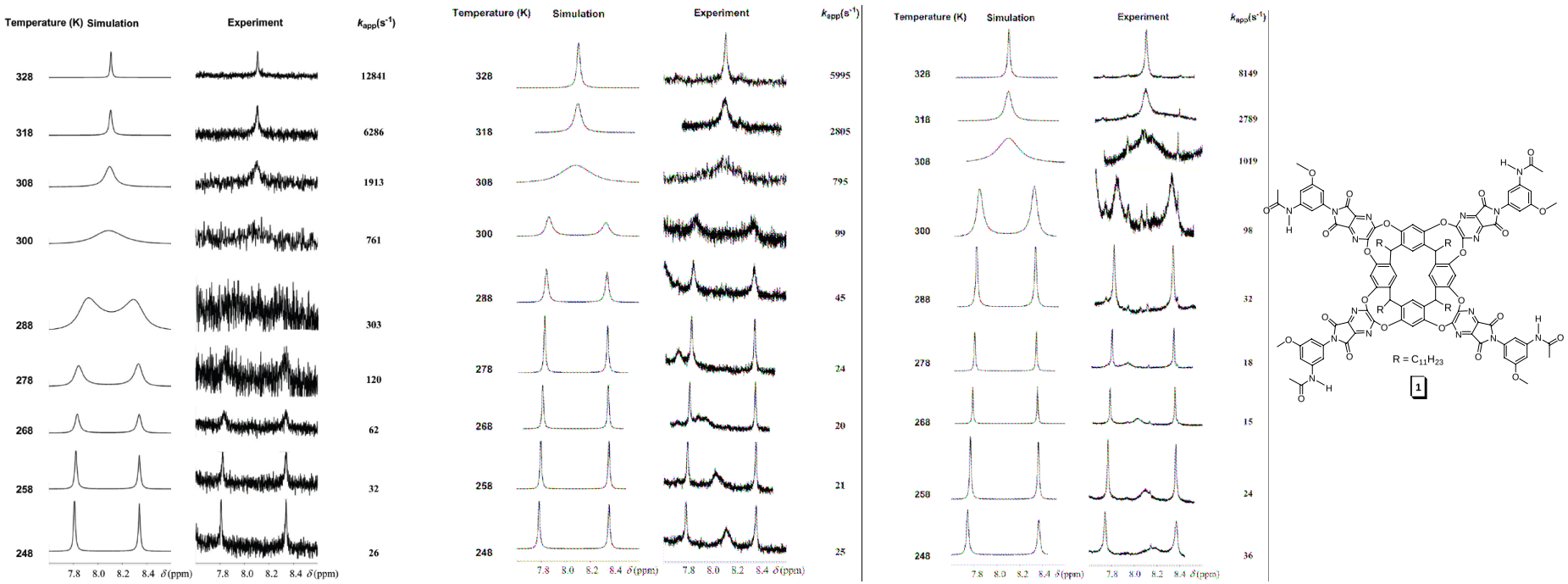
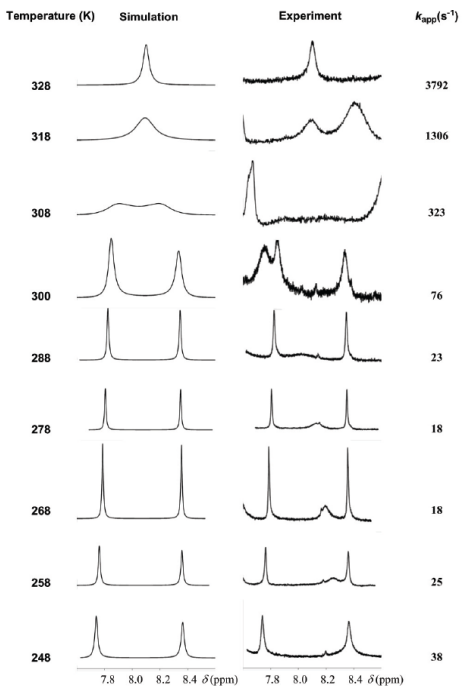


Figure S12. Experimental and simulated regions of ^{1}H NMR spectra (500 MHz) of **1** (6.85 mM in $CDCl_3$) showing H_b resonance, and containing: a) 1.37 mM, b) 6.80 mM, c) 21.1 mM, d) 48.4 mM, e) 116 mM, f) 185 mM trifluoroacetic acid (TFA) at various temperatures.

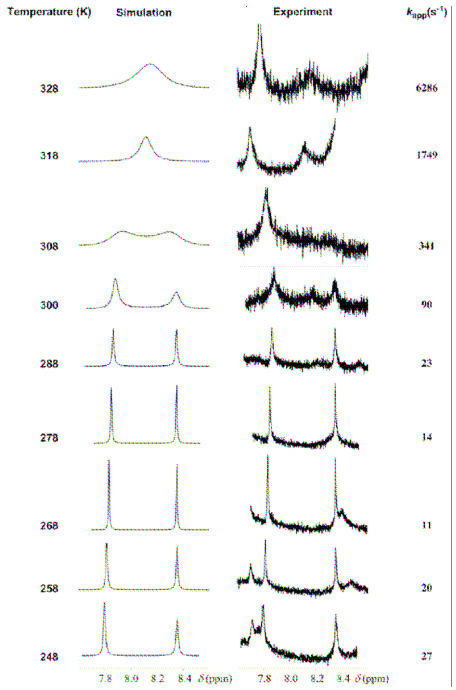
a) **b)** **c)**



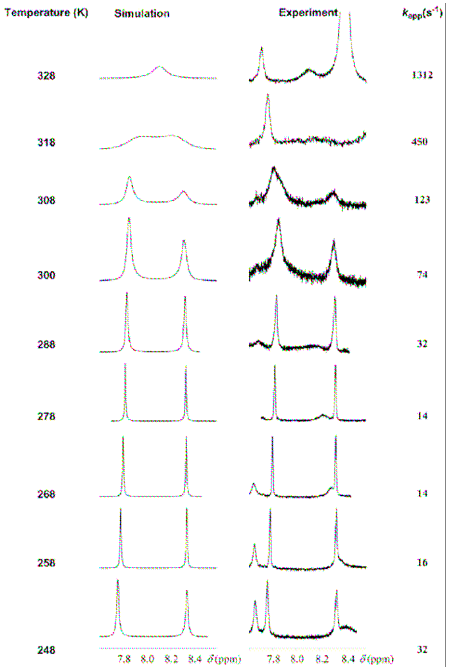
d)


Temperature (K)
Simulation
Experiment
$k_{app}(s^{-1})$
328
318
308
300
288
278
268
258
248
3792
1306
323
76
23
18
18
25
38
7.8 8.0 8.2 8.4 δ(ppm)
7.8 8.0 8.2 8.4 δ(ppm)

e)


Temperature (K)
Simulation
Experiment
$k_{app}(s^{-1})$
328
318
308
300
288
278
268
258
248
6286
1749
341
90
23
14
11
20
27
7.8 8.0 8.2 8.4 δ(ppm)
7.8 8.0 8.2 8.4 δ(ppm)

f)


Temperature (K)
Simulation
Experiment
$k_{app}(s^{-1})$
328
318
308
300
288
278
268
258
248
1312
450
123
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32
14
14
16
32
7.8 8.0 8.2 8.4 δ(ppm)
7.8 8.0 8.2 8.4 δ(ppm)

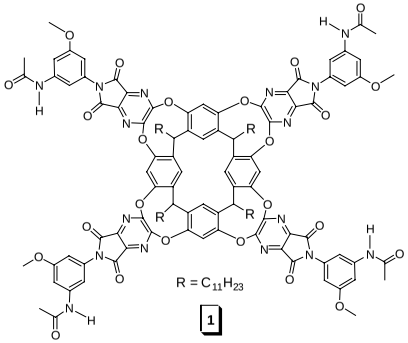
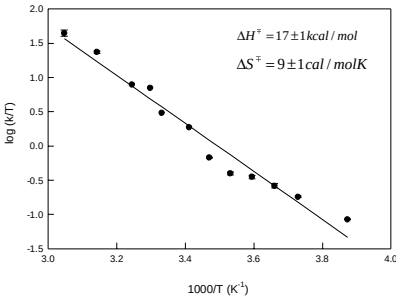
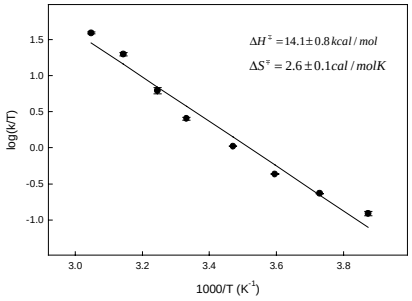

R = $C_{11}H_{23}$
1

Figure S13. Eyring plots (logk_{app}/T vs 1/T) for **1_a/1_b** conformational interconversion of **1** (6.85 mM) in $CDCl_3$ containing: a) 0 mM, b) 1.37 mM, c) 6.80 mM, d) 21.1 mM, e) 48.4 mM, f) 116 mM, g) 185 mM trifluoroacetic acid (TFA). The calculated activation parameters with the corresponding error margins are also shown.

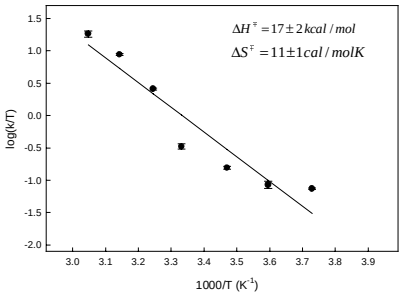
a)



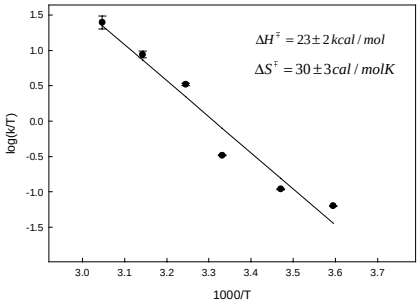
b)



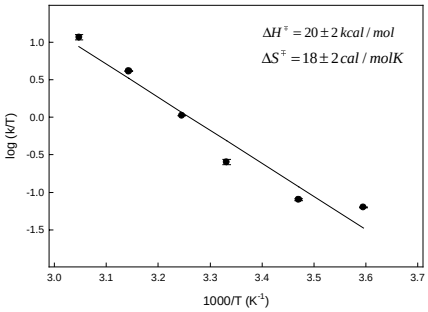
c)



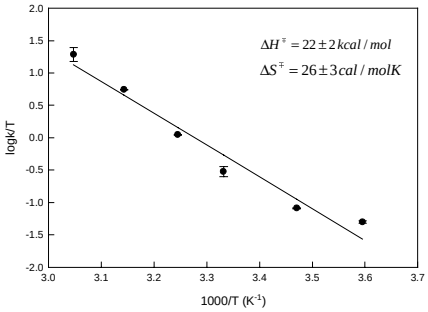
d)



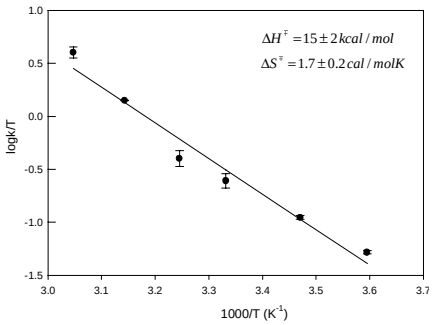
e)



f)



g)



IR Experiments. FT-IR spectra were recorded on a Perkin-Elmer Spectrum GX spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Spectra of 64 scans were obtained with 4 cm^{-1} resolution. Solvent subtraction was completed using a reference spectrum of a neat solvent. A long path, 10 mm, liquid cell (New Era) with KBr windows was used in IR experiments.

Figure S14. N-H stretching region of the infrared spectra of variously concentrated $CHCl_3$ solutions of **2** at 298 K.

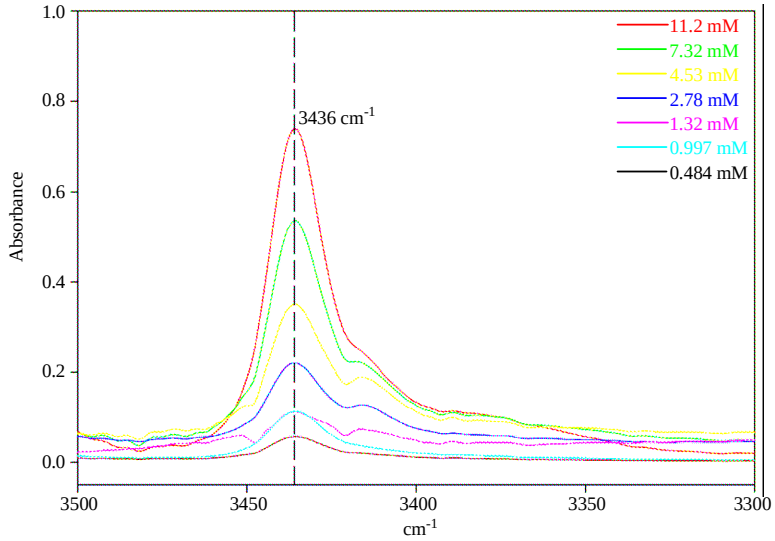


Figure S15. N-H stretching region of the infrared spectra of variously concentrated $CHCl_3$ solutions of **1** at 298 K.

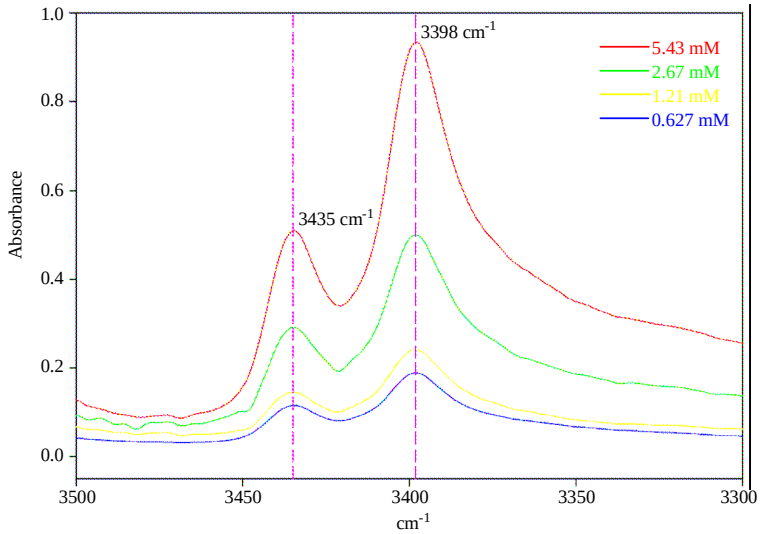


Figure S16. HRMS (ESI) mass spectrum of cavitand **1**.

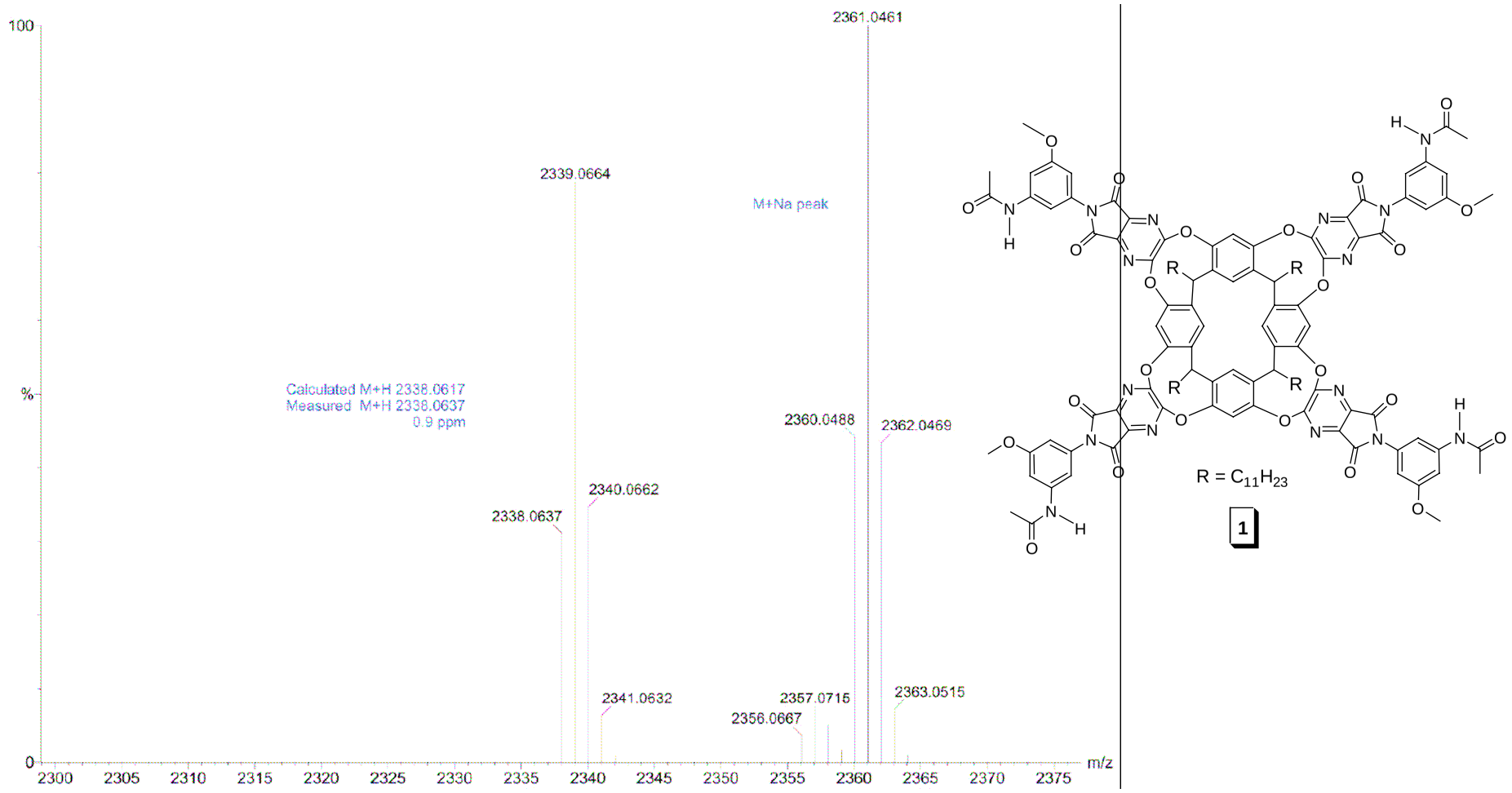
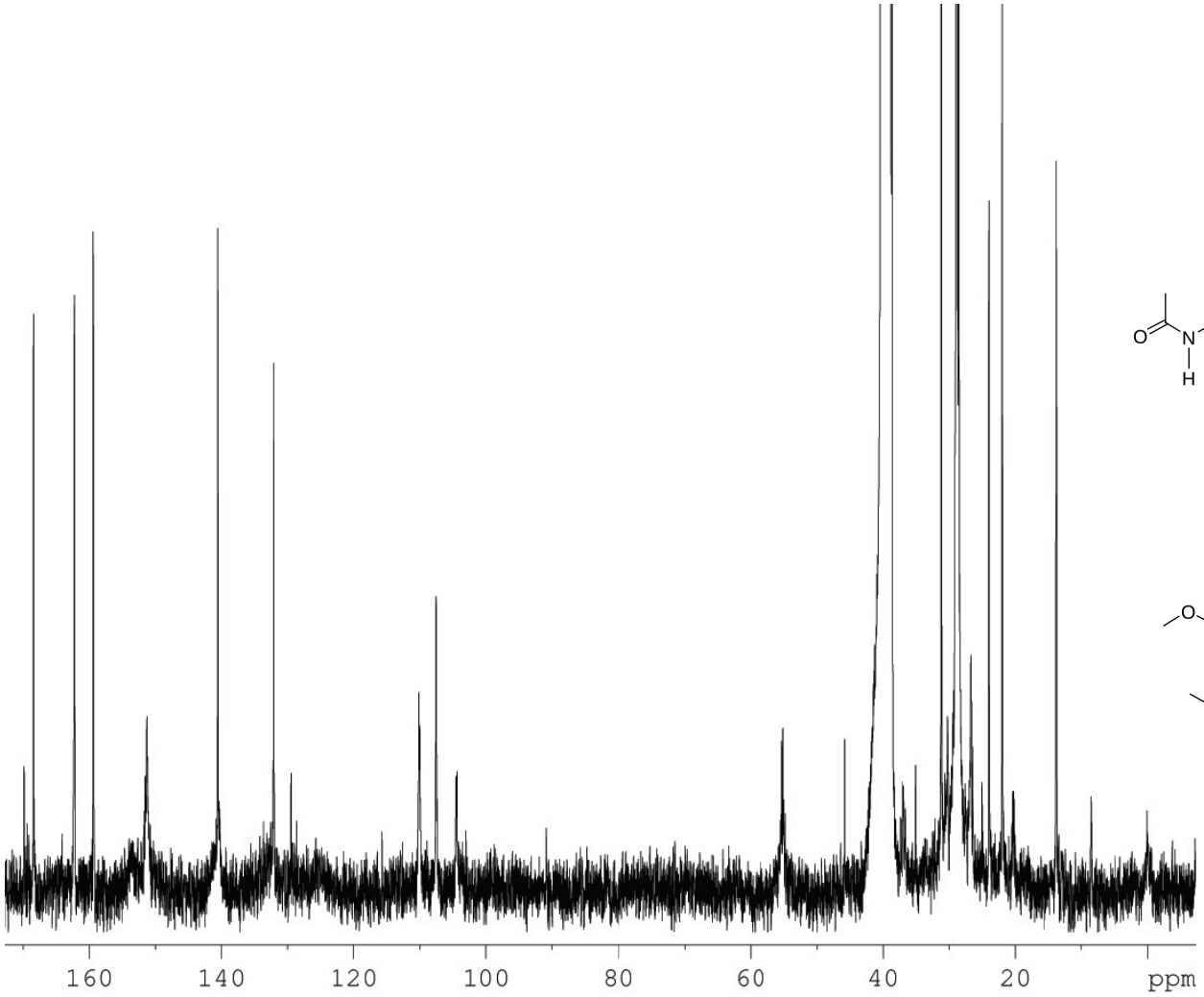
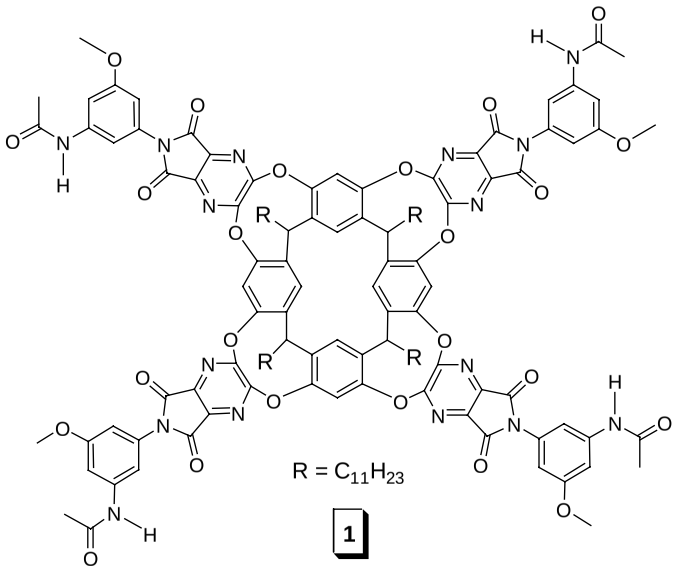


Figure S17. ^{13}C NMR (300MHz) spectrum of cavitand **1** (2.3 mM) in CD_3SOCD_3 at 310 K.





References:

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(4) Peters, J. A.; Van Bekkum, H. *Recueil des Travaux Chimiques des Pays-Bas*, **1981**, *100*, 21.
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(6) Reich H. J. WinDNMR: Dynamic NMR Spectra for Windows. *J. Chem. Educ. Software* **3D2**.
(7) See for instance: Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Weinheim, 1998.