Supporting information

Cavity-Containing Supramolecular Gels as a Tool for Orthogonal Self-assembly Crystallization Processes

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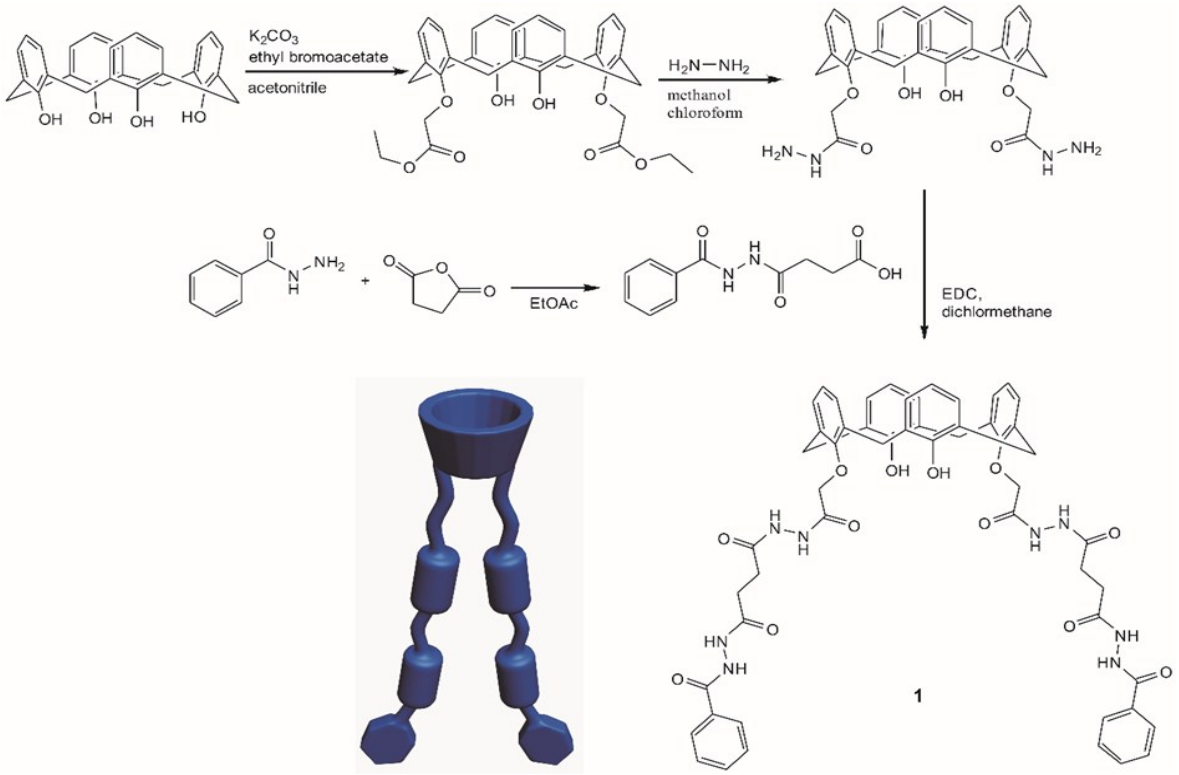
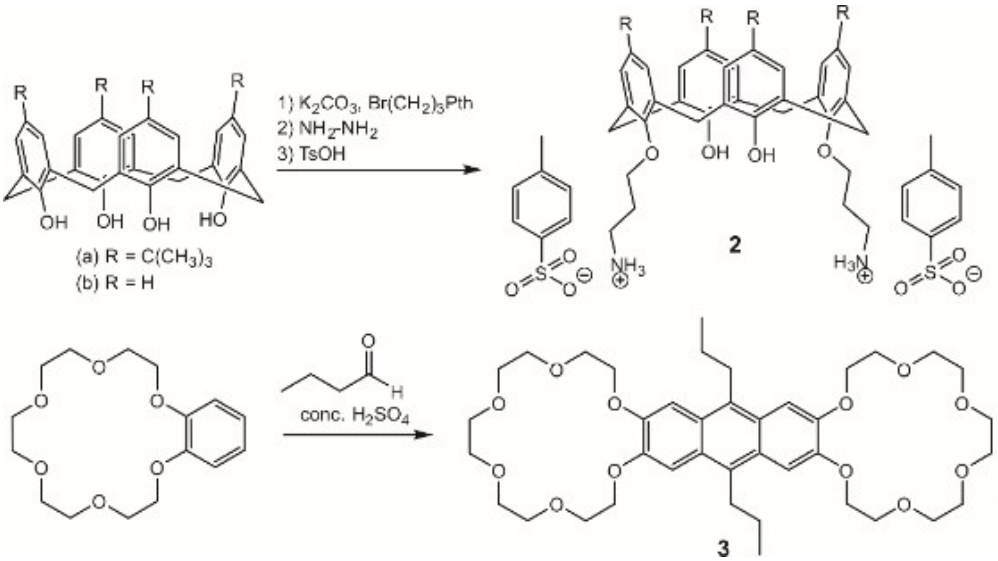
Experimental Data



Calixarene 1

The dihydrazine-calixarene precursor (E. Quinlan, S. E. Matthews and T. Gunnlaugsson, *Tetrahedron Lett.*, 2006, **47**, 9333) (500 mg, 0.88 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (380 mg, 1.9 mmol) was added and the mixture stirred for 10 minutes. 4-(2-benzoylhydrazinyl)-4-oxobutanoic acid (420 mg, 1.7 mmol) was added and the mixture was allowed to warm up to room temperature and stirred overnight. The crude product was purified by column chromatography (chloroform/methanol, 2%) to yield 370 mg (42%) white powder. ^{1}H NMR (400 MHz, $CDCl_3$): 2.53 (4H, broad, C=OCH_2), 2.68 (4H, broad, C=OCH_2), 3.48 (4H, d, *J* = 13.6 Hz, CH_2), 4.24 (4H, d, *J* = 13.6 Hz, CH_2), 4.77 (4H, s, C=OCH_2O), 6.70 (2H, t, *J* = 7.6 Hz, Ar-H), 6.85 (2H, t, *J* = 7.6 Hz, Ar-H), 6.99 (4H, d, *J* = 7.6 Hz, Ar-H), 7.09 (4H, d, *J* = 7.6 Hz, Ar-H), 7.39 (4H, t, *J* = 7.2 Hz, Ar-CH), 7.47 (2H, t, *J* = 7.2 Hz, Ar-CH), 7.92 (4H, m, Ar-CH), 8.44 (2H, s, OH), 9.89 (2H, broad, NH), 10.19 (2H, broad, NH), 10.53 (2H, broad, NH), 11.84 (2H, broad, NH) *ppm*, ^{13}C NMR (700 MHz, DMSO): 28.28, 28.32, 30.59, 73.26, 119.33, 125.58, 127.44, 127.54, 128.47, 128.65, 128.73, 129.14, 131.81, 132.47, 133.55, 152.27, 152.31, 165.45, 166.37, 169.97, 170.70 ppm, MS (ESI-FTICR-MS): 1027.35788 ($M+Na^+$, calc.: 1027.36024), 1043.33210 ($M+K^+$, calc.: 1043.33418) *m/z,* mp: 160 °C.



Calixarene 2a, R = $C(CH_3)_3$ (tosylate salt)

Toluenesulfonic acid (230 mg,1.3 mmol) was dissolved in methanol (3 mL) and cooled to 0° C. diamino calixarene (500 mg, 0.66 mmol) solved in acetonitrile/methanol mixture was slowly added. After warming up to room temperature the white solid was filtered, yielding 410 mg (56%) of a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (18 H, s, $C(CH_3)_3$), 1.33 (18 H, s, $C(CH_3)_3$), 2.19 (6H, s, CH_3), 2.35 (4H, m, CH_2), 3.26 (4H, d, *J* = 13.2, CH_2), 3.32 (4H, m, CH_2-NH_3^+), 3.86 (4H, m, CH_2O), 4.01 (4H, d, *J* = 13.2, CH_2), 6.73 (4 H, s, Ar-H), 6.80 (4H, d, *J* = 8.4 Hz, Ar-H), 7.08 (4H, s, Ar-H), 7.76 (4H, d, *J* = 8.4 Hz, Ar-H), 8.07 (4H, broad, NH_3^+) ppm, ^{13}C NMR (700 MHz, $CDCl_3$): 21.51, 27.93, 31.13, 31.24, 31.52, 32.00, 34.11, 38.98, 74.47, 125. 31, 125.70, 126.16, 128.03, 129.21, 132.19, 140.78, 142.19, 147.41, 149.28, 150.56 ppm, MS (ESI-FTICR-MS): 763.54281 (M-2TsOH$^-$-H$^+$, calc.763.54084) *m/z,* mp: 286 °C.

Calixarene 2b, R = H (tosylate salt)

Toluenesulfonic acid (160 mg, 0.9 mmol) was dissolved in methanol (2 mL) and cooled to 0° C. diamino calixarene (240 mg, 0.45 mmol) solved in acetonitrile/methanol mixture was slowly added. After warming up to room temperature the white solid was filtered, yielding in 240 mg (60%) white powder. 1H NMR (400 MHz, $CDCl_3$): 2.19 (6H, s, CH_3), 2.40 (4H, m, CH_2), 3.25 (4H, m, CH_2-NH_3^+), 3.33 (4H, d, *J* = 12.8, CH_2), 3.85 (4H, m, CH_2O), 4.04 (4H, d, *J* = 12.8, CH_2), 6.71 (4 H, m, Ar-H), 6.82 (8H, m, Ar-H), 7.09 (4H, d, *J* = 7.6 Hz, Ar-H, 7.76 (4H, d, *J* = 7.6 Hz, Ar-H), 8.10 (4H, broad, NH_3^+), ^{13}C NMR (700 MHz, DMSO): 20.77, 27.69, 30.58, 36.26, 73.44, 119.36, 125.46, 127.71, 128.14, 128.64, 129.00, 133.56, 137.91, 145.18, 151.42, 152.37 ppm, MS (ESI-FTICR-MS): 539.28709 (M-2TsOH$^-$-H$^+$, calc.539.29043) *m/z,* mp: 265 °C.

A preliminary X-ray crystal structure was obtained for this material which serves to confirm the gross structural details, however crystal quality was extremely poor. The structure exhibits severe disorder of the tosylate anions and chloroform solvent and the determination is not of sufficient quality to obtain quantitative information nor deposit in the CCDC. Data are available via the open data DOI for this paper. The crystallographic data are as follows: $C_{51}H_{56.75}Cl_{8.25}N_2O_{10}S_2$, *M* = 1214.31 g mol^{-1}, colourless block, 0.649×0.438×0.254 mm^3, triclinic, space group P-1 (No. 2), *a* = 10.1614(11) Å, *b* = 20.487(2) Å, *c* = 28.789(3) Å, α = 71.352(3)°, β = 85.650(3)°, γ = 84.669(3)°, *V* = 5647.1(11) Å^3, *Z* = 4, D_c = 1.428 g/cm^3, F_{000} = 2516, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, *T* = 120(2)K, $2\theta_{max}$ = 41.9°, 41571

reflections collected, 11924 unique (R_{int} = 0.0812). Final *GooF* = 1.992, *R1* = 0.1767, *wR2* = 0.4616, *R* indices based on 8664 reflections with I > 2σ(I) (refinement on F^2), 1248 parameters, 584 restraints. Lp and absorption corrections applied, μ = 0.541 mm^{-1}.

Calixarene 2a, R = $C(CH_3)_3$ ($CF_3SO_3^-$ Salt)

Trifluoromethansulfonic acid (40 mg, 0.26 mmol) was dissolved in methanol (1 mL) and cooled to 0° C. diamino calixarene (100 mg, 0.13 mmol) solved in acetonitrile/methanol mixture was slowly added. After warming up to room temperature the white solid was filtered, yielding in 80 mg (58%) white powder. 1H NMR (400 MHz, $CDCl_3$): 0.83 (18 H, s, $C(CH_3)_3$), 1.28 (18 H, s, $C(CH_3)_3$), 2.33 (4H, m, CH_2), 3.39 (4H, d, *J* = 13.6, CH_2), 3.41 (4H, m, CH_2-NH_3^+), 3.98 (4H, m, CH_2O), 4.05 (4H, d, *J* = 13.6, CH_2), 6.65 (4 H, s, Ar-H), 6.82 (4H, broad, NH_3^+), 7.09 (4H, s, Ar-H), ^{13}C NMR (400 MHz, $CDCl_3$): 27.29, 31.05, 31.14, 31.24, 31.88, 34.07, 34.12, 39.74, 75.31, 77.43, 125.39, 125.87, 128.01, 131.78, 142.88, 147.75, 149.00, 149.78 ppm, MS (ESI-FTICR-MS): 763.54770 (M-2TsOH$^-$-H$^+$, calc.763.54084) *m/z,* mp: 282 °C.

Calixarene 2a, R = $C(CH_3)_3$ (PF_6^- Salt)

Diamino calixarene (100 mg, 0.13 mmol) was dissolved in EtOH (10 mL) and concentrated HCl was added until pH < 2 and the mixture stirred for 2 hours. The solvent was removed and the solid suspended in acetone. Saturated NH_4PF_6 solution was added until the solution became clear. The solvent was removed and water was added. After stirring for 2 hours, filtration, washing with water and drying, it yielded in 85 mg (62%) white powder.1H NMR (400 MHz, $CDCl_3$): 0.85 (18 H, s, $C(CH_3)_3$), 1.30 (18 H, s, $C(CH_3)_3$), 2.38 (4H, m, CH_2), 3.38 (4H, d, *J* = 13.6, CH_2), 3.40 (4H, m, CH_2-NH_3^+), 4.01 (4H, m, CH_2O), 4.04 (4H, d, *J* = 13.6, CH_2), 6.67 (4 H, s, Ar-H), 7.09 (4H, s, Ar-H), 7.35 (4H, broad, NH_3^+), ^{13}C NMR (700 MHz, DMSO): 29.32, 30.90, 31.29, 31.41, 33.64, 34.07, 37.29, 74.13, 125.41, 125.75, 127.33, 133.09, 141.60, 147.38, 149.40, 149.94 ppm, MS (ESI-FTICR-MS): 763.53919 (M-2PF_6^--H$^+$, calc.763.54084) *m/z,* mp: 293 °C.

Gel formation

Vial inversion test

Gel **1**

5 mg of Calixarene **1** was dissolved in 0.5 mL 1,2 dibromoethane and heated up until it resulted in a clear soultion. After cooling down to rt the gel was formed within minutes

Gel **2a/b·3**

30 mg of a 1:1 mixture of Calixarenes of type **2** and crown ether **3** was dissolved in 0.5 mL 1,2,4 trichlorobenzene and heated up until it resulted in a clear soultion. After cooling down to room temperature the gels formed within minutes.

Rheology

Oscillatory stress-sweep experiments were carried out using a TA Instruments AR Rheometer 2000 with a parallel plate set up with a 25 mm rough plate geometry. Experiments were performed at 20 °C and at a fixed frequency of 1 Hz.

Gel **1**

Solvent: 1,2-dibromoethane
Concentration: 2 % w/v

Gel **2a/b·3**

Solvent: 1,2,4-trichlorobenzene
Concentration: 6 % w/v

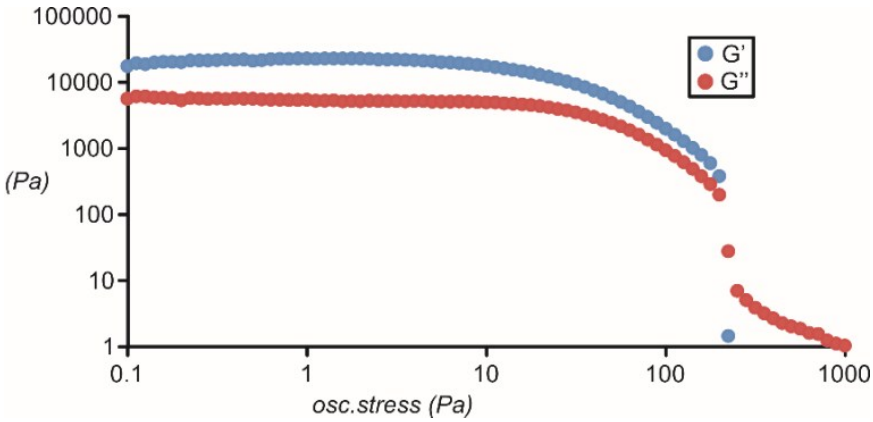


Figure S1 stress sweep rheology for gel **2a·3** in 1,3,5-trichlorobenzene (6% w/v).

SEM

A pre-formed gel sample was transferred onto the silicon wafer and the sample was dried *in vacuo* for 2 days. The sample was coated with 1 nm of platinum using a Cressington 328 Ultra High Resolution EM Coating System and the imaging was performed using an FEI Helios NanoLab DualBeam microscope in immersion mode, with beam settings of 1.5 kV and 43 pA.

Crystallization experiments

4-(4-Biphenyl)-4-oxobutyric acid

10 mg 4-(4-Biphenyl)-4-oxobutyric acid and 15 mg Calixarene **1** were dissolved in 1,2 Dibromoethane (0.5 mL) and heated up to give a clear solution. After cooling down to rt gel formation occured. Crystals grew within a few days. Unit cell indicates that the sample is the same solid state form as CSD refcode SAFNIW (Y. B. Kim, I. Y. Park, Y. H. Park, *Arch. Pharm. Res.*, 1988, *11*, 127).

Paracetamol

1 mg or 5 mg Paracetamol and 15 mg Calixarene **1** were dissolved in 1,2-dibromoethane (0.5 mL) and heated up to give a clear solution. After cooling down to room temperature gel formation occured. Crystals grew within a few days.

2 mg Paracetamol and 30 mg of a 1:1 mixture of Calixarene **2a** and crown ether **3** were dissolved in 1,2,4 Trichlorobenzene (0.5 mL) and heated up to give a clear solution. After slowly cooling down to rt gel formation occured. Crystals grew within a few days.

Unit cell indicates crystals are monoclinic form I CSD refcode HXACAN07 (C.Nichols, C.S.Frampton, *J. Pharm. Sci.*, 1998, *87*, 684).

4-Benzyloxyphenol

10 mg or 20 mg 4-Benzyloxyphenol and 30 mg of a 1:1 mixture of Calixarene **2a** and crown ether **3** were dissolved in 1,2,4-trichlorobenzene (0.5 mL) and heated up to give a clear solution. After slowly cooling down to room temperature gel formation occured. Crystals grew within a few days. Unit cell indicates that the sample is the same solid form as CSD refcode QQQCZV (B.Zaslow, J.L.Dubchansky, *J. Mol. Cryst.*, 1967, *3*, 297).

3-(*p*-Chlorophenoxy)propane-1,2-diol

5 mg of 3-(p-chlorophenoxy)propane-1,2-diol and 30 mg of a 1:1 mixture of Calixarene **2b** (tosylate salt) and crown ether **3** were dissolved in 1,2,4-trichlorobenzene (0.5 mL) and heated up to give a clear solution. After slowly cooling down to rt gel formation occured. Crystals grew within a few days.

X-ray crystal data: $C_{18}H_{22}Cl_2O_6$, M = 405.26, colourless plate, 0.16 × 0.14 × 0.06 mm^3, orthorhombic, space group $Pca2_1$ (No. 29), a = 12.3202(14), b = 4.6501(5), c = 32.022(4) Å, V = 1834.5(4) Å^3, Z = 4, D_c = 1.467 g/cm^3, F_{000} = 848, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 52.88°, 13672 reflections collected, 3747 unique (R_{int} = 0.0909). Final *GooF* = 1.030, *R1* = 0.0591, *wR2* = 0.0948, *R* indices based on 2489 reflections with I >2σ(I) (refinement on F^2), 242 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.386 mm^{-1}. Absolute structure parameter = 0.23(15). CCDC Deposition 1478493. OH hydrogen atoms were located by difference Fourier synthesis and allowed to ride on the parent atom with a fixed isotropic displacement parameter.

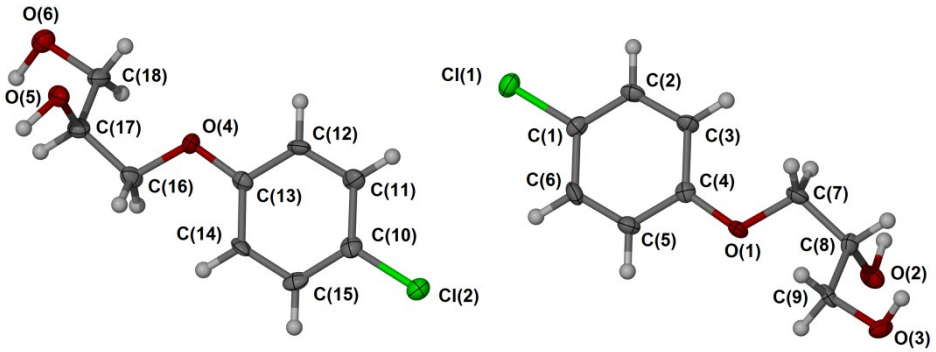


Figure S2. X-ray molecular structure of 3-(p-Chlorophenoxy)propane-1,2-diol.