Template-Directed One-Step Synthesis of Cyclic Trimers by ADMET

Hongyi Hou,[†] Ken C.-F. Leung,[‡] Daniela Larari,[‡] Alshakim Nelson,[†]
J. Fraser Stoddart*[‡] and Robert H. Grubbs*[†]

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, California Institute of Technology, 1200 East California Boulevard, Pasadena, California 91125

California NanoSystems Institute & Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095

Supporting Information

*Correspondence Addresses

Professor J Fraser Stoddart
California NanoSystems Institute and Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)
Tel: (+1)-310-206-7078
Fax: (+1)-310-206-1843
Email: stoddart@chem.ucla.edu

Professor Robert H. Grubbs
Arnold and Mabel Beckman Laboratory of Chemical Synthesis,
California Institute of Technology,
1200 East California Boulevard, Pasadena,
CA 91125 (USA)
Tel: (+1)-626-395-6003
Fax : (+1)-626-564-9297
Email: rhg@chem.ucla.edu

Materials

All reagents were obtained from Aldrich and used without further purification. Compound **3** was synthesized according to a literature procedure[1] while compound **4**-$H_3 \cdot 3PF_6$ was synthesized using a method similar to that described in the literature.[2]

Methods

Reversed-phase high-pressure liquid chromatography (HPLC) was conducted by using a Germini 5 micron C-18 column under a steady ramp (10% MeCN in 0.1% aqueous trifluoroacetic acid (TFA) to 100% MeCN over 90 min) with UV detection at 254 nm using a Beckman System Gold detector. Preparative HPLC was conducted by using a YMC-Pack pro C-18 column (5 micron) under a steady ramp (10% MeCN in 0.1% aqueous TFA to 100% MeCN over 26 min, then stay 100% MeCN for 9 min). ^{1}H NMR spectra were recorded at 300 MHz (Varian Mercury) or 500 MHz (Varian Mercury). Chemical shifts are quoted in parts per million (ppm) using residual protic solvent as the internal standard. Mass spectrometry samples were mixed with a UV absorbing matrix, α-cyanohydroxycinnamic acid, and analyzed by matrix-assisted laser desorption ionization (MALDI) using a Voyager DE-PRO time-of-flight mass spectrometer (Applied Biosystems), equipped with a 20-Hz nitrogen laser (337 nm) and delayed extraction technology. The instrument was calibrated externally with standards from ABI for the mass region of interest resulting in a mass accuracy of +/- 0.1%. The samples were also spiked with peptide standards for internal calibration. Isothermal titration calorimetry (ITC) was performed on a Microcal VP-ITC isothermal calorimeter using CH_2Cl_2 as the solvent at 293 K.

Synthesis of 4-H_3·3BAr_F

$NaBAr_F$ (292 mg, 0.3 mmol) in water (4 mL) was added to a suspension of compound **4**-H_3·3PF_6 (110 mg, 0.1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred vigorously at ambient temperature for 16 h. The organic layer was then isolated and dried ($MgSO_4$), before removing the solvent *in vacuo* to afford the product **4**-H_3·3BAr_F as a pale yellow solid in quantitative yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 4.43–4.49 (m, 12 H, –CH_2NH_2CH_2–), 6.25–6.45 (br, 6 H, –NH_2–), 7.32–7.64 (m, 21 H), 7.66–7.72 (m, 36 H), 7.74–7.85 (m, 9 H). For aromatic proton assignment, see **Figure S1**. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = –63.13 ppm (**Figure S2**).

Figure S1. ^{1}H NMR spectrum of the template **4-H_3·3BAr_F** (300 MHz, CD_2Cl_2, 298 K).

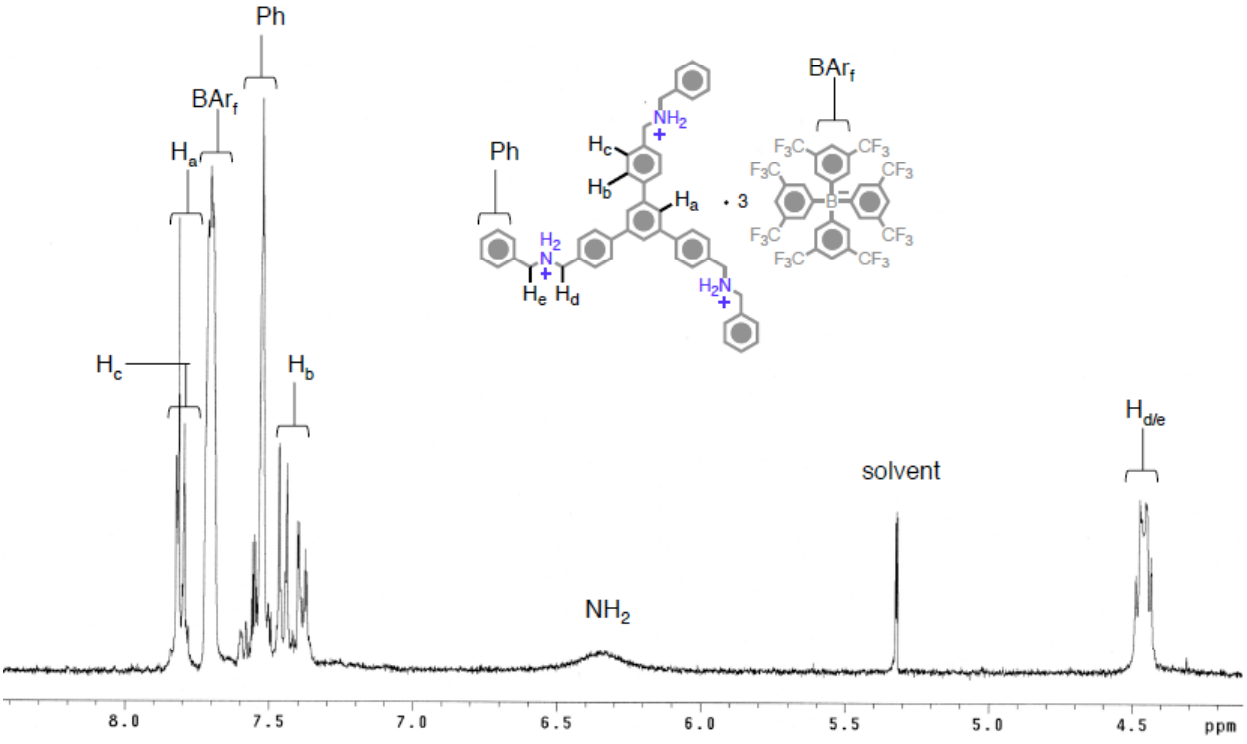
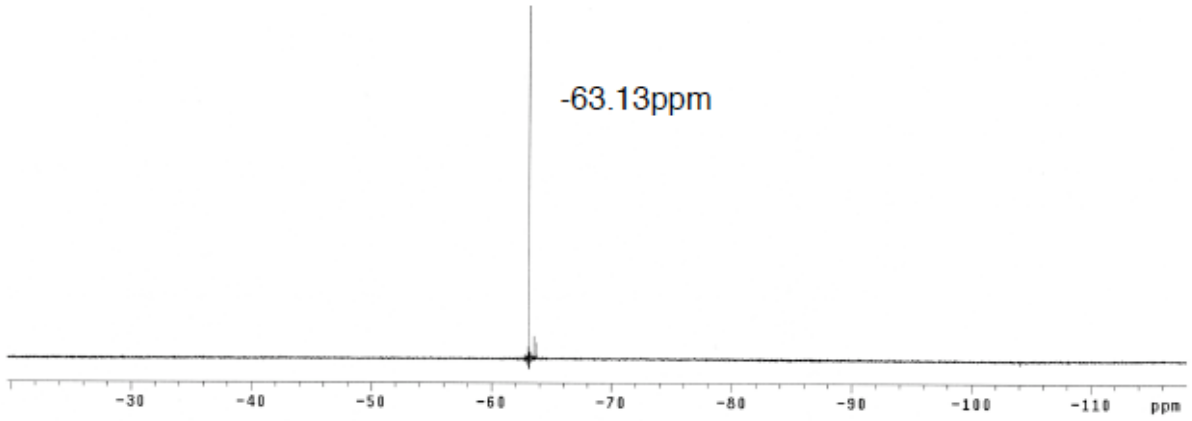


Figure S2. ^{19}F NMR spectrum of the template **4-H_3·3BAr_F** (282 MHz, CD_2Cl_2, 298 K).



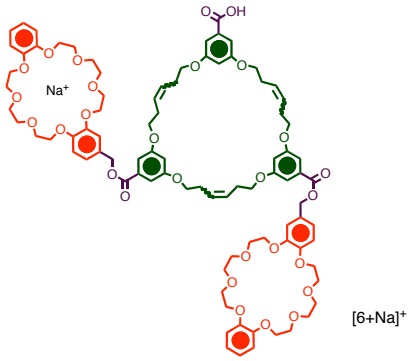
Synthesis of Trimer 5

A mixture containing the crown ether derivative **3** (**Figure S3**) (0.050 mmol) and the template **4**-H_3•3BAr_F (0.017 mmol) in CH_2Cl_2 (40 mL) was stirred at ambient temperature for 15 min. The complexation of monomer and the template was observed (**Figure S4**) by ^1H NMR spectroscopy. A solution of catalyst **2** in CH_2Cl_2 was added to the reaction mixture such that the final concentration of the crown derivative was 1.0 mM. The solution was then heated to 40 °C for 4 h, before quenching the catalyst with ethylvinyl ether (0.5 mL). The excess of solvent was removed under reduced pressure and the sample was subjected to preparative HPLC (steady ramp starting from 10% MeCN in 0.1% aqueous TFA to 100% MeCN over 26 min, then stay 100% MeCN for 9 min). The binding constant of crown ether derivatives with dibenzyl ammonium cation is significantly reduced in MeCN/H_2O mixture comparing with in CH_2Cl_2, so decomplexation of the trimer **5** and template **4**-H_3^{3+} occurs during HPLC separation to afford the pure trimer **5** (19 mg, 55% yield) as a white waxy solid. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.46–

2.54 (m, 12 H), 3.80 (m, 24 H), 3.90 (m, 24 H), 4.16 (m, 24 H), 3.98 (m, 12 H), 5.22 (m, 6 H), 5.60 (m, 6 H), 6.60 (m, 3 H), 6.88–6.98 (m, 21 H), 7.15 (m, 6 H) (**Figure S5**);

^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.0, 32.6, 67.0, 67.8, 68.1, 69.4, 69.5, 69.8, 71.1, 106.7, 106.8, 107.8, 108.6, 109.0, 114.1, 114.5, 114.6, 114.9, 121.9, 122.1, 122.3, 128.0, 128.7, 128.8, 129.5, 132.2, 132.3, 148.9, 149.0, 149.1, 160.1, 160.2, 166.5. (**Figure S6**).

MS(MALDI): calcd for $C_{114}H_{138}O_{36}Na$: *m/z* = 2105.8866; found *m/z* = 2105.8799 $[M+Na]^+$. A fragment of trimer **5** is also observed: calcd for $C_{89}H_{106}O_{28}Na$: *m/z* = 1645.6768; found *m/z* = 1645.6762, corresponding to the cleavage of one of the three DB24C8 connected with ester functionality ($[\mathbf{6}+Na]^+$).



When equimolar amount of the template **4**-H_3^{3+} was added to the isolated and purified trimer **5**, the tritopic complex [5⊃**4**-H_3]$^{3+}$ was not formed again even after 24 h, judging from the ^{1}H NMR spectrum. This result reveals that preorganization with the DB24C8 monomers and the template is crucial for the trimer formation under thermodynamic control.

Figure S3. ^{1}H NMR spectrum of monomer **3** (300 MHz, CD_2Cl_2, 298 K).

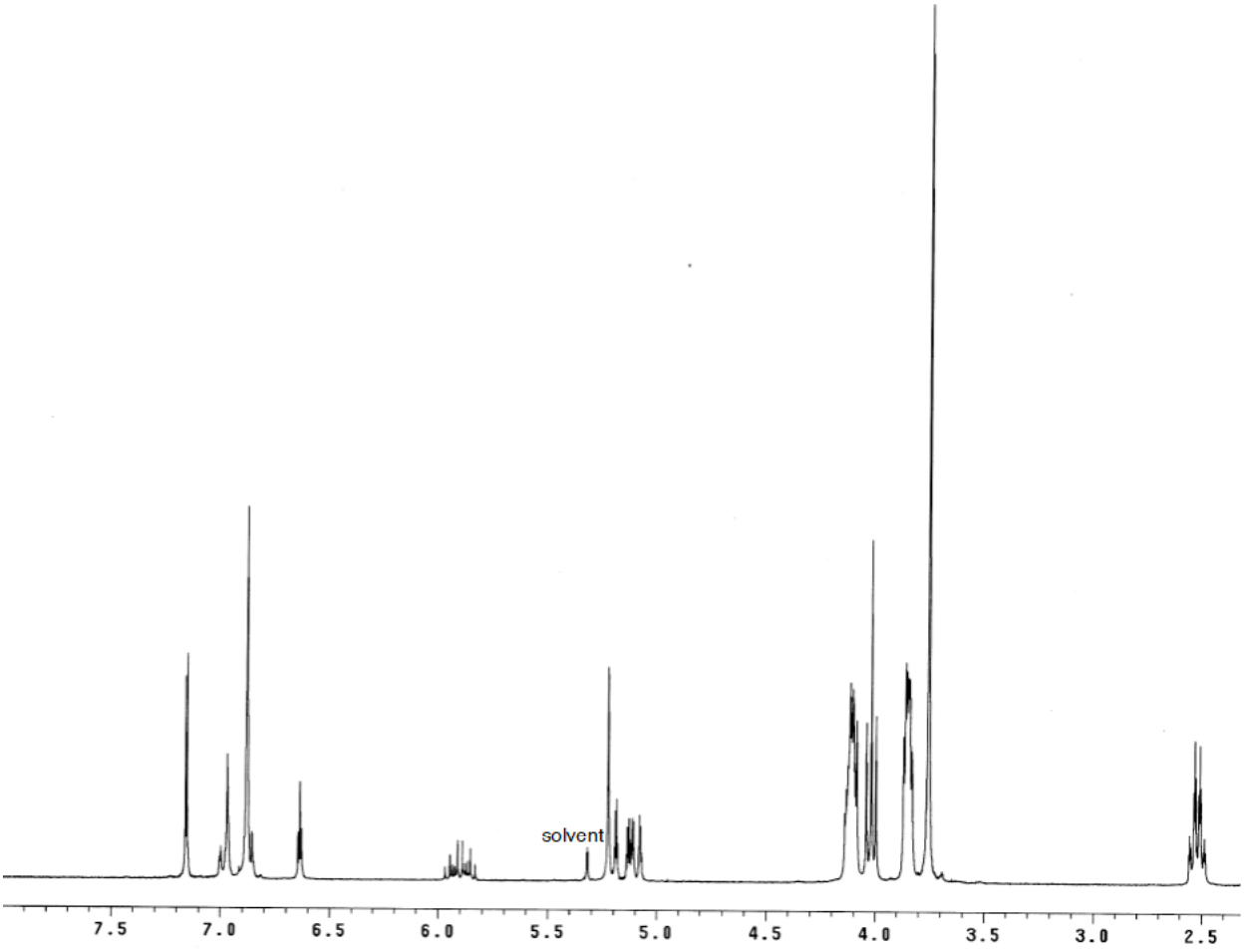


Figure S4. ^{1}H NMR spectrum of the complex $[(\mathbf{3})_3 \supset \mathbf{4}\text{-}H_3]^{3+}$ (300 MHz, CD_2Cl_2, 298 K).

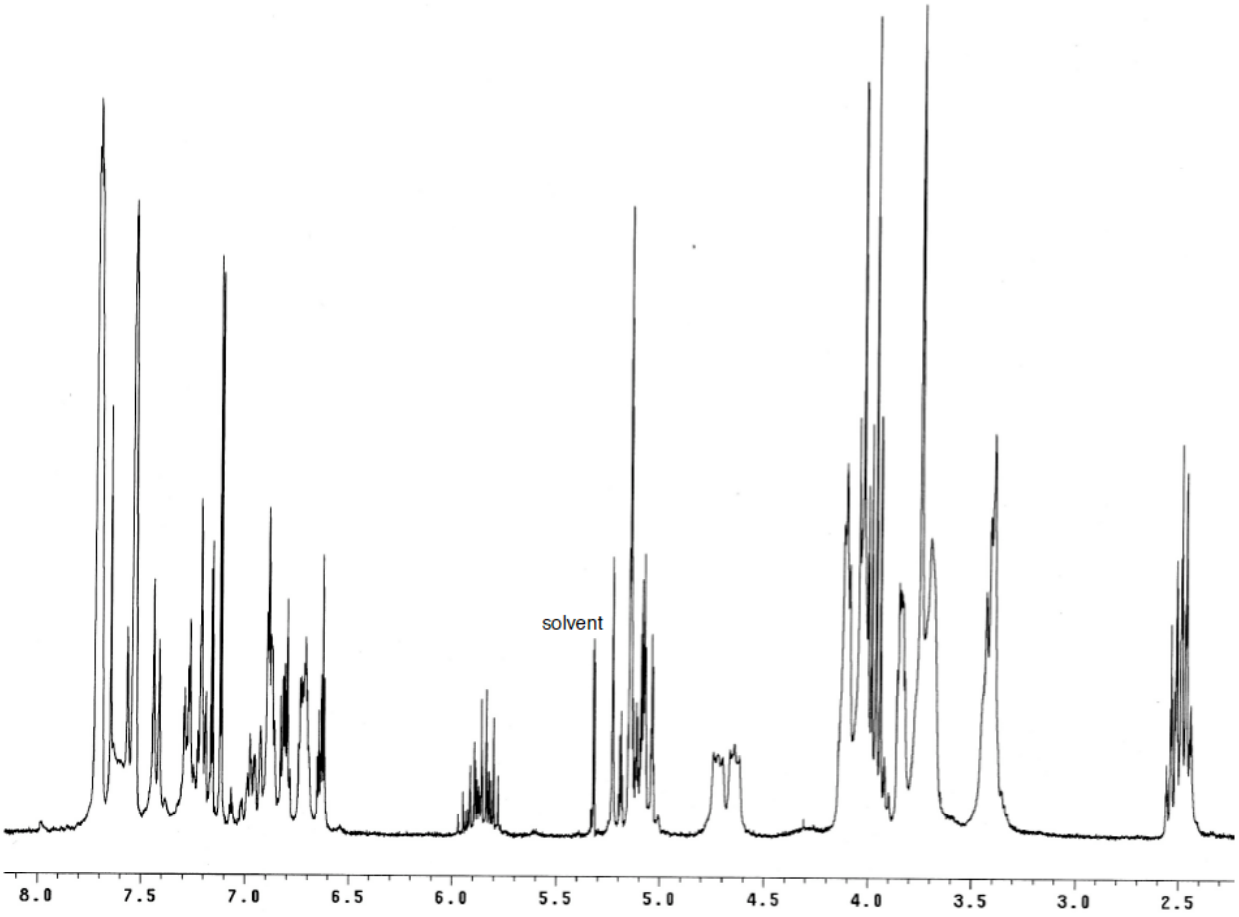


Figure S5. ^{1}H NMR spetrum of the trimer **5** (500 MHz, $CDCl_3$, 298 K).

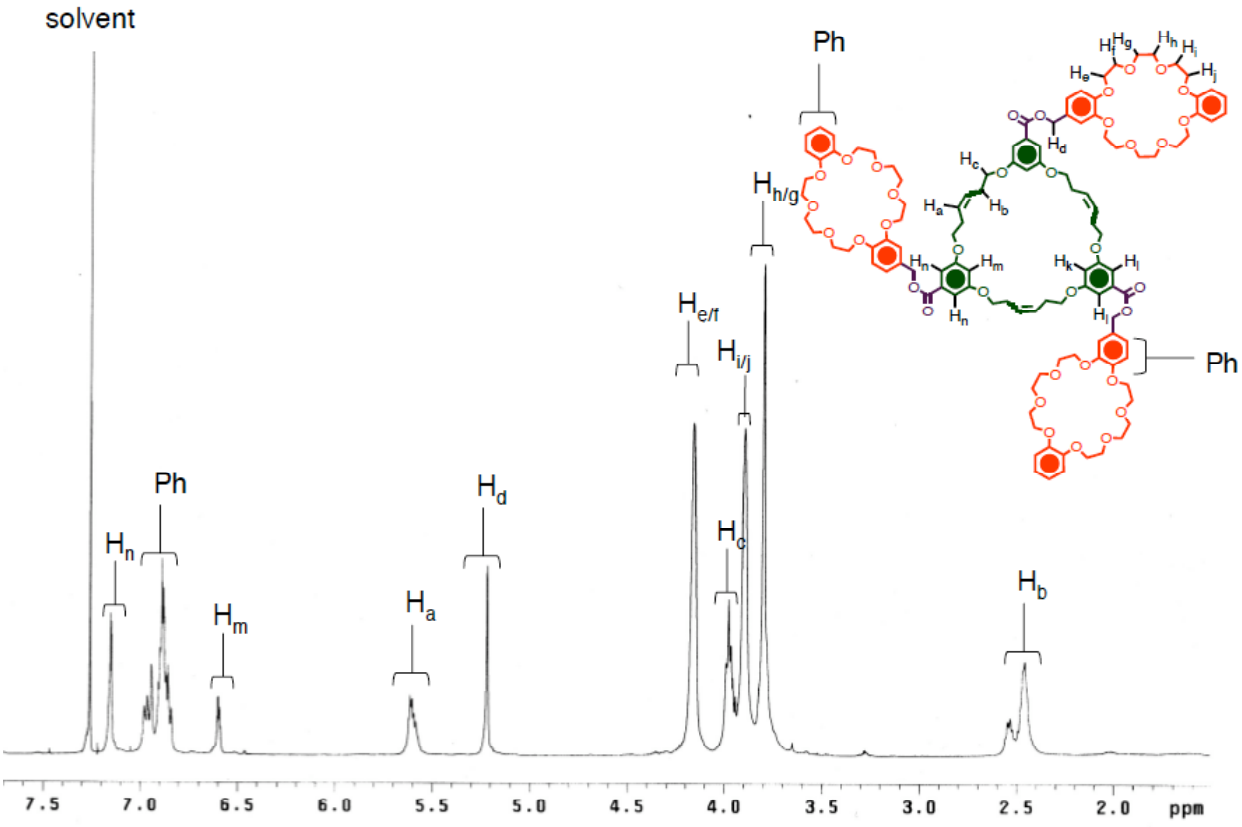
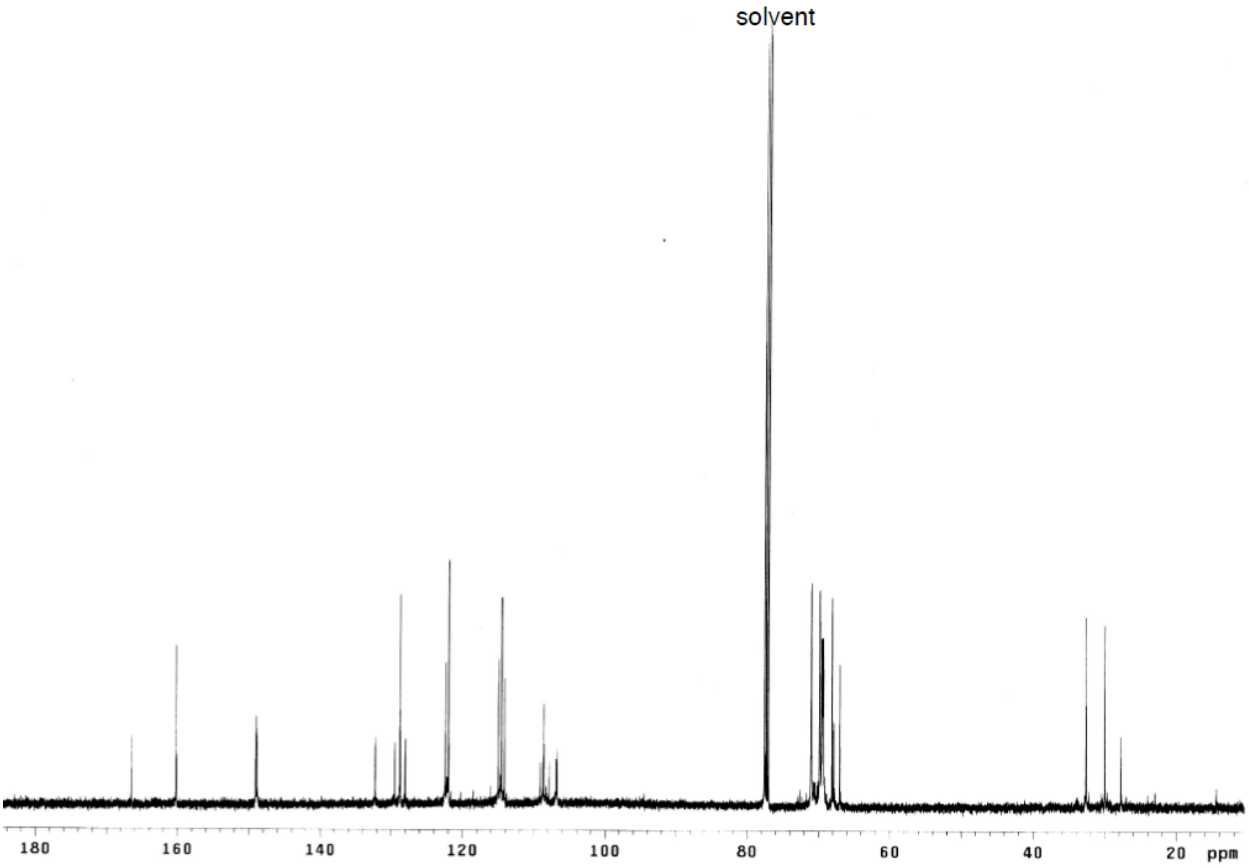


Figure S6. ^{13}C NMR spectrum of the trimer **5** (126 MHz, $CDCl_3$, 298 K).



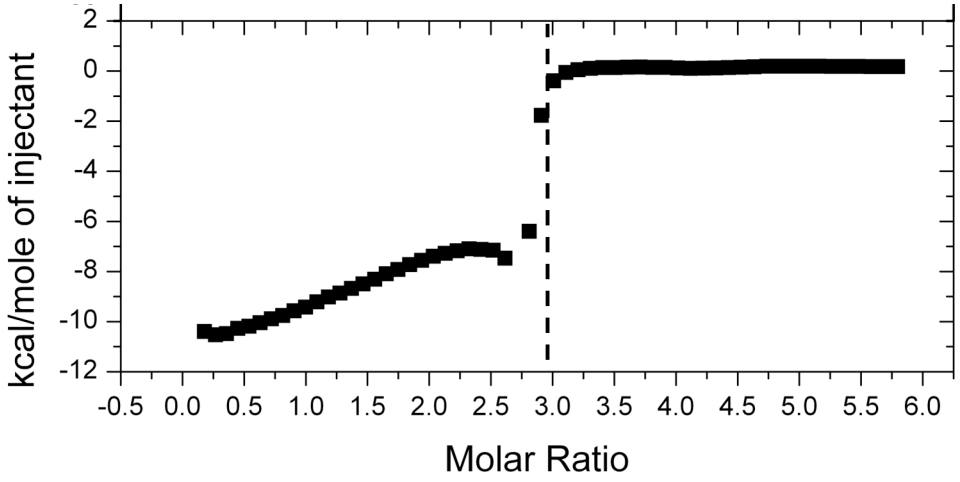
Background Reaction A (Table 1, Entry 2)

The catalyst **2** (20 mol%) in CH_2Cl_2 was added to a solution of the crown ether monomer **3** (0.007 mmol) in CH_2Cl_2. The final concentration of the crown ether monomer was 1.0 mM. The solution was heated to 40 °C for 4 h, before quenching the catalyst with ethylvinyl ether (0.5 mL). The excess of solvent was removed under reduced pressure and the residue was subjected to analytical HPLC (10% MeCN in 0.1% aqueous TFA to 100% MeCN over 90 min) separation. Yield: unreacted monomer (retention time = 66 min) 42%; dimer (retention time = 77 min) 58%.

Background Reaction B (Table 1, Entry 3)

A mixture containing the crown ether monomer **3** (0.007 mmol) and the single-site template **DBA•**BAr_F (0.007 mmol) in CH_2Cl_2 was stirred at ambient temperature for 15 min. The catalyst **2** in CH_2Cl_2 was added to the reaction mixture such that the final concentration of the crown derivative was 1.0 mM. The solution was then heated to 40 °C for 4 h, before quenching the catalyst with ethylvinyl ether (0.5 mL). The excess of solvent was removed under reduced pressure and the sample was subjected to analytical HPLC (10% MeCN in 0.1% aqueous TFA to 100% MeCN over 90 min) separation. Yield: unreacted monomer (retention time = 66 min) 83%; dimer (retention time = 77 min) 17%.

Figure S7. Isothermal titration calorimetric (ITC) isotherm of the complexation between crown ether derivative **3** (injectant) and trifurcate template **4**-H_3·3BAr_F in CH_2Cl_2 (293 K), showing the end-point at molar ratio of ~3.



References

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2. Aston, P. R.; Collins, A. N.; Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 59–62.