JOC The Journal of Organic Chemistry

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Tetranitro-oxacalix[4]crown-Based Host–Guest Recognition Motif and a Related [2]Rotaxane-Based Molecular Switch

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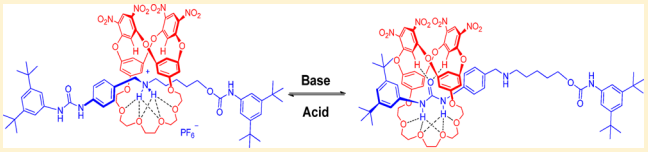
Supporting Information

ABSTRACT: Different from so far reported oxacalix[4]-crown-based host–guest motifs in which oxacalix[4]crowns act only as hydrogen bond acceptors, a [2]pseudorotaxane-type tetranitro-oxacalix[4]crown/urea host–guest recognition motif was developed in which tetranitro-oxacalix[4]crown played a role as both a hydrogen bond donor and an acceptor to stabilize the resulting supramolecular complex. Furthermore, on the basis of a [2]pseudorotaxane complex formed from a tetranitro-oxacalix[4]crown and an axle containing a secondary ammonium ion and a urea group, a [2]rotaxane-based molecular switch was created, in which the oxacalix[4]crown wheel was able to reversibly translocate between the secondary ammonium binding site and the urea binding site of the axle under acid–base stimulation.



INTRODUCTION

Molecular machines driven chemically, electrochemically, or photochemically have attracted an increasing amount of attention because of their broad potential applications.[1] As basic units of molecular machines, mechanically interlocked molecules (MIMs), such as rotaxanes and catenanes,[2] have been well studied with regard to their synthesis, regulation, and applications in molecular electronics,[3] organocatalysts,[4] organogels,[5] and functional molecular materials.[6] Given the increasing level of interest in developing MIMs with structural complexity and advanced functionality, there continues to be a need to develop new wheel–axle interaction motifs (pseudorotaxanes) for the construction of structurally distinct MIMs.[7]

Oxa(aza)calixcrowns,[8] structural analogues of calixcrowns,[9] are derived from oxa(aza)calixarenes[10] and crown ethers.[11] Previously, we have found that oxacalix[4]crowns, derived from an oxacalix[2]arene[2]pyrazine and oligoxyethylene chains, were able to form [2]pseudorotaxane-type host–guest complexes with either secondary ammonium salts[12] or paraquat derivatives.[13] Herein, we report an oxacalix[4]crown host, tetranitro-oxacalix[4]crown-6 [**H1** (Figure 1)], composed of a tetranitro-oxacalix[4]arene[14] and penta-oxyethylene chain, and its host–guest behavior with guests such as a secondary ammonium ion or a urea derivative. In particular, in the case of a urea guest, the host–guest complex motif was stabilized through a new [2]pseudorotaxane-type interaction of the tetranitro-oxacalix[4]crown with the urea group via C–H···O=C hydrogen bonds between the low-rim hydrogen atoms of the oxacalixcrown and the carbonyl group of the urea function. The development of a [2]rotaxane-based molecular switch on this basis of [2]pseudorotaxane complexes is also included.

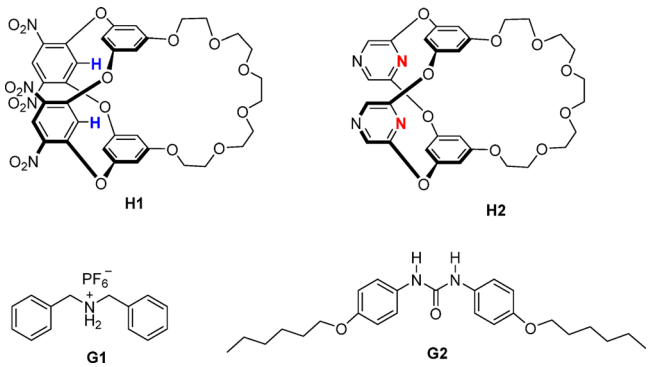


Figure 1. Structures of hosts (**H1** and **H2**) and guests (**G1** and **G2**).

RESULTS AND DISCUSSION

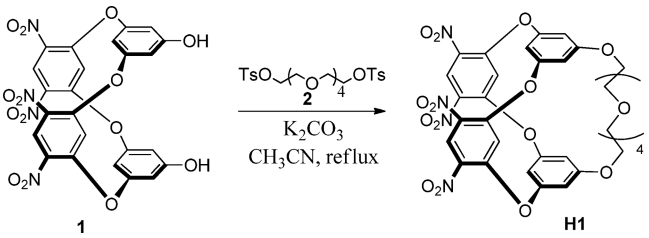
In the previously reported [2]pseudorotaxane [**H2** (Figure 1)],[13] the two low-rim pyrazine nitrogen atoms in the oxacalix[4]crown skeleton acted as hydrogen bond acceptors to stabilize complexes. It would be useful to determine what kind of host–guest behavior would be exhibited if the hydrogen bond acceptors in **H2** were replaced with hydrogen bond donors. We envisioned that via replacement of pyrazines in **H2** with dinitrobenzenes, the two low-rim hydrogen atoms in these oxacalix[4]crown hosts (highlighted in Figure 1) could act as hydrogen bond donors to stabilize host–guest complexes because of the electron withdrawing property of the nitro groups. Our investigation started from the synthesis of tetranitro-oxacalix[4]crowns **H1** that was achieved straightforwardly through a macrocyclization of **1**, prepared by following a

Received: May 9, 2016
Published: July 6, 2016

DOI: 10.1021/acs.joc.6b01082
J. Org. Chem. 2016, 81, 6457–6462

reported procedure,[14] with pentaethylene glycol ditosylate **2** under basic conditions (Scheme 1). **H1** was characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (Supporting Information).

Scheme 1. Synthesis of Tetranitro-oxacalix[4]crown Host H1



In our previous report,[12] pyrazine-derived oxacalix[4]crown **H2** formed a [2]pseudorotaxane-like complex with **G1** in acetone-d_6. In this investigation, it was found that no host–guest complexes were formed between **H1** and **G1** in acetone-d_6 as the ^{1}H NMR spectra of an equimolar mixture of **H1** and **G1** in acetone-d_6 [10 mM (Figure S1)] showed no change in chemical shifts compared to those of free species. It seemed that **H1** is a much weaker host toward secondary ammonium ion **G1** than pyrazine-derived oxacalix[4]crown **H2** is (Figure 1).[12] Thus, we used a less polar solvent, in which stronger hydrogen bonds were expected to form between the corresponding host **H1** and guest **G1**. The host–guest interactions between **H1** and **G1** were observed in a $CDCl_3$/CD_3CN mixed solvent [9/1 (v/v)], which is less polar than acetone-d_6, as indicated by the significant changes in chemical shifts of proton signals of the polyether chain and aromatic protons H_b and H_c of **H1** in the ^{1}H NMR spectrum of an equimolar mixture of **H1** and **G1** (10 mM), as shown in Figure 2.

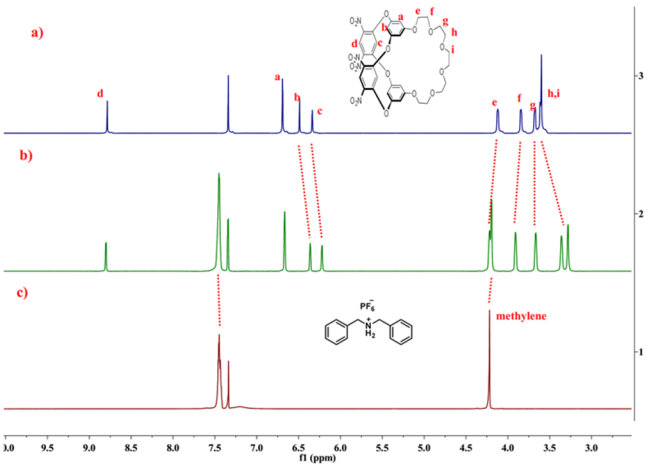


Figure 2. ^{1}H NMR spectra (500 MHz, 9/1 $CDCl_3$/CD_3CN, 298 K, c = 10 mM) of (a) **H1**, (b) **H1** and **G1**, and (c) **G1**.

Considering the guest urea moiety in **G2** has both H bond donors and acceptors, we envisioned **G2** could be more suitable for the formation of a stable complex with host **H1** through formation of multiple hydrogen bonds, but not with **H2** because only hydrogen bond acceptors exist in **H2**. This was proven experimentally. When guest **G2** was mixed with an equimolar **H2** in $CDCl_3$, there was no complex formation as no change in chemical shifts was observed in the ^{1}H NMR spectrum compared to those of free species [10 mM (Figure S2)]. As we expected, a complex of **G2** and **H1** was formed right upon mixing **G2** and **H1** in $CDCl_3$. We postulated that this was due to the electron withdrawing property of the two nitro groups in the dinitrophenyl rings of oxacalix[4]crown **H1**. The two low-rim hydrogen atoms in the two dinitrophenyl rings of **H1** are more acidic and could act as hydrogen bond donors to form hydrogen bonds with the carbonyl group of **G2**. The formation of a complex of **G2** and **H1** is evidenced by significant changes in chemical shifts in the ^{1}H NMR spectrum of an equimolar mixture of **H1** and **G2** in $CDCl_3$ compared to those of free **H1** and **G2** (10 mM), as shown in Figure 3. The upfield shifts for signals of protons H_a and H_b of **H1** (0.13 and 0.03 ppm, respectively), as well as signals of protons H_α and H_β of **G2** (0.07 and 0.15 ppm, respectively), signify the possible existence of shielding effect. A dramatic downfield shift (0.26 ppm) for signals of the low-rim protons H_c of **H1** implied the existence of hydrogen bonding interactions between protons H_c of **H1** and the carbonyl oxygen atom of **G2**. The downfield shift (0.37 ppm) for N–H protons of **G2** indicated the existence of hydrogen bonding interactions between the polyether oxygen atoms of **H1** and N–H groups of **G2**. The two-dimensional (2D) NOESY spectrum of an equimolar mixture of **H1** and **G2** in $CDCl_3$ [10 mM (Figure S3)] clearly showed the correlations of protons H_α of **G2** with phenyl protons H_a of **H1**, protons H_β of **G2** with phenyl protons H_a and H_c of **H1**, and N–H of **G2** with the protons of the polyether chain of **H1**. This evidence supports our proposed model of host–guest interaction between **H1** and **G2** within a threaded complex **G2⊂H1** (Figure 4). The optimized geometry of complex **G2⊂H1** was calculated using the semiempirical PM6 method as implemented in the Gaussian 09 program package (Supporting Information). The calculation showed the existence of hydrogen bond interactions between the two aromatic protons H_c of **H1** and the carbonyl oxygen atom of **G2** with bond lengths of 2.065 and 2.879 Å, respectively, as well as those between the polyether oxygen atoms of **H1** and the N–H protons of **G2** with bond lengths between 1.918 and 1.953 Å. Moreover, π–π staking interaction between one of the dinitrobenzene rings of **H1** and one of the benzene rings of **G1** was also observed in the optimized structure (Figure 5, Figure S4, and Table S1). Such a result of calculation supported our proposed model of the threaded host–guest complex **G2⊂H1**. The hydrogen bond interactions between the low-rim hydrogen atoms H_c of **H1** and the carbonyl group of **G2** were thus shown to play an important role in stabilization of the threaded host–guest complex. A Job plot (Figure S5) based on ^{1}H NMR data demonstrated that **H1** and **G2** formed a 1/1 complex in $CDCl_3$. The association constant (K_a) of complex **G2⊂H1** in $CDCl_3$ was determined to be 180 ± 23 M^{-1} with a ^{1}H NMR titration method (Figures S6–S8).

The results presented above indicate that host **H1**, possessing five oxyethylene units, has a suitable cavity for forming stable [2]pseudorotaxanes with either secondary ammonium salt **G1** or diphenylurea **G2** in weakly polar solvents. Given the host–guest behavior of **H1** and **G1** or **G2**, we attempted to create a [2]rotaxane-based molecular switch **R1** through a threading-followed-by-stoppering approach using a **H1**/secondary ammonium ion template. A [2]-pseudorotaxane-like complex **T⊂H1** was created through interaction of host **H1** with a guest **T** that contains both a

DOI: 10.1021/acs.joc.6b01082
J. Org. Chem. 2016, 81, 6457–6462

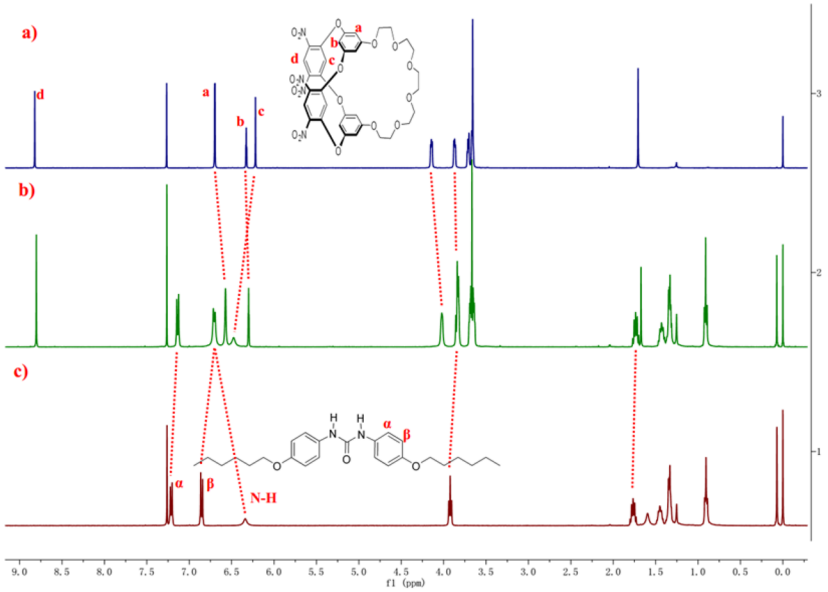


Figure 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) **H1**, (b) **G2** and **H1**, (c) **G2** (c = 10 mM).

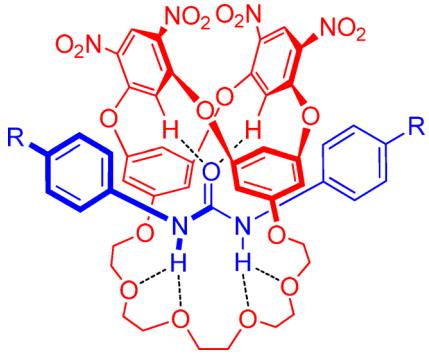


Figure 4. Proposed model of host–guest interaction between **H1** and **G2**.

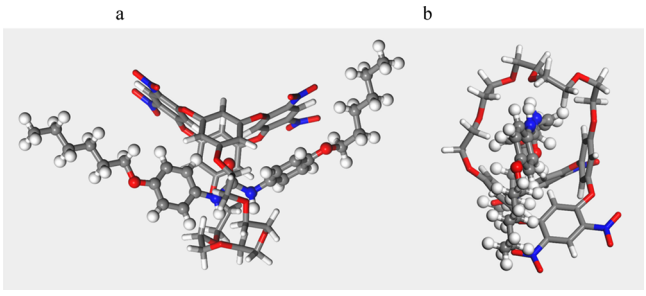


Figure 5. Optimized structure of complex **G2⊂H1** with **G2** as balls and sticks and **H1** as sticks. Color code: C, gray; N, blue; O, red; H, white. The structures in panels a and b were rotated 90° with respect to each other.

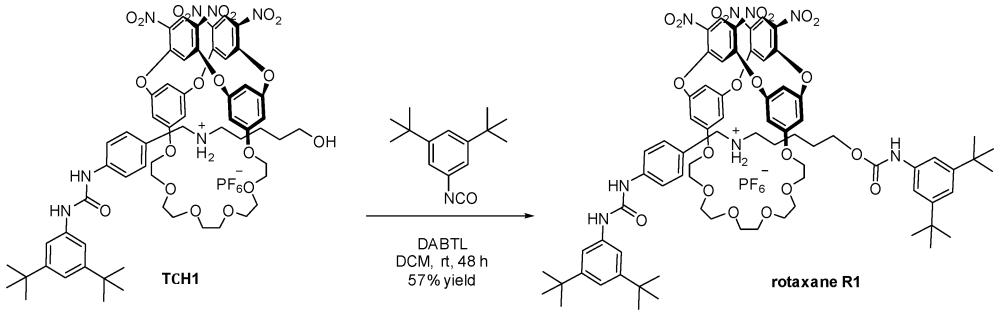
secondary ammonium unit and a urea unit, and subsequent coupling of complex **T⊂H1** with 1,3-di-*tert*-butyl-5-isocyanatobenzene afforded target [2]rotaxane **R1** (Scheme 2), which was characterized by ^{1}H NMR, ^{13}C NMR, and 2D NOESY spectroscopies [acetone-d_6 (Supporting Information)] and HRMS.

The ^{1}H NMR spectrum of [2]rotaxane **R1** in acetone-d_6 (Figure 6) showed the split of aromatic (H_a, H_c, and H_d) and oxyethylene proton signals of the macrocyclic component **H1**, and the appearance of two resonances for these protons is consistent with the reduction in symmetry of macrocycle **H1**, which manifested the existence of two magnetically inequivalent phenyl ring protons. Furthermore, H_7 and H_9 of axle **T1** obviously shifted upfield possibly because of the shielding effect, signifying the formation of [2]rotaxane **R1** with the macrocyclic component **H1** residing at the -NH_2^+- station of the axle component. This result showed that oxacalix[4]crown **H1** interacts stronger with secondary ammonium ion than that of urea (Figure S9).

We attempted to reversibly translocate macrocyclic component **H1** between the secondary ammonium -NH_2^+- station and the urea station of axle **T1**. Macrocyclic component **H1** was positioned at the -NH_2^+- station of axle **T1** because the interactions with secondary ammonium ion were stronger than those of urea. Upon addition of 2 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) to an acetone-d_6 solution of **R1** (10 mM), the ^{1}H NMR spectrum (Figure 7b) showed a significant upfield shift (0.70 and 0.87 ppm) for protons of the methylene groups adjacent to the NH group (H_7 and H_9, respectively) of **T1**, indicating deprotonation of -NH_2^+- function; upfield shifts experienced by aromatic protons H_2, H_5, and H_6 (0.07, 0.28, and 0.21 ppm, respectively) of **T1**, as well as H_a and H_a' (0.06 and 0.14 ppm, respectively) of **H1**, were possibly caused by the shielding effect of the aromatic rings of **H1** located at the urea station. Aromatic protons H_c and H_c' of **H1** obviously shifted downfield by 0.45 and 0.40 ppm, respectively, implying the existence of hydrogen bonds between these protons and the C═O group of the urea moiety of **T1**. On the basis of these changes in chemical shifts, we concluded that macrocyclic component **H1** in [2]rotaxane **R1** was translocated from the -NH_2^+- station to the urea station of thread **T1** upon deprotonation of the -NH_2^+- function. Next, we tried to bring **H1** back to the secondary ammonium -NH_2^+- station by adjusting the environment to an acidic one. We found that after addition of 5 equiv of aqueous hexafluorophosphoric acid (60 wt %) to the solution of deprotonated **R1** described above, relocation of the macrocyclic component **H1** ring to the -NH_2^+- station of thread **T1** was achieved, as was evidenced by the ^{1}H NMR spectrum (Figure 7c) that was

DOI: 10.1021/acs.joc.6b01082
J. Org. Chem. 2016, 81, 6457–6462

Scheme 2. Synthesis of Tetranitro-oxacalix[4]crown-Based [2]Rotaxane R1



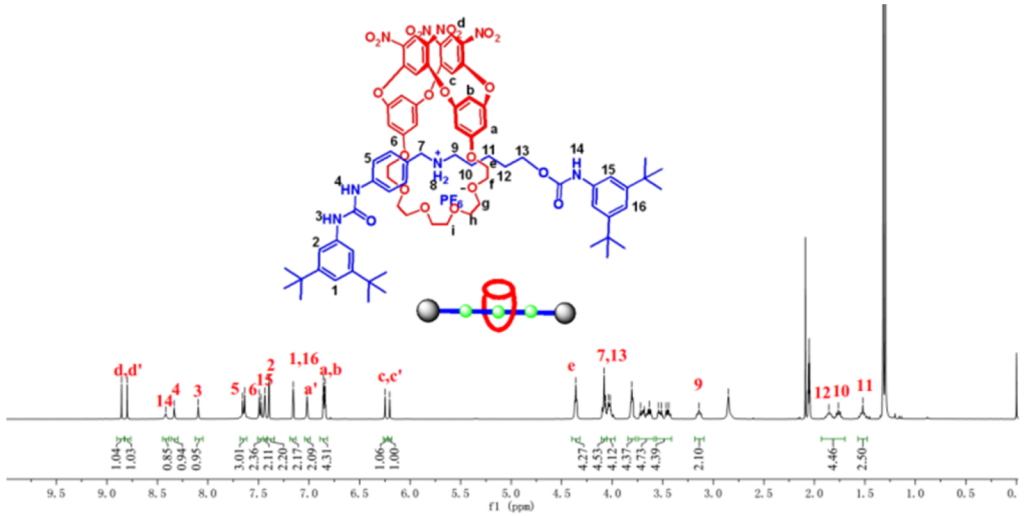


Figure 6. ^{1}H NMR spectrum of **R1** (400 MHz, acetone-d_6, 298 K).

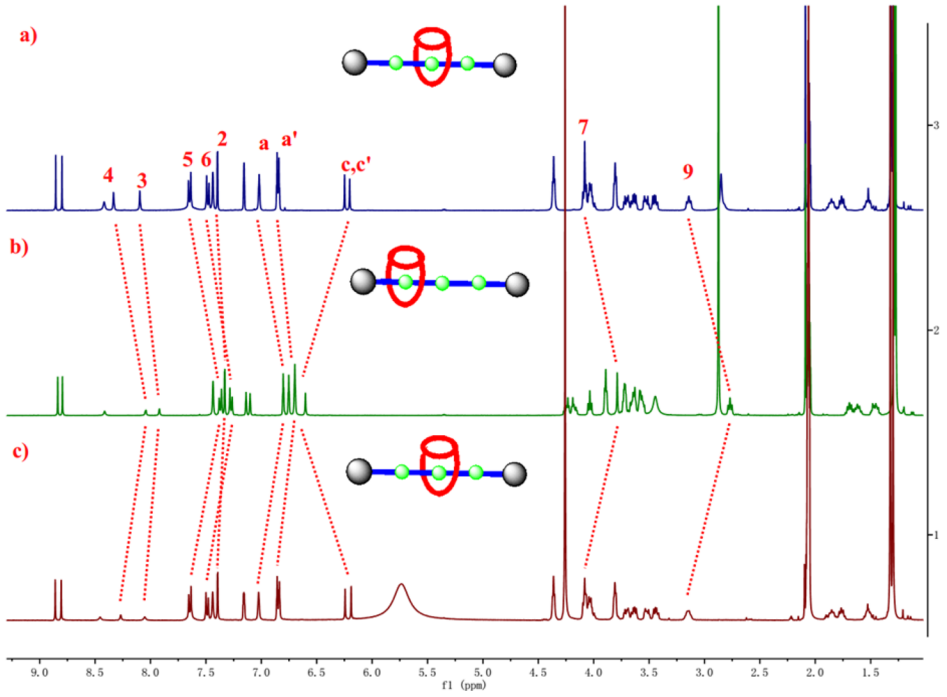


Figure 7. ^{1}H NMR spectra (400 MHz, acetone-d_6, c = 10 mM) of (a) **R1**, (b) **R1** and TABCO (2.0 equiv), and (c) **R1**, TABCO (2.0 equiv), and HPF_6 (5.0 equiv).

actually almost identical with that of **R1** before the acid/base-driven translocation (Figure 7a). Thus, we were able to use the translational isomerism of interlocked molecular switch **R1** by adjusting the pH of its solution in acetone-d_6.

DOI: 10.1021/acs.joc.6b01082
J. Org. Chem. 2016, 81, 6457−6462

In conclusion, oxacalixcrown **H1**, derived from a tetranitro-oxacalix[4]arene and a penta-oxyethylene chain, was found to form [2]pseudorotaxane-type complexes with either secondary ammonium ions or urea derivatives. A molecular switch based on these two complexes in which reversible translocation of the oxacalix[4]crown wheel was controlled by acid−base regulation between the secondary ammonium binding site and the urea binding site of axle was developed.

EXPERIMENTAL SECTION

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 500 MHz spectrometers with TMS as the reference. HRMS spectra were recorded on a micrOTOF-Q spectrometer (ESI) or a ultrafleX III TOF/TOF mass spectrometer (MALDI).

Tetranitro-oxacalix[4]crown-6 (H1). A mixture of tetranitro-oxacalix[4]arene **1** (174.0 mg, 0.3 mmol), pentaethylene glycol ditosylate **2** (164.1 mg, 0.3 mmol), and K_2CO_3 (124.2 mg, 0.9 mmol) in acetonitrile (50 mL) was refluxed for 24 h, cooled to room temperature, filtered, and concentrated under reduce pressure to yield a residue that was subjected to column chromatography [1/1 (v/v) petroleum ether/EtOAc] to afford oxacalixcrown **H1** as a yellow solid (147.5 mg, 63%): mp 160.3−161.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 2H), 6.70 (d, J = 2.0 Hz, 4H), 6.33 (t, J = 2.0 Hz, 2H), 6.22 (s, 2H), 4.17−4.12 (m, 4H), 3.89−3.85 (m, 4H), 3.73−3.69 (m, 4H), 3.68−3.64 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 156.1, 154.6, 132.7, 125.9, 106.8, 104.94, 104.91, 71.0, 70.7, 70.5, 69.4, 68.6; LRMS (ESI-TOF) m/z 782.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{34}H_{34}N_5O_{18}^+$ $[M + NH_4]^+$ 800.1893, found m/z 800.1890.

***N*-{4-[3-(3,5-Di-*tert*-butylphenyl)ureido]benzyl}-5-hydroxypentan-1-aminium Hexafluorophosphate (T).** After a solution of 5-amino-1-pentanol (29.1 mg, 0.28 mmol) and 1-(3,5-di-*tert*-butylphenyl)-3-(4-formylphenyl)urea (50.2 mg, 0.14 mmol) in MeOH (15 mL) was refluxed for 12 h and cooled to room temperature, $NaBH_4$ (37.0 mg, 1 mmol) was added to the reaction mixture; the mixture was then stirred for an additional 2 h, the reaction quenched by adding an aqueous HCl solution (5.0 M, 0.2 mL), and the mixture concentrated. The residue was partitioned between water (80 mL) and EtOAc (20 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were concentrated to result in a crude product that was dissolved in DCM (5 mL), acidified with an aqueous HCl solution (36%) until the pH reached <2, stirred for 30 min, and concentrated. The residue was subsequently dissolved in acetone (10 mL), combined with an aqueous saturated NH_4PF_6 solution (5 mL), stirred for 2 h, and evaporated to yield an aqueous suspension. The solid was collected by filtration, washed with water (3 × 5 mL), and dried to afford **T** (70.6 mg, 86%) as a yellow solid: mp 137.4−139.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.26 (s, 1H), 8.10 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 1.7 Hz, 2H), 7.16 (t, J = 1.7 Hz, 1H), 4.51 (s, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.44−3.38 (m, 2H), 1.96−1.86 (m, 2H), 1.59−1.49 (4, 1H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, acetone-d_6) δ 153.4, 151.9, 142.3, 139.9, 131.6, 125.2, 119.4, 117.3, 114.1, 61.8, 52.2, 48.7, 35.4, 32.6, 31.7, 30.6, 26.6, 23.6; LRMS (ESI-TOF) m/z 440.13 $[M - PF_6]^+$; HRMS (ESI-TOF) calcd for $C_{27}H_{42}N_3O_2^+$ $[M - PF_6]^+$ 440.3261, found m/z 440.3272.

Rotaxane R1. After a solution of **H1** (370.2 mg, 0.47 mmol) and **T** (139.9 mg, 0.24 mmol) in DCM (10 mL) had been refluxed for 24 h and cooled to room temperature, a catalytic amount of dibutyltin dilaurate (DBTDL) (13.0 mg, 0.02 mmol) and 3,5-di-*tert*-butylphenyl isocyanate (230.0 mg, 1.00 mmol) were added to the reaction mixture, which was then stirred at room temperature for 48 h and concentrated. The residue was subjected to chromatography [1/20 (v/v) MeOH/DCM] to afford rotaxane **R1** (219.2 mg, 57%) as a white solid: mp 106.7−108.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.86 (s, 1H), 8.80 (s, 1H), 8.42 (br, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.61−7.67 (3H), 7.48 (d, J = 8.5 Hz, 2H), 7.44 (s, 2H), 7.40 (d, J = 1.6 Hz, 2H), 7.16 (s, 2H), 7.02 (s, 2H), 6.86 (t, J = 2.0 Hz, 2H), 6.84 (t, J = 2.1 Hz, 2H), 6.25 (s, 1H), 6.20 (s, 1H), 4.36 (t, J = 3.7 Hz, 4H), 4.11−3.98 (m, 8H), 3.85−3.77 (m, 4H), 3.74−3.60 (m, 4H), 3.57−3.41 (m, 4H), 3.14 (t, J = 7.5 Hz, 2H), 1.90−1.71 (m, 4H), 1.59−1.47 (m, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ 162.8, 156.9, 156.9, 156.2, 154.6, 153.3, 152.1, 152.0, 142.8, 139.9, 139.5, 133.9, 132.1, 126.4, 126.3, 119.0, 117.6, 117.4, 114.1, 113.7, 108.0, 107.9, 107.8, 106.7, 106.6, 71.8, 71.6, 71.2, 69.9, 64.5, 52.7, 49.2, 35.5, 31.8, 30.6, 27.1, 23.8; LRMS (ESI-TOF) m/z 1454.33 $[M - PF_6]^+$; HRMS (MALDI-DHB) calcd for $C_{76}H_{93}N_8O_{21}^+$ $[M - PF_6]^+$ 1453.6425, found m/z 1453.6423.

5-{[(3,5-Di-*tert*-butylphenyl)carbamoyl]oxy}-*N*-{4-[3-(3,5-di-*tert*-butylphenyl)ureido]benzyl}pentan-1-aminium Hexafluorophosphate (T1). To a solution of **T** (140.2 mg, 0.24 mmol) in DCM (10 mL) were added dibutyltin dilaurate (DBTDL) (13.0 mg, 0.02 mmol) and 3,5-di-*tert*-butylphenyl isocyanate (230.1 mg, 1.00 mmol) to yield a mixture that was stirred at room temperature for 48 h and concentrated. The residue was subjected to chromatography [1/20 (v/v) MeOH/DCM] to afford **T1** (143.5 mg, 73%) as a colorless oil: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.61−7.44 (m, 8H), 7.11 (d, J = 9.7 Hz, 2H), 4.18 (s, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.01−1.85 (m, 2H), 1.70−1.55 (m, 2H), 1.54−1.45 (m, 2H), 1.28 (s, 38H); ^{13}C NMR (101 MHz, acetone-d_6) δ 153.7, 153.0, 151.0, 150.9, 141.1, 139.5, 138.7, 130.7, 125.2, 118.0, 116.3, 116.0, 112.9, 112.8, 64.1, 51.2, 47.7, 34.6, 34.5, 30.92, 30.88, 28.2, 25.9, 23.3; LRMS (ESI-TOF) m/z 671.4 $[M - PF_6]^+$; HRMS (MALDI-DHB) calcd for $C_{42}H_{63}N_4O_3^+$ $[M - PF_6]^+$ 671.4895, found m/z 671.4897.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01082.

Copies of NMR spectra, NOESY spectra, Job plot, titration data, and computation data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported by the National Natural Science Foundation of China (21371177) and the "Strategic Priority Research Program" of the Chinese Academy of Sciences (XDA01020304).

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