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A Switchable Open/closed Polyaromatic Macrocycle and its Reversible Binding of Long Hydrophilic Molecules

Kohei Kurihara,[a] Kohei Yazaki,[b] Munetaka Akita,[a] and Michito Yoshizawa*[a]

Abstract: In spite of wide-ranging previous studies on synthetic macrocycles, installation of open-close functions into the frameworks remains a knotty challenge. Here we present a new polyaromatic macrocycle capable of switching between open and closed forms in response to external stimuli, base and acid. The macrocycle, prepared in three steps, has a well-defined hydrophobic cavity with dimensions of ~1 nm, surrounded by four pH-responsive acridinium panels. The open and closed structures are definitely confirmed by X-ray single-crystal analysis. The cylindrical cavity can bind long hydrophilic molecules up to 2.7 nm in neutral water as well as release the bound guests through the open-to-closed structural change by simple addition of base, in a reversible fashion.

Reversible open-close motions triggered by external stimuli or forces are one of the most basic functions in our lives. Incorporation of such mechanical motions into synthetic molecular rings, tubes, and cages is highly promising for the development of functional nanoscale containers and machines.[1-3] There has been intensive study of covalent macrocyclic compounds, such as cyclodextrins, cyclophanes, cucurbiturils, and pillararenes, possessing definite cavities capable of binding wide-ranging organic molecules.[4] In addition, the electrostatic properties of the host frameworks can be occasionally changed by the addition of acids/bases or by oxidation/reduction reactions. Nevertheless, open-close switching of the cylindrical cavities by external stimuli (*e.g.*, heat, light, and pH) has been rarely achieved owing to their rigid constitutions.[5] Open-ended macrocyclic and tubular structures are expected to bind various guest molecules, even when the lengths are longer than that of the host cavities, in contrast to capsular and cage-like hosts with isolated cavities.[6] Therefore, installation of open-close functions into covalent macrocyclic hosts will open up their applications in stimuli-responsive molecular sensors and separators for, for example, long and complex biomolecules.

Here we report a new polyaromatic macrocycle switchable between open and closed states, reversibly (Figure 1a), in response to external stimuli, base and acid. Macrocycle **1** designed herein is composed of four pH-responsive acridinium panels connected alternately by *meta*-phenylene and *meta*-biphenyl spacers (Figure 1b). Both the open and closed structures are confirmed by X-ray crystallographic analysis. In neutral water, the cylindrical cavity with dimensions of ~1 nm can bind long hydrophilic molecules with a pyranose or steroid moiety (up to 2.7 nm in length). Remarkably, the bound guests are released from the cavity through the open-to-closed structural change of the host framework upon addition of base.

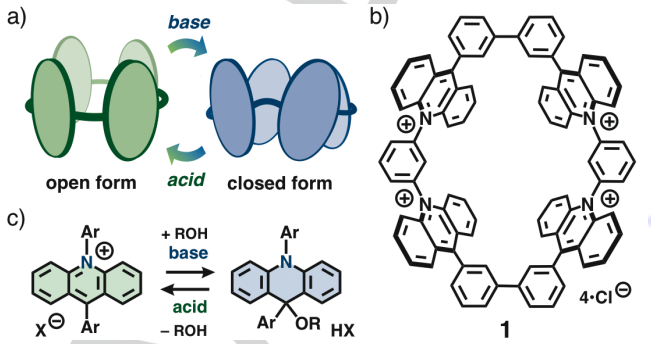

Figure 1. a) Cartoon of an open/closed structural change of a polyaromatic macrocycle and b) acridinium-based macrocyclic molecule **1** reported herein. c) General reactivity of a biarylacridinium salt with base (+ROH) and acid.

Biarylacridinium frameworks contain a rigid polyaromatic panel with a monocationic nitrogen atom (Figure 1c, left). Unlike common polyaromatic hydrocarbons (*e.g.*, anthracene, pyrene, and perylene), nucleophilic addition of alcohols or water to the acridinium panel under basic conditions gives rise to flexible acridane panels (Figure 1c, right). The resultant neutral frameworks can revert to the originals under acidic conditions. We expected that the incorporation of multiple acridinium panels into a shape-persistent polyaromatic tubular structure[7] could generate new pH-responsive macrocyclic molecule **1** (Figure 1b).[8] The tetracationic framework provides hydrophilic exterior surfaces so that the polyaromatic macrocycle is usable in water without the attachment of typical hydrophilic substituents. Importantly, the open macrocycle, prepared in only three-step reactions, can reversibly transform to the closed macrocycle (**2**) by simple addition of base (Figure 1a).

We synthesized water-soluble polyaromatic macrocycle **1** through nickel-catalyzed homocoupling of a diiododihydroacridine derivative followed by treatment with a HCl solution (step *iii* in Figure 2a).[9] The bent precursor was prepared in two steps starting from acridone and 1,3-diiodobenzene (steps *i* and *ii* in Figure 2a).[10] The macrocyclic structure of **1** was unambiguously confirmed by NMR, MS, and X-ray single-crystal analyses.[9,11] A ^{1}H NMR spectrum of **1** in D_2O showed eleven signals in the aromatic region (Figure 3b) due to the high symmetry (virtually D_{2h}). The ESI-TOF MS spectrum exhibited a prominent peak at *m/z* = 292.1 corresponding to the $[\mathbf{1} - 4\cdot Cl^-]^{4+}$ species (Figure S12). Single

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crystals of the macrocycle suitable for X-ray crystallographic analysis were obtained from the PF_6^- analogue **1"** in the presence of coumarin guest **3a** (Figure 2b).[12a] The molecular structure showed that the four acridinium panels are connected alternately by the non-substituted mono- or bisphenylene spacers, creating a cylindrical cavity with dimensions of 1.1 × 0.8 nm (Figure 2c). The ~1 nm-length cavity is fully occupied by the stacked two molecules of **3a** (1.5 nm in length) in an antiparallel fashion (Figure 2d). The interplanar guest-host (acridinium panels) and guest-guest distances of 3.4-3.8 Å indicate the existence of multiple π-π interactions.[13,14]

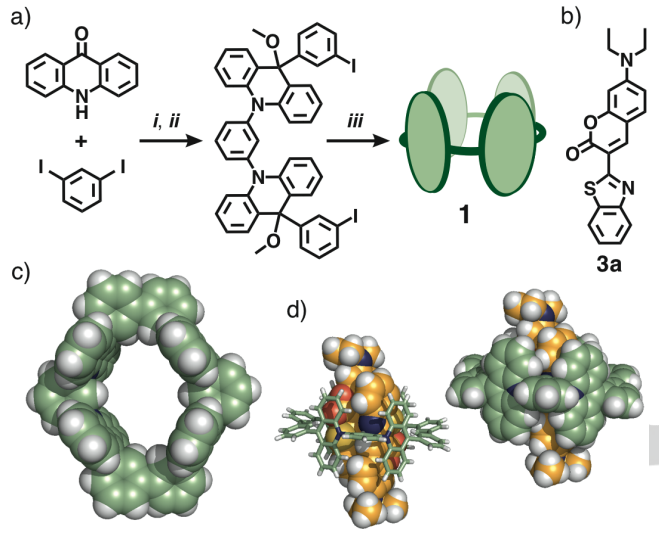

Figure 2. a) Synthesis of polyaromatic macrocycle **1** starting from acridone in three steps.[11] Conditions and reagents: (*i*) CuI, dipivaloylmethane, K_2CO_3, DMF, 160 ºC, (*ii*) 1,3-diiodobenzene, *n*-BuLi, THF, –80 ºC and then $NaHCO_3$, CH_3OH, r.t., (*iii*) $Ni(COD)_2$, 2,2'-bipyridyl, THF, 70 ºC and then CH_3OH, HCl aq., r.t. (24% total yield).[9] b) Coumarin **3a** as a guest molecule. Crystal structure of **1"•(3a)**$_2$ (counterions and solvent molecules are omitted for clarity): c) the top view without the guests (space-filling model) and d) the side views with the guests (cylinder and space-filling models).

An open-to-closed structural change of rigid polyaromatic macrocycle **1** was carried out under basic conditions in the presence of nucleophiles. For example, when macrocycle **1** and excess $NaHCO_3$ were stirred in a mixed solvent of CH_3CN and 2-ethyl-1-butanol for 15 h at 60 ºC, the yellow solution turned colorless to give a white precipitate. ^{1}H NMR analysis of the collected precipitate indicated the formation of closed macrocycle **2'** in 94% isolated yield.[9] The NMR spectrum of **2'** in toluene-d_8 showed three broad signals derived from the attached ethylbutyloxy groups in the range of 3.23 to 0.82 ppm (Figure 3c). The aromatic signals of **2'** were also broadened, most probably due to the restricted motion of the compressed structure. The infrared (IR) spectroscopy and elemental analysis (E.A.) of the product also proved the full conversion of the acridinium rings into the acridane rings (Figure S22). The closed structure of **2'** was finally evidenced by X-ray crystallographic analysis.[12b] In the crystal structure, the open cavity found in **1** completely disappeared due to flipping of the biphenyl rings inward through the structural change of the planar acridinium panels to the non-planar acridone panels (Figure 3e). The closed structure bearing the distorted four acridane panels remains intact even at 80 ºC, as indicated by variable temperature ^{1}H NMR analysis (Figure S21). Notably, open macrocycle **1** could be regenerated from closed macrocycle **2'** under acidic conditions. Addition of an aqueous HCl solution (~60 equiv.) to a CH_3OH suspension of **2'** followed by stirring for ~5 h at room temperature afforded a clear yellow solution including the original macrocycle (93% isolated yield) (Figure 3d).

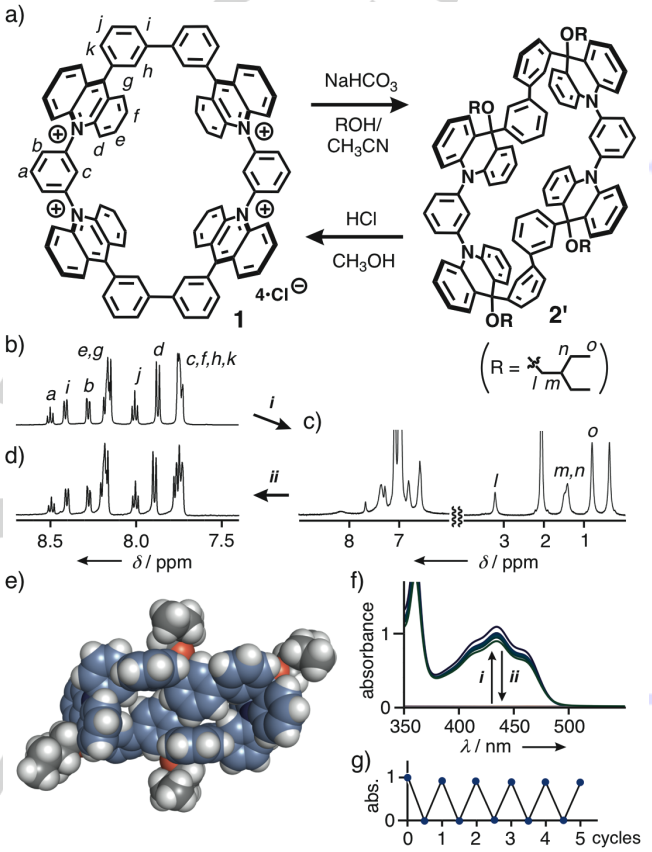

Figure 3. a) Schematic representation of the open/closed structural change of polyaromatic macrocycle **1**. ^{1}H NMR spectra (400 or 500 Hz, D_2O, r.t.) of b) **1**, c) closed macrocycle **2'** (in toluene-d_8), and d) **1** regenerated from **2'**. e) Crystal structure of **2'** (space-filling model; solvent molecules are omitted for clarity). f) UV-visible spectra (H_2O, r.t.) of **1** after alternate addition of (*i*) HCl aq and (*ii*) NaOH aq. (~20 equiv. based on **1**) and g) the open-closed switching cycles of **1** under basic/neutral conditions, monitored by the UV-visible spectra (plot of the absorption intensity at 434 nm).

Next we demonstrated that the open-closed switching process of **1** can be repeated several times in aqueous solutions Addition of an aqueous NaOH solution (~20 equiv.) to open macrocycle **1** in H_2O gave rise to closed macrocycle **2** (R = -OH) as a white precipitate within 1 h at room temperature. The resultant macrocycle reverted into the original one by the treatment with an aqueous HCl solution (~20 equiv. based on **2**) under similar conditions. The pH-responsive structural change was easily monitored by UV-visible spectroscopic analysis (Figure 3f). The absorption bands (λ_{max} = 434 nm) derived from the acridinium panels of **1** disappeared under basic conditions due to the formation of **2** precipitated out of the solution.[9,15] The

bands were recovered through neutralization upon addition of acid. Repeatability of the spectroscopic changes (five times) revealed that the opening-closing cycles of **1** occur efficiently in water at ambient temperature (Figure 3g).

In aqueous media, polyaromatic macrocycle **1** exhibited a binding ability toward water-soluble molecules, esculin (**3b**), sodium cholate (**3c**), and CHAPS (**3d**), whose lengths are longer than that of the cavity (Figure 4a). Simple mixing aqueous macrocycle **1** (1.2 μmol) with **3b** (2.3 μmol), with a length of 1.3 nm, in D_2O (1.0 mL) at room temperature led to the quantitative formation of 1:2 host-guest complex **1**•(**3b**)$_2$ within 5 min. In the ^{1}H NMR spectrum of the product (Figure 4c), proton signals derived from the coumarin moiety ($H_{A\text{-}D}$) of **3b** were observed in the range of 7.45 to 5.68 ppm with large upfield shifts ($\Delta\delta_{max}$ = 0.64 ppm). On the other hand, those derived from the pyranose moiety appeared around 5.0 and 4.7 ppm with slight shifts ($\Delta\delta$ <

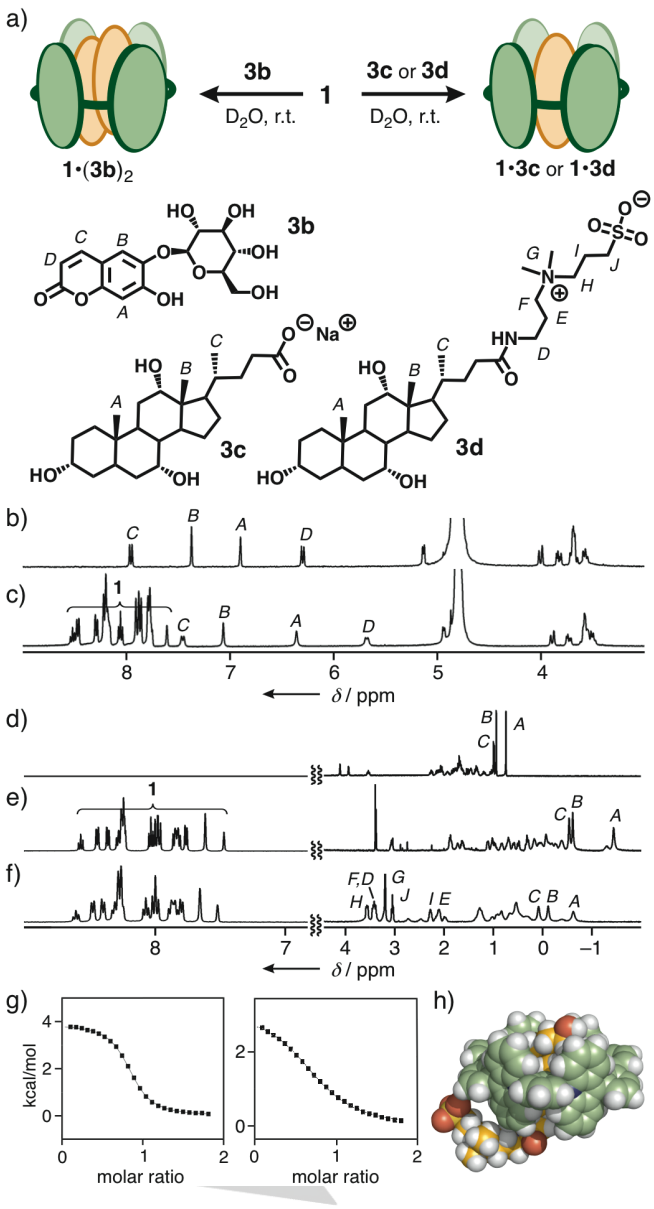

Figure 4. a) Schematic representation of the binding of hydrophilic molecules **3b-d** by open macrocycle **1** in water. ^{1}H NMR spectra (400 MHz, D_2O, r.t.) of b) **3b**, c) **1**•(**3b**)$_2$, d) **3c**, e) **1**•**3c**, and f) **1**•**3d**. g) Plots of the integrated heat for the ITC titrations of **3c** (left) and **3d** (right) into a H_2O solution of **1**. Black squares and black lines are experimental and calculated values, respectively. h) An optimized structure of **1**•**3d** (space-filling model).

0.12 ppm). These characteristic shifts, caused by aromatic shielding effects, indicate selective binding of the hydrophobic coumarin part of **3b** by the cylindrical cavity of **1** through the hydrophobic effect and π-stacking interactions. The ^{1}H NMR Job's plot identified the host-guest stoichiometry of the binding to be 1:2 (Figure S29). ESI-TOF MS analysis also confirmed the host-guest ratio (Figure S30).[16] In the same way, hydrophilic steroid derivatives **3c** and **3d** (1.5 and 2.7 nm in length, respectively) were quantitatively accommodated within **1** to give 1:1 host-guest complexes **1**•**3c** and **1**•**3d**, respectively. Upfield shifts of the methyl signals ($H_{A\text{-}C}$) on the steroid moieties were definitely observed in the ^{1}H NMR spectra (Figure 4e,f). The relatively large binding constant (K_a = 3.9 × 10^4 M^{-1}) and thermodynamic parameters (ΔH = 3.89 kcal mol^{-1} and ΔS = 34.0 cal mol^{-1} K^{-1}) toward the **1**•**3c** complex were determined by isothermal titration calorimetry (ITC; Figure 4g, left).[9] On the other hand, relatively long compound **3d** was bound by **1** with a moderate binding constant (7.3 × 10^3 M^{-1}; Figure 4g, right).[17] The optimized structure of **1**•**3d** by semiempirical calculations (PM6 level) reveals that most of the steroid moiety of **3d** is encircled by the acridinium panels of **1** (Figure 4h).[18,19]

We further examined the release of the bound guests from the cavity of **1** through the pH-responsive open-to-closed structural change at room temperature (Figure 5a). Addition of a base ($NaHCO_3$, ~20 equiv. based on **1**) to the aqueous solution of **1**•(**3b**)$_2$ evoked the rapid color change from yellow to colorless accompanying the precipitation of a white solid. The ^{1}H NMR spectrum showed the disappearance of the host signals and the large downfield shifts of the aromatic signals of guest **3b** ($\Delta\delta_{max}$ = +0.48 ppm) (Figure 5b,c). Similarly, the steroid signals (e.g., $H_{A\text{-}C}$) of **3d** bound in **1** were shifted downfield ($\Delta\delta_{max}$ = +1.09 ppm) upon addition of the base (Figure 5e,f). These spectral changes stem from the release of the bound guests from open macrocycle **1** in water.

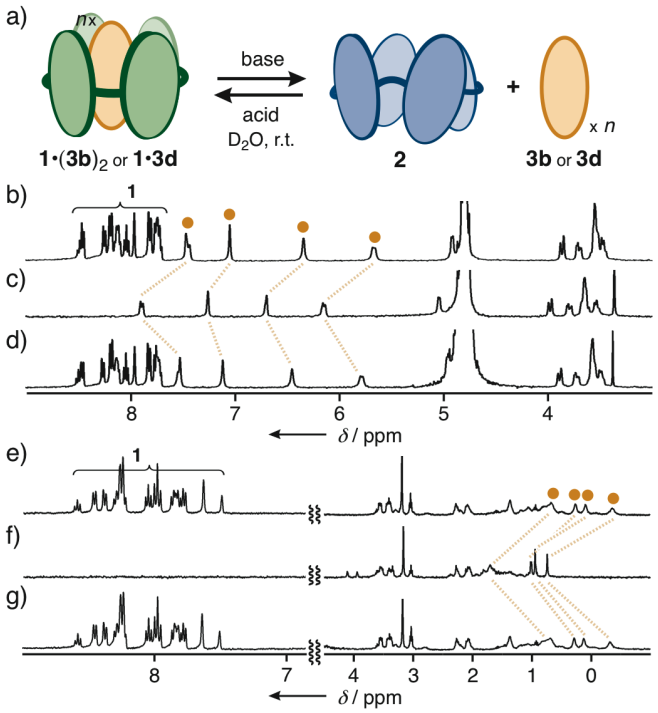

Figure 5. a) Schematic representation of pH-responsive catch and release of guests **3b** and **3d** by macrocycle **1** in water. ^{1}H NMR spectra (400 MHz, D_2O, r.t.) of **1**•(**3b**)$_2$ b) before and c) after addition of $NaHCO_3$, and d) after further addition of HCl aq. ^{1}H NMR spectra (400 MHz, D_2O, r.t.) of **1**•**3d** e) before and f) after addition of $NaHCO_3$ and g) after further addition of HCl aq.

Finally, rebinding of the released guests to the open macrocycle was readily achieved by adding acid to the resultant suspension of **2** and **3b** in water. Addition of an aqueous HCl solution (~20 equiv. based on **1**) caused rapid color change of the solution from colorless to yellow, accompanied with the dissolution of the precipitate, at room temperature. The ^{1}H NMR spectrum of the product (Figure 5d) was virtually identical to that of **1**•(**3b**)$_2$ (Figure 5b). The original **1**•**3d** complex was also regenerated exclusively by the same way (Figure 5g).

In conclusion, we have developed a new polyaromatic macrocycle providing (i) a open/closed switching function within the framework, (ii) a binding capability toward long hydrophilic molecules with the lengths longer than that of the cavity, and (iii) a releasing ability of the bound molecules in water at ambient temperature. The structures of the open and closed macrocycles are successfully confirmed by NMR, MS, and X-ray single-crystal analyses. In addition, reversible catch and release of the long molecules by the macrocycle are revealed by detailed NMR analysis. The key to the characteristics of the present macrocycle arises from the installation of pH-responsive polyaromatic panels (*i.e.*, acridinium ring) into a macrocyclic structure, which has never been reported so far.[20] Therefore, the guest release can be accomplished through not typical electrostatic repulsion or solvent effects but mechanical motions. Further studies on the finite open/closed switchable macrocycle, *e.g.*, incorporation of them into infinite polymer and inorganic matrixes, could exploit novel stimuli-responsive sensing and separating materials.

Acknowledgements

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Keywords: macrocycle, acridinium, catch and release, water, pH

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[9] See the Supporting Information.

[10] K. Yazaki, Y. Sei, M. Akita, M. Yoshizawa, *Chem. Eur. J.* **2016**, *22*, 17557–17561.

[11] The NMR spectra of **1** were fully characterized by using highly soluble analogous macrocycle **1'** having BF_4^- counterions.

[12] a) Single crystals of **1"**•(**3a**)$_2$ were obtained by slow diffusion of benzene into an acetonitrile solution of **1"** in the presence of **3a** (2 equiv.) for 2 d at room temperature; b) Single crystals of **2'** (R = -

$CH_2CH(CH_2CH_3)_2$) were obtained by slow concentration of a toluene solution of **2'** for 2 d at room temperature.

[13] a) C. Janiak, *J. Chem. Soc.*, *Dalton Trans.* **2000**, 3885–3896; b) C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc.*, *Perkin Trans. 2*, **2001**, 651–669; c) J. K. Klosterman, Y. Yamauchi, M. Fujita, *Chem. Soc. Rev.* **2009**, *38*, 1714–1725.

[14] The antiparallel orientation of the guest molecules is presumably attributed to the dipole-dipole interaction in the cavity. ^{1}H NMR spectra of **1**•(**3a**)$_2$ in CD_3CN showed broadened host and guest peaks (Figure S42a,b), indicating strong interactions between open macrocycle **1** and **3a**. In contract, closed macrocycle **2"** with ammonium groups showed no host-guest interaction with **3a** under the same conditions (Figure S42c,d).

[15] Closed macrocycle **2** (R = -H) insoluble in general organic solvents (e.g., acetone, $CHCl_3$, toluene, and DMSO) was characterized by FT-IR (Figure S22), E.A., and MALDI-TOF MS (Figure S25) analyses.

[16] However, these data cannot exclude the formation of a 1:1 host-guest complex (**1**•**3b**) as a minor product. The poor solubility of neutral guest **3b** in water precludes the ITC measurement.

[17] ^{1}H NMR Job's plots identified the formation of 1:1 host-guest complexes **1**•**3c** and **1**•**3d** (Figure S33 and S37). Thermodynamic parameters ΔH and ΔS for the **1**•**3d** complex were calculated to be 3.11 kcal mol^{-1} and 28.1 cal mol^{-1} K^{-1}, respectively.[9]

[18] Geometry optimization of **1**•**3d** was carried out in water without counterions by PM6 calculations with Gaussian 09 software. The solvent effect was taken into account using the self-consistent reaction field (SCRF) method.

[19] M. J. Frisch *et al.*, Gaussian 09, Gaussian, Inc., Wallingford, CT, **2009**.

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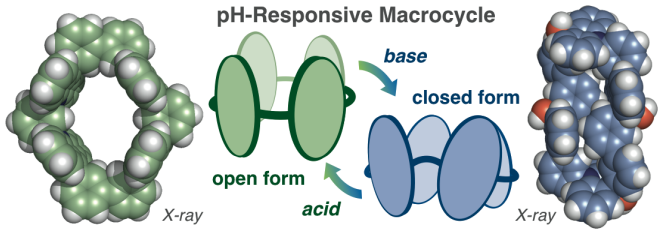

Here we present a new polyaromatic macrocycle capable of switching between open and closed forms in response to external stimuli. The macrocycle has a well-defined hydrophobic cavity with dimensions of ~1 nm, surrounded by four pH-responsive acridinium panels. The cylindrical cavity can bind long hydrophilic molecules in neutral water as well as release the bound guests through the open-to-closed structural change by addition of base, in a reversible fashion.

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