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Chemically Induced Breathing of Flexible Porphyrinic Covalent Cages

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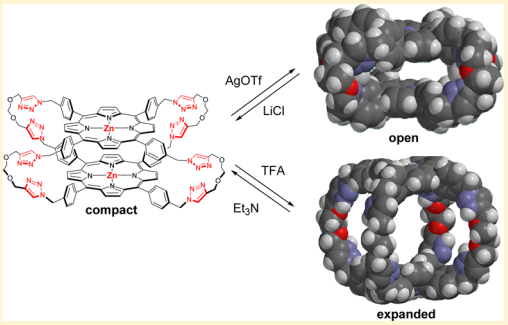
Supporting Information

ABSTRACT: The synthesis of two flexible bis-porphyrin cages **3** and **4**, incorporating respectively Zn(II) porphyrins and free-base porphyrins, is reported. In both cages, the four covalent linkers that bind the two porphyrins are functionalized with two 1,2,3-triazolyl ligands. These cages were characterized by NMR and HRMS, and for cage **3** incorporating 1,4-diazabicyclo[2.2.2]octane (DABCO), an X-ray crystallographic structure was obtained. Chemically induced conformational changes are studied and compared to those of two related cages with longer flexible linkers. Binding of four silver(I) ions to the peripheral ligands opens the flattened structures in solution and locks the two porphyrins in a face-to-face disposition. Addition of an excess of acid fully expands the cages due to electrostatic repulsion between the positively charged sites. These two reversible processes allow for a chemically induced breathing of the flexible structures.

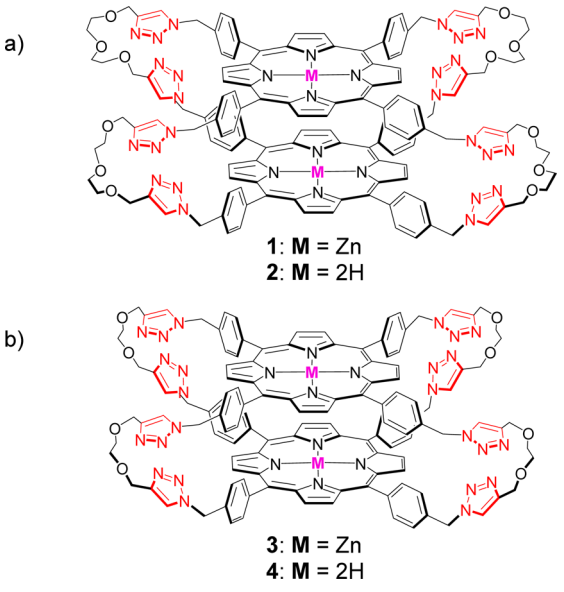


INTRODUCTION

The construction of molecular containers, capsules, or cage-like compounds represents an active field of research, and many chemical tools, in terms of bond formation (covalent, coordination, and hydrogen bonds) and synthesis pathway (self-assembly, templated synthesis, and dynamic combinatorial chemistry), have been exploited, leading to 3D architectures of high diversity.[1] As anticipated, these hollow structures were able to stabilize guest molecules according to their size, shape, and affinity for the host. Isolated from the bulk solvent, the encapsulated guest sometimes modifies to a large extent its physical and chemical properties. Therefore, molecular encapsulation enables one to stabilize reactive molecules or to perform chemical reactions inside molecular containers that behave as nanoreactors.[2] One way to control the binding and delivery of the guest molecule or the release of the reaction product is to incorporate constituents in the nanocontainer structure that respond to an external stimulus by triggering a large conformational change that modifies the host encapsulation properties. Some results in this area were obtained with multicomponent structures using photonic,[3] chemical,[4] or redox signal.[5]

In the large variety of conceivable molecular containers, the synthesis of covalent hollow structures incorporating several metalated or free-base porphyrins is attractive for the high chemical stability expected with covalent structures and for the aptitude of porphyrins to interact with various types of guest molecules through $\pi-\pi$ interactions or coordination bonds.[6] Several improved synthetic procedures were recently reported to afford such compounds.[7] Our aim was to synthesize covalent porphyrinic cages with additional active components in their structures. We have developed the synthesis of covalent cages consisting of two porphyrins connected by four flexible diethylene glycol linkers **1**−**2**, each incorporating two 1,2,3-triazolyl ligands (Scheme 1a).[8] In such structures, silver(I) was used as a chemical stimulus to control the cavity size. Herein, the DABCO-templated Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction leading to molecular cage **3**,

Scheme 1. (a) Cages 1 and 2 Already Reported;[8] and (b) Cages 3 and 4 of the Present Study in Which Shorter Linkers Connect the Porphyrins



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characterized by shorter covalent linkers between the zinc(II) porphyrins, is reported. The synthesis of cage **4**, incorporating two free-base porphyrins, is also described. The chemically induced conformational changes triggered by silver(I) coordination to the peripheral triazoles or by protonation of the free-base porphyrins and the triazoles are investigated and compared to those occurring in cages **1** and **2** with longer spacers. Addition of an acid allows for a greater expansion of cages **2** and **4** as compared to silver(I) complexation, due to the numerous repulsive protonated sites. The ^{1}H NMR and DOSY experiments provide evidence of the large size modifications of the flexible covalent structures associated with these reversible chemical processes.

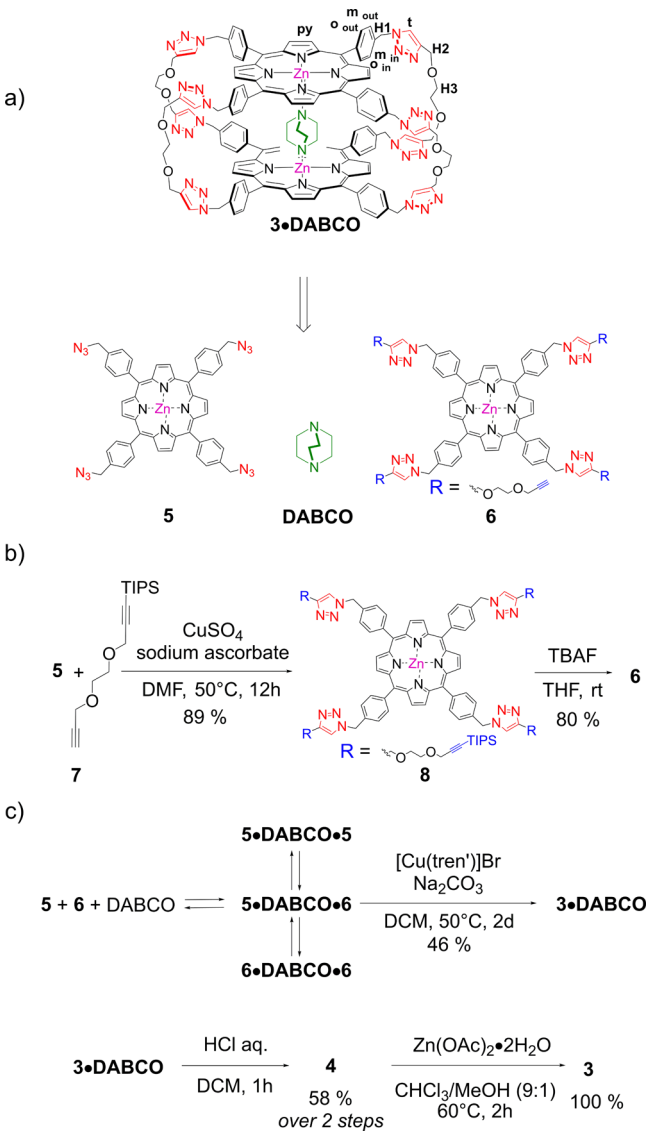
RESULTS AND DISCUSSION

The synthesis of cage **3** relies on a DABCO-templated CuAAC reaction from two porphyrinic precursors **5** and **6** (Scheme 2a). The CuAAC reaction enables one to introduce one triazolyl ligand in each of the four bis-porphyrin linkers while proceeding to the cyclization reaction between the tetraazide-functionalized porphyrin **5** and the tetraalkyne-functionalized porphyrin **6**. The two porphyrin precursors **5**[9] and **6** were prepared without difficulty at the hundred milligram scale. A first CuAAC reaction performed in DMF on the azide-functionalized Zn(II) porphyrin **5** in the presence of the triisopropylsilyl (TIPS)-monoprotected alkyne **7** and using $CuSO_4$ as catalyst led to porphyrin **8** in 89% yield (Scheme 2b). Classical removal of the TIPS protecting groups from porphyrin **8** using tetrabutylammonium fluoride (TBAF) afforded **6** in 80% yield. A mixture of three **DABCO·**porphyrin dimers was obtained upon addition of 1 equiv of DABCO to a millimolar solution of **5** and **6** in CH_2Cl_2 (Scheme 2c). The four intramolecular CuAAC click reactions proceed only from the **5·DABCO·6** hetero dimer, with [Cu(tren')]Br as catalyst[10] to avoid the decoordination of DABCO. After 2 days of reaction, the crude was submitted to column chromatographies to remove polymers and partially cyclized byproducts. The cage including DABCO, **3·DABCO**, was isolated as a purple solid in 46% yield. In another attempt to isolate **3**, the crude was treated with HCl to demetalate the porphyrins. Column chromatographies afforded cage **4** in 58% yield, and subsequent metalation of the free-base porphyrins with 2 equiv of $Zn(OAc)_2{\cdot}2H_2O$ gave **3** quantitatively.

The DABCO-templated cyclization reaction reported for cage **1** was performed in analogous conditions but afforded **1** in lower yield, 25%.[8] The DABCO-preorganization of the two porphyrin precursors is more effective in the present synthesis, due to the shorter linkers of precursor **6**. Furthermore, DABCO is more stable in cage **3** and was not partially removed during purification by column chromatography, making the purification of **3·DABCO** easier to handle.

Single crystals of **3·DABCO** were obtained by slow diffusion of pentane into a chloroform solution of the **3·DABCO** complex (Figure 1). The already mentioned X-ray crystal

Scheme 2. (a) DABCO-Templated CuAAC Strategy To Obtain Cage 3·DABCO; (b) Synthesis of Precursor 6; and (c) Synthesis of Cages 3·DABCO, 4, and 3



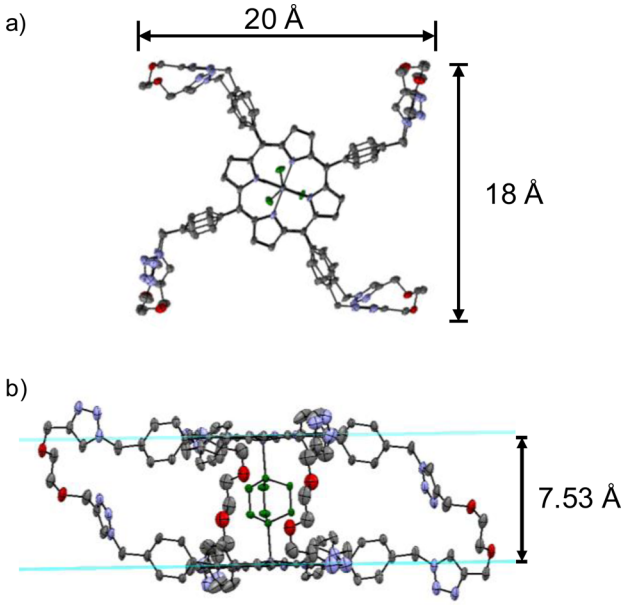


Figure 1. ORTEP representation of the molecular structure of the complex **3·DABCO**. (a) Top view and (b) side view. ORTEP ellipsoids are set at 30% probability. H atoms and solvent molecules are omitted for clarity (color code for the atoms: C, gray; N, blue; O, red; Zn, purple; DABCO, green).

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structure of **1·DABCO**[8] was of low quality, but with other crystallization attempts and by using slow diffusion of acetone into a DMF solution of the complex, we managed to obtain a nice structure (Figure S87 and Table S3). The two structures **3·DABCO** and **1·DABCO** are similar, with two eclipsed Zn(II) porphyrins. The shorter linkers of **3** ensure enough flexibility to accommodate DABCO inside the cavity without distortion of the porphyrins, and the Zn−N bond length, 2.19 Å, is typical for this kind of complexes. The mean planes of the porphyrins are separated by 7.53 Å, a distance close to that measured in cage **1·DABCO** (7.44 Å).

In solution, the ^{1}H NMR spectrum of **3·DABCO** is also consistent with an eclipsed disposition of the porphyrins and an average structure of C_4 symmetry (Figure 2a). DABCO

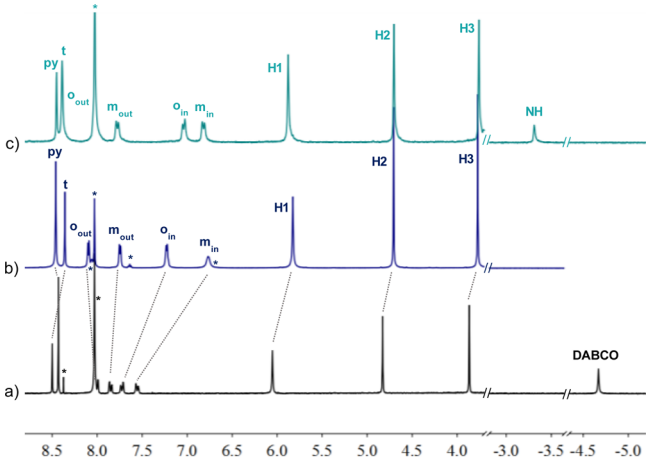

Figure 2. ^{1}H NMR spectra in DMF-d_7 (298 K) of (a) **3·DABCO** (400 MHz), (b) cage **3** (DMF-d_7 + 2% pyridine-d_5, 500 MHz), and (c) cage **4** (300 MHz). *Residual solvents.

coordinated to the zinc(II) porphyrins inside the cavity is affected by the strong ring current of the two porphyrins, resulting in a high upfield shifted signal at −4.67 ppm for its 12 protons.

After removal of DABCO with an excess of pyridine, cage **3** was soluble in polar coordinating solvents like DMSO, DMF/pyridine 2%, or in a mixture of $CHCl_3$/MeOH/pyridine (9:1:0.5). In the ^{1}H NMR spectra recorded in either of these deuterated solvents, important upfield shifts of the aromatic protons o_{in} and m_{in}, pointing inside the cavity, and less pronounced upfield shifts of protons H1, H2, and H3 of the linkers were noticed (Figure 2b). They demonstrate a conformational change of the cage leading to a closer proximity of the porphyrins favored by stabilizing $\pi-\pi$ interactions. Cage **4** incorporating free-base porphyrins displays chemical shifts close to those of cage **3** (Figure 2c), supporting a related flattened conformation for both cages as previously observed in solution for cages **1** and **2** and in the solid state for **1**.[8]

The modification of the shape and position of the Soret absorption band of the zinc(II) porphyrins in cage **3** upon inclusion of the guest illustrated also the cage rearrangement. The initial very broad Soret band is consistent with electronic interactions between close porphyrins in the conformational free structure of **3** in solution (Figure 3). Upon DABCO binding, the porphyrins move away from each other in agreement with a thinning and bathochromic shift of the Soret band. The 1:1 binding constants K of cages **1·DABCO** and **3·DABCO** were obtained by performing UV−visible

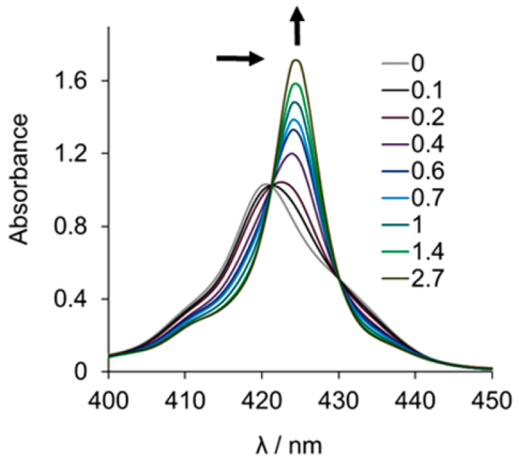

Figure 3. UV−vis titration of **3** with DABCO in $CHCl_3$/MeOH (9:1). The concentration of **3** was maintained constant at 1.2 μM. Number of equivalents added: 0, 0.1, 0.2, 0.4, 0.6, 0.7, 1.0, 1.4, and 2.7.

titrations in $CHCl_3$/MeOH (9:1) because they were too high to be determined in $CHCl_3$. The obtained association constant $K = 1.3 \times 10^7$ M^{-1} for **3·DABCO** is 67% higher than that of **1·DABCO**, $K = 7.8 \times 10^6$ M^{-1} (Figures S85 and S86 and Table S2). This increased binding affinity can be attributed to the shorter linkers of cage **3**, which ensure a better preorganization of the host structure for the guest molecule.

To control the cage conformation using a chemical stimulus, a solution of **3** or **4** in a mixture of CH_2Cl_2/$CHCl_3$/MeOH (5:5:1) was reacted with 4 equiv of AgOTf. The red solid that precipitated readily was dissolved in DMF and fully characterized by ^{1}H (COSY, NOESY, DOSY) and ^{13}C NMR as well as HRMS. The high-resolution mass spectrum attested the formation of the complex with a 4:1 silver/cage stoichiometry, with the detected $[\mathbf{Ag_4{\cdot}3}]^{4+}/4$ peak at m/z = 693.0854 whose isotopic profile was in accordance with the theoretical one. Another peak resulting from the loss of one silver ion in the ESI experiment was also detected. Whereas silver(I) coordination did not modify the number of proton signals in agreement with a structure of high symmetry, some important chemical shifts were observed on the ^{1}H NMR spectrum in DMF-d_7 (Figure 4). The downfield shift of 0.47 ppm of the triazole protons attested silver(I) binding to the triazolyl ligands. The large downfield shifts of the aromatic protons o_{in} ($\Delta\delta$ = 0.58 ppm) and m_{in} ($\Delta\delta$ = 0.67 ppm), as compared to those of o_{out} ($\Delta\delta$ = 0.01 ppm) and m_{out} ($\Delta\delta$ = 0.20 ppm), bring them at chemical shifts close to those observed for **3·DABCO** (Figure 4c) where the zinc(II) porphyrins are about 7 Å apart. These shifts indicate that silver(I) binding to the peripheral triazoles opens the flattened cage **3**.

The DOSY experiment corroborated this interpretation. The diffusion coefficient of **3** in DMF-d_7 decreased from 2.14×10^{-10} to 1.89×10^{-10} m^2 s^{-1} upon silver(I) coordination, which corresponds in a spherical model[11] to an increase of the hydrodynamic radius associated with the cage from 11.3 to 12.8 Å. Cage **1** in its collapsed conformation has a similar hydrodynamic radius of 10.9 Å, which also increases upon silver binding to 13.4 Å for $[\mathbf{Ag_4{\cdot}1}](\mathbf{OTf})_4$ (Table S1). It must be noticed that silver complexes $[\mathbf{Ag_4{\cdot}1}](\mathbf{OTf})_4$ and $[\mathbf{Ag_4{\cdot}3}](\mathbf{OTf})_4$ are very stable in the presence of an excess of silver(I) because no noticeable change occurred on the ^{1}H and DOSY NMR spectra from 4 to 200 equiv of added silver(I) ion

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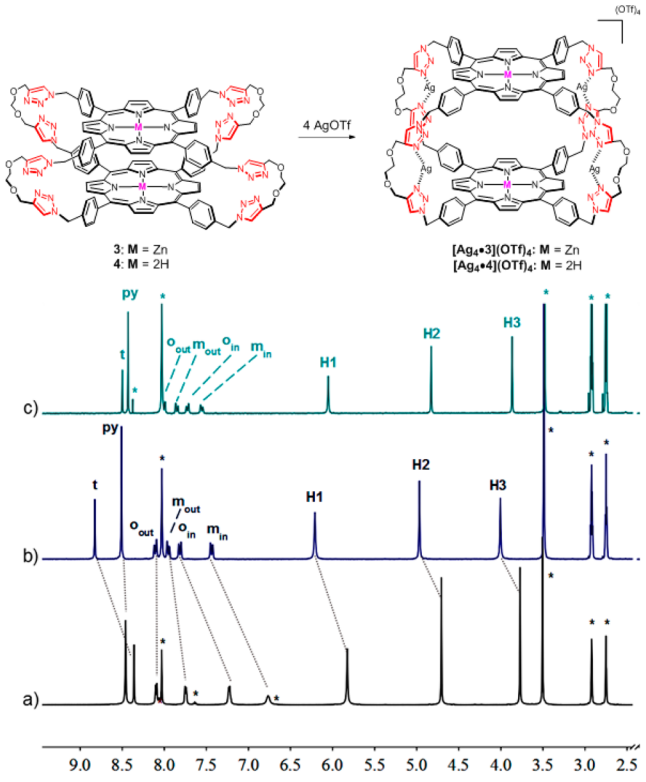

Figure 4. ^{1}H NMR spectra (500 MHz, 298 K) in DMF-d_7 of (a) cage **3**, (b) cage $[\mathbf{Ag_4{\cdot}3}](\mathbf{OTf})_4$, and (c) cage **3·DABCO**. *Residual solvents.

(Figures S44–46). Solubilizing the silver cage $[\mathbf{Ag_4{\cdot}1}]^{4+}$ or $[\mathbf{Ag_4{\cdot}3}]^{4+}$ in a solvent of low polarity such as DCM was possible by exchanging triflate with $BArF^-$ ($BArF^-$: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) anions. With $BArF^-$ as counterion, the hydrodynamic radii of $[\mathbf{Ag_4{\cdot}1}](\mathbf{BArF})_4$ and $[\mathbf{Ag_4{\cdot}3}](\mathbf{BArF})_4$ were almost identical, 13.9 and 13.8 Å, respectively. These results show that silver(I) coordination fixes the conformation of the flexible cages **1** and **3** with a cofacial disposition of the porphyrins, leading to very close hydrodynamic radii. The same conclusions could be drawn from the DOSY results obtained when binding of silver(I) was performed on cages **2** and **4**, which incorporate free-base porphyrins (Table S1). Such metal-induced conformational changes are reversible, and switching from the open silver-complexed cages back to the flattened conformations could be easily achieved by removal of the silver(I) in the presence of an excess of chloride anions (Figure S47).

To enlarge the cavity size further than by coordinating silver(I), protonation of the various basic sites was considered. Protonation of the eight triazoles and of the two free-base porphyrins of cages **2** and **4** could lead to 12 positively charged species. Thanks to the flexible linkers, expansion of both cages is expected in response to strong electrostatic repulsion. Cage **4** gave a green solution in CD_2Cl_2 upon addition of deuterated trifluoroacetic acid (TFA-*d*). Its ^{1}H NMR spectrum (Figure 5b–c) attested that the two porphyrins are moving away from each other by the progressive downfield chemical shifts of the o_{in} and m_{in} aromatic protons. After addition of 24 equiv of TFA-*d* (Figure 5b), all of the signals were downfield shifted, indicative of the cage expansion. The broadness of all signals was attributed to a slow exchange between partially protonated cages. Upon addition of a large excess of acid, all signals became

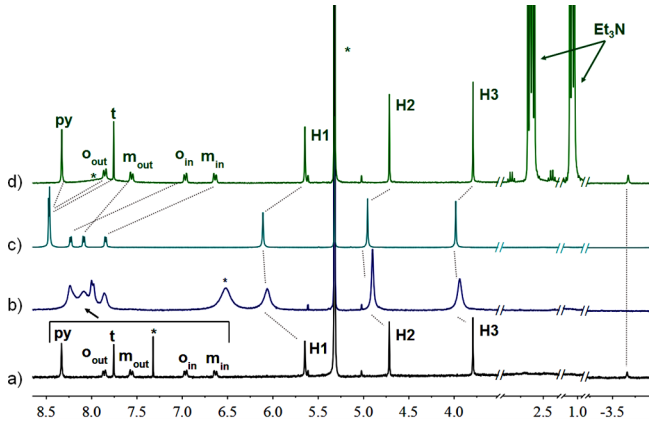

Figure 5. ^{1}H NMR spectra (300 MHz, 298 K) in CD_2Cl_2 of (a) cage **4**, (b) cage **4** after addition of 24 equiv of TFA-*d*, (c) cage **4** after addition of 1200 equiv of TFA-*d*, and (d) protonated cage **4** after neutralization with Et_3N. *Residual solvents.

sharp, and the chemical shifts of the o_{in} and m_{in} protons were closer to those of protons o_{out} and m_{out} (Figure 5c). The use of an excess of TFA-*d* ensured a fully protonated and soluble cage.

The DOSY experiment confirmed an increased volume for the protonated cage **4** with a hydrodynamic radius of 15.6 Å (Figure S76), consistent with the repulsion of the numerous positively charged sites. The open form could be shrunk back to its flattened conformation by addition of a base (Figure 5d). The same protonation reaction performed on cage **2** gave, as expected on the basis of the longer chemical linkers, a molecule of larger size, with a hydrodynamic radius of 16.2 Å (Figure S84). Despite several attempts, no crystal suitable for X-ray diffraction analysis of cages in their expanded states, either by protonation or by silver(I) coordination, could be obtained.

Molecular models (PM6, Spartan '16) of the 12-time protonated cages **4** (Figure 6a) and **2** (Figure 6c) gave

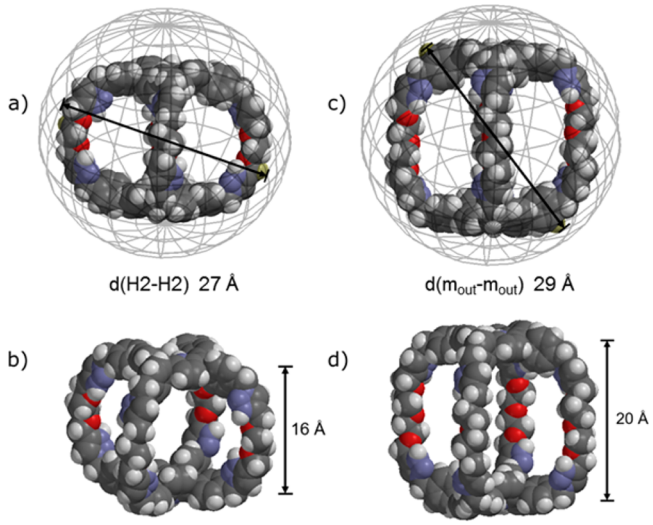

Figure 6. Energy-minimized structures (PM6, Spartan '16) of protonated cages **4** (a,b) and **2** (c,d). The largest distance in the minimized structures is indicated in (a) and (c). The hydrodynamic radii obtained from DOSY experiments for the spheres represented are 15.6 Å (a) and 16.2 Å (c). The mean plane distances between the porphyrins in the protonated cages **4** and **2** are indicated in (b) and (d), respectively.

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structures that fit well in spheres with hydrodynamic radii deduced from the DOSY experiments. From these models, the estimated mean plane distances between the porphyrins in the protonated cages **4** and **2** are substantial, respectively, 16 and 20 Å (Figure 6b,d). Whereas in cage **1**, the flattened porphyrins are separated by 3.81 Å in the compact conformation according to the X-ray structure,[8] protonation fully expands the cage and increases this distance in solution to around 20 Å.

CONCLUSION

The DABCO-templated CuAAC reaction was effective to afford in 46% yield a bis-Zn(II)porphyrin cage **3·DABCO** assembled with four flexible covalent linkers each incorporating two triazolyl ligands. Demetalation afforded quantitatively cage **4** incorporating two free-base porphyrins. The compact conformation that **3** adopts in solution expands by coordination of DABCO to the Zn-porphyrins. The flexibility of the linkers as well as the two types of constituents (porphyrin and triazole) incorporated in cages **3** and **4** and in the related cages **1** and **2** enable a chemically induced breathing of the structure, based on reversible complexation or protonation reaction. The distance between the porphyrins can thus be increased by silver(I) coordination to the peripheral triazoles and maximized by protonation of the basic sites of cages **2** and **4**. These results demonstrated two ways of controlling large and reversible chemically induced conformational changes in 3D structures that are particularly promising for the development of switchable receptors, sensors, or reactors.

EXPERIMENTAL SECTION

General Methods. All chemicals were of the best commercially available grade and used without further purification. CH_2Cl_2 and $CHCl_3$ were distilled over CaH_2 before use. THF was dried using dry-station GT S100 or distilled over sodium/benzophenone before use. Anhydrous DMF was purchased from ACROS organics. Column chromatography was carried out using silica gel (Merck, silica gel 60, 63−200 or 40−63 μm). Mass spectra were obtained by using a Bruker MicroTOF spectrometer in electrospray mode (ESI). Nuclear magnetic resonance (NMR) spectra for ^1H were acquired on Bruker AVANCE 300, 400, 500 spectrometers. ^{13}C spectra were acquired on a Bruker AVANCE 500 spectrometer. ^{19}F spectra were acquired on a Bruker AVANCE 300 spectrometer. ^{11}B spectra were acquired on a Bruker AVANCE 400 spectrometer. The ^1H and ^{13}C spectra were referenced to residual solvent peaks ($CDCl_3$, 7.24 and 77.16; CD_2Cl_2, 5.32 and 53.84; DMSO, 2.50 and 39.52; DMF, 8.03 and 163.15). Measures of self-diffusion coefficients were performed on a Bruker 600 MHz spectrometer-Avance III, equipped with a DOTY (high strength z gradient probe DOTY Scientific, developing a pulse field gradient of 50 G/cm/A) or a BBI probe (Bruker BBI probe, developing a pulse field gradient of 5 G/cm/A). The sample was thermostated at 298 K. Diffusion NMR data were acquired using a Stimulated Echo pulse sequence with bipolar z gradients. Limited Eddy current delay was fixed to 5 ms. The diffusion time and the duration of the gradients were optimized for each sample. A recycling delay of 3 s was respected between scans. DOSY spectra were generated by the DOSY module of the software NMRNotebook, using Inverse Laplace Transform (ILT) driven by maximum entropy, to build the diffusion dimension. The diffusion coefficients were corrected by using DMF as an internal reference ($\eta = 9.04 \times 10^{-4}$ Pa s and $D_{DOTY} = 1.45 \times 10^{-10}$ m^2 s^{-1}; $D_{BBI} = 1.41 \times 10^{-10}$ m^2 s^{-1}). UV−visible spectra were recorded on a Kontron Instruments UVIKON 860 spectrometer at 21 °C with a 1 cm path cell.

Monoprotected Dialkyne ***7***. A solution of lithium bis-(trimethylsilyl)amide (1 M in THF, 11 mmol, 11 mL, 1.5 equiv) was added to a stirred solution of α,ω-bis(*O*-propargyl)ethylene glycol[12] (7.29 mmol, 1 g, 1 equiv) in dry THF (600 mL) at room temperature under argon. After 10 min, TIPSCl (6.77 mmol, 1.45 mL, 0.9 equiv) was added to the reaction mixture. After 25 min, aqueous KOH (1 M, 200 mL) was added. After removal of THF under reduced pressure, the aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was purified by column chromatography on silica gel (petroleum ether/AcOEt 9:1) to afford **7** as a colorless oil (724 mg, 36% yield). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.23 (2H, s, H_6), 4.19 (2H, d, ^4J = 2.4 Hz, H_3), 3.72 (4H, m, H_{4-5}), 2.41 (1H, t, ^4J = 2.4 Hz, H_1), 1.05 (21H, s, H_{TIPS}). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ (ppm) 103.1 (C_7), 88.0 (C_8), 79.7 (C_2), 74.7 (C_1), 68.9 (C_4), 68.5 (C_5), 59.3 (C_6), 58.5 (C_3), 18.7 (C_{10}), 11.3 (C_9). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{30}NaO_2Si$ 317.1907, found 317.1899 (100); $[2M + Na]^+$ calcd for $C_{34}H_{60}NaO_4Si_2$ 611.3922, found 611.3900 (16).

TIPS-Protected Porphyrin ***8***. To a stirred solution of **7** (1.80 mmol, 608 mg) and zinc(II) [5,10,15,20-tetrakis(*p*-(azidomethyl)phenyl)-porphyrin] **5** (0.39 mmol, 352 mg, 1 equiv) in anhydrous DMF (39 mL) were added $CuSO_4{\cdot}5H_2O$ (0.39 mmol, 98 mg, 1 equiv) and sodium ascorbate (1.36 mmol, 270 mg, 3.5 equiv). The reaction mixture was degassed (three vacuum-argon cycles) and stirred at 50 °C overnight under argon. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water (3 × 200 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was purified by column chromatography on silica gel (CH_2Cl_2/MeOH from 100/0 to 90/10) to afford **8** as a purple solid (974 mg, 89% yield). ^1H NMR (300 MHz, $CDCl_3$ + pyridine-d_5): δ (ppm) 8.78 (8H, s, H_{py}), 8.15 (8H, d, ^3J = 7.9 Hz, H_o), 7.80 (4H, s, H_t), 7.57 (8H, d, ^3J = 7.9 Hz, H_m), 5.83 (8H, s, H_1), 4.77 (8H, s, H_2), 4.24 (8H, s, H_5), 3.75−3.79 (16H, m, H_{3-4}), 1.01 (84H, s, TIPS). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$ + pyridine-d_5): δ (ppm) 149.9 (C_2), 145.8 (C_{10}), 144.0 (C_4), 135.2 (C_5), 133.7 (C_7), 131.8 (C_1), 126.0 (C_6), 123.0 (C_9), 119.8 (C_3), 103.2 (C_{15}), 87.9 (C_{16}), 69.8 (C_{12}), 68.7 (C_{13}), 64.9 (C_{11}), 59.3 (C_{14}), 54.2 (C_8), 18.7 (C_{18}), 11.2 (C_{17}). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{116}H_{152}N_{16}O_8Si_4Zn$ 2073.0342, found 2073.0329 (100). UV−vis: (CH_2Cl_2) λ_{max} nm (ε M^{-1} cm^{-1}) 423 (395 000), 552 (4360), 597 (16 300); mp > 360 °C.

Alkyne-Functionalized Porphyrin ***6***. TBAF·3H_2O (998 μmol, 315 mg, 4.5 equiv) was added to a stirred solution of **8** (224 μmol, 466 mg, 1 equiv) in THF (50 mL). The reaction mixture protected from light was stirred overnight at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2. The organic layer was washed with water, the aqueous phase was extracted several times with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was purified by column chromatography on silica gel (CH_2Cl_2/MeOH from 100/0 to 97/3) to afford **6** as a purple solid (258 mg, 80% yield). ^1H NMR (300 MHz, $CDCl_3$ + pyridine-d_5): δ (ppm) 8.76 (8H, s, H_{py}), 8.12 (8H, d, ^3J = 7.9 Hz, H_o), 7.77 (4H, s, H_t), 7.53 (8H, d, ^3J = 7.9 Hz, H_m), 5.79 (8H, s, H_1), 4.74 (8H, s, H_2), 4.17 (8H, d, ^3J = 2.4 Hz, H_5), 3.76−3.71 (16H, m, H_{3-4}), 2.39 (4H, t, ^3J = 2.4 Hz, H_{Alkyne}). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$ pyridine-d_5): δ (ppm) 149.9 (C_2), 145.7 (C_{10}), 143.9 (C_4), 135.1 (C_5), 133.7 (C_7), 131.7 (C_1), 126.0 (C_6), 122.9 (C_9), 119.8 (C_3), 79.6 (C_{15}), 74.8 (C_{16}), 69.7 (C_{12}), 69.1 (C_{13}), 64.9 (C_{11}), 58.5 (C_{14}), 54.2 (C_8). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{80}H_{73}N_{16}O_8Zn$ 1449.5083, found 1449.5062 (100); mp > 360 °C.

Synthesis of Cage ***3·DABCO***. A solution of DABCO in CH_2Cl_2 (1 mL, 141 μmol, 16.0 mg, 1 equiv) was added to a stirred solution of **6** (141 μmol, 206 mg, 1 equiv) and zinc [5,10,15,20-tetrakis(*p*-(azidomethyl)phenyl)porphyrin] **5** (141 μmol, 127 mg, 1 equiv) in dry and degassed CH_2Cl_2 (140 mL, 1 mM). The reaction mixture, protected from light, was stirred at room temperature under argon for 1 h. [Cu(tren')]Br (172 μmol, 310 mg, 1.2 equiv) and Na_2CO_3 (670 μmol, 70 mg, 4.8 equiv) were added, and the reaction mixture was refluxed under argon for 2 days. The mixture was cooled to room temperature, washed with water (3 × 150 mL) and brine (150 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography on alumina ($CHCl_3$/MeOH 98/2) to afford **3·DABCO** as a purple solid (159.6 mg, 46%

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J. Org. Chem. 2017, 82, 5845−5851

yield). ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$ 9:1): δ (ppm) 8.33 (16H, s, H_{py}), 7.97 (8H, s, H_t), 7.77 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.54 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.50 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.45 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.76 (16H, s, H1), 4.70 (16H, s, H2), 3.78 (16H, s, H3), −5.07 (12H, s, H_{DABCO}). ^{1}H NMR (400 MHz, DMF-d_7): δ (ppm) 8.50 (16H, s, H_t), 8.43 (8H, s, H_{py}), 7.99 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.85 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.73 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.56 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 6.05 (16H, s, H1), 4.83 (16H, s, H2), 3.87 (16H, s, H3), −4.67 (12H, s, H_{DABCO}). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$/methanol-d_4 9:1): δ (ppm) 149.5 (C_2), 145.7 (C_{12}), 143.1 (C_4), 134.8 (C_5), 134.8 (C_7), 133.9 (C_9), 131.4 (C_1), 126.7 (C_6), 125.7 (C_8), 123.4 (C_{11}), 119.5 (C_3), 70.1 (C_{14}), 64.8 (C_{13}), 54.1 (C_{10}), 38.4 (C_{DABCO}). HRMS (ESI) m/z: $[M + 3H]^{3+}$ calcd for $C_{134}H_{119}N_{34}O_8Zn_2/3$ 819.9506, found 819.9511 (95). UV−vis: ($CHCl_3$/MeOH (9:1)) λ_{max} nm (ε M^{-1} cm^{-1}) 424 (985 000), 560 (36 400), 601 (7620); mp > 360 °C.

Synthesis of Cage **4**. Cage **4** was obtained starting from the reaction mixture that afforded **3·DABCO**. It was cooled to room temperature, washed with water (3 × 150 mL), and HCl 37% wt (5 mL) was then added to demetalate quantitatively the porphyrins. The organic phase was then neutralized by adding 150 mL of an aqueous saturated solution of Na_2CO_3, washed with distilled water (3 × 150 mL), brine (150 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by several column chromatographies on silica gel (CH_2Cl_2/MeOH (9:1)) to afford cage **4** as a purple solid (181 mg, 58% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.38 (16H, s, H_{py}), 8.30 (8H, s, H_t), 8.00 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.60 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 6.81 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 6.11 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.56 (16H, s, H1), 4.58 (16H, s, H2), 3.66 (16H, s, H3), −3.19 (4H, s, NH). ^{1}H NMR (500 MHz, DMF-d_7): δ (ppm) 8.45 (16H, s, H_{py}), 8.39 (8H, s, H_t), 8.02 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.78 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.04 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 6.82 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.88 (16H, s, H1), 4.70 (16H, s, H2), 3.76 (16H, s, H3), −3.31 (4H, s, NH). ^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm) 8.33 (16H, s, H_{py}), 7.86 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.76 (8H, s, H_t), 7.56 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 6.96 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 6.63 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.65 (16H, s, H1), 4.72 (16H, s, H2), 3.79 (16H, s, H3), −3.66 (4H, s, NH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ (ppm) 144.4 (C_{12}), 140.3 (C_4), 135.4 (C_9), 133.9 (C_{5+7}), 131.1 (C_1), 126.0 (C_6), 124.8 (C_8), 124.6 (C_{11}), 119.2 (C_3), 69.0 (C_{14}), 63.6 (C_{13}), 52.2 (C_{10}); pyrrolic ^{13}C C_2 are too enlarged to be observed at 298 K. HRMS (ESI) m/z: $[M + 2H]^{2+}$ calcd for $C_{128}H_{110}N_{32}O_8/2$ 1111.4587, found 1111.4560 (100); $[M + H]^+$ calcd for $C_{128}H_{109}N_{32}O_8$ 2221.9101, found 2222.9086. UV−vis: (dmso) λ_{max} nm (ε M^{-1} cm^{-1}) 417 (780 000), 516 (34 600), 552 (16 300), 590 (10 200), 646 (8880); mp > 360 °C.

Synthesis of Cage **3**. $Zn(OAc)_2{\cdot}2H_2O$ (49.5 μmol, 11 mg, 2.2 equiv) was added to a stirred solution of cage **4** (22.5 μmol, 50 mg, 1 equiv) in 20 mL of $CHCl_3$/MeOH (9:1). After 2 h at 60 °C, the solvents were removed under reduced pressure. The residue was then washed with MeOH to remove the unreacted $Zn(OAc)_2{\cdot}2H_2O$ and dried under vacuum to afford cage **3** as a purple solid (52.8 mg, 22.5 μmol, 100%). ^{1}H NMR (500 MHz, DMF-d_7 + pyridine-d_5): δ (ppm) 8.46 (16H, s, H_{py}), 8.36 (8H, s, H_t), 8.10 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.75 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.23 (8H, d, $H_{o\ in}$), 6.77 (8H, br s, $H_{m\ in}$), 5.83 (16H, s, H1), 4.71 (16H, s, H2), 3.77 (16H, s, H3). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.37 (16H, s, H_{py}), 8.29 (8H, s, H_t), 8.01 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.59 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 6.97 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 6.26 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.61 (16H, s, H1), 4.60 (16H, s, H2), 3.68 (16H, s, H3). $^{13}C\{^1H\}$ NMR (126 MHz, DMF-d_7 + pyridine-d_5): δ (ppm) 150.6 (C_2), 146.2 (C_{12}), 143.7 (C_4), 136.4 (C_9), 135.8 (C_7), 135.5 (C_5), 132.4 (C_1), 127.2 (C_6), 126.4 (C_8), 125.4 (C_{11}), 120.9 (C_3), 70.7 (C_{14}), 65.4 (C_{13}), 54.0 (C_{10}). HRMS (ESI) m/z: $[M + 2H]^{2+}$ calcd for $C_{128}H_{106}N_{32}O_8Zn_2/2$ 1173.3722, found 1173.3729 (100). UV−vis: (DMSO) λ_{max} nm (ε M^{-1} cm^{-1}) 424 (1 100 000), 560 (41 100), 601 (19 700); ($CHCl_3$/MeOH (9:1)) λ_{max} nm 420, 558, 594); mp > 360 °C.

Silver(I)-Complexed Cage **[Ag_4·3](OTf)$_4$**. AgOTf (25.5 μmol, 6.56 mg, 4 equiv) was added at room temperature to a stirred solution of cage **3** (6.39 μmol, 15.0 mg, 1 equiv) in distilled $CHCl_3/CH_2Cl_2$/MeOH (5:5:1, 25 mL), protected from light. A purple precipitate formed immediately. The solvent was removed, and the residue was dried under vacuum to afford a purple solid (21.6 mg, quantitative yield). ^{1}H NMR (500 MHz, DMF-d_7): δ (ppm) 8.83 (8H, s, H_t), 8.51 (16H, s, H_{py}), 8.11 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.95 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.81 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.44 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 6.21 (s, 16H, H1), 4.97 (s, 16H, H2), 4.01 (s, 16H, H3). $^{13}C\{^1H\}$ NMR (126 MHz, DMF-d_7): δ (ppm) 150.5 (C_2), 146.9 (C_{12}), 144.0 (C_4), 136.2 (C_7), 136.0 (C_9), 135.8 (C_5), 132.3 (C_1), 127.5 (C_6), 126.4 (C_8), 125.6 (C_{11}), 122.6 (q, $^1J_{C-F}$ = 320 Hz, OTf), 120.8 (C_3), 70.7 (C_{14}), 63.9 (C_{13}), 55.1 (C_{10}). $^{19}F\{^1H\}$NMR (282 MHz, DMF-d_7): δ (ppm) −79.63. HRMS (cryospray ESI) m/z: $[M - 4OTf]^{4+}$ calcd for $C_{128}H_{104}Ag_4N_{32}O_8Zn_2/4$ 693.0870, found 693.0855 (10); $[M - 4OTf - Ag]^{3+}$ calcd for $C_{128}H_{104}Ag_3N_{32}O_8Zn_2/3$ 888.4811, found 888.4790 (100); mp > 360 °C.

Silver(I)-Complexed Cage **[Ag_4·3](BArF)$_4$**. NaBArF (25.5 μmol, 22.6 mg, 4 equiv) was added to a stirred suspension of cage **[Ag_4·3](OTf)$_4$** (6.39 μmol, 21.6 mg, 1 equiv) in CH_2Cl_2. After 1 h, the compound was completely soluble. The reaction mixture was then washed with water (3 × 20 mL), dried over Na_2SO_4, and the solvent was removed under vacuum to obtain a purple solid (39.0 mg, 98% yield). ^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) 8.61 (16H, s, H_{py}), 8.21 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.88 (8H, s, H_t), 7.76 (32H, m, H_o BArF), 7.72 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.62 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.58 (16H, m, H_p BArF), 7.41 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 5.85 (16H, s, H1), 4.73 (16H, s, H2), 3.83 (16H, s, H3). ^{1}H NMR (500 MHz, DMF-d_7): δ (ppm) 8.83 (8H, s, H_t), 8.54 (16H, s, H_{py}), 8.16 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), 7.97 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.81 (48H, m, BArF), 7.78 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.44 (d, ^3J = 7.6 Hz, 8H, $H_{m\ in}$), 6.21 (s, 16H, H1), 4.97 (s, 16H, H2), 4.01 (s, 16H, H3). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2): δ (ppm) 162.1 (q, $^1J_{B-C}$ = 50 Hz, BArF), 150.1 (C_2), 145.9 (C_{12}), 143.6 (C_4), 135.9 (C_7), 135.2 (s, BArF), 134.5 (C_5), 133.4 (C_9), 131.9 (C_1), 129.2 (q, $^2J_{C-F}$ = 31.5 Hz, BArF), 126.5 (C_6), 125.8 (C_8), 124.9 (q, $^1J_{C-F}$ = 272 Hz, BArF), 122.8 (C_{11}), 120.2 (C_3), 117.9 (s, BArF), 70.6 (C_{14}), 63.6 (C_{13}), 55.6 (C_{10}). $^{19}F\{^1H\}$ NMR (282 MHz, CD_2Cl_2): δ (ppm) −63.89. ^{11}B NMR (96 MHz, CD_2Cl_2): δ (ppm) −6.59. HRMS (ESI) m/z: $[M - 4BArF]^{4+}$ calcd for $C_{128}H_{104}Ag_4N_{32}O_8Zn_2/4$ 693.0870, found 693.0881 (100); $[M - 4BArF - Ag]^{3+}$ calcd for $C_{128}H_{104}Ag_3N_{32}O_8Zn_2/3$ 888.4811, found 888.4842 (41); $[M - 3BArF]^{3+}$ calcd for $C_{128}H_{104}Ag_4BF_{24}N_{32}O_8Zn_2/3$ 1211.8045, found 1211.8067 (10); mp > 360 °C.

Silver(I)-Complexed Cage **[Ag_4·4](OTf)$_4$**. AgOTf (7.20 μmol, 1.85 mg, 4 equiv) was added at room temperature to a stirred solution of cage **4** (1.80 μmol, 4.00 mg, 1 equiv) in distilled $CHCl_3/CH_2Cl_2$/MeOH (5:5:1, 11 mL), protected from light. A purple precipitate formed immediately. After 20 min, the solvent was removed, and the residue was dried under vacuum to afford a purple solid (5.9 mg, quantitative yield). ^{1}H NMR (500 MHz, DMF-d_7): δ (ppm) 8.82 (8H, s, H_t), 8.59 (16H, s, H_{py}), 8.25 (8H, d, ^3J = 7.6 Hz, $H_{o\ out}$), versus 8.05 (8H, d, ^3J = 7.6 Hz, $H_{m\ out}$), 7.81 (8H, d, ^3J = 7.6 Hz, $H_{o\ in}$), 7.46 (8H, d, ^3J = 7.6 Hz, $H_{m\ in}$), 6.23 (16H, s, H1), 4.96 (s, 16H, H2), 4.00 (16H, m, H3), −3.45 (4H, s, NH). $^{13}C\{^1H\}$ NMR (126 MHz, DMF-d_7): δ (ppm) 146.8 (C_{12}), 142.5 (C_4), 136.7 (C_9), 136.3 (C_7), 135.6 (C_5), 131.9 (br, C_1), 127.9 (C_6), 126.8 (C_8), 125.6 (C_{11}), 122.6 (q, $^1J_{C-F}$ = 322 Hz, OTf), 120.6 (C_3), 70.7 (C_{14}), 64.2 (C_{13}), 54.8 (C_{10}). $^{19}F\{^1H\}$ NMR (282 MHz, DMF-d_7): δ (ppm) −79.64. HRMS (ESI) m/z: $[M - 4OTf]^{4+}$ calcd for $C_{128}H_{108}Ag_4N_{32}O_8/4$ 662.1302, found 662.1311 (100); $[M - 4OTf - Ag]^{3+}$ calcd for $C_{128}H_{108}Ag_3N_{32}O_8/3$ 847.2055, found 847.2085 (55); mp > 360 °C.

Recovering Cage **3** *from* **[Ag_4·3](OTf)$_4$**. An excess of LiCl (16 μmol, 0.7 mg, 10 equiv) was added at room temperature to a stirred solution of cage **[Ag_4·3](OTf)$_4$** (1.6 μmol, 5.5 mg, 1 equiv) in DMF-d_7. A white precipitate formed immediately. After filtration, the solvent was removed, and the residue was washed with methanol and centrifugated. The residue was dried under vacuum to afford a purple solid (3.5 mg, 90% yield).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00698.

X-ray crystallographic data for **1·DABCO** (CIF)
X-ray crystallographic data for **3·DABCO** (CIF)
^{1}H, ^{13}C, 2D NMR, DOSY spectra and HRMS of new compounds and crystallographic data for **1·DABCO** (CCDC 1535914) and **3·DABCO** (CCDC 1535953) (PDF)

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Notes

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