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Templated synthesis of a large and flexible covalent porphyrinic cage bearing orthogonal recognition sites†

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A large covalent cage incorporating two porphyrins attached by four long and flexible polyether chains each bearing two 3-pyridyl ligands was synthesized from a DABCO-templated olefin metathesis reaction. The X-ray structure of the cage with the DABCO coordinated inside the cavity to the two zinc(II) porphyrins reveals a highly symmetric structure.

Molecular cages are particularly attractive when their three-dimensional cavity is active, being associated with guest encapsulation,[1] chemical reactions,[2] catalysis[2c,3] or drug delivery.[4] The synthesis of such molecules relies on a multi-component reaction involving the formation of either strong[5] or reversible covalent bonds,[6] or on a self-assembly process based on hydrogen bonds[7] or coordination bonds formation.[1f,g,8] Covalent cage synthesis can be a tough work when it is based on a stepwise construction, whereas efficient cage construction was demonstrated when templated synthesis is chosen.[5d,9] Covalent cages present a high structural stability particularly important for high turnover in catalysis or for medical applications. Stabilizing molecules or reactants inside a capsule relies mostly on hydrophobic forces, van der Waals interactions or hydrogen bonds.[10] Metalloporphyrins incorporated in a cage can stabilize guest molecules to a larger extent *via* strong coordination bonds and can also participate in the preorganisation of the hollow structure in a templated reaction.[9c,11] Incorporating various active components in a cage framework is of significant interest since it will diversify and enhance the possible functions associated with the cavity, and when these components are orthogonal, an allosteric regulation of the cage activity can be expected.[12]

In the present work, we describe the templated synthesis of a covalent cage incorporating two cofacial pyridyl functionalized porphyrins connected by four long polyether chains. The covalent cage, with a 1,4-diazabicyclo[2.2.2]octane (DABCO) coordinated inside the cavity to both zinc porphyrins, was characterized in solution and in the solid state by X-ray crystallography.‡ The free-base porphyrinic cage with a ligand free cavity was also obtained. There have been only few covalent four-linked cofacial porphyrinic containers synthesized so far,[13] none with a one step templated ring-closure procedure and only one was recently reported with an X-ray structure analysis.[13j]

The cage was designed in order to have two cofacial metallated porphyrins able to coordinate strongly ditopic ligands of different sizes inside the adaptable cavity, thanks to the four long and flexible chains connecting the two porphyrins. The length of the polyether chain (14 atoms) was optimized using a CPK-model to prevent intramolecular cyclisation reactions in the final cage closing-step between the terminal olefins of the porphyrin monomer. According to this model, the porphyrin–porphyrin distance will be able to change to a large extent in the cage structure, from 5 to 15 Å. In addition, four 3-pyridyl groups are attached distal to each porphyrin core through a rigid and face hindering 2,6-dimethylphenyl linker. Therefore, the cage framework contains two components with orthogonal functionalities, the metalloporphyrins to coordinate ligands and the 3-pyridyl ligands to trap transition metals, both disposed in a way to prevent mutual interactions. The metalloporphyrins are also the key elements to preorganise a DABCO porphyrin dimer to efficiently close the cage *via* ring-closing metathesis (RCM).

The precursor **3** is a porphyrin derivative bearing four allyl functionalized polyether chains (Fig. 1). It was prepared in one step from **1**, a porphyrin bearing four 3-pyridyl groups remote from the porphyrin core, which was obtained in a limited number of steps from a triflate porphyrin derivative.[14] The four-fold Williamson reaction, carried out in dry DMF with sodium hydride and 2-(allyloxy)ethyl 4-methylbenzenesulfonate **2** (Fig. 1), afforded the porphyrin **3** in a very good yield (85%).

To favour the cage formation *via* RCM,[5d,9c,d,15] preorganisation of the precursor **3** with DABCO, which forms a stable face to face porphyrinic dimer, was realized.[16] Half an equiv. of DABCO was mixed with one equiv. of porphyrin derivative **3** (Fig. 2a) at room temperature in deuterated DCM. The highly upfield shifted NMR signal of the DABCO protons at −4.13 ppm characterized the sandwich complex **4** (Fig. 2b).[16] Moreover, two signals corresponding to the methyl groups and to the aromatic protons on the 2,6-dimethylphenyl group were split upon dimer formation due to the non-equivalence of the porphyrin faces in the DABCO dimer. This gave rise to two sets of signals, one corresponding to the protons pointing

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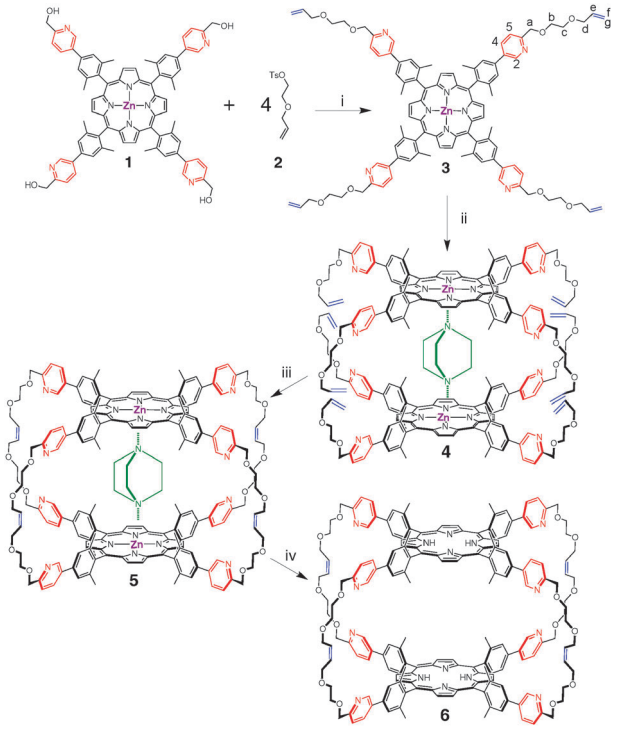

Fig. 1 Synthesis of molecular cages (i) NaH, DMF; (ii) 0.5 equiv. DABCO, CH_2Cl_2; (iii) Grubbs' 2nd-gen. catalyst, CH_2Cl_2; (iv) TFA, CH_2Cl_2.

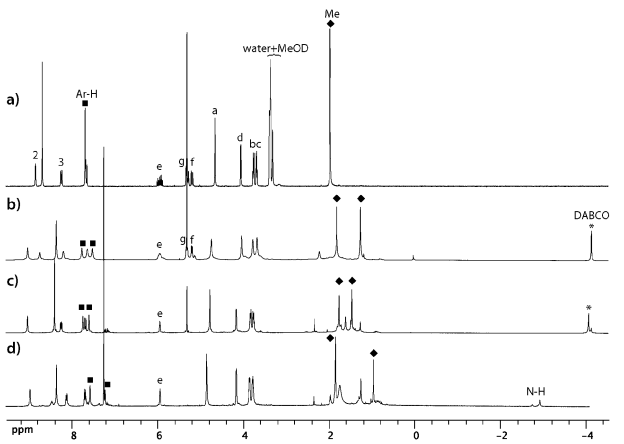

Fig. 2 ^{1}H NMR spectra in CD_2Cl_2 of **3** (a), of **4** at 223 K (b), of cage **5** and (c) of cage **6** in $CDCl_3$ (d).

inside the dimer, more upfield shifted than the other ones pointing outside the cavity.

A DABCO-templated olefin metathesis of the covalent cage was then performed (Fig. 1). After mixing **3** (1 equiv.) with DABCO (0.5 equiv.) in dichloromethane under argon, the second generation Grubbs' catalyst (1 equiv.) was added and the mixture was stirred for 14 h at room temperature. The desired molecular cage **5** was obtained in a 40% yield after purification by size-exclusion chromatography. This templated RCM reaction is very effective considering that four carbon–carbon double bonds are formed in one step.

Compound **5** was fully characterized by ^{1}H and ^{13}C NMR, ES-MS, UV-vis spectroscopy and X-ray diffraction. The two terminal olefinic signals (Hg and Hf) observed in the ^{1}H NMR spectrum at 5.32 and 5.20 ppm for the coordination dimer **4** (Fig. 2b) disappear and only one broad singlet, at 5.94 ppm, corresponding to the 8 alkene protons was detected for **5** (Fig. 2c). This is in favour of the formation of only one isomer of the cage, corresponding to the same configuration of all double bonds, either all *cis* or all *trans*. According to the CPK-model, the all *cis* stereoisomer is favoured, leading to less constrained chains. The methyl groups and the aromatic protons of the 2,6-dimethylphenyl units gave two sets of peaks, clearly showing the different chemical environment of the protons pointing either inside or outside the cavity. At room temperature, the chemical shift of the DABCO protons observed at −4.07 ppm characterizes its coordination to the zinc(II) porphyrins inside the cavity (Fig. 2c).[17] Two NOESY correlations were observed with the DABCO protons, one with the methyl groups pointing inside the cavity and one with the pyrrolic protons of the porphyrin nuclei. The four polyether chains are long and flexible enough to allow a close face to face disposition of the two porphyrins coordinated to DABCO. The diffusion ordered spectroscopy (DOSY) NMR experiment in DCM showed a single species characterized by a lower diffusion coefficient of 369 $\mu m^2\ s^{-1}$ for this large molecule compared to that of porphyrin $\mathbf{H_2 3}$ (470 $\mu m^2\ s^{-1}$).

After several trials, purple single crystals of the DABCO cage complex **5** were obtained by slow diffusion of MeOH into a $CHCl_3$ solution. The molecular structure, represented in Fig. 3, is highly symmetric: the top view shows clearly that the two zinc(II) porphyrins are eclipsed and the 2,6-dimethylphenyl groups superimposed whereas the side view shows the DABCO ligand coordinated inside the cavity to the cofacial porphyrins.

The overall dimensions of the molecule 25 × 21 × 15 Å (width × depth × height) were estimated from the distance between two adjacent polyalkylene chains and between the

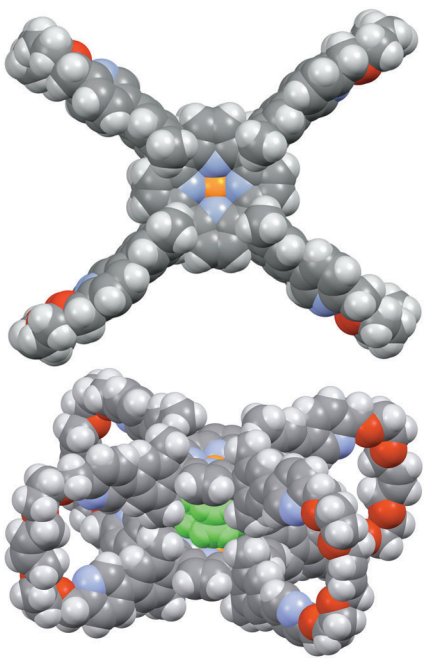

Fig. 3 Crystallographic structure of **5** top view (above), side view with DABCO shown in green color (below) (C: grey, N: blue, O: red, Zn: orange).

opposing methyl of the dimethylbenzene moieties of the porphyrin skeleton. The DABCO is complexed in between the porphyrinic units through regular N–Zn bonds (2.15 Å) indicating no strain in the complex. The cavity into which the DABCO is complexed is formed by the porphyrins and the four orthogonally oriented 2,6-dimethylphenyl units with a volume of *ca.* 200 Å^3. The packing coefficient PC is 63.5% [127 Å^3/200 Å^3; DABCO volume/cavity volume], which is somewhat larger value than in non-covalent encapsulation where the PC = 55%.[18]

Molecular cage **5** was finally subjected to acidic conditions (TFA 50% v/v solution in DCM) to remove both the zinc atoms and the DABCO. After purification, the uncoordinated cage **6** was obtained with a quantitative yield and characterized by NMR spectroscopy, ES-MS and UV-vis spectroscopy.† Despite the conformational flexibility of cage **6**, the proton NMR spectrum in DCM is consistent with an average stable and highly symmetric conformation in solution on the NMR time scale (Fig. 2d). Only one singlet was observed at 8.37 ppm for the pyrrolic protons of the two porphyrins and the only new signal at −2.92 ppm corresponds to the high field chemical shift of the NH porphyrinic protons, which experience the ring current of two porphyrins (for $\mathbf{H_2}$**3**, δNH = −2.43 ppm). The cage **6** was also characterized by its diffusion coefficient of 350 μm^2 s^{-1} in a DCM solution, obtained from a DOSY experiment. This value is close to that of the cage **5**, which is somehow surprising since removal of DABCO should allow the cage to expand. The UV-vis spectrum showed the characteristic bands of the free base porphyrins of the cage with a slight hypsochromic shift of 3 nm of the Soret band (*vs.* $\mathbf{H_2}$**3**), which could indicate some excitonic coupling between the porphyrins in a face to face disposition.

The present work reports the successful synthesis and the X-ray structure of a covalent cage obtained from a templated olefin metathesis reaction, which allows us, in one step, to quadruply bridge two porphyrins. The template could be removed to obtain the molecular cage with a ligand free cavity. The presence of two porphyrins and four pyridyl components in the cage framework will enable us to adjust the cavity size and shape with different kinds of external chemical signals and opens different ways to tune the activity within the covalent cage.

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Notes and references

‡ X-Ray crystallographic data: $C_{200}H_{213}N_{18}O_{21}Zn_2Cl_{15}$, M_r = 3903.44, monoclinic, space group *C*2/*m*, *a* = 36.835(3) Å, *b* = 27.126(2) Å, *c* = 22.4881(12) Å, α = 90.00°, β = 103.306(3)°, γ = 90.00°, *V* = 21867(3) Å^3, *Z* = 4, ρ_{calc} = 1.186 g cm^{-3}, μ = 0.464 mm^{-1}, *T* = 123.0(1) K, radiation MoKα (λ = 0.71073 Å), θ_{max} = 25.25°, no. of meas. reflns: 40 910, no. of indep. reflns: 20 049, R_{int} = 0.1124, R_1 = 0.1686, wR_2 = 0.4577. CCDC 867933.

1 (*a*) J. M. Lehn, *Supramolecular chemistry concepts and perspectives*, VCH, 1995; (*b*) M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi and K. Ogura, *Nature*, 1995, **378**, 469; (*c*) N. Branda, R. M. Grotzfeld, C. Valdes and J. Rebek, *J. Am. Chem. Soc*., 1995, **117**, 85; (*d*) D. L. Caulder, R. E. Powers, T. N. Parac and K. N. Raymond, *Angew. Chem., Int. Ed*., 1998, **37**, 1840; (*e*) P. Ballester, *Chem. Soc. Rev*., 2010, **39**, 3810; (*f*) W. J. Meng, B. Breiner, K. Rissanen, J. D. Thoburn, J. K. Clegg and J. R. Nitschke, *Angew. Chem., Int. Ed*., 2011, **50**, 3479; (*g*) S. Turega, M. Whitehead, B. R. Hall, M. F. Haddow, C. A. Hunter and M. D. Ward, *Chem. Commun*., 2012, **48**, 2752.

2 (*a*) D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev*., 2005, **105**, 1445; (*b*) T. S. Koblenz, J. Wassenaar and J. N. H. Reek, *Chem. Soc. Rev*., 2008, **37**, 247; (*c*) M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem., Int. Ed*., 2009, **48**, 3418.

3 (*a*) M. Kuil, T. Soltner, P. W. N. M. van Leeuwen and J. N. H. Reek, *J. Am. Chem. Soc*., 2006, **128**, 11344; (*b*) S. J. Lee, S. H. Cho, K. L. Mulfort, D. M. Tiede, J. T. Hupp and S. T. Nguyen, *J. Am. Chem. Soc*., 2008, **130**, 16828; (*c*) M. D. Pluth, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res*., 2009, **42**, 1650.

4 (*a*) B. Therrien, G. Suss-Fink, P. Govindaswamy, A. K. Renfrew and P. J. Dyson, *Angew. Chem., Int. Ed*., 2008, **47**, 3773; (*b*) Y. Hatakeyama, T. Sawada, M. Kawano and M. Fujita, *Angew. Chem., Int. Ed*., 2009, **48**, 8695; (*c*) S. Walker, R. Oun, F. J. McInnes and N. J. Wheate, *Isr. J. Chem*., 2011, **51**, 616.

5 (*a*) C. Seel and F. Vögtle, *Angew. Chem., Int. Ed. Engl*., 1992, **31**, 528; (*b*) G. Mori, N. Aratani and A. Osuka, *Tetrahedron*, 2007, **63**, 7916; (*c*) V. Steinmetz, F. Couty and O. R. P. David, *Chem. Commun*., 2009, 343; (*d*) S. Hiraoka, Y. Yamauchi, R. Arakane and M. Shionoya, *J. Am. Chem. Soc*., 2009, **131**, 11646.

6 M. Mastalerz, *Angew. Chem., Int. Ed*., 2010, **49**, 5042.

7 (*a*) J. Rebek, *Acc. Chem. Res*., 2009, **42**, 1660; (*b*) S. Singh, A. Aggarwal, C. Farley, B. A. Hageman, J. D. Batteas and C. M. Drain, *Chem. Commun*., 2011, **47**, 7134.

8 (*a*) Y. R. Zheng, Z. G. Zhao, M. Wang, K. Ghosh, J. B. Pollock, T. R. Cook and P. J. Stang, *J. Am. Chem. Soc*., 2010, **132**, 16873; (*b*) R. W. Saalfrank, H. Maid and A. Scheurer, *Angew. Chem., Int. Ed*., 2008, **47**, 8794; (*c*) M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res*., 2005, **38**, 369; (*d*) N. Fujita, K. Biradha, M. Fujita, S. Sakamoto and K. Yamaguchi, *Angew. Chem., Int. Ed*., 2001, **40**, 1718.

9 (*a*) D. A. Makeiff, D. J. Pope and J. C. Sherman, *J. Am. Chem. Soc*., 2000, **122**, 1337; (*b*) T. Inomata and K. Konishi, *Chem. Commun*., 2003, 1282; (*c*) K. T. Youm, S. T. Nguyen and J. T. Hupp, *Chem. Commun*., 2008, 3375; (*d*) T. Ishida, Y. Morisaki and Y. Chujo, *Tetrahedron Lett*., 2006, **47**, 5265.

10 M. D. Pluth and K. N. Raymond, *Chem. Soc. Rev*., 2007, **36**, 161.

11 (*a*) S. Anderson, H. L. Anderson and J. K. M. Sanders, *Acc. Chem. Res*., 1993, **26**, 469; (*b*) A. Ikeda, M. Ayabe, S. Shinkai, S. Sakamoto and K. Yamaguchi, *Org. Lett*., 2000, **2**, 3707; (*c*) E. Stulz, S. M. Scott, A. D. Bond, S. J. Teat and J. K. M. Sanders, *Chem.–Eur. J*., 2003, **9**, 6039.

12 (*a*) S. D. Starnes, D. M. Rudkevich and J. Rebek, *J. Am. Chem. Soc*., 2001, **123**, 4659; (*b*) N. C. Gianneschi, M. S. Masar and C. A. Mirkin, *Acc. Chem. Res*., 2005, **38**, 825; (*c*) A. Lledo, S. Kamioka, A. C. Sather and J. Rebek, *Angew. Chem., Int. Ed*., 2011, **50**, 1299; (*d*) M. Yamanaka, M. Kawaharada, Y. Nito, H. Takaya and K. Kobayashi, *J. Am. Chem. Soc*., 2011, **133**, 16650; (*e*) M. Zhang, B. Zheng and F. Huang, *Chem. Commun*., 2011, **47**, 10103.

13 (*a*) N. E. Kagan, D. Mauzerall and R. B. Merrifield, *J. Am. Chem. Soc*., 1977, **99**, 5484; (*b*) K. H. Neumann and F. Vögtle, *J. Chem. Soc., Chem. Commun*., 1988, 520; (*c*) B. C. Bookser and T. C. Bruice, *J. Am. Chem. Soc*., 1991, **113**, 4208; (*d*) R. Karaman, S. W. Jeon, O. Almarsson and T. C. Bruice, *J. Am. Chem. Soc*., 1992, **114**, 4899; (*e*) M. Kreysel and F. Vögtle, *Synthesis*, 1992, 733; (*f*) G. Markl, M. Reiss, P. Kreitmeier and H. Noth, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2230; (*g*) W. H. Chen, J. M. Yan, Y. Tagashira, M. Yamaguchi and K. Fujita, *Tetrahedron Lett*., 1999, **40**, 891; (*h*) F. Hajjaj, K. Tashiro, H. Nikawa, N. Mizorogi, T. Akasaka, S. Nagase, K. Furukawa, T. Kato and T. Aida, *J. Am. Chem. Soc*., 2011, **133**, 9290; (*i*) C. X. Zhang, Q. Wang, H. Long and W. Zhang, *J. Am. Chem. Soc*., 2011, **133**, 20995; (*j*) J. Zhang, Y. Li, W. Yang, S.-W. Lai, C. Zhou, H. Liu, C.-M. Che and Y. Li, *Chem. Commun*., 2012, **48**, 3602.

14 J. Taesch, T. T. Dang and V. Heitz, *Tetrahedron Lett*., 2012, **53**, 333.

15 A. R. Mulholland, C. P. Woodward and S. J. Langford, *Chem. Commun*., 2011, **47**, 1494.

16 P. Ballester, A. Costa, A. M. Castilla, P. M. Deya, A. Frontera, R. M. Gomila and C. A. Hunter, *Chem.–Eur. J*., 2005, **11**, 2196.

17 The tiny peak at −4.13 ppm could be assigned either to the coordinated DABCO inside the cage in a conformation that differs from the major one by rotation around the Zn···Zn axis or to a trace of a *cis*,*cis*,*cis*,*trans* stereoisomer.

18 S. Mecozzi and J. Rebek, *Chem.–Eur. J*., 1998, **4**, 1016.

