Enlarged cavitand-based coordination cages

Nicola Cuminetti,[a] Maurits H. K. Ebbing,[b] Pilar Prados,[b] Javier de Mendoza[b] and
Enrico Dalcanale[a,*]

[a]*Dipartimento di Chimica Organica e Industriale, Università di Parma, Parco Area delle Scienze 17/A, I-43100 Parma, Italy*
[b]*Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco E-28039 Madrid, Spain*

Abstract—Two new coordination cages **1a,b** were prepared via metal-directed self-assembly of the tetrakis(benzonitrile) cavitands **2a,b** with Pt(dppp)(CF$_3$SO$_3$)$_2$. Their large portals allow fast exchange on the NMR timescale of encapsulated counterions or guests with solvent molecules. © 2001 Elsevier Science Ltd. All rights reserved.

Metal-directed self-assembly has proven to be a highly efficient methodology for the formation of cage molecules.[1] Its appeal resides in the thermodynamically driven, quantitative formation of the desired structure by direct mixing of the preorganised components in the correct stoichiometric ratio. The demand for cages with internal cavities of nanoscopic dimensions able to encapsulate large guests,[2] stabilise reactive intermediates,[3] or be used as reaction chambers,[4] can be fulfilled either by increasing the number of self-assembled components[5] or by enlarging the size of the reacting ligands. The second approach, widely used for the construction of nanoscale molecular squares and other supramolecular architectures,[6] is unprecedented for coordination cages.
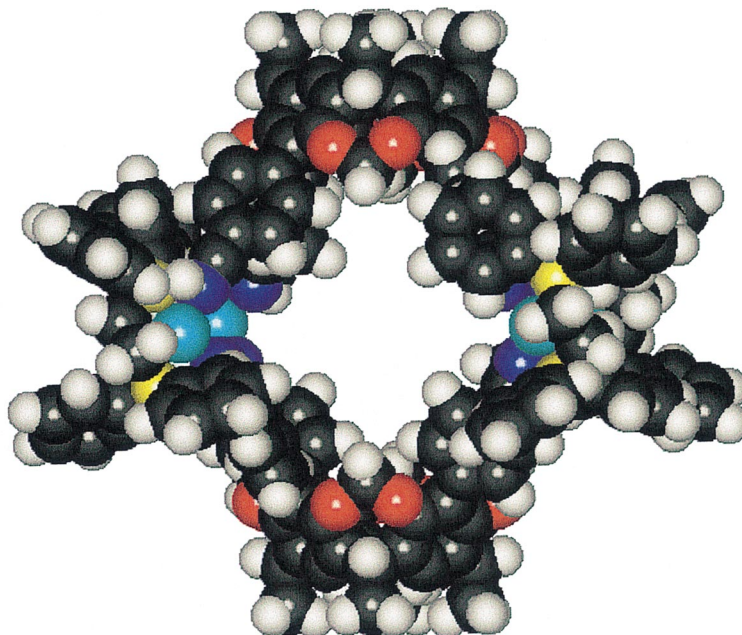
In previous studies, self-assembly of coordination cages composed of two rigidly preorganised tetracyano cavitand ligands connected through four Pd^{II} or Pt^{II} square-planar complexes was reported.[7] Encapsulation of one triflate anion was observed by ^{19}F NMR and
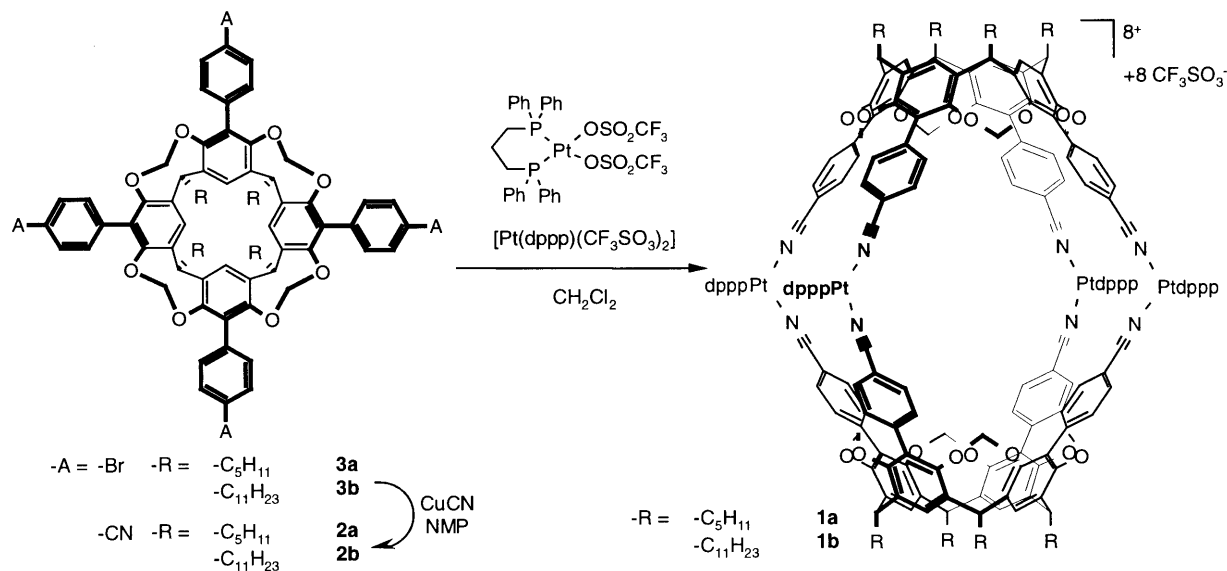
Scheme 1.

Figure 1. Molecular structure of **1**. Long alkyl chains are replaced by methyl groups. Colour code: carbon, black; hydrogen, white; oxygen, red; nitrogen, blue; phosphorus, yellow; platinum, cyan.

confirmed by X-ray diffraction.[8] The volume of the internal cavity has been estimated to be 250 Å, based on calculations with GRASP on the crystal structure.[†]

Here self-assembly of nanosize coordination cages **1a**,**b** using enlarged tetradentate cavitand ligands **2a**,**b** is reported. Phenyl groups were chosen as spacers introduced at the upper rim of **2** in order to extend the cavity size, while retaining the relative orientation of the cyano groups and the rigidity of the cavitand framework, both essential for cage formation. Although molecular modelling[‡] showed for **2** a rotation of 42° for the biphenyl angle, it takes place along the *para* axis, leaving intact the coordination ability of the nitriles to form square planar complexes.

The first attempt to synthesise **2** was performed starting from a known tetrabromocavitand[10] through a Suzuki coupling with 1,4-dibromobenzene or 1-bromo-4-cyanobenzene. Unfortunately in both cases the main product was the unsubstituted parent cavitand. Nitriles **2a**,**b** were thus synthesised by a known procedure[11] from the corresponding tetrakis(bromophenyl) cavitands **3a**,**b** (see Scheme 1).[12] Reaction of **3a**,**b** with CuCN in NMP gave the desired **2a**,**b** in 21 and 34% yield respectively after flash column chromatography of the crude mix-

ture.[§] In the case of **2b**, the major isomer with all four undecyl feet in the axial configuration (rccc isomer) is contaminated with a small amount (<10%) of the rctt isomer having two adjacent undecyl feet in the equatorial configuration, which retains the same coordination properties. The two isomers are not separable using standard preparative chromatographic techniques. The origin of the second isomer has been traced in the resorcinarene condensation reaction, in which the concurrent presence of large substituents in the 2-position of the resorcinol and long alkyl chains at the lower rim favours the formation of a small amount of the rctt isomer. In the subsequent methylene bridging reaction the rctt isomer underwent ring inversion,[13] forming the corresponding cavitand with two equatorial feet.

[†] A spherical probe of 1.7 Å was used. See Ref. 9.

[‡] Molecular modelling was performed by minimisation of the structural energy using the MM+ Force Field in vacuum as implemented in Hyperchem 5.1™.

[§] Synthesis of **2a**,**b**: A solution of 0.40 mmol of **3a** (0.17 mmol of **3b**) and 2.80 mmol (1.22 mmol) of CuCN in 30 ml (15 ml) NMP was refluxed for 40 h. It was then cooled to 80°C and 3.0 mmol (1.4 mmol) FeCl$_3$, dissolved in 7 ml (4 ml) 2.5 M HCl, were added and the mixture was stirred for a further 1 h. After cooling to rt the solution was filtered and washed with CH$_2$Cl$_2$, the solvent evaporated under reduced pressure and the solid purified by flash column chromatography (silica gel, 2% EtOAc in CH$_2$Cl$_2$). Yield 21% (34%). Selected data for **2a**: ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.94$ (t, 12H, CH_3), 1.40 (bs, 24H, CH$_3$(CH_2)$_3$), 2.35 (m, 8H, CH_2CH), 4.14 (d, 4H, CH_{in}, $J = 6.8$ Hz), 4.82 (t, 4H, CH$_2$CH), 5.21 (d, 4H, CH_{out}, $J = 6.8$ Hz), 7.14 (d, 8H, ArH_m, $J = 7.9$ Hz), 7.36 (s, 4H, ArH), 7.62 (d, 8H, ArH_o, $J = 7.9$ Hz). MS (CI): $m/z = 1221$ ([M]$^+$, 100%). FT-IR (KBr): $v = 2216$ cm^{-1} (C≡N). **2b**: ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.88$ (t, 12H, CH_3), 1.28 (bs, 64H, CH$_3$(CH_2)$_8$), 2.33 (m, 8H, CH_2CH), 4.15 (d, 4H, CH_{in}, $J = 6.8$ Hz), 4.82 (t, 4H, CH$_2$CH), 5.23 (d, 4H, CH_{out}, $J = 6.8$ Hz), 7.13 (d, 8H, ArH_m, $J = 8.3$ Hz), 7.35 (s, 4H, ArH), 7.64 (d, 8H, ArH_o, $J = 8.3$ Hz). MS (FAB+): $m/z = 1558.7$ ([M]$^+$, 100%).

Cages **1a,b** were obtained in a quantitative yield mixing **2a,b** with Pt(dppp)(CF$_3$SO$_3$)$_2$ in a 1:2 molar ratio in dichloromethane at room temperature (Scheme 1).¶ The less soluble cage **1a** precipitated out of the solution and was collected in its pure form by filtration. The high symmetry of the cages (D_{4h}) is reflected in their simplified ^{31}P and ^{1}H NMR spectra. MALDI-TOF gave the [M−CF$_3$SO$_3^-$]$^+$ ion in both cases. Compound **1a** was also characterised using ESI-MS showing prominent peaks for the [M−2CF$_3$SO$_3^-$]$^{2+}$ ion either in dichloromethane or acetone. The ^{31}P NMR spectra indicated the equivalence of all eight phosphorus atoms, featuring sharp singlets, with appropriate Pt satellites. The large upfield shift of the aromatic protons *ortho* and *meta* to the nitriles (0.5 ppm for the *ortho* ones) is diagnostic of cage formation since from one side they are pointing toward the cage interior and on the other side they are in proximity of the dppp phenyl rings. Self-assembly was attempted using **2b** and Pd(dppp)(CF$_3$SO$_3$)$_2$ as an organometallic precursor. Its ^{1}H and ^{31}P NMR spectra were consistent with cage formation; however, neither MALDI-TOF nor ESI-MS gave indicative peaks. This different behaviour results from the weaker CN–Pd dative bond compared to CN–Pt.

No permanent inclusion of the CF$_3$SO$_3^-$ counterions was observed by ^{19}F NMR even at low temperature. Rapid exchange with solvent molecules occurs due to the large dimensions of the lateral portals. Their dimensions, as well as the internal cavity volume, were evaluated by modelling the cage structure (Fig. 1). The distance between two adjacent Pt atoms delimiting the portals in the equatorial region is about 13.8 Å, while the longitudinal opening between two methylene bridges is 11.5 Å. The internal volume is ca. 1100 Å^3, over four times that of its short analogue.‖

Table 1. Encapsulation studies on cage **1b**

Candidate guests	Observed effect
NaSbF$_6$[a]	No complexation
NBu$_4$PF$_6$	No complexation
K$_2$TiF$_6$[a]	No complexation
NBu$_4$PhCOO	Complete disassembly
TPP[b]	No complexation
ZnC$_6$OAP[c]	No complexation
Ru$_3$(CO)$_{12}$	Partial disassembly
(NBu$_4$)$_3$PW$_4$O$_{24}$	Partial disassembly

[a] Guest dissolved in CD$_3$NO$_2$.
[b] TPP = 5,10,15,20-tetraphenylporphyrin.
[c] ZnC$_6$OAP = (octahexylporphyrin-2,3,8,12,13,17,18-octaacetate)zinc.

Eight different anionic and neutral guests have been evaluated as guests for encapsulation (see Table 1). Complexation experiments were performed adding stepwise several equivalents of the candidate guest to a CD$_2$Cl$_2$ solution of **1b** and monitoring the changes by ^{1}H and ^{19}F NMR. The three spherical hexafluoro anions SbF$_6^-$, PF$_6^-$ and TiF$_6^{2-}$ were not permanently encapsulated in the cage, even at low temperatures. The benzoate anion led to complete disassembly of **1b**, successfully competing with the nitriles in coordinating to the metal centres. The remaining four candidate guests were checked by docking simulations small enough to fit the cavity space and too large to escape through the lateral portals. The two porphyrins, having four *meso* phenyl (TPP) and eight β-hexyl (ZnC$_6$OAP) substituents,[14] respectively, gave no complexation.** Ru$_3$(CO)$_{12}$ and (NBu$_4$)$_3$PW$_4$O$_{24}$†† instead, produced a partial disassembly of the cage, monitored by the appearance of two sets of signals attributed to **2b** and residual **1b**.

In conclusion, two new nanosize coordination cages have been obtained by metal-directed self-assembly. Enlarging the size of the tetracyano cavitand ligands has proven to be a viable route for the preparation of large cages. The drawback of such an approach is the concomitant widening of the lateral portals, which prevents permanent inclusion of suitable guests.

Acknowledgements

¶ Synthesis of **1**: [Pt(dppp)(OTf)$_2$] (9.0 mmol) was added to a solution of **2** (4.5 mmol) in 10 ml CH$_2$Cl$_2$ and mixed for a few minutes. The solvent was then evaporated to dryness obtaining **1** in a quantitative yield. Selected data for **1a**: ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, high dilution): $\delta = 0.95$ (t, 24H, CH_3), 1.42 (bs, 48H, CH$_3$(CH_2)$_3$), 2.31 (m, 16H, CH_2CH), 2.51 (bs, 8H, (Ph$_2$PCH$_2$)$_2$CH_2), 3.02 (bs, 16H, (Ph$_2$PCH_2)$_2$CH$_2$), 4.24 (d, 8H, CH_{in}, $J = 7.2$ Hz), 4.71 (bt, 8H, CH$_2$CH), 5.06 (d, 8H, CH_{out}, $J = 7.2$ Hz), 6.98 (bd, 16H, ArH_m), 7.11 (bd, 16H, ArH_o), 7.30–7.45 (bm, 56H, Ar$H_{m,p}$-dppp+ArH), 7.74 (bs, 32H, ArH_o-dppp). ^{19}F NMR (188.3 MHz, CDCl$_3$): $\delta = -79.0$ (s, CF_3SO$_3^-$ external only). ^{31}P NMR (81 MHz, CDCl$_3$): $\delta = -13.1$, $J_{\text{Pt-P}} = 3400$ Hz. MS (ESI, CH$_2$Cl$_2$): $m/z = 2884.3$ [M−2CF$_3$SO$_3^-$]$^{2+}$, 1872.6 [M−3CF$_3$SO$_3^-$]$^{3+}$; (ESI, acetone): $m/z = 2884.0$ [M−2CF$_3$SO$_3^-$]$^{2+}$. MS (MALDI-TOF): $m/z = 5917.6$ [M−CF$_3$SO$_3^-$]$^+$. **1b**: ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 38°C): $\delta = 0.90$ (t, 24H, CH_3), 1.30 (bs, 128H, CH$_3$(CH_2)$_8$), 2.32 (bs, 24H, CH_2CH+Ph$_2$PCH$_2$)$_2$CH_2), 3.04 (bs, 16H, (Ph$_2$PCH_2)$_2$CH$_2$), 4.27 (d, 8H, CH_{in}, $J = 7.3$ Hz), 4.72 (t, 8H, CH$_2$CH), 5.06 (d, 8H, CH_{out}, $J = 7.3$ Hz), 7.02 (d, 16H, ArH_m, $J = 8.3$ Hz), 7.14 (d, 16H, ArH_o, $J = 8.3$ Hz), 7.36 (s, 8H, ArH), 7.50 (m, 48H, Ar$H_{m,p}$-dppp), 7.75 (m, 32H, ArH_o-dppp). ^{19}F NMR (188.3 MHz, CDCl$_3$): $\delta = -78.9$ (s, CF_3SO$_3^-$ external only). ^{31}P NMR (81 MHz, CDCl$_3$): $\delta = -13.5$, $J_{\text{Pt-P}} = 3420$ Hz. MS (MALDI-TOF): $m/z = 6590.5$ [M−CF$_3$SO$_3^-$]$^+$.

‖ Calculated using GRASP with a 2.8 Å spherical probe.

** Encapsulation of the large porphyrin guests requires the activation of the cage dissociation–recombination process. Time- (up to 8 hours) and temperature- (up to 50°C) dependent NMR complexation experiments were performed to rule out the possibility of a very slow encapsulation rate determined by an eventual high kinetic stability of **1b**. Moreover, addition of Pt(dppp)(OTf)$_2$ to a CDCl$_3$ solution of **2b** and ZnC$_6$OAP led to cage formation without detectable inclusion of the guest.

†† (NBu$_4$)$_3$PW$_4$O$_{24}$ is the precursor of an highly efficient epoxidation catalyst. See Ref. 15.

References

1. (a) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853–908. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1018–1033.
2. (a) Ikeda, A.; Yoshimura, M.; Udzu, H.; Fukuhara, C.; Shinkai, S. *J. Am. Chem. Soc.* **1999**, *121*, 4296–4297. (b) Fox, O. D.; Drew, M. G. B.; Wilkinson, E. J. S.; Beer, P. D. *Chem. Commun.* **2000**, 391–392.
3. Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 6311–6312.
4. Kang, J. M.; Rebek, Jr., J. *Nature* **1997**, *385*, 50–52.
5. (a) Takeda, N.; Umemoto, K.; Yamaguchi, K.; Fujita, M. *Nature* **1999**, *398*, 794–796. (b) Olenyuk, B.; Whiteford, J. A.; Fechtenkötter, A.; Stang, P. J. *Nature* **1999**, *398*, 796–799.
6. Manna, J.; Kuehl, C. J.; Whiteford, J. A.; Stang, P. J.; Muddiman, D. C.; Hofstadler, S. A.; Smith, R. D. *J. Am. Chem. Soc.* **1997**, *119*, 11611–11619.
7. Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613–615.
8. Dalcanale, E.; Rissanen, K. et al., manuscript in preparation.
9. Mecozzi, S.; Rebek, Jr., J. *Chem. Eur. J.* **1998**, *4*, 1016–1022.
10. Timmerman, P.; Boerrigter, H.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Incl. Phenom. Mol. Recognit. Chem.* **1994**, *19*, 167–191.
11. Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795–5802.
12. (a) von dem Bussche-Hünnefeld, C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1085–1087. (b) von dem Bussche-Hünnefeld, C.; Helgeson, R. C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *Croat. Chem. Acta* **1996**, *69*, 447–458.
13. Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2075–2080.
14. Paganuzzi, V.; Guatteri, P.; Riccardi, P.; Sacchelli, T.; Barberà, J.; Costa, M.; Dalcanale, E. *Eur. J. Org. Chem.* **1999**, 1527–1539.
15. Venturello, C.; D'Aloisio, R.; Bart, J. C. J.; Ricci, M. *J. Mol. Catal.* **1985**, *32*, 107–118.