ORGANIC
LETTERS

2002
Vol. 4, No. 3
319−321

Metal Ligation Regulates Conformational Equilibria and Binding Properties of Cavitands

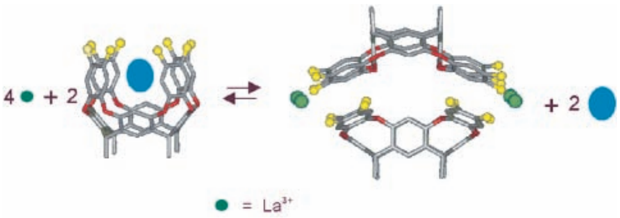
Patrick Amrhein, Paul L. Wash, Alexander Shivanyuk, and Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and The Department of Chemistry,
The Scripps Research Institute, MB-26, 10550 North Torrey Pines Rd.,
La Jolla, California 92037

jrebek@scripps.edu

Received September 17, 2001

ABSTRACT



A self-folding cavitand binds quinuclidinium cation in its vase conformation and lanthanum ions in its kite conformation. Metal coordination provides a novel switching mechanism for the uptake and release of guests.

Self-folding cavitands[1] **1** act as hosts to complementary guests in apolar solvents,[2] in methanol, and in water.[3] The intramolecular hydrogen bonds of the host resist the conformational changes required for guest exchange. Accordingly, exchange rates are slow on the NMR time scale at ambient temperatures, even though the binding affinities are usually moderate (2−3 kcal/mol). Much higher affinities (7−10 kcal/mol) are seen with cavitands outfitted with an introverted carboxy group[4] or a metalated porphyrin.[5]

The present research was undertaken to examine the interplay of the binding sites of cavitands **4**—the vase-shaped cavity and the metal ligating groups fixed on the rim.[6] We attached eight carbamoylmethyl phosphonate (CMPO) groups to the cavitand's upper rim[7] for binding to lanthanide ions. The octanitro compound **2a** was reduced to octaamine **2b** with $SnCl_2$ and then acylated with bromoacetyl chloride (K_2CO_3, AcOEt/H_2O) to give octabromacetamide **3** in 64% yield. Arbuzov reaction with triethyl or tripropyl phosphite afforded the respective octaphosphonates **4** in preparative yields.

The ^1H NMR spectrum of **4b** measured in CD_2Cl_2 or $CDCl_3$ at 295 K (Figure 2a) features one triplet for the methine protons of the bridges at 5.77 ppm and one set of signals for the protons of the resorcinol rings and cavitand walls; this pattern is characteristic of a vase conformation (Figure 3).[8] Like the parent cavitand **1a**, the compounds **4**

---

[1] Reviews: (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Stoddart, F., Ed.; The Royal Society of Chemistry: London, 1994. (b) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663. (c) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org Chem.* **1999**, 1991. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer Academic Publishers: Dordrecht, Boston, London, 2001.

[2] (a) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 12216. (b) Shivanyuk, A.; Rissanen, K.; Körner, S.; Rudkevich, D. M.; Rebek, J., Jr. *Helv. Chim. Acta* **2000**, *83*, 1778.

[3] Haino, T.; Rudkevich, D. M.; Shivanyuk, A.; Rissanen, K.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 3797.

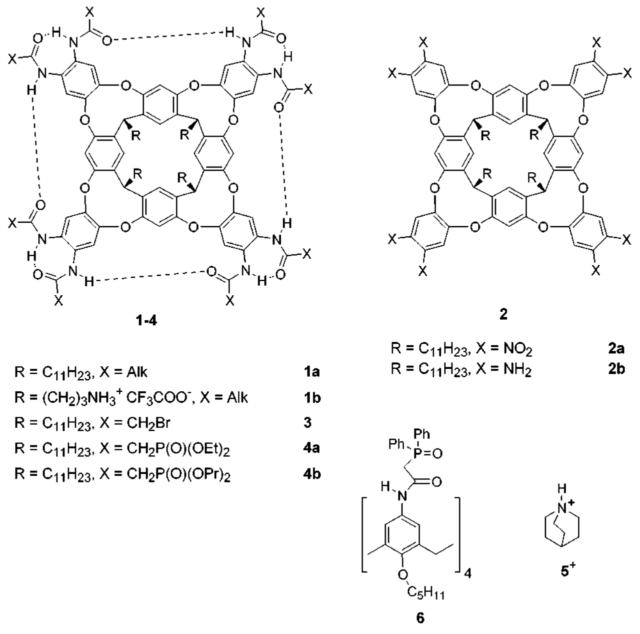
[4] (a) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int Ed.* **2000**, *39*, 3281. (b) Wash, P. L.; Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int Ed.* **2001**, *40*, 1221.

[5] Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 4659.

[6] For metallo-cavitands fixed in a crown conformation, see: Xu, W.; Vittal, J. J.; Puddephat, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 8362.

[7] For recent examples of CMPO-calixarenes and cavitands, see: (a) Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Jakobi, R. A.; Kraft, D.; Mauprivez, O.; Rouquette, J.; Schwing-Weil, M.-J.; Simon, N.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1175. (b) Arduini, A.; Böhmer, V.; Daelmau, L.; Desreux, J.-F.; Dozol, J.-F.; Garcia Carrera, M. A.; Lambert, B.; Musigmann, C.; Pochini, A.; Shivanyuk, A.; Ugozoli, F. *Chem. Eur. J.* **2000**, *6*, 2135. (c) Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, *62*, 7148.

10.1021/ol0167661 CCC: $22.00



1-4

R = $C_{11}H_{23}$, X = Alk **1a**

R = $(CH_2)_3NH_3^+ CF_3COO^-$, X = Alk **1b**

R = $C_{11}H_{23}$, X = CH_2Br **3**

R = $C_{11}H_{23}$, X = $CH_2P(O)(OEt)_2$ **4a**

R = $C_{11}H_{23}$, X = $CH_2P(O)(OPr)_2$ **4b**

2

R = $C_{11}H_{23}$, X = NO_2 **2a**

R = $C_{11}H_{23}$, X = NH_2 **2b**

6

5$^+$

Figure 1. Compounds **1**−**6**.

form kinetically stable 1:1 complexes with derivatives of adamantane and quinuclidine in these solvents. Unlike the parent cavitand **1a**, the hydrophilic dialkoxy phosphoryl groups of **4** impart solubility in alcohols. The ^{1}H NMR spectrum of **4b** in CD$_3$OD is an incomprehensible set of broad signals, while the ^{31}P NMR spectrum contained one broadened singlet centered at 23.4 ppm. The addition of **5**$^+$Cl$^-$ to this solution results in a sharp spectrum for the complex, characteristic of the vase conformation (Figure 2b). Two upfield signals emerge that correspond to the methylene and methine protons of the encapsulated **5**$^+$ cation. The complex is stable on the NMR time scale at 295 K, and the integration of corresponding signals reveals its 1:1 stoichiometry. One sharp signal was observed in the ^{31}P NMR spectrum, corresponding to a C_{4V}-symmetric structure of the vase conformer.[8] The stability constant of **4b**·**5**$^+$ could not be accurately determined from the NMR data because of the unknown state of "free" **4b**.

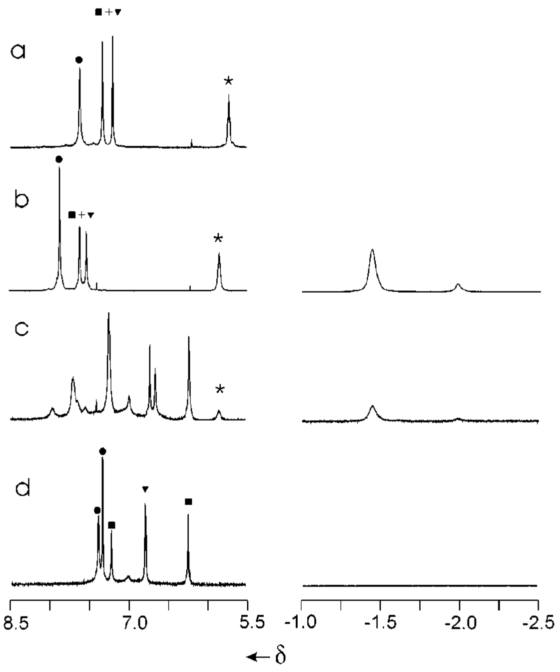


Figure 2. Upfield and downfield regions of the ^{1}H NMR spectra ([**4b**]= 4 mM, 295 K, 600 MHz): (a) **4b** in CD$_2$Cl$_2$; (b) **4b**·**5**$^+$ in CD$_3$OD; (c) as in (b) after the addition of 1 molar equiv of La(OTf)$_3$; (d) as in (b) after the addition of 2 equiv of La(OTf)$_3$. Asterisks represent methine bridges. Protons of the resorcinol rings: (■) at 5-positions; (▼) at 2-positions; (●) the protons of the cavitand walls.

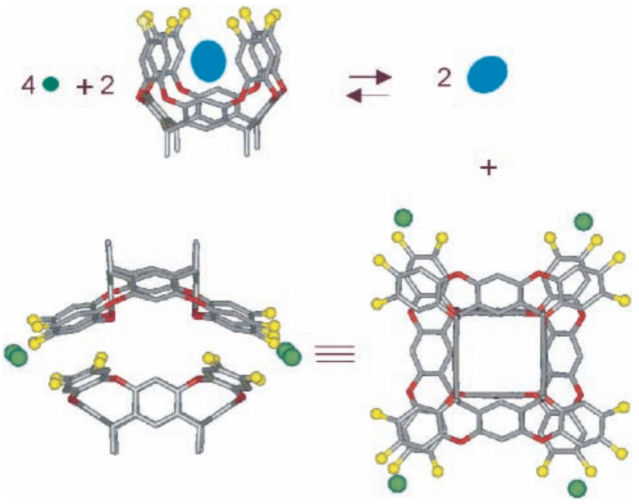


Figure 3. Schematic presentation of the equilibrium between vase and kite conformers of cavitands (top) and the dimeric velcrand (bottom). Yellow balls: CMPO fragments. Green balls: La^{3+}. Blue ellipse: **5**$^+$.

The addition of lanthanum(III)triflate to the solution of the complex **4b**·**5**$^+$ resulted in the appearance of a new set of NMR signals[9] (Figure 2c). The new set grows at the expense of the original set on further addition of La^{3+}, and at $[\mathrm{La}^{3+}]_{\mathrm{total}}/[\mathbf{4b}]_{\mathrm{total}} = 2$ no signals of the original quinuclidinium complex remain. The ligation of La^{3+} releases **5**$^+$ from the cavity of **4b**.

The characteristics of the metal complex, as deduced from the 2D-ROESY spectrum, reveals a C_{2V}-symmetrical kite conformation (Figure 3).[10] The signal for the methine bridge protons shifts upfield to 4.1 ppm, and two signals were found in the ^{31}P NMR spectrum at 22.70 and 24.22 ppm.

The effects of the metal ion ligation are reversible. Addition of calixarene ligand **6**[7](a high-affinity CMPO-type

---

(8) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707.

(9) No interaction was detected between cavitands **1** and La(OTf)$_3$ in a 1:1 mixture of methanol-d_4 and CDCl$_3$.

(10) Very recently it was shown that protonation stabilizes the kite conformation of quinoxaline cavitand: Skinner, P. J.; Cheetham, A. G.; Beeby, A.; Gramlich, A.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2146.

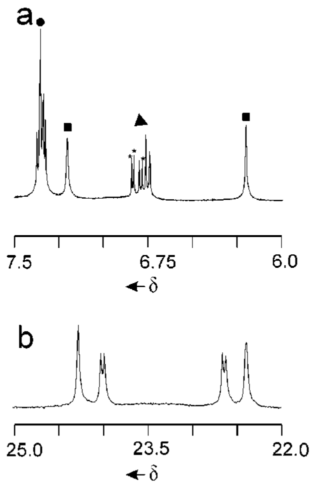


Figure 4. The ^{1}H (a) and ^{31}P (b) NMR spectra of **4a**+**4b** with 10 equiv of La(OTf)$_3$. Groups of signals are indicated. Protons of the resorcinol rings: (■) 5-positions; (▲) 2-positions; (●) protons of the cavitand walls. The signals of the heterodimer are indicated by asterisks; CDCl$_3$ (10%) was added to the solution in CD$_3$OD to prevent precipitation of the complex.

ligand) to the methanol solution of the metal complex of **4b** and free **5**$^{+}$Cl^{-} restored the quinuclidinium complex, **4b**·**5**$^{+}$. The same result could be achieved by the addition of tetrabutylammonium nitrate, as the bidentate nitrate provides effective complexation of La^{3+}. The addition of chloride ions, on the other hand, did not result in the conformational change from the kite to the vase. The kite conformer of the lanthanum complex was stable at temperatures between 233 and 313 K. This is in contrast to simpler quinoxaline cavitands whose kite conformations could be detected by NMR only at lower temperatures.

An additional clue to the structure of the metal complexes was revealed by the spectrum of a 1:1 mixture of La^{3+} complexes of **4a** and **4b**. Seven singlets (ratio 1:1:1:1:2:1:1) are seen for the protons at 2-positions of the resorcinol rings of **4a** and **4b** (Figure 4a). Moreover, the ^{31}P NMR spectrum of this mixture contains six singlets in a 2:1:1:1:1:2 ratio (Figure 4b). These results indicate a dimeric, velcrand-like structure for the La^{3+} complex. The additional set of signals is due to the heterodimeric complex formed in a statistical (2:1:1) ratio with respect to the homodimeric complexes. Only a lower limit of the dimerization constant ($>10^{4}$ M^{-1}) could be derived from dilution experiments.

The ESI-mass spectrum of this solution shows peaks at *m/z* 1279 and 1309 Da corresponding to [**4a**·**4b** + 2La − H]$^{5+}$ and [**4a**·**4b** + 2La + OTf]$^{5+}$. The spectrum also showed cations [2**4b** + 2La + OTf − H]$^{4+}$, [**4a**·**4b** + 2La + 2OTf]$^{4+}$, and [**4a**·**4b** + 4La + 8OTf]$^{4+}$ with *m/z* of 1693, 1674, and 1967 Da, respectively.

A cartoon of the velcraplex-like dimer is proposed in Figure 3. This arrangement offers four CMPO-like binding sites on each of the four edges of the dimer. Hence, 2 equiv of La^{3+} are necessary to disrupt one complex of **4**·**5**$^{+}$. The detailed structure of the La-bound dimers[11] awaits crystallographic studies.

In summary, the interaction between **4** and La^{3+} in CD$_3$OD changes the cavitands' conformations from vase to kite and expels the resident guests from the cavity.[12] This process can be reversed by the addition of strong ligands for La^{3+}. The metal regulates quantitatively the molecular recognition capabilities of the cavitands.

Acknowledgment. We are grateful to the Skaggs Foundation and the National Institutes of Health for financial support. P.W. and A. S. are Skaggs Postdoctoral Fellows; P. A. is a Lynen Fellow of the Alexander von Humboldt Foundation.

Supporting Information Available: Synthetic procedures and characterization of compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0167661

---

[11] Tucci, F.; Rudkevich, D. M.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 1007.

[12] For regulation of hydrogen bonding by metal complexation in calixarenes, see: (a) Murakami, H.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1533. (b) Rudkevich, D. M.; Shivanyuk, A. N.; Brzozka, Z.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2124. (c) Scheerder, J.; Van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1090.