CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002013

A pH Switchable Pseudorotaxane Based on a Metal Cage and a Bis-anionic Thread

Guido H. Clever[b] and Mitsuhiko Shionoya*[a]

Following the examples of nature, movable parts have proven to be a key feature in the developing field of molecular machinery.[1] In particular, rotaxanes are exquisite building blocks to achieve control over molecular motions. The state of the art in rotaxane chemistry is beautifully illustrated by the systems presented by the groups of Stoddart,[2] Leigh,[3] Sauvage,[4] and others,[5] comprising shuttle-bus rotaxanes controlled by external stimuli, surface-bound architectures, and rotaxanes integrated into complicated frameworks. The number of basic recognition systems underlying rotaxane formation is, however, still limited, mainly comprising the interaction between two (charged) organic compounds that are attracted by Coulomb forces, hydrogen bonds, or held together by coordination of a metal ion between them.

Herein, we introduce a new kind of rotaxane based on the attractive interaction between a bis-anionic organic thread and positively charged but coordinatively saturated metal complexes of a metal–organic coordination cage molecule.[6] Except for the recent report on a hybrid organic–inorganic rotaxane,[7] we believe this is the first example of a rotaxane in which the contained metal ions are not directly bound by the thread, but only provide their positive charges for attraction of the negatively charged thread.[8] Recently, we reported the quantitative encapsulation of bis-anionic guests inside Pd^{II}-mediated cage **1a** comprising two spatially preorganized, coordinatively saturated Pd^{II} centers serving as electrostatic anchors (Scheme 1b).[9] The X-ray structure showed that the assembly of the four concave-shaped ligands around the two Pd^{II} ions generates a hollow space amenable to the incorporation of suitably sized guests such as 1,1′-ferrocene bis-sulfonate.[10]

Realizing that this binding principle could be utilized for the construction of more complex molecular assemblies, such as rotaxanes, we subsequently examined the encapsulation of a variety of bis-sulfonates of suitable sizes.

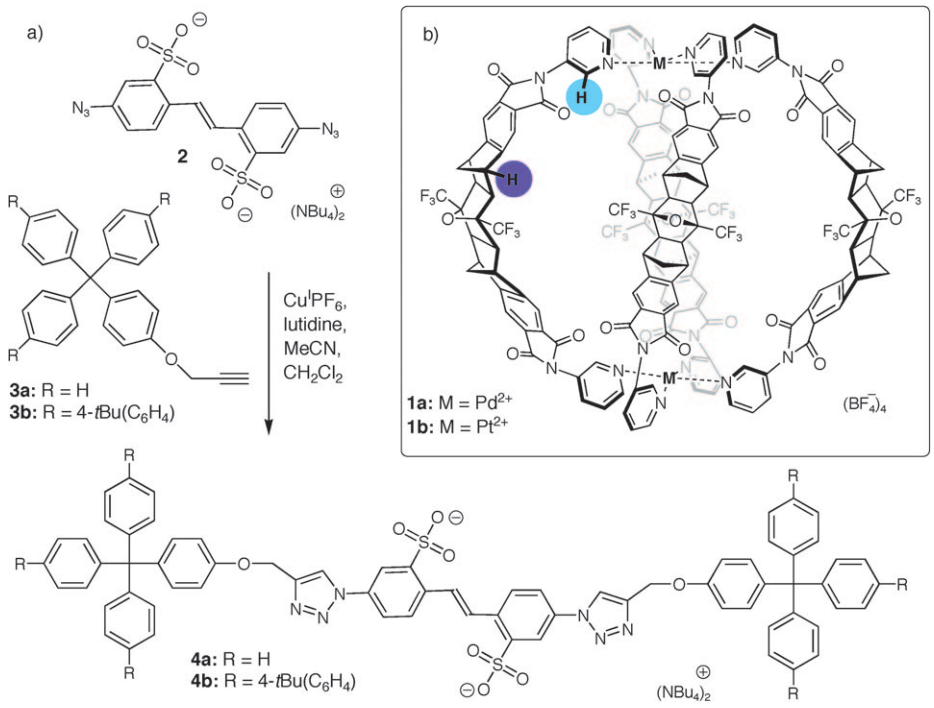
Bis-sulfonate **2** was found to be readily incorporated into **1a**, as shown by a characteristic upfield shift of the guest signals in a ^{1}H NMR titration experiment and a diffusion oriented spectroscopy (DOSY) NMR experiment showing the increase of effective molecular size of the guest by the incorporation of **2** inside the cage. The peak at m/z 1825 observed in the ESI mass spectrum can be assigned to the $[\mathbf{2}@\mathbf{1a}]^{2+}$ ion (see the Supporting Information). Furthermore, compound **2** is perfectly functionalized for our intended use, since it contains the two necessary sulfonate groups in a suitable distance and two azide functionalities amenable to derivatization by click chemistry. Furthermore, it features a photoswitchable stilbene double bond.[11] The Cu^I-catalyzed cycloaddition with alkynes such as **3a** or **3b** smoothly yielded rodlike molecules **4a** and **4b** as their tetrabutylammonium salts (Scheme 1a).[12] Indeed, stepwise addition of **4a** to a solution of cage **1a** in CD_3CN resulted in immediate and quantitative uptake of the rodlike molecule inside the metal–organic cage molecule in the fashion of a pseudorotaxane (Figure 1a).

The NMR titration in Figure 2 shows that upon addition of 0.5 equivalents of guest **4a**, half of the Pd^{II} cage **1a** has taken up the guest without showing fast intermolecular exchange, as determined by the splitting of the cage's NMR signals into two subsets. After one equivalent of **4a** had been added, all of the cage molecules had taken up one guest, which gave rise to one set of sharp NMR signals. The NMR spectrum reveals which parts of the rodlike molecule **4a** are located inside the shielding environment of the cage and which are protruding through two of the cage's four portals: the signals of the guest's central stilbene and tria-

[a] Prof. Dr. M. Shionoya
Department of Chemistry, Graduate School of Science
The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku
Tokyo 113-0033 (Japan)
Fax: (+81) 3-5841-8061
E-mail: shionoya@chem.s.u-tokyo.ac.jp

[b] Prof. Dr. G. H. Clever
Institut für Anorganische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 4
37077 Göttingen (Germany)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002013.



Scheme 1. a) Synthesis of guests **4a** and **4b**; b) formula of metal cages **1a** and **1b**.

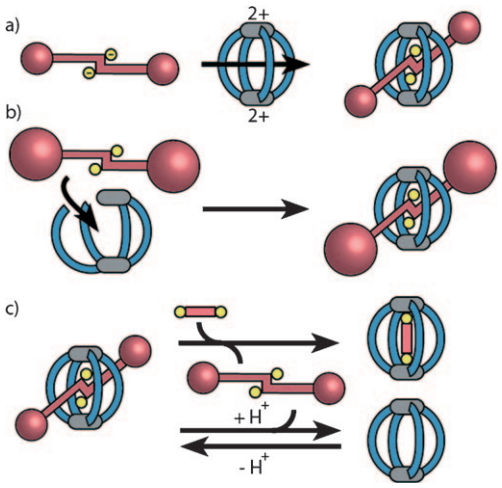


Figure 1. a) Proposed mechanism for the uptake of rodlike guests **4a** with a small stopper into cage **1a**; b) uptake of guest **4b** carrying a large stopper into cage **1a**; c) top: guest **4a** can be replaced by a stronger binder such as guest **5**; bottom: reversible switching of encapsulation by a change in pH.

zole moieties (H11–H15) undergo a characteristic upfield shift due to the interaction with the interior of the cage. In contrast, the signals of the parts that lay within the portals of the cage (H5 and H6) are shifted downfield due to their position with respect to the aromatic rings of the cage. All of the residual signals of the tetraphenyl methane groups undergo no significant shifts. Second, the signals of the cage's inward pointing hydrogen atoms (H_i, light blue in Scheme 1 and Figure 2) are shifted downfield upon encapsulation of the negatively charged guest, which is in accordance with our previous observations.[9] Most interesting, however, is that the NMR spectra even reveal the topology of the pseudorotaxane, which is not trivial, since the cage has four portals and the guest could in principle protrude through two neighboring or two opposite portals.[13] The NMR signals of the cage's hydrogen atoms lining the sides of the portals (H_d, dark blue in Scheme 1 and Figure 2) show that guest **4a** is incorporated with both ends of the rod protruding through oppositely arranged portals of the cage. In the NMR spectrum of the "empty" cage, these protons give rise to only one singlet due to the high D_{4h} symmetry of the cage in solution. In the rotaxane, however, the signal is split into two singlets, indicating that these hydrogen atoms now have fallen into two groups with one signal representing the hydrogen atoms lining the two open portals and one signal representing the two oppositely arranged portals filled by the guest molecule.

Upon addition of a second equivalent of the guest **4a** to the host–guest complex **4a@1a**, two sets of guest signals can be distinguished: one for the encapsulated equivalent and the other for the free excess guest molecules outside the cage. In a comparison of the DOSY NMR spectra of the free thread **4a** and the pseudorotaxane **4a@1a**, again an increase in hydrodynamic radius was observed due to the formation of the host–guest complex (see the Supporting Information). In this case, the formed complex was even found to be significantly bigger than the "empty" cage **1a** alone;[9] this is explained by the two tetraphenyl methane residues of **4a** protruding from the cage's portals and thereby contributing to the hydrodynamic radius. The measurement of a NOESY NMR spectrum revealed two close contacts between the cage **1a** and guest **4a** (see the Supporting Information). Additionally, the formation of the host–guest complex **4a@1a** gave rise to the observation of a single strong signal in the ESI-TOF mass spectrum at m/z 2200, attributable to the ion $[\mathbf{4a@1a}]^{2+}$ (see the Supporting Information).

Free guest molecule **4a** is highly fluorescent when excited at 326 nm (emission maximum at 400 nm). Upon encapsulation, we found that the fluorescence was quenched, presumably by an energy transfer to **1a**.[14] Furthermore, free guest **4a** (a 18 μM solution in $CHCl_3/CH_3CN$ (1:1), N_2 purged) can be isomerized into its *cis* isomer by irradiation at 365 nm

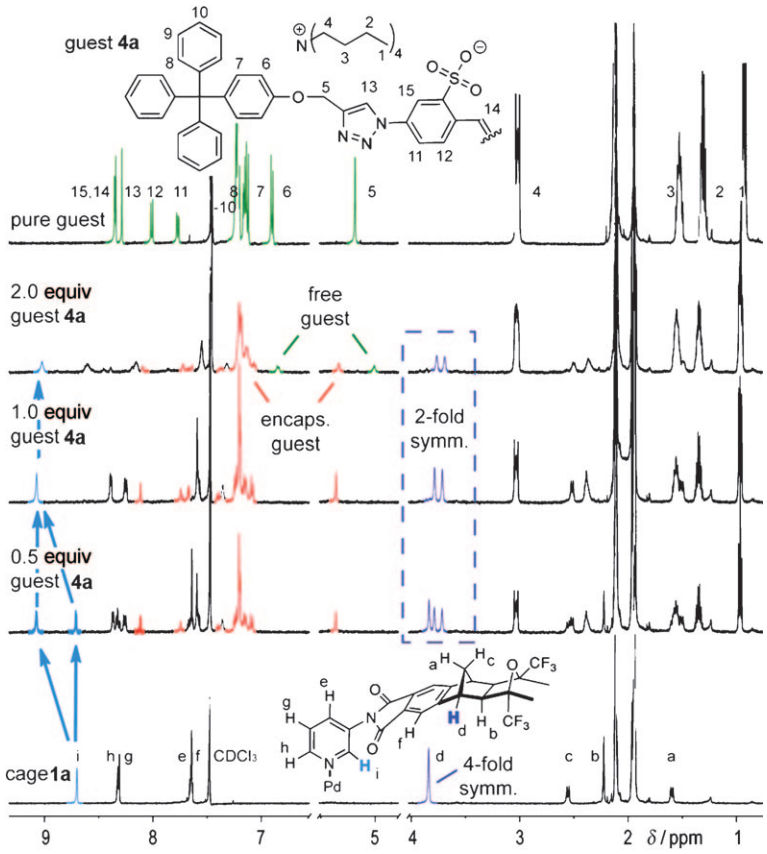


Figure 2. ^{1}H NMR titration of **1a** with **4a**. (500 MHz, CD_3CN, 293 K).

within 10 s, whereas encapsulated **4a** is protected from the photoisomerization within the cage **1a** (see the Supporting Information).[11]

Surprisingly, the uptake of **4a** into **1a** was finished within seconds, and therefore, in light of considerably slow ligand exchange with Pd^{II} ions, this occurs too quickly for a mechanism that involves the decomplexation of the ligands from the Pd^{II} centers of the cage. Furthermore, repeating the uptake experiment with the corresponding Pt^{II} cage **1b**, which is expected to have a structure similar to that of cage **1a**, indicated a similar quick encapsulation despite the fact that the ligand exchange in Pt^{II} complexes is known to be much slower than in Pd^{II} complexes (see the Supporting Information).

To further elucidate the rotaxanation mechanism, we synthesized guest **4b**, which has much larger stopper groups at both ends (Scheme 1 and Figure 1b). Interestingly, the encapsulation of **4b** into **1a** takes about 90 min at room temperature as indicated by the NMR and ESI spectra (see the Supporting Information). Inclusion of **4b** into **1b** was not observed at room temperate, but several days of heating the mixture of **1b** and **4b** to 80 °C in CD_3CN also resulted in rotaxanation in this case (along with partial dissociation of the cage).

These observations and a comparison of the sizes of the stopper groups of **4a** and **4b** with the big openings of the cage **1** led us to conclude that the rodlike guest molecule **4a** can easily enter the cage through its portals in contrast to the bigger guest **4b**, which can only be encapsulated by an alternative, slower mechanism requiring a (partial) decomplexation of the pyridine ligands from the metal centers. This interpretation is in good agreement with the insights about the relative sizes of the cage's portals and the guests **4a** and **4b** gained from molecular modeling studies (Figure 3 and the Supporting Information).

Next, we examined the reversibility of the rotaxanation process. 2,6-Naphthyl bis-sulfonate **5** (Figure 4a) was envisioned to be a perfectly fitting guest for cage **1a** from the results obtained by molecular modeling. Indeed, this compound is quantitatively incorporated inside the cage upon addi-

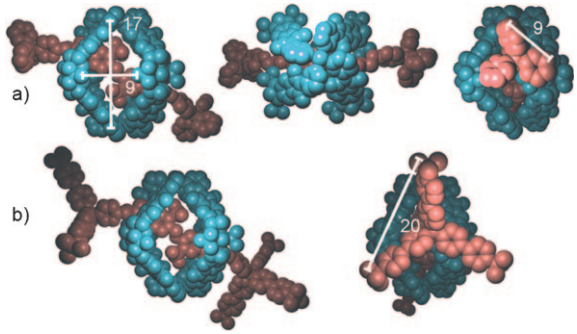


Figure 3. MMFF[15] molecular models of a) **4a**@**1a** and b) **4b**@**1a** based on the X-ray structure of **1a**.[9] Numbers denote distances in Å.[15]

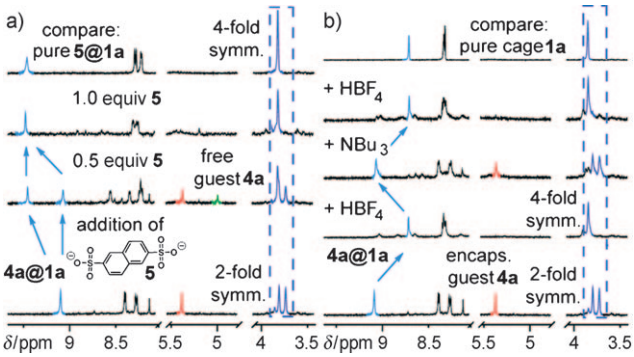


Figure 4. a) Replacement of **4a** from the inside of **1a** by guest **5**; b) reversible switching of encapsulation of **4a** in **1a** by a change in pH. (^{1}H NMR spectra, 500 MHz, $CD_3CN/CDCl_3$ (1:1), 293 K, [**1a**] = 0.35 mM).

tion of one equivalent of its tetrabutylammonium salt to a solution of cage **1a** in CD_3CN. Furthermore, guest **5** is able to quantitatively replace guest **4a** from the inside of cage **1a** as seen from the NMR spectroscopic data shown in Figure 4a.

Upon addition of 0.5 equivalents of bis-sulfonate **5** to the **4a@1a** complex, in half of the cages the rodlike guest **4a** is replaced by **5** and after the addition of one equivalent of **5**, all of **4a** is replaced by **5** inside the cages. The resulting NMR spectrum is in accordance with the spectrum of the pure **5@4** complex, especially regarding the shift of the cage's inward pointing hydrogen atom (light blue in Figure 4). Furthermore, the 2-fold symmetry of the **4a@1a** complex is lost (dark blue in Figure 4) and again 4-fold symmetry is adapted, which can be explained by the ability of the small guest **5** to freely rotate inside **1a**.

Finally, we examined the effect of pH changes on the rotaxanation process. Upon addition of an acid such as HBF_4 to pseudorotaxane **4a@1a**, dethreading occurred, as determined from the signal changes observed in the NMR spectrum (Figure 4b). The process is reversible upon addition of tributylamine and can be repeated several times in cycles (see the Supporting Information). Going along with this pH switching, however, is partial dissociation of the coordination compound releasing the free ligand, as indicated by the emergence of characteristic NMR signals, most probably due to a concomitant protonation of the ligand's pyridine rings and thus breaking of the coordinate bonds.

In conclusion, we have presented a new approach to the synthesis of rotaxanes based on the combination of two binding principles: metal coordination for assembly of the cage and Coulomb interactions for guest binding. Rotaxanation is thermodynamically highly favorable and kinetic control can be achieved by the choice of stopper size and metal ion. In terms of topology, our system presented herein falls into a small class of rotaxanes in which the thread is not surrounded by a simple circular macrocycle, but by a molecular cage that might be described as four hemicycles, the ends of which are collectively joined by two nodes (the metal ions).[13,16] Here, we only made use of two of the cage's four gates. We imagine that the fourfold symmetry of the cage might allow the extension of rotaxane chemistry from the first into the second dimension by the inclusion of an orthogonal pair of threads inside the cage.

Most gratifying, however, is that our experiments indicated two independent possibilities of switching the rotaxanation process, which might prove useful for the use of our system in information processing applications.

Experimental Section

Compounds **4a** and **4b** were synthesized by the Cu^I-catalyzed click reaction from bis-azide **2** by using alkynes **3a** or **3b** (6 equiv), respectively, $[Cu(CH_3CN)_4][PF_6]$ (6 mol%) and lutidine (6 equiv) in degassed CH_3CN/CH_2Cl_2. Pt^{II} cage **1b** was prepared according to the procedure for synthesizing Pd^{II} cage **1a**[9] from the bis-pyridyl ligand and $[Pt(CH_3CN)_4][BF_4]_2$,[17] allowing a prolonged reaction time of 12 h at 80 °C (for details, see the Supporting Information). Unless otherwise noted, the NMR spectroscopy titrations were carried out by using 0.70 mM cage solutions in CD_3CN and 8.75 mM stock solutions of the respective guest compounds (**4a** and **4b** in $CDCl_3$, **5** in CD_3CN).

Acknowledgements

G.C. thanks JSPS and the Alexander v. Humboldt Foundation for a postdoctoral scholarship. This work was supported by Grants-in-Aid from MEXT of Japan and the Global COE Program for Chemistry Innovation.

Keywords: anion recognition · cage compounds · host–guest systems · rotaxanes · supramolecular chemistry

[1] a) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem.* **2007**, *119*, 72; *Angew. Chem. Int. Ed.* **2007**, *46*, 72; b) W. R. Browne, B. L. Feringa, *Nat. Nanotechnol.* **2006**, *1*, 25; c) K. Kinbara, T. Aida, *Chem. Rev.* **2005**, *105*, 1377; d) V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3484; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348; e) *Molecular Catenanes, Rotaxanes and Knots* (Eds.: J.-P. Sauvage, C. Dietrich-Buchecker), Wiley-VCH, Weinheim, **1999**.

[2] a) A. Coskun, D. C. Friedman, H. Li, K. Patel, H. A. Khatib, J. F. Stoddart, *J. Am. Chem. Soc.* **2009**, *131*, 2493; b) S. Angelos, Y.-W. Yang, K. Patel, J. F. Stoddart, J. I. Zink, *Angew. Chem.* **2008**, *120*, 2254; *Angew. Chem. Int. Ed.* **2008**, *47*, 2222; c) V. Balzani, M. Clemente-Leon, A. Credi, B. Ferrer, M. Venturi, A. H. Flood, J. F. Stoddart, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1178.

[3] a) S. M. Goldup, D. Leigh, P. J. Lusby, R. T. McBurney, A. M. Z. Slawin, *Angew. Chem.* **2008**, *120*, 3429; *Angew. Chem. Int. Ed.* **2008**, *47*, 3381; b) A. Fernandes, A. Viterisi, F. Coutrot, S. Potok, D. A. Leigh, V. Aucagne, S. Papot, *Angew. Chem.* **2009**, *121*, 6565; *Angew. Chem. Int. Ed.* **2009**, *48*, 6443.

[4] a) A. I. Prikhodko, J.-P. Sauvage, *J. Am. Chem. Soc.* **2009**, *131*, 6794; b) J.-P. Collin, F. Durola, J. Lux, J.-P. Sauvage, *Angew. Chem.* **2009**, *121*, 8684; *Angew. Chem. Int. Ed.* **2009**, *48*, 8532.

[5] a) M. J. Chmielewski, L. Zhao, A. Brown, D. Curiel, M. R. Sambrook, A. L. Thompson, S. M. Santos, V. Felix, J. J. Davis, P. D. Beer, *Chem. Commun.* **2008**, 3154; b) W. Jiang, H. D. F. Winkler, C. A. Schalley, *J. Am. Chem. Soc.* **2008**, *130*, 13852; c) T. Umehara, H. Kawai, K. Fujiwara, T. Suzuki, *J. Am. Chem. Soc.* **2008**, *130*, 13981; d) G. Wenz, B.-H. Han, A. Müller, *Chem. Rev.* **2006**, *106*, 782; e) S. J. Loeb, *Chem. Commun.* **2005**, 1511; f) J. Terao, A. Tang, J. J. Michels, A. Krivokapic, H. L. Anderson, *Chem. Commun.* **2004**, 56; g) O. Lukin, T. Kubota, Y. Okamoto, F. Schelhase, A. Yoneva, W. M. Müller, U. Müller, F. Vögtle, *Angew. Chem.* **2003**, *115*, 4681; *Angew. Chem. Int. Ed.* **2003**, *42*, 4542; h) K. Kim, *Chem. Soc. Rev.* **2002**, *31*, 96; i) Y. Makita, N. Kihara, T. Takata, *J. Org. Chem.* **2008**, *73*, 9245.

[6] a) S. J. Dalgarno, N. P. Power, J. L. Atwood, *Coord. Chem. Rev.* **2008**, *252*, 825; b) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry: Second Edition*, Wiley, Chichester, UK, **2009**; c) M. Fukuda, R. Sekiya, R. Kuroda, *Angew. Chem.* **2008**, *120*, 718; *Angew. Chem. Int. Ed.* **2008**, *47*, 706.

[7] C.-F. Lee, D. A. Leigh, R. G. Pritchard, D. Schultz, S. J. Teat, G. A. Timco, R. E. P. Winpenny, *Nature* **2009**, *458*, 314.

[8] *Anion Receptor Chemistry* (Eds.: J. L. Sessler, P. A. Gale, W.-S. Cho), RSC Publishing, Cambridge, **2006**.

[9] a) G. H. Clever, S. Tashiro, M. Shionoya, *Angew. Chem.* **2009**, *121*, 7144; *Angew. Chem. Int. Ed.* **2009**, *48*, 7010; b) G. H. Clever, S. Tashiro, M. Shionoya, *J. Am. Chem. Soc.* **2010**, *132*, 9973.

[10] We have recently reported coordination-based internal modification of coordination capsules using bis-sulfonate ligands, see S. Hiraoka, M. Kiyokawa, M. Shionoya, *Angew. Chem.* **2010**, *122*, 142; *Angew. Chem. Int. Ed.* **2010**, *49*, 138.

[11] O. Karthaus, M. Shimomura, M. Hioki, R. Tahara, H. Nakamura, *J. Am. Chem. Soc.* **1996**, *118*, 9174.
[12] B. M. J. M. Suijkerbuijk, B. N. H. Aerts, H. P. Dijkstra, M. Lutz, A. L. Spek, G. van Koten, R. J. M. Klein Gebbink, *Dalton Trans.* **2007**, 1273.
[13] a) C.-F. Lin, Y.-H. Liu, C.-C. Lai, S.-M. Peng, S.-H. Chiu, *Angew. Chem.* **2006**, *118*, 3248; *Angew. Chem. Int. Ed.* **2006**, *45*, 3176; b) C.-F. Lin, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Eur. J.* **2007**, *13*, 4350.
[14] In our case fluorescence is totally quenched by encapsulation, for an example of emissive host–guest complexes, see: J. K. Klosterman, M. Iwamura, T. Tahara, M. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 9478.
[15] Molecular mechanics (MMFF) energy minimizations computed with Spartan 08, Wavefunction Inc., Irvine USA (see also the Supporting Information). Owing to the number and symmetry of the NMR signals of the host–guest complexes in solution, the guests are believed to be able to quickly rock or tumble inside the cage.
[16] L. M. Klivansky, G. Koshkakaryan, D. Cao, Y. Liu, *Angew. Chem.* **2009**, *121*, 4249; *Angew. Chem. Int. Ed.* **2009**, *48*, 4185.
[17] A. de Renzi, A. Panunzi, A. Vitagliano, G. Paiaro, *J. Chem. Soc. Chem. Commun.* **1976**, 47.

Received: July 16, 2010
Published online: September 17, 2010

