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Cucurbit[8]uril Rotaxanes

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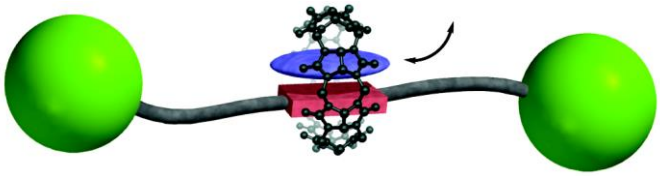
ABSTRACT



The synthesis of [2]rotaxanes, each comprising a viologen core threaded through a cucurbit[8]uril (Q8, Figure 1) macrocycle and stoppered by tetraphenylmethane groups, and their binding to second guests as inclusion complexes in organic and aqueous media is described. Stoppering was observed to have little effect on binding. Chemical modification of the threaded guest was used to control solubility and binding characteristics, thus demonstrating a novel approach to making artificial receptors with readily modifiable properties.

The recent boom in the area of cucurbit[n]uril (Qn) chemistry[1] can be attributed to an increasing awareness of the potential of this family of macrocycles as receptors for a myriad of small molecules with equilibrium association constant (K_a) values that span over twelve orders of magnitude.[2] Most remarkably, this supramolecular chemistry takes place in water, a medium of great interest for its biological relevance and of great frustration to organic chemists seeking to mimic biology.[3] Qn chemistry has already been applied broadly in areas including catalysis, sensing, polymer chemistry, drug delivery, controlled release, biomolecular recognition, affinity purification, enzyme assays, waste remediation, electrochemistry, photochemistry, and molecular machines.[1]

Despite their promise, however, the full potential of cucurbiturils will not be realized until further progress is made in the area of chemical synthesis. In particular, we need straightforward methods for chemical derivatization so that useful properties such as solubility, guest binding, and chemical reactivity (e.g., conjugation, catalysis) can be modulated and, ideally, optimized. As with other macrocyclic compounds (e.g., cyclodextrins, porphyrins, and calixarenes), chemical modification of cucurbiturils is possible[4] but problematic due to their stable and repetitive structures and their limited solubility.

We have sought to develop methods for altering the properties of Qn receptors without the need for chemically modifying the macrocycle itself. This work focuses on Q8 (Figure 1) and takes advantage of its rare ability to bind two guests simultaneously. In their seminal paper,[5] Kim and coworkers showed that Q8 binds to one molecule of methyl viologen (**1**), and the resulting Q8•**1** complex binds selectively to one molecule of 2,6-dihydroxynaphthalene (**2**). Formation of the heteroternary complex results in aromatic guest stacking face-to-face in the cavity of Q8, the formation of a new visible charge-transfer absorbance, and the quenching of naphthalene fluorescence. Heteroternary Q8•X•Y complexes have since enabled the construction of supramolecular assemblies,[6] multivalent receptors,[7] supramolecular block copolymers,[8] and aromatic sensors.[9] In each of these examples, binding occurs sequentially (Figure 1a), and the properties (solubility, optical,

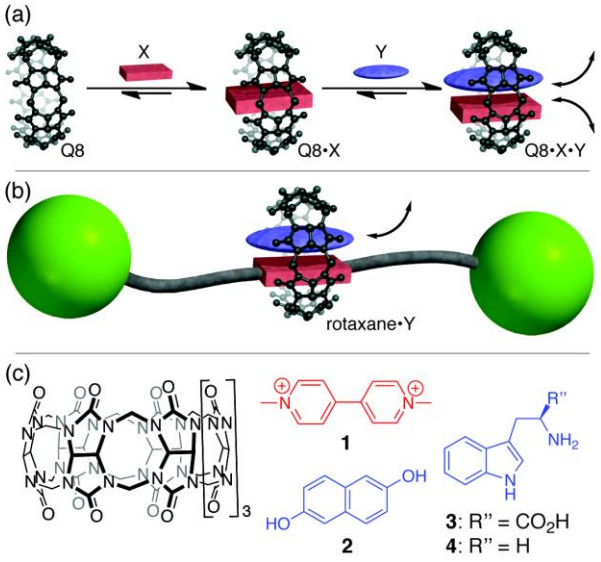
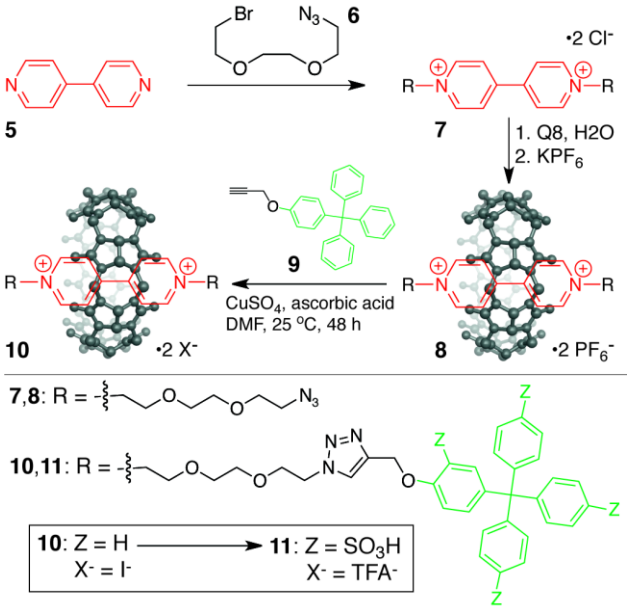


Figure 1. (a) sequential binding in ternary complexation versus (b) binary complexation by a rotaxane; (c) chemical formulas.

activity, binding, material) of the first guest, X, influence the properties of the resulting Q8•X complex, which then acts as a receptor for the second guest, Y. The remarkable characteristic of this system is the reversible joining of X and Y mediated by Q8. The chief limitation, however, is the ability of the Q8•X complex to dissociate before binding Y, a problem exacerbated at low concentrations (esp. lower than K_a^{-1}) and in the many potential applications involving a solid support. Here we present an approach that overcomes this limitation by mechanically linking Q8 to X as a rotaxane.[10]

Numerous examples of Qn-based rotaxanes exist,[11] but this paper presents the first example of a Q8 rotaxane. The chief advantage of a Q8 rotaxane, versus those of smaller Qn homologues, is that a Q8 rotaxane should have the capacity to bind a second guest while not allowing dissociation of the first guest (Figure 1b). The concept of a [2]rotaxane binding a second guest as an inclusion complex was demonstrated by Anderson and coworkers on a stilbene-threaded γ-cyclodextrin that binds a cationic cyanine dye. Such a rotaxane molecule could in principle be modified, via the threaded guest, to affect the binding of the second guest, thus obviating derivatization of the macrocycle. Our design (**10**, **11**, Scheme 1) uses a viologen core to guide Q8 threading and to promote the selective binding of a second guest. Q8 is large, and thus large stopper groups were needed; we chose tetraphenylmethane for synthetic convenience and for its potential to be chemically modified. Oligo(ethylene glycol) linkers between the viologen and stopper groups were installed to allow sufficient space for a second guest to access the Q8 cavity.

Scheme 1. Rotaxane Synthesis



The synthesis of rotaxane **10** (Scheme 1) comprised three steps from known reagents. The linkers were attached to the core by coupling 4,4'-dipyridyl (**5**) with excess alkyl halide **6**[12] to produce the viologen **7** in 24% recovery after column chromatography. Viologen **7** was mixed with equimolar Q8 in water to form a water-soluble pseudorotaxane. We wanted access to a wide range of stopper groups and coupling chemistries, and thus we needed an organic soluble pseudorotaxane. Wang and Kaifer showed recently that Qn•guest complexes can be transferred efficiently to organic solvent by precipitation from water as the hexafluorophosphate salt followed by resuspension in polar aprotic solvents.[13] Therefore, we treated the water-soluble pseudorotaxane with excess aqueous KPF_6 and obtained the hexafluorophosphate salt **8** as precipitate in 75% overall recovery from **7**. Pseudorotaxane **8** was combined with an excess of stopper group **9**[14] under Huigsen 1,3-dipolar cycloaddition conditions in DMF solution to obtain crude rotaxane **10** in 45% yield. This mixture also contains 10-15% excess Q8,[15] which was removed as the insoluble material by repeated trituration with acetonitrile, giving pure **10** in 25% overall recovery. It is worth noting that the ^{1}H NMR signals of the glycol linker peaks in **7** shift upfield upon forming pseudorotaxane **8** and then return downfield upon stoppering (Figure 2), indicating the positioning of Q8 centrally over the viologen core in rotaxane **10**.[16] This result suggests a steric influence of the stopper groups that forces the linker(s) out of the cavity.

Rotaxane **10** is insoluble in water, presumably due to the dominating hydrophobicity of the

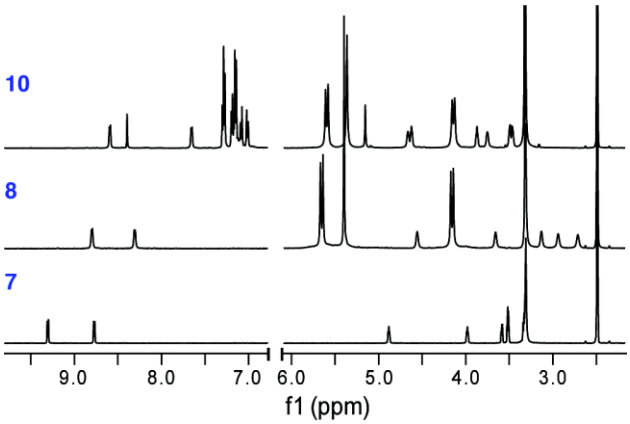


Figure 2. ^{1}H NMR spectra of viologen **7** (bottom), pseudorotaxane **8** (middle), and rotaxane **10** (top) in DMSO-D6, showing the influence of Q8 binding (**7** to **8**) and stoppering (**8** to **10**) on the inclusion of the threaded guest.

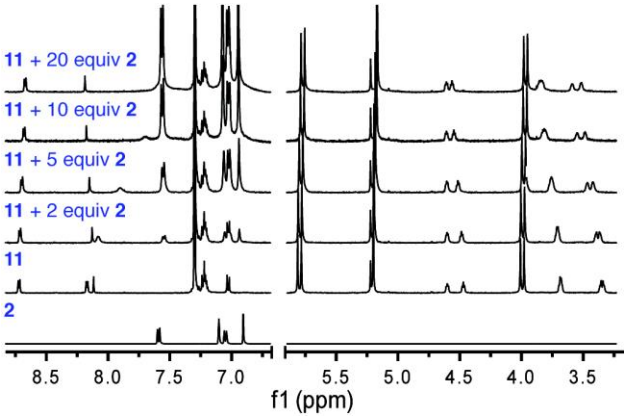


Figure 3. ^{1}H NMR spectral overlay of the titration of viologen **10** with second guest **2** in acetonitrile-D3, showing perturbation of numerous viologen signals.

stopper groups. It was, however, soluble in acetonitrile (up to ~0.4 mM) and DMSO (up to ~0.9 mM). We saw this as a rare opportunity to study an unmodified cucurbituril binding in organic solution. Wang and Kaifer observed stable complexes of cucurbit[7]uril, but poor solubility of the host in organic media precluded the measurement of equilibrium association constants.[13] We titrated rotaxane **10** with the neutral second guest **2** in DMSO-D6 and acetonitrile-D3 solutions and looked for changes in the ^{1}H NMR spectra. In DMSO-D6 we found no change in the spectrum of **10** upon adding ten equivalents of **2**.[17] In acetonitrile-D3 solution, however, we observed a clear upfield perturbation in chemical shift of the inner viologen aromatic protons and downfield perturbation in chemical shift of several linker protons and the triazole proton of **10** upon addition of **2** (Figure 3). This observation indicates simultaneous binding of **2** and the viologen core of the threaded axle inside the cavity of Q8. We observed no perturbation of chemical shift of the stopper signals, indicating little if any participation by these groups in the binding of **2**. The numerous responsive signals allowed us to quantify the chemical shift perturbation of a given signal and fit the data to a binary equilibrium binding model to obtain a K_a value of 90 (±16) M^{-1}. This value is small, but it is important because very little thermodynamic information is currently available on the binding of cucurbituril homologues in organic solvent.[18] The **10•2** complex was confirmed by ESI mass spectrometry (Supporting Information).

We wanted a water-soluble rotaxane and considered modification of the stopper groups by electrophilic aromatic substitution. Organic-soluble rotaxane **10** was treated with chloro-sulfonic acid at room temperature followed by heating in water to obtain the octasulfonated rotaxane **11** in 20% recovery after HPLC purification. Surprisingly, rotaxane **11** was soluble in water up to a concentration of ~15 mM, 1000-fold higher than Q8 and 10-fold higher than the analogous Q8•**1** complex. This result demonstrates that a single chemical reaction on the threaded guest was sufficient to alter the solubility from aqueous insoluble to highly aqueous soluble.

Substantial changes in the ^{1}H NMR spectrum of **11** in the presence of small amounts of second guest suggested that binding was much stronger in aqueous solution than observed for rotaxane **10** in acetonitrile-D3. We wanted to quantify binding and, importantly, to determine the influence of the linker and stopper groups. The binding of second guests **2**, **3**, and **4** to Q8•**1** is known to result in the quenching of naphthalene or indole fluorescence,[5,9b] and thus it should be possible to use fluorescence spectroscopy to monitor the binding of these guests to rotaxane **11**. Indeed, we observed quenching of fluorescence upon addition of rotaxane **11** or Q8•**1** in 5 mM sodium phosphate buffer, pH 7.4 (Figure 4), indicating that the

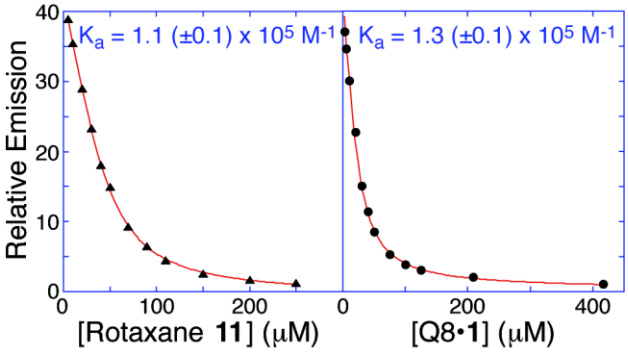


Figure 4. Representative fluorescence titration experiments of the binding of tryptamine **4** to rotaxane **11** (left) and the Q8•**1** complex (right) at 25 °C in 5 mM sodium phosphate, pH 7.4.

rotaxane binds in a similar fashion as Q8•**1** to second guests, with the second guest and the viologen portion of the rotaxane in close proximity, likely within the cavity of Q8. The titration data were fit to a binary equilibrium binding model to obtain K_a values (Table 1) for each of the three guests with the two receptors.

Table 1. Equilibrium Binding Data (K_a values in M^{-1})

guest	rotaxane **11**[*]	Q8•MV[*]
2	1.3 (±0.1) x 10^5	7.3 (±0.6) x 10^5
3	1.8 (±0.2) x 10^4	8.4 (±0.5) x 10^4
4	1.1 (±0.1) x 10^5	1.3 (±0.1) x 10^5

[*]Average values from three experiments at 25 °C in 5.0 mM sodium phosphate, pH 7.4, with standard deviations in parentheses.

Values for the Q8•**1** complexes were similar to those reported in other aqueous media.[9b,19] Values for the rotaxane complexes were similar in magnitude but lower than the analogous Q8•**1** complexes, with a modest energetic penalty of 0.14-1.0 kcal/mol for the addition of linker and stopper groups.

With these data we were able to compare binding in organic vs. aqueous media. The binding affinity of rotaxane **11** to second guest **2** in aqueous buffer (1.3 x 10^5 M^{-1}) is >1000-fold stronger than that of rotaxane **10** in acetonitrile-D3 (90 M^{-1}). This comparison may be tainted somewhat by the fact that the two rotaxanes are not identical. We do not expect, however that the additional steric bulk and negative charge afforded by rotaxane **11** should aid in the binding of the neutral guest. This result underscores the importance of the hydrophobic effect for HN binding and merits further study.[20]

This paper describes the first rotaxanes based on Q8, and a new approach to the modification of cucurbiturils, which is a major problem in the field. The Q8 rotaxanes reported here also constitute a new class of artificial receptors that bind neutral and cationic guests with high affinity in aqueous solution. The water-soluble rotaxane **11** behaves similarly to the Q8•**1** complex but does not dissociate[21] and thus can be used in a broader range of conditions and applications. The threaded guest can be modified to change the properties of the receptor, as demonstrated here by substantially altering the solubility and binding characteristics. We anticipate more detailed quantitative studies of the effects of solvent on cucurbituril binding, as well as an exploration of larger homologues (e.g., cucurbit[10]uril and nor-seco-cucurbit[10]uril)[22] and other mechanically interlocked structures (e.g., catenanes).[23] Most importantly, modifying the threaded guest provides a complementary method for conjugating cucurbiturils to solid support for affinity purification[24] and allows for changes in the binding and catalytic properties of the receptor while circumventing difficult chemistry on the macrocycle itself. We will report our progress in these areas in due course.

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Supporting Information Available. Detailed experimental procedures, characterization data, NMR and mass spectra, titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lagona, L.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4844. (b) Nau, W. M.; Scherman, O. A. *Israel J. Chem.* **2011**, *51*, 492.

(2) (a) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367. (b) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618. (c) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540. (d) Day, A. I.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094. (e) Jeon, W. S.; Moon, K.; Park, S. H.; Chun, H.; Ko, Y. H.; Lee, J. Y.; Lee, E. S.; Samal, S.; Selvapalam, N.; Rekharsky, M. V.; Sindelar, V.; Sobransingh, D.; Inoue, Y.; Kaifer, A. E.; Kim, K. *J. Am. Chem. Soc.* **2005**, *127*, 12984. (f) Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 15959. (g) Rekharsky, M. V.; Mori, T.; Yang, C.; Young, H. K.; Selvapalam, N.; Kim, H.; Sobransingh, D.; Kaifer, A. E.; Liu, S.; Isaacs, L.; Chen, W.; Moghaddam, S.; Gilson, M. K.; Kim, O.; Inoue, Y. *Proc. Natl. Acad. Sci.* **2007**, *104*, 20737.

(3) (a) Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 2366. (b) Schneider, H.-J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3924.

(4) (a) Day, A.; Arnold, A. P.; Blanch, R. J. *Molecules* **2003**, *8*, 74. (b) Jon, S. Y.; Selvapalam, N.; Oh, D. H.; Kang, J.-K.; Kim, S. Y.; Jeon, Y. J.; Lee, J. W.; Kim, K. *J. Am. Chem. Soc.* **2003**, *125*, 10186. (c) Kim, K.; Selvapalam, N.; Ko, Y. H.; Park, K.-M.; Kim, D.; Kim, J. *Chem. Soc. Rev.* **2007**, *36*, 267.

(5) Kim, H.-J.; Heo, J.; Jeon, W. S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1526.

(6) (a) Appel, E. A.; Ruwald, U.; Jones, S.; Zayed, J. M.; Scherman, O. A. *J. Am. Chem. Soc.* **2010**, *132*, 14251. (b) Ko, Y. H.; Kim, E.; Hwang, I.; Kim, K. *Chem. Comm.* **2007**, 1305.

(7) Reczek, J. J.; Kennedy, A. A.; Halbert, B. T.; Urbach, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 2408.

(8) Rauwald, U.; Scherman, O. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3950.

(9) (a) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621. (b) Bush, M. E.; Bouley, N. D.; Urbach, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 14511. (c) Ling, Y.; Wang, W.; Kaifer, A. E. *Chem. Comm.* **2007**, 610. (d) Biedermann, F.; Ruwald, U.; Cziferszky, M.; Williams, K. A.; Gann, L. D.; Guo, B. Y.; Urbach, A. R.; Bielawski, C. W.; Scherman, O. A. *Chem. Eur. J.* **2010**, *87*, 13716.

(10) Arico, F.; Badjic, J. D.; Cantrill, S. J.; Flood, A. H.; Leung, K. C.-F.; Liu, Y.; Stoddart, J. F. *Top. Curr. Chem.* **2005**, *249*, 203.

(11) (a) Jeon, Y.-M.; Whang, D.; Kim, J.; Kim, K. *Chem. Lett.* **1996**, *7*, 503. (b) Liu, S.; Xiaojun, W. U.; Huang, Z.; Yao, J.; Liang, F.; Chengtai, W. U. *J. Incl. Phenom.* **2004**, *50*, 203. (c) Sindelar, V.; Moon, K.; Kaifer, A. E. *Organic Letters* **2004**, *6*, 2665. (d) Tuncel, D.; Unal, O.; Artar, M. *Israel J. Chem.* **2011**, *51*, 525. (e) Wego, A.; Jansen, K.; Buschmann, H.-J.; Schollmeyer, E.; Dopp, D. *J. Incl. Phenom.* **2002**, *43*, 201.

(12) Lu, G. L.; Burgess, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3902.

(13) Wang, W.; Kaifer, A. E. *Supramol. Chem.* **2010**, *22*, 710.

(14) Skorobogatyi, M. V.; Pchelintseva, A. A.; Petrunina, A. L.; Stepanova, I. A.; Andronova, V. L.; Galegov, G. A.; Malakhov, A. D.; Korshun, V. A. *Tetrahedron* **2006**, *62*, 1279.

(15) The excess Q8 derives from the pseudorotaxane, which appears to be a mixture of 1:1 and 2:1 (Q8:viologen) complexes.
(16) Moon, K.; Kaifer, A. E. *Org. Lett.* **2004**, *6*, 185.
(17) This result was surprising given the observation by Leventis and coworkers[17] that several pyridinium derivatives bind to cucurbit[7]uril with K_a values in excess of 10^3 M^{-1} in DMSO solution. It would be interesting to know whether the 0.1 M salt used in their experiments had an influence on binding in organic solvent.
(18) Thangavel, A.; Rawashdeh, A. M. M.; Sotiriou-Leventis, C.; Leventis, N. *Org. Lett.* **2009**, *11*, 1595.
(19) Rauwald, U.; Biedermann, F.; Deroo, S.; Robinson, C. V.; Scherman, O. A. *J. Phys. Chem. B* **2010**, *114*, 8606.
(20) Nau, W. M.; Florea, M.; Assaf, K. I. *Israel J. Chem.* **2011**, *51*, 559.
(21) The stability of rotaxane **11** to unthreading was confirmed by NMR experiments in which no change was observed upon adding 3,5-dimethyladamantylamine (data not shown).
(22) (a) Liu, S. M.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 16798. (b) Huang, W. H.; Liu, S. M.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2006**, *128*, 14744.
(23) Sauvage, J. P.; Dietrich-Buchecker, C. *Catenanes, Rotaxanes, and Knots: A Journey Through the World of Molecular Topolgy*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1999.
(24) (a) Hwang, I.; Baek, K.; Jung, M.; Kim, Y.; Park, K. M.; Lee, D.-W.; Selvapalam, N.; Kim, K. *J. Am. Chem. Soc.* **2007**, *129*, 4170. (b) Lee, D.-W.; Park, K. M.; Banerjee, M.; Ha, S. H.; Lee, T.; Suh, K.; Paul, S.; Jung, H.; Kim, J.; Selvapalam, N.; Ryu, S. H.; Kim, K. *Nature Chem.* **2011**, *3*, 154.