Macrocycle Synthesis

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One-Pot Formation of Large Macrocycles with Modifiable Peripheries and Internal Cavities**

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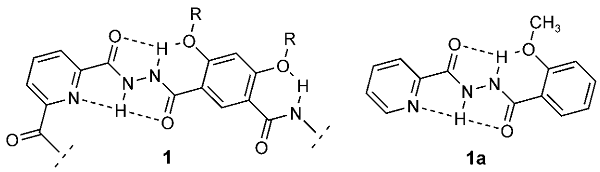
Macrocycles with persistent shape and large, noncollapsible lumens have attracted increasing interest because of their unique properties and potential applications.[1] Although most of the macrocycles with well-defined shape have hydrocarbon backbones formed from the stepwise coupling of sp- or sp^2-hybridized carbon atoms,[1a,b,d,2] macrocycles with other rigid backbones have also been reported.[3] For example, we discovered a series of aromatic oligoamide macrocycles that could be generated in high yield by a one-pot macrocyclization process.[4] These readily available macrocycles contain hydrophilic cavities that are rich in carbonyl oxygen atoms. With their persistent shape and noncollapsible cavities, these macrocycles have demonstrated unique features such as binding large cations with high affinity and specificity,[5] and self-assembling into highly conducting transmembrane pores.[6] The latest mechanistic study[4b] indicates that the folding of uncyclized oligoamide intermediates and precursors, which belong to a class of folding oligoamides with well-defined crescent conformations and tapelike backbones,[7] plays a critical role in the observed high efficiency of the one-pot macrocyclization. The folding of the intermediates and precursors facilitates the one-pot cyclization,[8] and at the same time impedes the formation of "overshooting" oligomers longer than the direct precursor of a macrocycle through remote steric hindrance.[4b] Herein we report that macrocycles with backbones other than aromatic oligoamides can also be formed with very high efficiency. Specifically, macrocycles with rigidified oligohydrazide backbones and nanosized cavities containing well-positioned, modifiable convergent sites can be obtained nearly exclusively in one step.

Similar to the crescent and helical oligoamides we had previously synthesized, the aromatic oligohydrazides consisting of *meta*-linked benzene rings are also known to fold into conformations with tapelike, hydrogen-bond-rigidified backbones.[9] General structure **1** represents an unknown class of aromatic oligohydrazides consisting of *meta*-linked benzene



1 **1a**

and pyridine residues that should have a hydrogen-bond-enforced, curved backbone. The basic unit of **1** consists of a hydrogen-bonded hydrazide group flanked by pyridyl N and ether O atoms that act as hydrogen-bond acceptors. The planar conformation of such a basic unit is illustrated by the optimized structure of hydrazide **1a**.[10] The structure of **1a** is rigidified by two highly favorable, three-center hydrogen bonds that are placed on either side of its hydrazide unit. These three-center hydrogen bonds enforce **1a** to be planar. An oligomer consisting of such rigidified hydrazide units and *meta*-linked aromatic rings will be forced to fold into a crescent shape, which will allow cyclization to occur once it reaches a length that brings its two ends into proximity. Thus, oligomers based on **1** should have a folded, crescent-shaped backbone that may facilitate macrocyclization, thus leading to the corresponding macrocycle.

To test this possibility, acid chloride **2** (1 equiv) was treated with hydrazide **3** (1 equiv) in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) at 0 °C (Scheme 1). The reaction mixture was allowed to warm to room temperature, and was then heated under reflux for 24 h. The crude product was precipitated by adding diethyl ether. The MALDI mass spectrum of this product revealed a dominant signal ($m/z = 1515.0$) that corresponded to the $[M+Na^+]$ ion of the six-residue macrocycle **4**. Purification by column chromatography gave pure **4** as a pale yellow solid in 73 % yield. The ^1H and ^{13}C NMR spectra of **4** also revealed signals that are fully consistent with the symmetrical structure of this molecule.[10] The highly efficient, nearly exclusive formation of **4** demonstrates that folding-assisted macrocyclization can indeed be extended to the preparation of macrocycles with a

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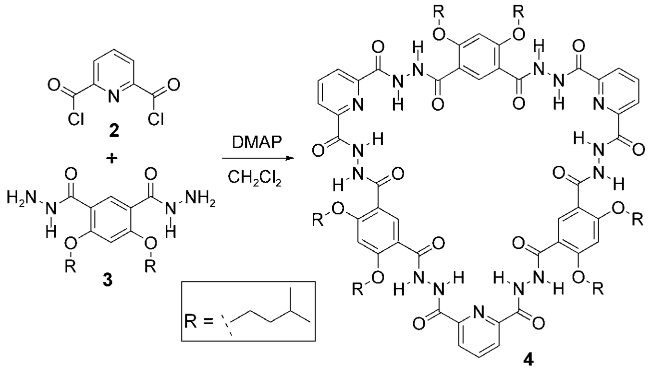


Scheme 1. One-pot formation of oligohydrazide macrocycle **4** consisting of *meta*-linked pyridine and benzene residues.

rigidified backbone besides that offered by aromatic oligoamides.

The six-residue **4** represents the first member of a new series of macrocycles. An exciting possibility offered by shape-persistent macrocycles involves the creation of modifiable internal cavities by placing well-positioned, multiple functionalities in a convergent fashion. Unfortunately, most currently known systems,[11] including the oligoamide macrocycles we reported previously and macrocycle **4** described here, do not allow for easy modification of their internal cavities. Shape-persistent macrocycles with internal cavities of readily tunable size and properties could be formed in high yields by choosing a rigidified, curved backbone that allows the convergent placement of functional groups.

An oligohydrazide consisting of alternating *meta*- and *para*-linked benzene residues, as exemplified by general structure **5** (Figure 1 a), should have a hydrogen-bond-enforced, curved backbone with a convex edge and a concave edge. Macrocycles based on such a backbone should have both divergently (R^1) and convergently (R^2) placed side chains. The size and, more importantly, the function of the internal cavities can be tuned by adjusting the convergent groups. An additional feature provided by this design is that the presence of the *para*-linked residues leads to an overall reduced curvature of the backbone of **5**, macrocycles based on which should have cavities of expanded sizes.

The structure of **5** is supported by the X-ray structure of **5a**[9] (Figure 1 b), which adopts a completely planar conformation that is enforced by two sets of highly favorable, three-center hydrogen bonds.[12] The reported noncyclic aromatic oligohydrazides were based on *meta*-linked benzene residues, and thus trimer **5b** was examined by 2D (ROESY) ^{1}H NMR to provide insights into the folding of the *meta/para*-linked **5**. The ROESY spectrum of **5b** recorded at room temperature (Figure 2) revealed significant ROE interactions between protons *a* and *f*, *a* and *g*, and *b* and *c*, which suggests that **5b** indeed adopts the expected crescent conformation that is enforced by intramolecular hydrogen bonds.

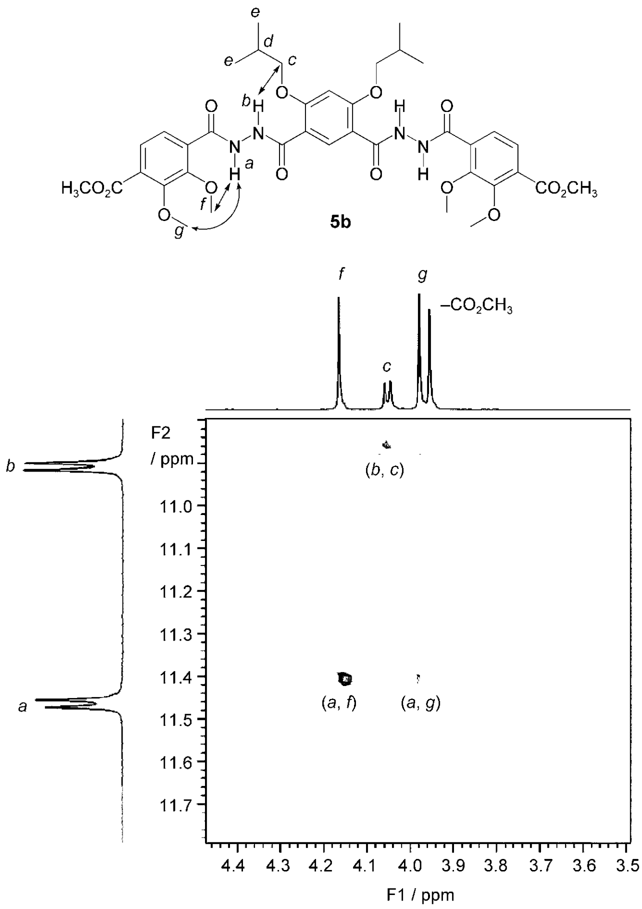


Figure 2. Partial ROESY ^{1}H NMR spectrum of trimer **5b** recorded in $CDCl_3$ (500 MHz, 298 K, mixing time = 0.3 s).

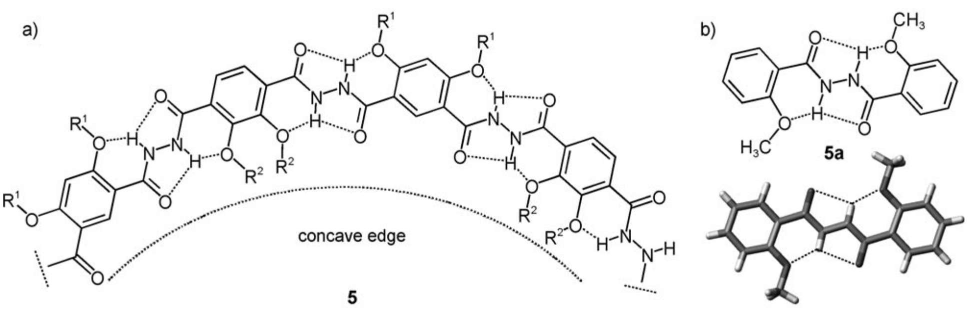
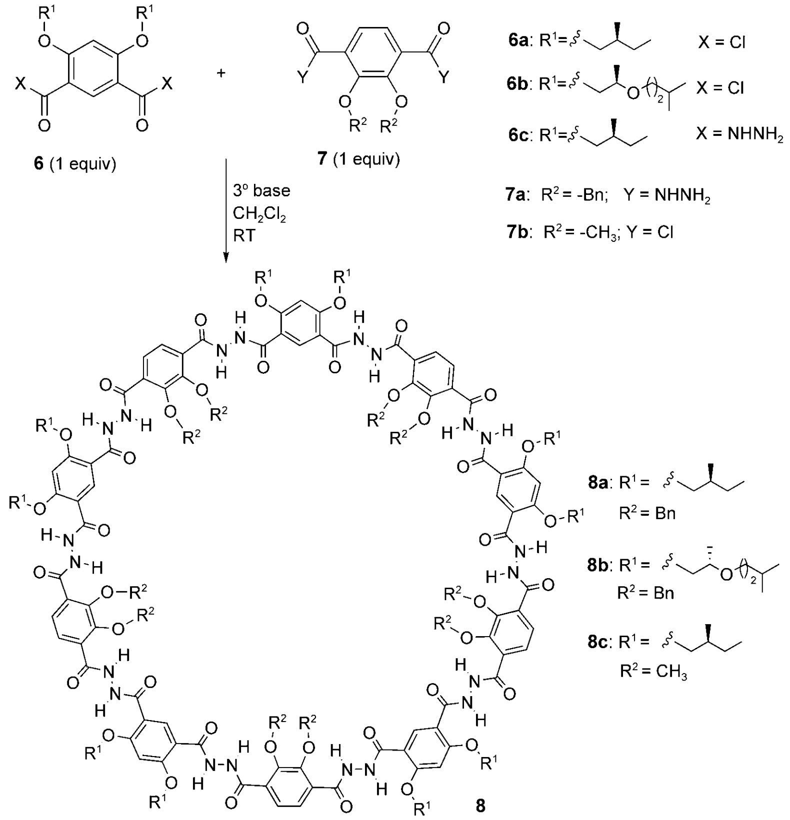


Figure 1. a) The general structure shared by oligohydrazides containing alternating *meta*- and *para*-linked benzene residues connected by hydrogen-bond-rigidified hydrazide groups. Such an oligomer has a concave edge and a convex edge, to which convergently and divergently side chains are attached. b) The structure of **5** is supported by the known crystal structure of **5a**, which shows a completely planar conformation that is enforced by two sets of three-center hydrogen bonds.

With the inclusion of *para*-linked residues, it was not clear whether the reaction between a diacid chloride and a dihydrazide (Scheme 2) would lead to the formation of cyclic product(s), linear



Scheme 2. One-pot formation of oligohydrazide macrocycles **8** consisting of alternating *meta*- and *para*-linked benzene residues. Bn = benzyl.

oligomers, or both. Thus, acid chloride **6a** (1 equiv) was treated with hydrazide **7a** (1 equiv) in CH_2Cl_2 at room temperature. The crude product was obtained in 72% yield after removing the solvent, re-dissolving the solid residue in CH_2Cl_2, simple washing, and recrystallization from methanol. The crude product was analyzed by MALDI mass spectrometry, which revealed a dominant signal ($m/z = 3564.9$) that corresponded to the $[M+Na^+]$ ion of the ten-residue macrocycle **8a**. Extensive purification by column chromatography (silica gel, chloroform/methanol) yielded **8a** in 54% yield.

The very high efficiency of this one-pot macrocyclization reaction was further demonstrated by treating acid chloride **6b** with hydrazide **7a** under similar conditions. Examining the crude products from this reaction by MALDI mass spectrometry revealed that the corresponding macrocycle **8b** ($m/z = 4144.2$, $[M+Na^+]$) existed as the dominant species. Washing a solution of the crude product in CH_2Cl_2 with aqueous HCl and NaCl afforded essentially pure (by ^{1}H NMR spectroscopy) macrocycle **8b** in 97% yield.[10]

In addition to the evidence provided by the MALDI mass spectra, the cyclic structures of macrocycles **8a** and **8b** were clearly demonstrated by the simplicity of their ^{1}H NMR spectra.[10] The ^{1}H NMR signals corresponding to those of the hydrazide and aromatic protons (6.0–12.0 ppm) of each macrocycle can be unambiguously assigned to the two types of monomeric residues (Figure 3). Consistent with the symmetrical nature of their structures, the ^{13}C NMR spectra of these compounds also exhibit similar simplicity.[10]

The persistency of the three-center hydrogen bonds that rigidify the hydrazide groups and thus the backbone of **8b** was demonstrated by intense NOE interactions between protons *a* and *e*, *b* and *c*, and *b* and *d* in its NOESY spectrum (Figure 4).

Compounds **6** and **7** can be readily prepared by procedures previously described,[13] and allows the preparation of other ten-residue macrocycles that share the same backbone as **8a,b** but carry a wide variety of divergent (R^1) and convergent (R^2) groups. The preparation of macrocycle **8c** from diacid chloride **7b** and hydrazide **6c** (Scheme 2) demonstrated that neither R^1 nor R^2 had any effect on the efficiency of the one-pot condensation. Crude macrocycle **8c** was obtained in 91% yield after washing the reaction mixture in CH_2Cl_2 with aqueous HCl and brine, and in 62% yield after purification by column chromatography. The cyclic structure of **8c** was confirmed by the $[M+Na^+]$ signal ($m/z = 2804.5$) in its MALDI mass spectrum, along with the isotope distribution pattern of this signal.[10] However, attempts to characterize **8c** by ^{1}H and ^{13}C NMR spectroscopy have so far resulted in spectra with either very poor resolution (^{1}H NMR) or no signals (^{13}C NMR), which was most likely a consequence of strong intermolecular aggregation of **8c**.

A unique feature offered by the general design of **8** is that the multiple convergent sites in the internal cavities of these macrocycles can be adjusted, either by incorporating monomers carrying the desired side chains or

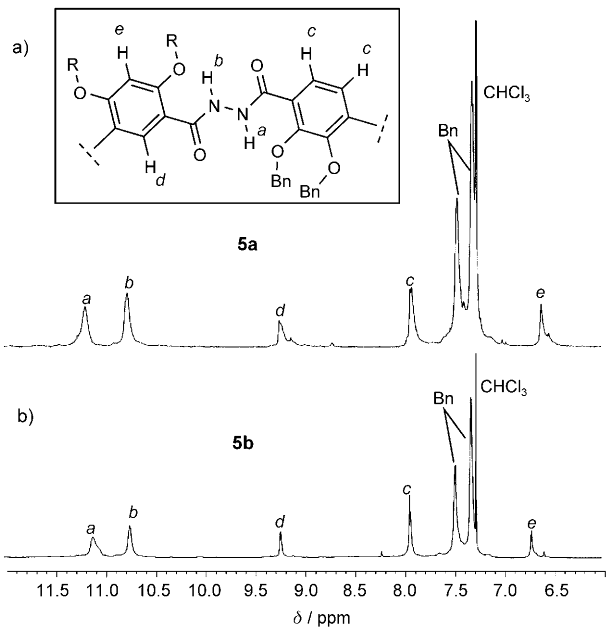


Figure 3. The ^{1}H NMR spectra of a) **8a** and b) **8b** recorded in $CDCl_3$ (500 MHz).

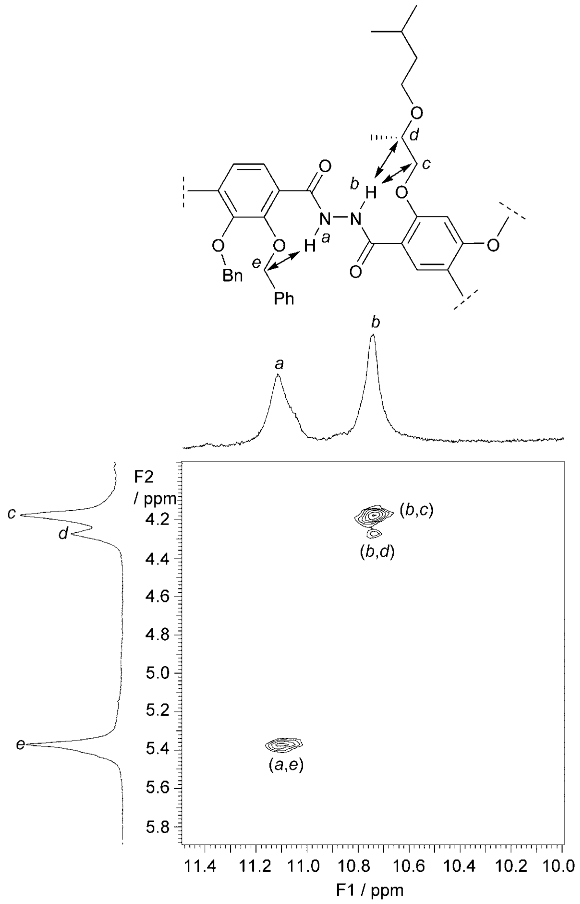


Figure 4. Partial 2D (NOESY) ^{1}H NMR spectrum of **8b** recorded in $CDCl_3$ (500 MHz, 293 K, mixing time = 70 ms).

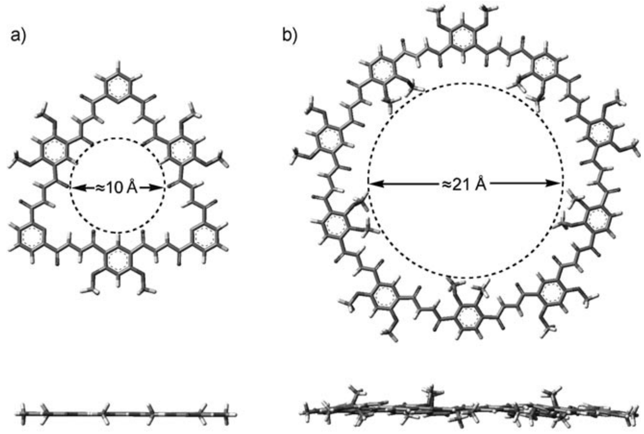


Figure 5. Top and side views of the structures of macrocycles a) **4**, and b) **8** optimized at the B3LYP/6-31(g)d level. All side chains were replaced with methyl groups to save computational time.

by performing a post-cyclization modification. For example, removing the benzyl groups of **8a** and **8b** should expose the hydroxy groups of the catechol moieties. Functional groups could then be introduced through ester, ether, acetal, or other linkages. Furthermore, the hydroxy groups of the catechol moieties should provide multiple sites for the binding of metal ions, thereby leading to cavities with catalytic capability.

The structures of macrocycles **4** and **8** (R replaced with methyl) were optimized by using an ab initio method at the B3LYP/6-31(g)d level of theory.[14] These macrocycles have flat backbones rigidified by three-center hydrogen bonds (Figure 5). The planar shape of both **4** and **8** reflects the high strength of the three-center hydrogen bonds, which enforces the hydrogen-bond donor and acceptors involved to be coplanar. Macrocycle **4** has a triangular shape, with an internal cavity of approximately 10 Å diameter. Macrocycle **8** is much larger than **4**, with an overall round shape and an internal cavity that provides ten well-positioned, multiple convergent sites. In the optimized structure of **8**, the ten convergent methyl groups project above and below the plane of the macrocyclic backbone, thus leading to a cavity with a diameter of about 21 Å.

In summary, the highly efficient, one-pot formation of new shape-persistent macrocycles having hydrogen-bond-rigidified oligohydrazide backbones has been described. The one-pot reactions use readily available starting materials and should lead to large quantities of a variety of macrocycles. Adjusting the divergent side chains allows the peripheries, and thus the solubility, of the macrocycles to be tuned. With their flat backbones and large diameters, these macrocycles should undergo self-organization typical of disclike molecules,[15] thereby leading to columnar aggregates containing nanosized channels. The efficient formation of **8a–c** has opened up a new approach to constructing shape-persistent macrocyles with internal cavities containing multiple convergent sites. Incorporating different functionalities into these convergent sites will lead to noncollapsible cavities with systematically tunable sizes and properties, which will enable hosts to be designed that are capable of targeting guests that are otherwise difficult to recognize. Despite the kinetic nature of the bond-forming reaction, the one-pot nearly exclusive formation of **4** and the much larger **8**, along with the previously reported one-pot generation of aromatic oligoamide macrocycles,[4] rival those observed for macrocyclization reactions under thermodynamic conditions.[16] Thus, these systems have established folding-assisted macrocyclization as a new, general method for the efficient synthesis of shape-persistent macrocycles from folded intermediates and precursors.

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[1] a) C. Grave, A. D. Schlüter, *Eur. J. Org. Chem.* **2002**, 3075; b) S. Höger, *Chem. Eur. J.* **2004**, *10*, 1320; c) Z. R. Laughrey, B. C. Gibb, *Top. Curr. Chem.* **2005**, *249*, 67; d) W. Zhang, J. S. Moore, *Angew. Chem.* **2006**, *118*, 4524; *Angew. Chem. Int. Ed.* **2006**, *45*, 4416; e) M. J. MacLachlan, *Pure Appl. Chem.* **2006**, *78*, 873.

[2] a) M. Mayor, C. Didschies, *Angew. Chem.* **2003**, *115*, 3284; *Angew. Chem. Int. Ed.* **2003**, *42*, 3176; b) K. Nakao, M. Nishimura, T. Tamachi, Y. Kuwatani, H. Miyasaka, T. Nishinaga, M. Iyoda, *J. Am. Chem. Soc.* **2006**, *128*, 16740.

[3] a) H. Jiang, J. M. Leger, P. Guionneau, I. Huc, *Org. Lett.* **2004**, *6*, 2985; b) L. Y. Xing, U. Ziener, T. C. Sutherland, L. A. Cuccia, *Chem. Commun.* **2005**, 5751; c) C. Rotger, M. N. Pina, M. Vega, P. Ballester, P. M. Deya, A. Costa, *Angew. Chem.* **2006**, *118*, 6998; *Angew. Chem. Int. Ed.* **2006**, *45*, 6844; d) J. Sakamoto, A. D. Schlüter, *Eur. J. Org. Chem.* **2007**, 2700; e) F. Campbell, J. Plante, C. Carruthers, M. J. Hardie, T. J. Prior, A. J. Wilson, *Chem. Commun.* **2007**, 2240; f) J. M. Holub, H. J. Jang, K. Kirshenbaum, *Org. Lett.* **2007**, *9*, 3275; g) J. B. Lin, X. N. Xu, X. K. Jiang, Z. T. Li, *J. Org. Chem.* **2008**, *73*, 9403; h) I. Alfonso, M. Bolte, M. Bru, M. I. Burguete, S. V. Luis, J. Rubio, *J. Am. Chem. Soc.* **2008**, *130*, 6137; i) B. Qin, X. Y. Chen, X. Fang, Y. Y. Shu, Y. K. Yip, Y. Yan, S. Y. Pan, W. Q. Ong, C. L. Ren, H. B. Su, H. Q. Zeng, *Org. Lett.* **2008**, *10*, 5127.

[4] a) L. H. Yuan, W. Feng, K. Yamato, A. R. Sanford, D. G. Xu, H. Guo, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 11120; b) W. Feng, K. Yamato, L. Q. Yang, J. S. Ferguson, L. J. Zhong, S. L. Zou, S. L. H. Yuan, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 2629; c) B. Gong, *Acc. Chem. Res.* **2008**, *41*, 1376.

[5] A. R. Sanford, L. H. Yuan, W. Feng, K. Yamato, R. A. Flowers, B. Gong, *Chem. Commun.* **2005**, 4720.

[6] A. J. Helsel, A. L. Brown, K. Yamato, W. Feng, L. H. Yuan, A. J. Clements, S. V. Harding, G. Szabo, Z. F. Shao, B. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 15784.

[7] a) J. Zhu, R. D. Parra, H. Q. Zeng, E. Skrzypczak-Jankun, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2000**, *122*, 4219; b) B. Gong, et al., *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11583; c) L. H. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. S. Atreya, D. K. Sukumaran, T. Szyperski, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 16528.

[8] For some examples of macrocyclizations promoted by conformational preorganization, see a) F. J. Carver, C. A. Hunter, R. J. Shannon, *J. Chem. Soc. Chem. Commun.* **1994**, 1277; b) J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, 1949.

[9] J. L. Hou, X. B. Shao, G. J. Chen, Y. X. Zhou, X. K. Jiang, Z. T. Li, *J. Am. Chem. Soc.* **2004**, *126*, 12386.

[10] See the Supporting Information for details.

[11] For examples of macrocycles containing convergently arranged functionalities prepared by template-directed synthesis, see a) M. Fischer, G. Lieser, A. Rapp, I. Schnell, W. Mamdouh, S. De Feyter, F. C. De Schryver, S. Höger, *J. Am. Chem. Soc.* **2004**, *126*, 214; b) S. H. Jung, W. Pisula, A. Rouhanipour, H. J. Rader, J. Jacob, K. Mullen, *Angew. Chem.* **2006**, *118*, 4801; *Angew. Chem. Int. Ed.* **2006**, *45*, 4685; c) for a recent example of compounds containing cages with convergent functional groups, see M. Mastalerz, *Chem. Commun.* **2008**, 4756.

[12] R. D. Parra, H. Q. Zeng, J. Zhu, C. Zheng, X. C. Zeng, B. Gong, *Chem. Eur. J.* **2001**, *7*, 4352.

[13] L. H. Yuan, A. R. Sanford, W. Feng, A. M. Zhang, J. S. Ferguson, K. Yamato, J. Zhu, H. Q. Zeng, B. Gong, *J. Org. Chem.* **2005**, *70*, 10660.

[14] M. J. Frisch, et al. GAUSSIAN 03 (Gaussian, Pittsburg, 2004), Revision C. 02.

[15] S. Laschat, A. Baro, N. Steinke, F. Giesselmann, C. Hagele, G. Scalia, R. Judele, E. Kapatsina, S. Sauer, A. Schreivogel, M. Tosoni, *Angew. Chem.* **2007**, *119*, 4916; *Angew. Chem. Int. Ed.* **2007**, *46*, 4832.

[16] a) A. J. Gallant, M. J. MacLachlan, *Angew. Chem.* **2003**, *115*, 5465; *Angew. Chem. Int. Ed.* **2003**, *42*, 5307; b) A. J. Gallant, J. K.-H. Hui, F. E. Zahariev, Y. A. Wang, M. J. MacLachlan, *J. Org. Chem.* **2005**, *70*, 7936; c) W. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **2006**, *128*, 11863; d) C. S. Hartley, J. S. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 11682.

