Foldamers

International Edition: DOI: 10.1002/anie.201701693
German Edition: DOI: 10.1002/ange.201701693

Metal-Coordination-Assisted Folding and Guest Binding in Helical Aromatic Oligoamide Molecular Capsules

Maxime Horeau, Guillaume Lautrette, Barbara Wicher, Virginie Blot, Jacques Lebreton, Muriel Pipelier, Didier Dubreuil, Yann Ferrand, and Ivan Huc**

Abstract: *The development of foldamer-based receptors is driven by the design of monomers with specific properties. Herein, we introduce a pyridazine-pyridine-pyridazine diacid monomer and its incorporation into helical aromatic oligoamide foldamer containers. This monomer codes for a wide helix diameter and can sequester metal ions on the inner wall of the helix cavity. Crystallographic studies and NMR titrations show that part of the metal coordination sphere remains available and may then promote the binding of a guest within the cavity. In addition to metal coordination, binding of the guest is assisted by cooperative interactions with the helix host, thereby resulting in significant enhancements depending on the foldamer sequence, and in slow guest capture and release on the NMR time scale. In the absence of metal ions, the pyridazine-pyridine-pyridazine monomer promotes an extended conformation of the foldamer that results in aggregation, including the formation of an intertwined duplex.*

Aromatic foldamers,[1] that is, foldamers with aryl groups in their main chain, have emerged as powerful tools for the production of molecular containers able to recognize small molecules or ions with high selectivity and affinity.[1a,2] As natural receptors demonstrate, folding is an efficient approach to organize arrays of functional groups in space around a binding cavity. In this respect, aromatic sequences possess the advantage that their folded structures are largely predictable, which allows for some level of prediction of their molecular recognition properties as well. They give access to a variety of shapes, among which helices with an inner cavity large enough to accommodate guests are attractive because of their simplicity, in contrast with the intricate tertiary folds required to generate binding sites in proteins. The inner cavity of an aromatic helix is lined with the edges of the backbone aryl rings, which allows for the straightforward introduction of desirable substituents, a feature that has also proven useful in some macrocyclic and self-assembled cages.[3] Open-ended aromatic helical receptors[4] rapidly bind and release small guests; they may also slowly wind around dumbbell-shaped molecules.[5] An intriguing geometry is that of helical capsule sequences that combine a wide diameter in the center and a reduced diameter at both ends, which eventually closes the cavity and completely isolates guests from the solvent.[6] Such helices are inherently asymmetrical (or C_2 symmetrical) and are thus suitable for generating complex arrays of functionalities complementary to chiral guests. For example, exquisite selectivity for β-fructopyranose, tartaric acid, and malic acid have been observed.[6b,c]

The modular nature of foldamer sequences constitute a key feature: sequence variants with added, deleted, or mutated monomers can quickly be produced to iteratively improve binding properties.[6b,c,7] Modulation of recognition has also been achieved through strand intercalation[8] or in situ modification of a monomer,[9] both of which can alter cavity size and recognition. Since binding properties are directly related to features imparted by the monomers, the development of foldamer-based receptors can be said to be monomer-driven. New monomers enrich the tool kit of available building blocks and may be exploited in a variety of contexts. In the following, we introduce a pyridazine-pyridine-pyridazine diacid monomer pyz-pyr-pyz (Figure 1 b) to sequester a metal ion at the inner wall of aromatic oligoamide helical capsules while leaving some coordination sites available for the metal to contribute to guest recognition. The intention here is to take advantage of the strength of coordination bonds for binding affinity,[10] with the capsule shell ensuring guest shape and guest size selectivity. The new monomer is inspired by aza-aromatic sequences and their conformational changes upon binding to metal ions.[11] It possesses carboxylic acid functions for aromatic amide compatibility and consists of a central terpyridine-like tridentate metal binding site. The second endocyclic nitrogen atoms of the peripheral pyridazine rings hydrogen bond to the adjacent amide protons and control backbone conformation. We incorporated this monomer into the foldamer sequences **1** and **2** (Figure 1 d). We show that these sequences aggregate and do not produce a binding cavity upon folding in the absence of metal ions, while the addition of metal ions induces folding into helical capsules that exhibit metal-coordination-assisted guest binding (Figure 1 a).

Oligomers **1** and **2** were designed to fold into helical capsules according to well-established principles,[6] in the presence of metal ions. Monomers P, N, A, and pyz-pyr-pyz display their amine and/or acid functions at the same angle

[*] Dr. M. Horeau, Dr. V. Blot, Prof. J. Lebreton, Dr. M. Pipelier, Prof. D. Dubreuil
UMR 6230—CEISAM, Univ. Nantes—CNRS
Faculté des Sciences et des Techniques
2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3 (France)
E-mail: muriel.pipelier@univ-nantes.fr
Dr. G. Lautrette, Dr. B. Wicher, Dr. Y. Ferrand, Dr. I. Huc
UMR 5248—CBMN
Univ. Bordeaux—CNRS—Institut Polytechnique de Bordeaux
Institut Européen de Chimie et Biologie
2 rue Robert Escarpit, 33600 Pessac (France)
E-mail: i.huc@iecb.u-bordeaux.fr
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201701693.

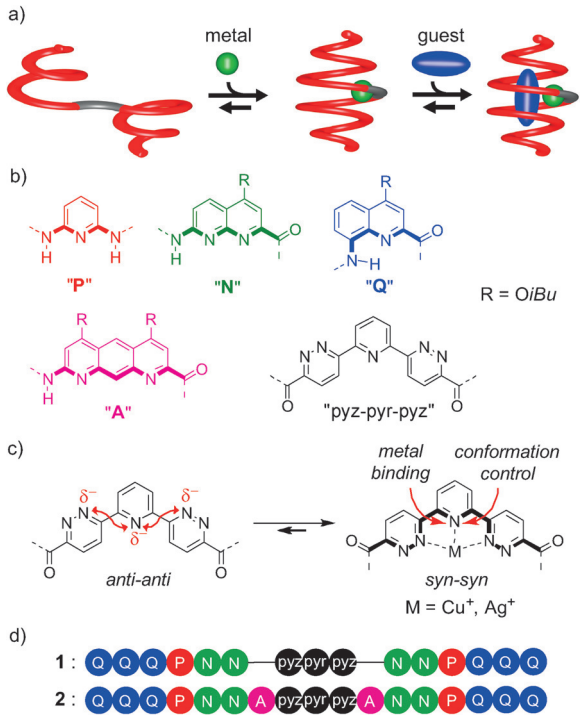

Figure 1. a) Principle of helical-capsule folding upon metal coordination and guest binding in the capsule cavity assisted by the metal ion. b) Letter and color codes of the amino acid, diamine, and diacid monomers used in oligoamide sequences **1** and **2**. The bonds marked with thick lines delineate the inner rim of the helically folded sequences. c) Preferred conformations of pyz-pyr-pyz in the absence of metal ions and upon metal coordination. d) Oligoamide sequences **1** and **2**. Note that amide orientation with respect to the sequence is inverted at each of the diamine and diacid sites. The two terminal Q units have an 8-nitro group and not an 8-amino function.

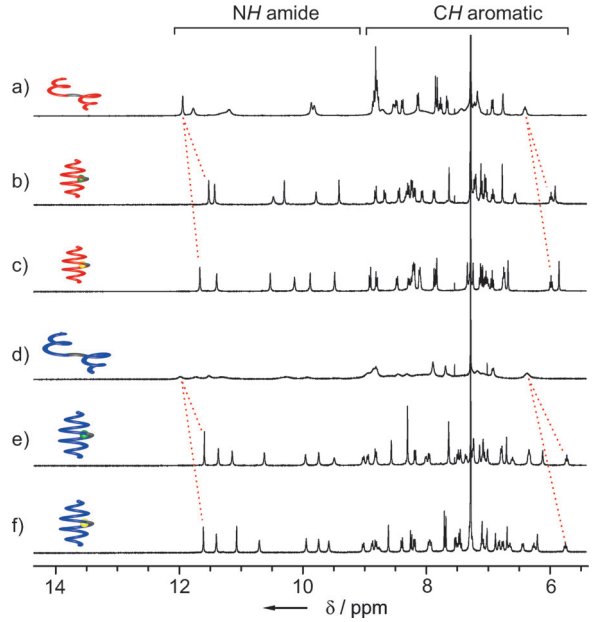

Figure 2. Excerpts from the 400 MHz ^{1}H NMR spectra showing the amide and aromatic resonances at 1 mM in $CDCl_3/CD_3CN$ (95:5 vol/vol): a) **1**; b) **1** + $CuBF_4(MeCN)_4$ (1 equiv); c) **1** + $AgBF_4$ (1 equiv); d) **2**; e) **2** + $CuBF_4(MeCN)_4$ (1 equiv); f) **2** + $AgBF_4$ (1 equiv).

(equivalent to a *meta* substitution, ca. 120°) and thus produce a similar curvature (number of units per turn). However, their widths correspond to one, two, three, or four fused benzenic rings, respectively, giving rise to an increasing helix diameter when assembled in the order P→N→A→pyz-pyr-pyz. The flanking Q_3 segments have a reduced diameter and serve as end caps. The syntheses of pyz-pyr-pyz and **1** and **2** are described in detail in the supporting information. In the absence of metal ions, the ^{1}H NMR spectra of **1** and **2** are not sharp (Figure 2a,d) and show concentration dependence (Figures S1, S2 in the Supporting Information). This is indicative of some aggregation, which does not occur in related capsule sequences.[6] A crystal structure of **1** revealed the formation of a discrete dimer with a unique architecture in which two strands show different levels of reciprocal intercalation (Figure 3a,b,d) and some double helical intertwining (Figure 3c). As expected, the Q_3PN_2 segments adopt a helical conformation, and the central pyz-pyr-pyz unit is found in an *anti-anti* extended conformation favored by repulsion between endocyclic nitrogen atoms (Figures 1c and 3d). This extended shape apparently promotes intermolecular contacts. In $CDCl_3$, the concentration dependence of the NMR spectra indicates dimerization constants larger than 1000 $L\,mol^{-1}$ for **2** and smaller than 10 $L\,mol^{-1}$ for **1**. Interestingly, the aggregation of **2** is suppressed upon adding DMSO, and sharp NMR lines are then observed (Figure S7). Some aromatic signals of monomeric **2** are shifted upfield in DMSO, thus suggesting the buildup of aromatic stacking, which would not occur in an extended conformation. DMSO thus apparently promotes the folding of **2** into a helix in the absence of any metal ions, possibly by reducing the effect of the intramolecular electrostatic repulsion that favors the *anti-anti* conformer of pyz-pyr-pyz. Overcoming a local conformation preference to produce a well folded capsule has previously been observed in a pyridazine-pyrrole-pyridazine segment.[9]

Upon adding metal ions such as Ag^+ or Cu^+ to solutions of **1** in $CDCl_3/CD_3CN$ mixtures, a new set of sharp NMR signals emerge that are no longer concentration-dependent (Figure 2b,c and Figures S5, S6). Metal complexes thus form that are in slow exchange on the NMR timescale with uncomplexed **1**. This contrasts with the metal-binding properties of an isolated pyridazine-pyridine-pyridazine precursor of pyz-pyr-pyz, which also binds metal ions but allows for rapid exchange (Figure S10). Titrations indicate that **1** binds exactly one equivalent of metal ions. This was confirmed by a crystal structure of **1**-Cu^{2+} (Figure 3g–j). Crystals were grown by liquid–liquid diffusion in a solution of **1**-Cu^+ without any protection from oxygen. However, the deep green color of the crystals and the square planar geometry of the complex leave little doubt about the Cu^{II} oxidation state after a prolonged incubation. The metal ion is bound to the pyz-pyr-pyz unit selectively, despite multiple other nitrogen donors being available in the sequence. This stabilizes the *syn-syn* conformation, thereby resulting in the folding of the strand into a single helix with a cavity to which the metal ion is exposed. Furthermore, a fourth coordination site of the metal ion is occupied by an acetonitrile molecule, which fills a large part

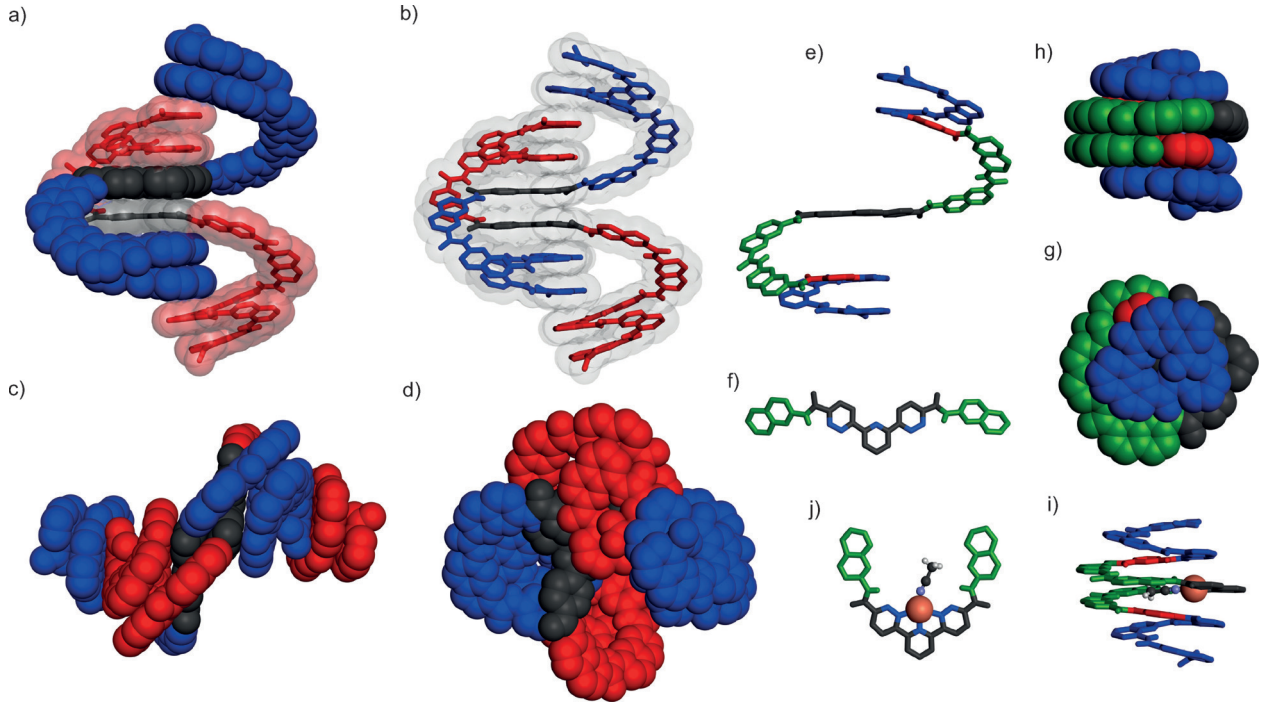

Figure 3. Solid-state structures of $(\mathbf{1})_2$ (a–f) and $\mathbf{1}$-Cu^{2+} (g–j). Different views of the intertwined dimer $(\mathbf{1})_2$ in space-filling or tube representations are shown in (a–d). e) A single strand of the duplex. f) A top view of the central N–pyz-pyr-pyz–N segment of **1** in its extended, metal-free conformation to be compared to the bent metal bound conformation shown in (j). A coordinated acetonitrile molecule is shown in ball and stick representation in (i) and (j). The space-filling views of $\mathbf{1}$-Cu^{2+} (h–g) show that the helical capsule completely sequesters the metal complex from the solvent. In (e–j), monomers are color coded as in Figure 1. Isobutoxy side chains and included solvent molecules are omitted for clarity.

of the capsule inner cavity. It is likely that a coordinating solvent molecule also completes the Cu^+ coordination sphere in solutions of $\mathbf{1}$-Cu^+. However, we could not identify NMR signals of the bound solvent owing to signal overlap in the aliphatic region where its resonance would be expected.

The structure of the complex $\mathbf{1}$-Cu^{2+}-CH_3CN thus validates the proposed design principles and the possibility to have guests bound to a metal ion within a foldamer capsule. Sequence **2**, which has two additional A units, was then prepared to enlarge the available space around the metal ion. This sequence is the first that makes use of A units lacking any substituent in position 9.[8] These A units leave more space in the helix cavity, but also lack features that could be useful for molecular recognition.

Titration of **2** with Cu^+ and Ag^+ produced the complexes **2**-Cu^+ and **2**-Ag^+ as well-defined species as judged by their sharp ^{1}H NMR lines (Figure 2e,f). These complexes were not designed to bind to any particular guests but their resemblance to some saccharide-binding capsule sequences,[6b] the estimated available space in the capsule cavity, and the fact that metal ions can assist sugar binding[12] all encouraged us to screen for binding to saccharides. The results, however, were disappointing since only weak and ill-defined (broad and/or complex) NMR spectra were observed (not shown). We then turned to guests with known coordination abilities and found that imidazole forms a well-defined complex with **2**-Cu^+. An NMR titration is shown in Figure 4 and reveals the progressive appearance of a new species in slow exchange on the NMR time scale with capsule **2**-Cu^+. The identity of the **2**-Cu^+-imidazole complex was also supported by mass spectrometry. The NMR spectrum features a distinct sharp resonance at 13.1 ppm that could be assigned to the encapsu-

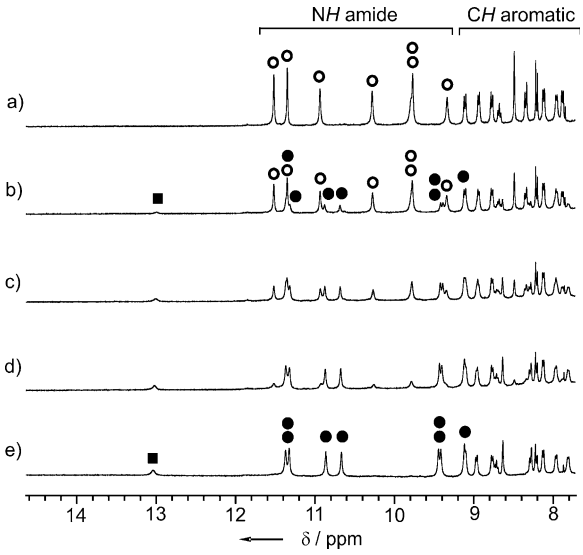

Figure 4. Excerpts from the 400 MHz ^{1}H NMR spectra in 80:20 $CDCl_3$/[D_6]DMSO (vol/vol) at 298 K of capsule **2**-Cu^+ (1 mM) without guest (a) and in the presence of 0.25 equiv (b), 0.50 equiv (c), 0.75 equiv (d), 1 equiv (e) of imidazole. The amide signals of the host–guest complex **2**-Cu^+-imidazole are marked with solid circles and those of the empty capsule are marked with empty circles. The resonance at 13.1 ppm corresponds to the N*H* of imidazole.

lated imidazole NH, and that presumably reflects its involvement in a hydrogen bond. The K_a of imidazole binding by **2**-Cu^+ was found to be in the range 10^5–10^6 L mol^{-1} in 80:20 $CDCl_3$/[D_6]DMSO (vol/vol) at 298 K. Higher values might be expected upon decreasing the proportion of DMSO since DMSO could possibly compete for Cu coordination. In contrast, **2** alone does not bind to imidazole, nor does it undergo any conformational change in its presence (Figure S8).

Since imidazole is not much larger than the acetonitrile molecule found in the cavity of **1**-Cu^{2+}, we also titrated **1**-Cu^+ with imidazole and eventually observed the formation of a new species in slow exchange on the NMR timescale that we assigned as **1**-Cu^+-imidazole (Figure S9). The K_a value was measured to be 6000 L mol^{-1}, which is significantly lower than for **2**-Cu^+. In addition, the ^{1}H NMR spectrum of the **1**-Cu^+-imidazole complex does not feature the distinct signal at 13.1 ppm. The imidazole NH resonance apparently overlaps with aromatic signals or is broad.

In summary, we have validated the incorporation of a metal-binding monomer within helical aromatic foldamer sequences. The inherent conformational preference of the pyz-pyr-pyz unit promotes undesired aggregation, but this disappears and proper helix folding occurs in the presence of metal ions. Part of the metal coordination sphere remains available and may then promote the binding of a guest. In addition to metal coordination, binding of the guest is assisted by cooperative interactions with the helix host, which results in significant enhancements depending on the foldamer sequence, and also in slow guest exchange on the NMR time scale. Metal-binding monomers thus extend the potential for tight and selective guest binding by helical aromatic foldamer hosts. Our current efforts aim at exploiting this property for the recognition of complex guests, including saccharides.

Acknowledgements

This work was supported by the Conseil Interprofessionnel du Vin de Bordeaux (predoctoral fellowship to G.L.) and by the European Research Council under the European Union's Seventh Framework Programme (grant agreement no. ERC-2012-AdG-320892, post-doctoral fellowship to G.L. and B.W.).

Conflict of interest

The authors declare no conflict of interest.

Keywords: foldamers · helical conformation · host–guest chemistry · metal coordination · molecular recognition

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 6823–6827
Angew. Chem. **2017**, *129*, 6927–6931

[1] a) D.-W. Zhang, X. Zhao, J.-L. Hou, Z.-T. Li, *Chem. Rev.* **2012**, *112*, 5271–5316; b) I. Huc, *Eur. J. Org. Chem.* **2004**, 17–29; c) I. Saraogi, A. D. Hamilton, *Chem. Soc. Rev.* **2009**, *38*, 1726–1743; d) B. A. Ikkanda, B. L. Iverson, *Chem. Commun.* **2016**, *52*, 7752–7759; e) R. V. Nair, K. N. Vijayadas, A. Roy, G. J. Sanjayan, *Eur. J. Org. Chem.* **2014**, 7763–7780.

[2] a) H. Juwarker, K.-S. Jeong, *Chem. Soc. Rev.* **2010**, *39*, 3664–3674; b) H. Juwarker, J.-m. Suk, K.-S. Jeong, *Chem. Soc. Rev.* **2009**, *38*, 3316–3325.

[3] a) W. Cullen, M. C. Misuraca, C. A. Hunter, N. H. Williams, M. D. Ward, *Nat. Chem.* **2016**, *8*, 231–236; b) S. Löffler, J. Lübben, A. Wuttke, R. A. Mata, M. John, B. Dittrich, G. H. Clever, *Chem. Sci.* **2016**, *7*, 4676–4684; c) S. Löffler, J. Lübben, L. Krause, D. Stalke, B. Dittrich, G. H. Clever, *J. Am. Chem. Soc.* **2015**, *137*, 1060–1063; d) G. Joshi, A. P. Davis, *Org. Biomol. Chem.* **2012**, *10*, 5760–5763; e) T. Ichijo, S. Sato, M. Fujita, *J. Am. Chem. Soc.* **2013**, *135*, 6786–6789; f) W. J. Ramsay, F. J. Rizzuto, T. K. Ronson, K. Caprice, J. R. Nitschke, *J. Am. Chem. Soc.* **2016**, *138*, 7264–7267.

[4] a) J.-L. Hou, X.-B. Shao, G.-J. Chen, Y.-X. Zhou, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2004**, *126*, 12386–12394; b) C. Li, G.-T. Wang, H.-P. Yi, X.-K. Jiang, Z.-T. Li, R.-X. Wang, *Org. Lett.* **2007**, *9*, 1797–1800; c) L.-Y. You, S.-G. Chen, X. Zhao, Y. Liu, W.-X. Lan, Y. Zhang, H.-J. Lu, C.-Y. Cao, Z.-T. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 1657–1661; *Angew. Chem.* **2012**, *124*, 1689–1693; d) M. Waki, H. Abe, M. Inouye, *Angew. Chem. Int. Ed.* **2007**, *46*, 3059–3061; *Angew. Chem.* **2007**, *119*, 3119–3121; e) H. Abe, H. Machiguchi, S. Matsumoto, M. Inouye, *J. Org. Chem.* **2008**, *73*, 4650–4661; f) K.-J. Chang, B.-N. Kang, M.-H. Lee, K.-S. Jeong, *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215; g) Y. Hua, A. H. Flood, *J. Am. Chem. Soc.* **2010**, *132*, 12838–12840.

[5] a) T. Nishinaga, A. Tanatani, K. Oh, J. S. Moore, *J. Am. Chem. Soc.* **2002**, *124*, 5934–5935; b) A. Tanatani, T. S. Hughes, J. S. Moore, *Angew. Chem. Int. Ed.* **2002**, *41*, 325–328; *Angew. Chem.* **2002**, *114*, 335–338; c) A. Petitjean, L. A. Cuccia, M. Schmutz, J.-M. Lehn, *J. Org. Chem.* **2008**, *73*, 2481–2495; d) Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Grélard, H. Jiang, I. Huc, *Science* **2011**, *331*, 1172–1175; e) Y. Ferrand, Q. Gan, B. Kauffmann, H. Jiang, I. Huc, *Angew. Chem. Int. Ed.* **2011**, *50*, 7572–7575; *Angew. Chem.* **2011**, *123*, 7714–7717; f) Q. Gan, Y. Ferrand, N. Chandramouli, B. Kauffmann, C. Aube, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* **2012**, *134*, 15656–15659.

[6] a) J. Garric, J.-M. Léger, I. Huc, *Angew. Chem. Int. Ed.* **2005**, *44*, 1954–1958; *Angew. Chem.* **2005**, *117*, 1990–1994; b) N. Chandramouli, Y. Ferrand, G. Lautrette, B. Kauffmann, C. D. Mackereth, M. Laguerre, D. Dubreuil, I. Huc, *Nat. Chem.* **2015**, *7*, 334–341; c) G. Lautrette, B. Wicher, B. Kauffmann, Y. Ferrand, I. Huc, *J. Am. Chem. Soc.* **2016**, *138*, 10314–10322; d) Y. Hua, Y. Liu, C–H. Chen, A. H. Flood, *J. Am. Chem. Soc.* **2013**, *135*, 14401–14412.

[7] Fine tuning of guest binding by combining different monomers has also been implemented in shape-persistent foldamer-based macrocycles: Y. Liu, J. Shen, C. Sun, C. Ren, H. Zeng, *J. Am. Chem. Soc.* **2015**, *137*, 12055–12063.

[8] M. L. Singleton, G. Pirotte, B. Kauffmann, Y. Ferrand, I. Huc, *Angew. Chem. Int. Ed.* **2014**, *53*, 13140–13144; *Angew. Chem.* **2014**, *126*, 13356–13360.

[9] G. Lautrette, C. Aube, Y. Ferrand, M. Pipelier, V. Blot, C. Thobie, B. Kauffmann, D. Dubreuil, I. Huc, *Chem. Eur. J.* **2014**, *20*, 1547–1553.

[10] For examples of metal assisted molecular recognition of organic guests, see: a) G. Izzet, B. Douziech, T. Prangé, A. Tomas, I. Jabin, Y. Le Mest, O. Reinaud, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6831–6836; b) H. Bakirci, A. L. Koner, M. H. Dickman, U. Kortz, W. M. Nau, *Angew. Chem. Int. Ed.* **2006**, *45*, 7400–7404; *Angew. Chem.* **2006**, *118*, 7560–7564; c) U. Darbost, O. Sénèque, Y. Li, G. Bertho, J. Marrot, M.-N. Rager, O. Reinaud, I. Jabin, *Chem. Eur. J.* **2007**, *13*, 2078–2088; d) N. Le Poul, B. Douziech, J.

Zeitouny, G. Thiabaud, H. Colas, F. Conan, N. Cosquer, I. Jabin, C. Lagrost, P. Hapiot, O. Reinaud, Y. Le Mest, *J. Am. Chem. Soc.* **2009**, *131*, 17800 – 17807.

[11] a) M. Barboiu, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5201 – 5206; b) N. Giuseppone, J.-L. Schmitt, J.-M. Lehn, *Angew. Chem. Int. Ed.* **2004**, *43*, 4902 – 4906; *Angew. Chem.* **2004**, *116*, 5010 – 5014; c) N. Giuseppone, J.-L. Schmitt, J.-M. Lehn, *J. Am. Chem. Soc.* **2006**, *128*, 16748 – 16763.

[12] a) G. Chen, Z. Guan, C.-T. Chen, L. Fu, V. Sundaresan, F. H. Arnold, *Nat. Biotechnol.* **1997**, *15*, 354 – 357; b) T. Mizutani, T. Kurahashi, T. Murakami, N. Matsumi, H. Ogoshi, *J. Am. Chem. Soc.* **1997**, *119*, 8991 – 9001; c) S. Striegler, M. Dittel, *J. Am. Chem. Soc.* **2003**, *125*, 11518 – 11524; d) O. Alptürk, O. Rusin, S. O. Fakayode, W. Wang, J. O. Escobedo, I. M. Warner, W. E. Crowe, V. Kràl, J. M. Pruet, R. M. Strongin, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9756 – 9760.

Manuscript received: February 15, 2017
Version of record online: May 4, 2017

