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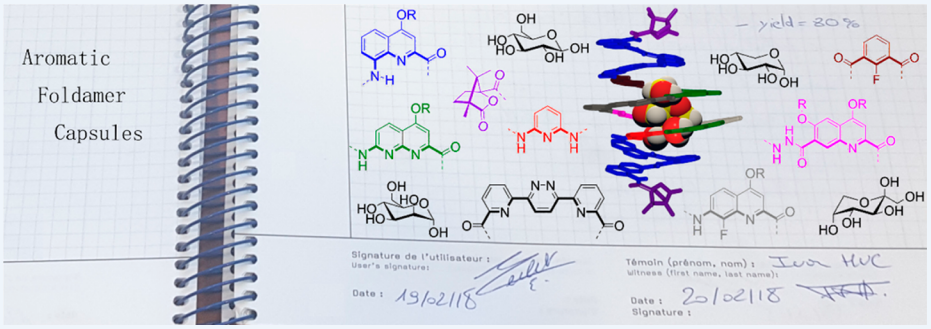
Designing Helical Molecular Capsules Based on Folded Aromatic Amide Oligomers

Yann Ferrand*,† and Ivan Huc*,‡

†Université de Bordeaux, CNRS, Bordeaux Institut National Polytechnique, CBMN (UMR 5248), Institut Européen de Chimie et Biologie, 2 Rue Escarpit, 33600 Pessac, France

‡Department Pharmazie, Ludwig-Maximilians-Universität, Butenandtstraße 5-13, D-81377 München, Germany



CONSPECTUS: The ab initio rational structure-based design of a synthetic molecular receptor for a given complex biomolecular guest remains an elusive objective, yet remarkable progress has been achieved in recent years. This Account deals with the use of folded artificial aromatic amide oligomers, also termed aromatic foldamers, inspired from biopolymer structures, for the design of helical molecular capsules that can recognize guest molecules, completely surround them, and isolate them from the solvent, thus giving rise to a sort of guest encapsulation associated with slow binding and release kinetics. The development of new amino acid, diacid, and diamine monomers, a main source of creativity in this field, progress in their assembly into ever longer oligoamide sequences, and the predictability of the folded structures due to their inherent rigidity and simple folding principles, allowed for the design and preparation of unimolecular and bimolecular capsule shapes. These capsules consist of molecular helices having a large diameter in the middle and a narrow diameter at both ends thus creating a cavity suitable for binding a guest molecule. The understanding of molecular recognition properties within these bioinspired containers has greatly progressed. Recognition of simple guests such as diols or amino-alcohols may thus be predicted, and hosts can be proposed for guests as complex as saccharides using first principle design. Taking advantage of the modular nature of oligomeric sequences, of their synthetic accessibility and of their propensity to grow into crystals suitable for X-ray crystallographic analysis, a structure-based iterative design methodology has been developed that eventually yielded exquisite guest selectivity, affinity, and diastereoselectivity. This methodology involves rational negative design steps during which changes in the foldamer capsule sequence are not intended to improve binding to the targeted guest but instead to exclude the binding of other guests while preserving key interactions with the target. Metal ions can also be introduced at the inner rim of foldamer capsules and eventually assist the binding of an organic guest. These results demonstrate the viability of an ab initio approach to abiotic receptor design based on aromatic foldamers. The dynamic of the capsules associated with their self-organized nature provides opportunities to not only tune guest binding and selectivity, but also guest capture and release kinetics as well as cavity size and shape. Controlled release thus emerges as a realistic objective. Recent progress thus opens up multiple perspectives for the development of tailored hosts, sensors, and carriers structurally and conceptually different from earlier generations of macrocyclic-based receptors or from supramolecular containers produced by self-assembly.

1. INTRODUCTION

Folding of molecular strands is the method nature has selected to position chemical groups in space with atomic precision over nanometric distances and endow biopolymers with such extraordinary functions as enzyme catalysis in proteins and genetic information storage in nucleic acids.[1,2] During the last 25 years, chemists have thoroughly demonstrated that various non-natural backbones also have a propensity to fold.[3] These synthetic oligomers or polymers, termed foldamers,[4] may adopt folded conformations such as sheets or helices as found in biopolymers. But they may also give access to original structures and functions, and so all the more that their chemical composition differs from peptides and nucleotides. In this context, important efforts including our own have focused on oligoamide skeletons having aromatic rings in their main chain.[5] The rigidity imparted by aromatic rings restricts the space of accessible conformations and allows for a good

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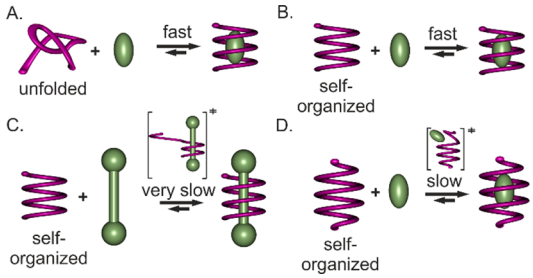

Figure 1. Schematic representations of different recognition modes of a guest molecule (olive green oval) by a helix (purple tube): (A) Helical folding induced by the guest. (B) Guest recognition in the cavity of a preformed helix. (C) Unfolding and refolding of a preorganized helix around a dumbbell shaped guest. (D) Encapsulation of a substrate in a helix whose cavity is closed at both ends.

predictability of folded structures. As developed in this article, the prediction of structures in turns allows for a certain degree of prevision of properties, and in particular of molecular recognition properties.

Molecular recognition rests on the convergence of arrays of chemical functions toward a cavity where a complementary guest may be bound. Early artificial receptors relied on the preorganization of recognition functions in relatively rigid molecules such as macrocycles and macropolycycles.[6] As a different approach, self-assembly may produce large supramolecular containers with cavities that can also host guest molecules.[7] These containers may form from remarkably simple molecular building blocks and most of the time possess a high degree of symmetry. In contrast, natural peptidic or nucleotidic receptors adopt complex conformations with low or no symmetry. In addition, peptides and nucleotides are inherently modular due to their oligomeric nature. Each monomer may be modified in order to adjust the structure, the dynamics and the properties of the folded conformation. Modularity and the variety of molecular shapes that can be obtained through folding are the very features that foldamer-based receptor development intends to take advantage from. In particular, aromatic foldamers have been shown to fold into helices having a cavity large enough to accommodate a guest. Depending on the host's and guest's shapes, different types of equilibria may come into play. For example, the binding event may promote helix formation from a not completely folded state through some kind of induced fit mechanism (Figure 1A).[8] If the helix is stable in the absence of guest, binding and release of the guest through the open helix cavity is a fast event (Figure 1B),[9] unless the guest has a dumbbell shape in which case the helix has to unwind and rewind around the guest (Figure 1C).[10] An original architecture derives from a helix whose ends have a reduced diameter and that can thus completely surround its guest and seclude it from the solvent (Figure 1D). This account focuses on this very type of structure, which we consider to be the most amenable to selective and tight molecular recognition and, eventually, to controlled release. The other recognition modes shown in Figure 1 are not discussed further but are all well documented in the literature.

2. MONOMER DESIGN AND PREDICTABILITY OF FOLDED STRUCTURES

Folded conformation control in aromatic oligoamides rests on the interactions depicted in Figure 2A. Conjugation sets a preference for amide bonds and adjacent aryl rings to be

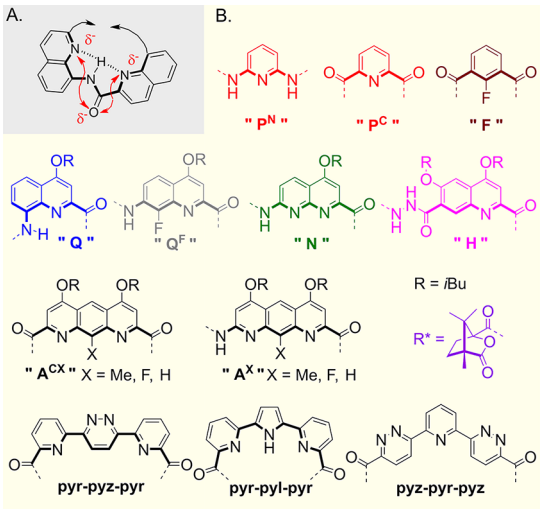

Figure 2. (A) Local interactions that govern aromatic oligoamide folding. Conjugation, hydrogen bonds (dotted lines), and electrostatic repulsions (arrows) all contribute to the stabilization of a preferred conformation at each aryl-amide bond. In a long enough sequence, the resulting curvature gives rise to a helix. Aromatic stacking within the helix also contributes to its stability in particular through solvophobic effects in protic media. (B) Formula of main chain units derived from diamine, diacid and amino acid monomers that constitute helical capsules. Each monomer is associated with a letter and a color code. "R" groups diverge from the folded objects and determine their solubility. With R = *i*Bu, capsules are well soluble in chlorinated and aromatic organic solvents.

coplanar. Local attractive and repulsive interactions between each amide function and endocylic nitrogen atoms or exocylic substituents in adjacent aryl rings then set a preferred relative orientation at each aryl-amide linkage,[5a] thus defining a local curvature that depends on the unit size—large units code for a large diameter (i.e., low curvature)—and of the amine and acid substituents' positions on each aryl ring—a *para* substitution does not promote curvature. Thus, the folded shape simply results from a linear combination of local conformational preferences which makes it prediction particularly simple. Upon introducing monomers that code for a high curvature (small helix diameter) at the end of a sequence and monomers that code for a weak curvature (large helix diameter) in the middle of a sequence, one obtains a helical capsule (Figure 1D) that can completely surround a complementary guest molecule and seclude it from the solvent.[11] The capture and release of the guest in solution entail a transient local unfolding of the helix.[12] It follows that both processes become slower as guest size increases.

The design of molecular capsules based on aromatic oligoamides led to the development of a toolbox of heterocyclic amino acid, diacid and diamine monomers (Figure 2B). In these building blocks, the endocyclic nitrogen atoms are essential to conformational stability (Figure 2A). Neither the synthesis nor their assembly into oligoamide sequences are presented in detail here. References to the preparation of each of these units are associated with the description of sequences that contain them (see below). It remains that monomer development is an essential source of creativity in the field of foldamers. Research in this area can be said to be monomer driven.[13] An original aspect of these molecules is that, unlike peptides and nucleotides, main chain features and not just side chains are varied along the sequences. Our work has made

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extensive use of amide linkages between aryl rings because their synthesis is high yielding, an important parameter when many couplings are required to build a sequence, and because they provide hydrogen bonding features useful to bind to polar guests. In addition, aryl−aryl,[14] aryl-alkyne,[8c,9a] triazoles,[8d−g] and oxadiazole[15] linkages may also be introduced with the considerable advantage that all these functions give rise to similar aromatic helices and can thus be combined at will.

3. FIRST CAPSULES AND PREDICTABILITY OF MOLECULAR RECOGNITION

A proof of concept of the feasibility of a helical capsule from an aromatic oligoamide strand was first described in 2005.[11] The

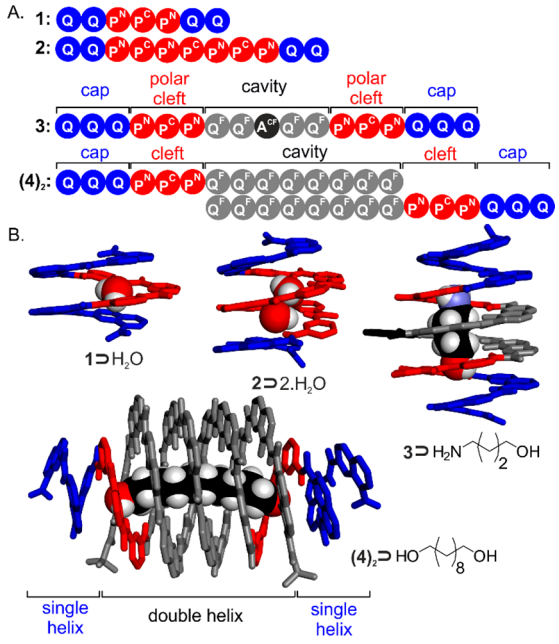

Figure 3. (A) Sequences of first generation capsules (**1** and **2**) and of second generation capsules (**3** and **4**). Capsules **1**, **2**, and **3** consist of a unimolecular strand, whereas capsule **4** self-assembles into an antiparallel double helix. (B) Crystal structures of host−guest complexes: **1**⊃H_2O, **2**⊃2H_2O, **3**⊃4-aminobutanol, and (**4**)$_2$⊃1,10-decanediol. Capsules are shown as tubes with their units color coded as in Figure 2. Guest molecules are shown as CPK models.

first capsule consisted in a short sequence of seven units combining three kinds of aromatic monomers, P^N, P^C, and Q (Figure 2B): sequence **1** consists of a central tripyridine carboxamide $P^NP^CP^N$ flanked at each end by a Q_2 dimer. The latter serve as end-caps of the polar cavity generated by the central segment which binds to a single water molecule through hydrogen bonds both in the solid state and in solution. Indeed, Q units encode for high strand curvature, crystal structures show that their inner rim coincides with a penta-aza 15-crown-5 and molecules as small as water are too large to escape through the narrow channel of Q_n oligomers.[16] The crystal structure of the **1**⊃H_2O complex shown in Figure 3B confirms the seclusion of the guest by the host. Upon increasing the number of pyridine rings in the central segment to seven (capsule **2**), the cavity becomes large enough to host two water molecules.[17] The crystal structure of **2**⊃2H_2O is shown in Figure 3B.

By extension of prototypes **1** and **2**, a second generation helical capsule was developed. Each extremity of sequence **3** consists of a quinoline trimer (Q_3) as an end-cap and of a polar segment ($P^NP^CP^N$) that can hydrogen bond to a polar hydroxyl or amine function. The central segment is composed of wider Q^F and A^F monomers that generate a channel large enough to accommodate an *n*-alkane. The 17 units of **3** eventually fold in a unimolecular helix that selectively binds complementary guests such as 1,4-butanediol or 4-amino-1-butanol with binding constants of the order of 10^3 L·mol^{-1} in chloroform (Figure 3B).[18] In contrast, 1,5-pentanediol is too long and does not fit in the cavity of **3** in any detectable level. Nevertheless, one could design a complementary receptor upon increasing the number of Q^F units in the center of the sequence. This very principle was exploited in sequence **4** that contains only one Q_3 end-cap and whose long $(Q^F)_8$ segment has a strong propensity to self-assemble into an antiparallel double helix. Double helical dimer (**4**)$_2$ thus has two terminal end-caps, two polar segments and a central segment comprised of 2 × 8 Q^F units. It recognizes selectively 1,10-decanediol (Figure 3B).[19] In summary, not only helical shapes but also the recognition of simple guests may be designed with a good level of predictability. Predictability was also used to a good advantage by Flood et al. to produce a capsule selective to chloride[20] and by Dong et al., who described a potassium selective container.[15]

4. ENCAPSULATION OF CHIRAL ORGANIC ACIDS

The next capsule generation was intended to recognize polar and chiral organic molecules with the idea to take advantage of the inherent chirality of the helical host to discriminate

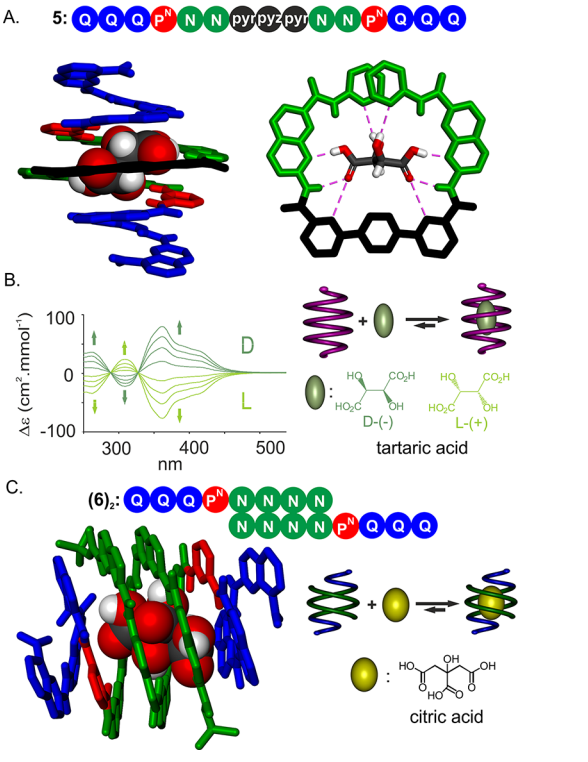

Figure 4. (A) Sequence of a third generation capsule for the recognition of tartaric acid (top). Side view of the crystal structure of the *P*-**5**⊃D-tartaric acid complex. Top view of the central segment of the complex showing hydrogen bonds between the host and guest (purple dashed lines). (B) Circular dichroism monitoring of the titration of capsule **5** by D- (dark green) or L- (light green) tartaric acid. (C) Sequence **6** and its association in antiparallel double helix (**6**)$_2$ (top) and crystal structure of the (**6**)$_2$⊃citric acid complex.

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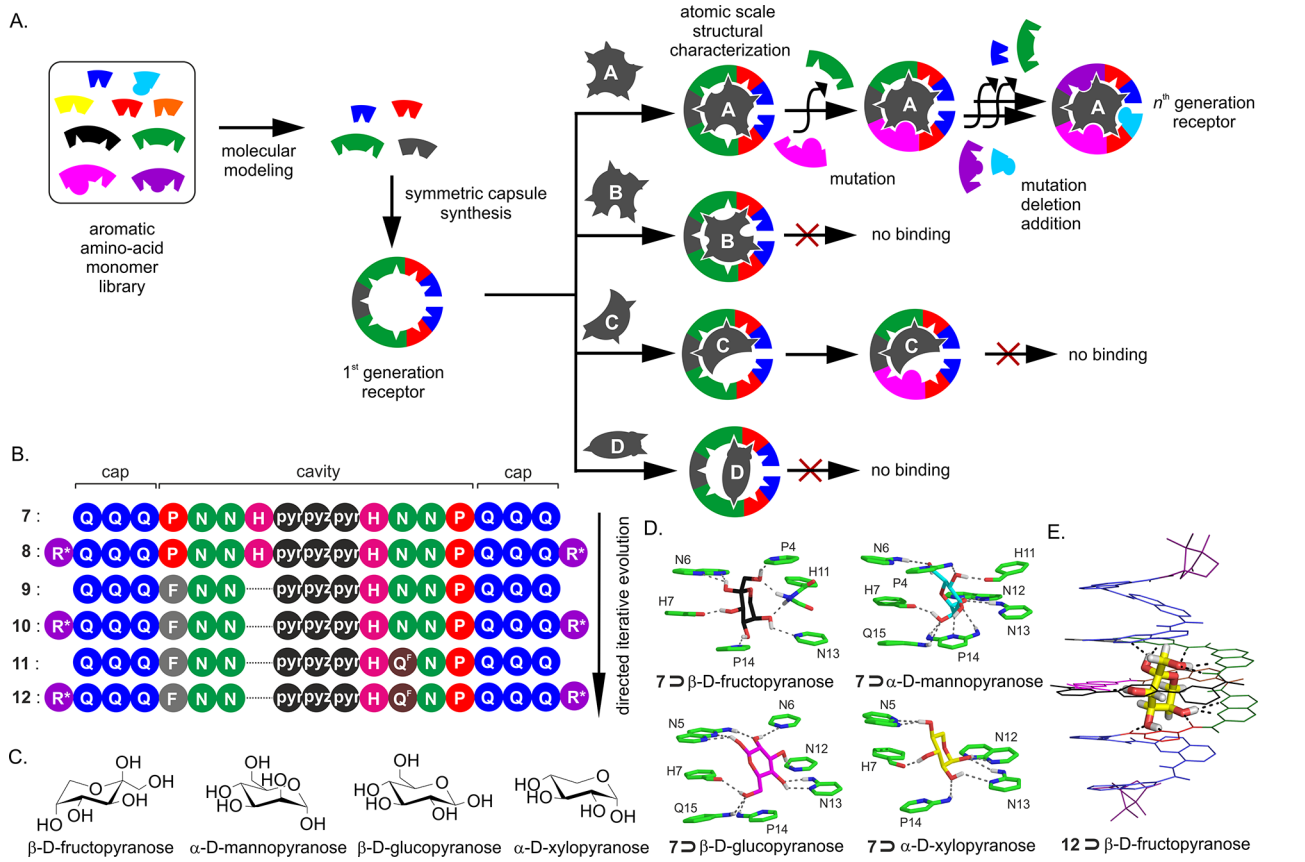

Figure 5. (A) Schematic representation of the structure-based iterative evolution of a foldamer sequence using a "negative design" strategy that consists in implementing mutations, additions and deletions in order to exclude the association with some guests while preserving the association with an initial guest. (B) Alignment of sequences produced during the iterative evolution of sequence **7** into sequence **12**, a highly selective host for *β*-fructopyranose. (C) Formulas of monosaccharide guests for which a host–guest complex structure with a foldamer host was elucidated by X-ray crystallography. (D) Detailed view of crystal structures of host–guest complexes of sequence **7** with *β*-fructopyranose, *α*-mannopyranose, *β*-glucopyranose, and *α*-xylopyranose. Only the heterocycles hydrogen bonded to the guest are shown along with their letter code and their position in the sequence. (E) Structure of the complex between sequence **12** and *β*-fructopyranose determined by NMR.

enantiomers of the guest. In this new design, the Q^F units used in the previous generation were replaced by naphthyridines, noted N, in order to make the space occupied by fluorine atoms available to the guest and thus enlarge the cavity volume. This replacement also made available an *ortho*-aminopyridine motif that can hydrogen bond to carboxylic acid functions. Sequence **5** is thus composed of two helical cones $Q_3P^NN_2$ connected by a central pyr-pyz-pyr diacid unit that codes for a large diameter (Figure 4A). This sequence showed a large affinity (K_a as high as 10^6 L·mol^{-1}) and selectivity for tartaric acid.[21] Moreover, tartaric acid encapsulation proved to be completely diastereoselective: the D-tartaric acid enantiomer is recognized quantitatively (i.e., as far as NMR can detect) by the right-handed (*P*) helix. Due to the dynamic nature of the helical conformation, *P* and *M* conformers can interconvert and the equilibrium is shifted toward one or the other helix sense upon adding one or the other tartaric acid enantiomer (Figure 4B).[22] As for earlier designs, we anticipated that deleting one Q_3 end-cap at one end of sequence **5** along with an increase of the length of the naphthyridine segment would generate a self-assembled double helical capsule. Indeed, sequence **6** forms a double helix $(\mathbf{6})_2$ whose cavity is large enough to host a citric acid molecule (crystal structure in Figure 4C).[23]

As shown in Figure 4, tartaric and citric acid binding is driven by hydrogen bonding. Yet binding was found to be strong enough to occur in the presence of polar and protic solvents that compete for hydrogen bonding with the guests. For example, citric acid binding exceeds 1000 L·mol^{-1} in 9:1 acetone/methanol (v/v).[23] Tartaric acid binding is effective in pure methanol (2000 L·mol^{-1}) and even observed in water (20 L·mol^{-1}).[24] These latter measurements entailed the synthesis of water-soluble capsules, i.e., sequences in which the isobutoxy chains of **3** are replaced by 3-amino-propyloxy chains. The availability of these new building blocks and the observation of binding in water open up the prospect to develop probes selective for biologically relevant analytes. One can speculate that aromatic monomers that would display hydrophobic groups at the inner rim of the helix could tightly and selectively bind hydrophobic guests.

5. ENCAPSULATION OF SACCHARIDES, ITERATIVE EVOLUTION, AND NEGATIVE DESIGN

In order to target more complex guests such as saccharides (polyhydroxylated molecules that do not differ much from each other (Figure 5C)), a novel receptor design strategy was necessary. As shown above, molecular recognition properties may be predicted to a certain extent, yet the ab initio design of a synthetic host for a complex guest remains beyond the reach of current design capabilities: advanced and specific computational tools are much needed. However, it is possible to predict the volume of a foldamer cavity, the number and nature of

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hydrogen bond donors and acceptors that point toward the cavity as well as its chiral nature, to propose that a sequence such as **7** (Figure 5B) has potential to recognize monosaccharides, as was validated experimentally.[25] To transform this first principle design into a very selective receptor of a particular sugar, we then took advantage of (i) the ability to obtain accurate structural information through crystallographic and solution studies (Figure 5D); (ii) the inherent modularity of an oligoamide sequence, for which variants can be synthesized with minimal changes to the synthetic plan; and (iii) the original concept of "negative design". Starting from an initial host–guest complex with a given saccharide, this concept consists in not trying to enhance binding with the starting saccharide but instead in modifying the sequence of the host in order to prevent the binding of any other guest while preserving the interactions responsible of the initial association (Figure 5A). In practice, this first entailed the deletion of one monomer H of sequence **8** to produce sequence **9** in the next iteration. A deletion causes a quite drastic reduction of cavity size. Other changes were far more subtle as they consisted in introducing exocyclic fluorine atoms in place of endocyclic nitrogen atoms to create small bulges in the capsule cavity. For example a P unit was mutated into an F unit when going from **8** to **9**, and an N unit was mutated into a Q^F unit when going from **10** to **11**. Using this approach, a few iterations allowed us to make sequence **7** evolve into sequence **12** that possesses an unmatched selectivity and an almost perfect complementarity for *β*-D-fructopyranose (Figure 5E).[24] This strategy was validated a second time through the successful iterative evolution of a sequence that selectively binds to tartaric acid (Figure 4A) into a sequence that selectively recognizes malic acid, a guest that differs from tartaric acid by a single oxygen atom and the absolute configuration of a stereogenic center.[26] In this case, about ten iterations were necessary to revert the initial tartaric vs malic acid selectivity from over 100:1 to less than 1:100. Thus, the combination of first principle design, guest screening structural elucidation and structure-based improvements proved able to meet challenging objectives.

6. METAL ASSISTED BINDING AND METAL HYDRATE RECOGNITION

The inner rims of the helical sequences shown in Figures 3–5 possess multiple endocyclic nitrogen atoms. This may hint at the possibility to bind metal ions at these sites, either because metal recognition is the aim, or as a means to assist the binding of another guest within the capsule cavity through coordination to the metal when its coordination sphere is not saturated by the helix wall (Figure 6A,B). In fact, the presence of the amide protons next to the endocyclic nitrogen atoms make it difficult to achieve tight direct metal binding. However, a suitably designed pyz–pyr–pyz ligand can provide a well-defined anchor point to sequester a metal ion in the capsule cavity (Figure 6B).[27,15] The conformation of the ligand differs in the presence and in the absence of metal, and metal binding gives rise to a rearrangement of the capsule folding similar to some helix-linear strand transitions (Figure 6).[28] We found that some metal ions like Cu^+ and Ag^+ may effectively coordinate to pyz-pyr-pyz via first coordination sphere interactions and therefore assist the binding of another, organic, guest (Figure 6D).[27a] Surprisingly, metal ions such as Mg^{2+}, Ca^{2+}, and Ba^{2+} are bound as hydrates through second coordination sphere interactions, thus behaving like polar polyhydroxylated guest similar to saccharides (Figure 6E).[27b] The inner walls of *meta*-

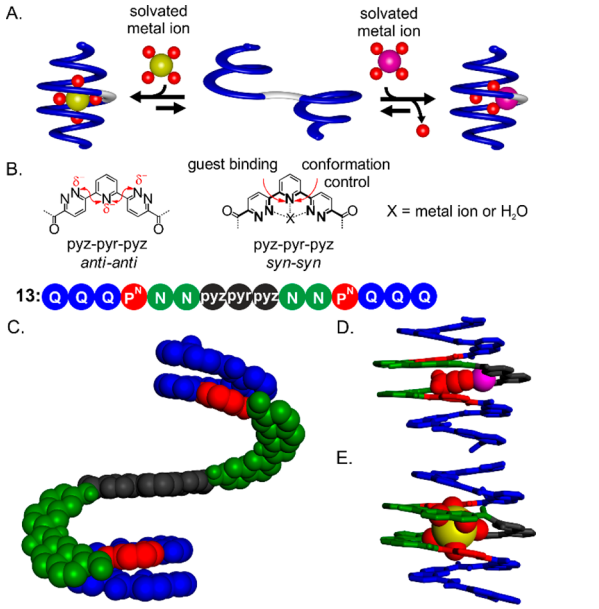

Figure 6. (A) Schematic representation of metal-induced folding modes of a helical-capsule: second-sphere coordination (left) and first-sphere coordination (right). (B) Preferred conformations of pyz–pyr–pyz (left) in the free form and in the presence of a guest (right), and sequence **13**. Solid state structures of (C) sequence **13** in the absence of metal, (D) **13**-Cu^{2+} with a molecule of acetonitrile (red) acting as a ligand for the copper (magenta), and (E) **13**-Ca^{2+}. The calcium (yellow) is surrounded by seven water molecules (red balls) in its first coordination sphere, with the foldamer playing the role of a second coordination sphere.

ethynylpyridinyl helices have also been used advantageously by Abe and Inouye to facilitate alkyl glucoside binding assisted by Cu^{2+} coordination.[29]

7. DYNAMIC ASPECTS OF ENCAPSULATION

Foldamer architectures are self-organized and stabilized by noncovalent interactions. They are thus relatively dynamic. This aspect enriches their solution behavior and makes their study a fascinating endeavor. For example, helix handedness inversion and chiral guest capture and release occur at very different time scales, the former being much slower than the latter. This allowed us to observe that the two enantiomers of a guest form diastereomeric complexes with a host having a given handedness at similar rates, before helix handedness inversion has time to occur. What distinguishes the complexes is the release rates of the two guests. The most stable disatereomeric complex is longer lived. Thus, chiral guests do not distinguish helix handedness from the outside, i.e., upon entering the host, but only from the inside, i.e., by having different times of residence in the host's cavity (Figure 7A). This means that the prevailing diastereoselective interactions occur inside the helix cavity.

It was also possible to demonstrate that the overall length of an aromatic oligoamide sequence influences the rate of capture and release of a chiral guest (tartaric acid in this case) because helix length influences the overall helix stability even when the binding site remains unchanged.[21] These observations were easy to make because the time scales of guest binding and release and of helix handedness inversion range from second to minutes or hours, which are convenient laboratory time scales. It is possible however to combine helices with curved sheet

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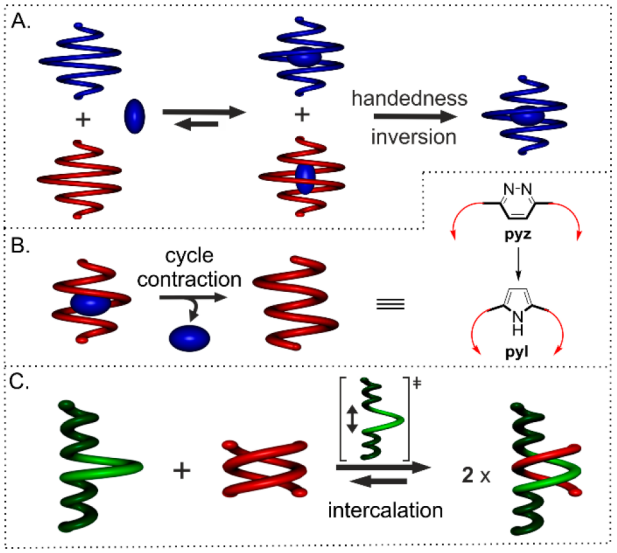

Figure 7. (A) Schematic representation of the encapsulation of an enantiomerically pure guest molecule by a racemic mixture of helices (*P* helices are shown in blue and *M* helices in red). Two complexes are initially obtained that constitute a pair of supramolecular diastereoisomers. At equilibrium, after handedness inversion of *M* helices induced by the guest, only the *P* complex is observed. (B) Schematic representation of the chemical transformation of a foldamer backbone leading to a change of cavity size and to substrate release. (C) Schematic representation of the intercalation of a single strand from a double helix into a single helical capsule that possesses a reduced diameter at both extremities. The outcome is the extension of the green strand and the increase of the cavity volume of the bimolecular host.

architectures to produce capsule-like objects that possess a permanent window through which a guest may go in and out. In this case, binding and release rates are fast on the NMR time scale.[30]

As another dynamic aspect of foldamer based encapsulation, we demonstrated the possibility of an "in situ" modification of a foldamer skeleton to elicit a conformational change that results in a significant change of the thermodynamic guest binding parameters (e.g., substrate release). Specifically, the ring contraction of a central pyridazine unit (Figure 4A) in a pyrrole was implemented using chemical and electrochemical methods (Figure 7B).[31] Aromatic foldamer structures can also be modified in situ in a reversible manner using light.[20,32]

As a last example in this non exhaustive overview of dynamic aspects of foldamer capsules, it was shown that self-assembly allows for the postsynthetic modification of the cavity volume of a helical container without altering its sequence. Thus, a short helical strand may be designed to specifically intercalate into the central segment of a unimolecular capsule, causing the extension of the latter like the extension of a spring, and therefore a significant increase of the cavity volume (Figure 7C).[33] The process is driven by the fact that the dissociation of a single homomeric duplex allows for the formation of two heteromeric duplexes. The dimerization constant of the former thus competes with the square of the association constant of the latter.

8. CONCLUSION

Considerable progress has been made in the know-how of aromatic amino acid monomer synthesis and their assembly into ever longer oligoamide sequences, as well as in the understanding of molecular recognition properties of helical molecular capsules. The results summarized here demonstrate the viability of an ab initio approach to abiotic receptors taking advantage of the modular nature of oligomeric sequences, their synthetic accessibility and, in the case of aromatic oligoamides, their propensity to grow into crystals suitable for X-ray crystallographic structural analysis. A desirable extension to facilitate receptor design is the development of dedicated molecular modeling tools to orient strategic choices during iterative design. The chemical synthesis of these capsules is rich and complex and its presentation would deserve a separate article. Current solution phase methods will eventually be replaced by more efficient solid phase methodologies that may be automated to reach even longer sequences to encapsulate larger and more complex guests and to accelerate iterative improvements of the foldamer recognition properties. Architectures other than the helical capsules can be considered as Figure 1 illustrates. Cone-shaped helices may for example allow for the recognition of a subcomponent of a very large molecule such as a saccharide covalently bound to the surface of a molecule. Other developments concern the possible usages of these selective receptors, e.g., as carriers, or as sensors when molecular recognition is coupled to the emission of a signal such as fluorescence. There are thus multiple prospects ahead.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: y.ferrand@iecb.u-bordeaux.fr.
*E-mail: ivan.huc@cup.lmu.de.

ORCID

Yann Ferrand: 0000-0002-6552-6914
Ivan Huc: 0000-0001-7036-9696

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Yann Ferrand is a CNRS researcher and a group leader at the Institute of Chemistry and Biology of Membranes and Nano-objects of the University of Bordeaux (France). He was appointed as a CNRS research associate in 2007. He studied chemistry at the University of Rennes (France) where he received his PhD degree in 2005. Then, he worked as a postdoc in the School of Chemistry of the University of Bristol (United Kingdom) from 2005 until 2007. His research focuses on the design and synthesis of synthetic macromolecules (e.g., foldamers) for the recognition of complex molecular targets and their use as sensors.

Ivan Huc is a full Professor at the Department of Pharmacy of the Ludwig-Maximilians-Universität in Munich (Germany). Prior to his appointment at LMU he was a group leader, as CNRS researcher then as research director, at the European Institute of Chemistry and Biology in Bordeaux, France, from 1998 until 2017. He studied chemistry at the Ecole Normale Supérieure (ENS) in Paris, France and obtained his doctorate from the Univ. of Paris VI in 1994 for work performed at the ENS and at MIT in Cambridge, MA. He then did a postdoc and worked as a research associate at the University of Strasbourg from 1995 until 1998. His group focuses on the design,

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synthesis and characterization of aromatic foldamers and their applications including pharmacological aspects.

REFERENCES

(1) Anfinsen, C. B. Principles that govern the folding of protein chains. *Science* **1973**, *181*, 223−230.

(2) Watson, J. D.; Crick, F. H. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* **1953**, *171*, 737−738.

(3) Guichard, G.; Huc, I. Synthetic foldamers. *Chem. Commun.* **2011**, *47*, 5933−5941.

(4) Gellman, S. H. Foldamers: a manifesto. *Acc. Chem. Res.* **1998**, *31*, 173−180.

(5) (a) Huc, I. Aromatic oligoamide foldamers. *Eur. J. Org. Chem.* **2004**, *2004*, 17−29. (b) Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. Aromatic amide foldamers: structures, properties, and functions. *Chem. Rev.* **2012**, *112*, 5271−5316.

(6) Wipff, G.; Kollman, P. A.; Lehn, J. M. Macrocyclic receptor chemistry: experimental and theoretical studies on molecular recognition. *J. Mol. Struct.: THEOCHEM* **1983**, *93*, 153−165.

(7) Lützen, A. Self-assembled molecular capsules - even more than nano-sized reaction vessels. *Angew. Chem., Int. Ed.* **2005**, *44*, 1000−1002.

(8) (a) Berl, V.; Krische, M. J.; Huc, I.; Lehn, J.-M.; Schmutz, M. Template-induced and molecular recognition directed hierarchical generation of supramolecular assemblies from molecular strands. *Chem. - Eur. J.* **2000**, *6*, 1938−1946. (b) Chang, K.-J.; Kang, B.-N.; Lee, M.-H.; Jeong, K.-S. Oligoindole-based foldamers with a helical conformation induced by chloride. *J. Am. Chem. Soc.* **2005**, *127*, 12214−12215. (c) Inouye, M.; Waki, M.; Abe, H. Saccharide-dependent induction of chiral helicity in achiral synthetic hydrogen-bonding oligomers. *J. Am. Chem. Soc.* **2004**, *126*, 2022−2027. (d) Meudtner, R. M.; Hecht, S. Helicity inversion in responsive foldamers induced by achiral halide ion guests. *Angew. Chem., Int. Ed.* **2008**, *47*, 4926−4930. (e) Juwarker, H.; Lenhardt, J. M.; Pham, D. M.; Craig, S. L. 1,2,3-Triazole CH···Cl^- Contacts guide Anion Binding and Concomitant Folding in 1,4-Diaryl Triazole Oligomers. *Angew. Chem., Int. Ed.* **2008**, *47*, 3740−3743. (f) Hua, Y.; Ramabhadran, R. O.; Karty, J. A.; Raghavachari, K.; Flood, A. H. Two levels of conformational pre-organization consolidate strong CH hydrogen bonds in chloride−triazolophane complexes. *Chem. Commun.* **2011**, *47*, 5979−5981. (g) Wang, Y.; Xiang, J.; Jiang, H. Halide-guided oligo(aryl-triazole-amide)s foldamers: receptors for multiple halide ions. *Chem. - Eur. J.* **2011**, *17*, 613−619.

(9) (a) Prince, R. B.; Barnes, S. A.; Moore, J. S. Foldamer-based molecular recognition. *J. Am. Chem. Soc.* **2000**, *122*, 2758−2762. (b) Hou, J.-L.; Shao, X.-B.; Chen, G.-J.; Zhou, Y.-X.; Jiang, X.-K.; Li, Z.-T. Hydrogen bonded oligohydrazide foldamers and their recognition for saccharides. *J. Am. Chem. Soc.* **2004**, *126*, 12386−12394.

(10) (a) Tanatani, A.; Hughes, T. S.; Moore, J. S. Foldamers as dynamic receptors: probing the mechanism of molecular association between helical oligomers and rodlike ligands. *Angew. Chem., Int. Ed.* **2002**, *41*, 325−328. (b) Gan, Q.; Wang, X.; Kauffmann, B.; Rosu, F.; Ferrand, Y.; Huc, I. Translation of rod-like template sequences into homochiral assemblies of stacked helical oligomers. *Nat. Nanotechnol.* **2017**, *12*, 447−452.

(11) Garric, J.; Léger, J.-M.; Huc, I. Molecular apple peels. *Angew. Chem., Int. Ed.* **2005**, *44*, 1954−1958.

(12) Abramyan, A. M.; Liu, Z.; Pophristic, V. Mechanistic and dynamic insights into ligand encapsulation by helical arylamide foldamers. *Phys. Chem. Chem. Phys.* **2014**, *16*, 20406−20410.

(13) Singleton, M. L.; Castellucci, N.; Massip, S.; Kauffmann, B.; Ferrand, Y.; Huc, I. Synthesis of 1,8-diazaanthracenes as building blocks for internally functionalized aromatic oligoamide foldamers. *J. Org. Chem.* **2014**, *79*, 2115−2122.

(14) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. Helicity coding: programmed molecular self-organization of achiral nonbiological strands into multiturn helical superstructures: synthesis and characterization of alternating pyridine−pyrimidine oligomers. *Chem. - Eur. J.* **1999**, *5*, 3471−3481.

(15) Wang, W.; Zhang, C.; Qi, S.; Deng, X.; Yang, B.; Liu, J.; Dong, Z. A switchable helical capsule for encapsulation and release of potassium ion. *J. Org. Chem.* **2018**, *83*, 1898−1902.

(16) Jiang, H.; Léger, J.-M.; Huc, I. Aromatic δ-peptides. *J. Am. Chem. Soc.* **2003**, *125*, 3448−3449.

(17) Garric, J.; Léger, J.-M.; Huc, I. Encapsulation of small polar guests in molecular apple peels. *Chem. - Eur. J.* **2007**, *13*, 8454−8462.

(18) Bao, C.; Kauffmann, B.; Gan, Q.; Srinivas, K.; Jiang, H.; Huc, I. Converting sequences of aromatic amino acid monomers into functional three-dimensional structures: second-generation helical capsules. *Angew. Chem., Int. Ed.* **2008**, *47*, 4153−4156.

(19) Bao, C.; Gan, Q.; Kauffmann, B.; Jiang, H.; Huc, I. A self-assembled foldamer capsule: combining single and double helical segments in one aromatic amide sequence. *Chem. - Eur. J.* **2009**, *15*, 11530−11536.

(20) Hua, Y.; Liu, Y.; Chen, C.-H.; Flood, A. H. Hydrophobic collapse of foldamer capsules drives picomolar-level chloride binding in aqueous acetonitrile solutions. *J. Am. Chem. Soc.* **2013**, *135*, 14401−14412.

(21) Ferrand, Y.; Kendhale, A. M.; Kauffmann, B.; Grélard, A.; Marie, C.; Blot, V.; Pipelier, M.; Dubreuil, D.; Huc, I. Diastereoselective encapsulation of tartaric acid by a helical aromatic oligoamide. *J. Am. Chem. Soc.* **2010**, *132*, 7858−7859.

(22) Ferrand, Y.; Chandramouli, N.; Kendhale, A. M.; Aube, C.; Kauffmann, B.; Grélard, A.; Laguerre, M.; Dubreuil, D.; Huc, I. Long-range effects on the capture and release of a chiral guest by a helical molecular capsule. *J. Am. Chem. Soc.* **2012**, *134*, 11282−11288.

(23) Chandramouli, N.; Ferrand, Y.; Kauffmann, B.; Huc, I. Citric acid encapsulation by a double helical foldamer in competitive solvents. *Chem. Commun.* **2016**, *52*, 3939−3942.

(24) Chandramouli, N.; El-Behairy, M. F.; Lautrette, G.; Ferrand, Y.; Huc, I. Polar solvent effects on tartaric acid binding by aromatic oligoamide foldamer capsules. *Org. Biomol. Chem.* **2016**, *14*, 2466−2384.

(25) Chandramouli, N.; Ferrand, Y.; Lautrette, G.; Kauffmann, B.; Mackereth, C. D.; Laguerre, M.; Dubreuil, D.; Huc, I. Iterative design of a helically folded aromatic oligoamide sequence for the selective encapsulation of fructose. *Nat. Chem.* **2015**, *7*, 334−341.

(26) Lautrette, G.; Wicher, B.; Kauffmann, B.; Ferrand, Y.; Huc, I. Iterative evolution of an abiotic foldamer sequence for the recognition of guest molecules with atomic precision. *J. Am. Chem. Soc.* **2016**, *138*, 10314−10322.

(27) (a) Horeau, M.; Lautrette, G.; Wicher, B.; Blot, V.; Lebreton, J.; Pipelier, M.; Dubreuil, D.; Ferrand, Y.; Huc, I. Metal-coordination-assisted folding and guest binding in helical aromatic oligoamide molecular capsules. *Angew. Chem., Int. Ed.* **2017**, *56*, 6823−6827. (b) Mateus, P.; Wicher, B.; Ferrand, Y.; Huc, I. Alkali and alkaline earth metal ion binding by a foldamer capsule: selective recognition of magnesium hydrate. *Chem. Commun.* **2017**, *53*, 9300−9303.

(28) Barboiu, M.; Stadler, A.-M.; Lehn, J.-M. Controlled folding, motional, and constitutional dynamic processes of polyheterocyclic molecular strands. *Angew. Chem., Int. Ed.* **2016**, *55*, 4130−4154.

(29) Takashima, S.; Abe, H.; Inouye, M. Copper(II)/phenanthroline-mediated CD-enhancement and chiral memory effect on a meta-ethynylpyridine oligomer. *Chem. Commun.* **2012**, *48*, 3330−3302.

(30) Lamouroux, A.; Sebaoun, L.; Wicher, B.; Kauffmann, B.; Ferrand, Y.; Maurizot, V.; Huc, I. Controlling dipole orientation through curvature: aromatic foldamer bent β-sheets and helix−sheet−helix architectures. *J. Am. Chem. Soc.* **2017**, *139*, 14668−14675.

(31) Lautrette, G.; Aube, C.; Ferrand, Y.; Pipelier, M.; Blot, V.; Thobie, C.; Kauffmann, B.; Dubreuil, D.; Huc, I. Tuning the guest-binding ability of a helically folded capsule by in situ modification of the aromatic oligoamide backbone. *Chem. - Eur. J.* **2014**, *20*, 1547−1553.

(32) Steinwand, S.; Yu, Z.; Hecht, S.; Wachtveitl, J. Ultrafast dynamics of photoisomerization and subsequent unfolding of an oligoazobenzene foldamer. *J. Am. Chem. Soc.* **2016**, *138*, 12997−13005.

DOI: 10.1021/acs.accounts.8b00075
Acc. Chem. Res. 2018, 51, 970−977

(33) Singleton, M. L.; Pirotte, G.; Kauffmann, B.; Ferrand, Y.; Huc, I. Increasing the size of an aromatic helical foldamer cavity by strand intercalation. *Angew. Chem., Int. Ed.* **2014**, *53*, 13140−13144.

DOI: 10.1021/acs.accounts.8b00075
Acc. Chem. Res. 2018, 51, 970−977