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HIGHLIGHT

Synthetic foldamers†

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Foldamers are artificial folded molecular architectures inspired by the structures and functions of biopolymers. This highlight focuses on important developments concerning foldamers produced by chemical synthesis and on the perspectives that these new self-organized molecular scaffolds offer. Progress in the field has led to synthetic objects that resemble small proteins in terms of size and complexity yet that may not contain any α-amino acids. Foldamers have introduced new tools and concepts to develop biologically active substances, synthetic receptors and novel materials.

Folding is the process nature has selected to control the conformation of its molecular machinery and carry out unsurpassed chemical functions such as enzyme catalysis, information storage and duplication in nucleic acids, as well as energy capture and conversion. Nature uses a very limited set of building blocks—*e.g.* twenty amino acids in proteins and four nucleobases in DNA—with specific abilities to impart well-defined folds. However, these building blocks emerged not only because they are well suited, but also because they complied with evolutionary constraints, in particular the initial obligation to be within a few steps of prebiotic chemicals. In contrast, chemists can make molecules that escape evolutionary pressure. Over the years, they have worked to expand the registry of structures and functions of folded biopolymers through the use of non-natural building blocks, or through the arrangement of natural building blocks into non-natural sequences. This broad ensemble of "*artificial folded molecular architectures*" has been defined as "*foldamers*".[1] Foldamers are produced in a diverse range of contexts: from folded oligomers synthesized stepwise and structured synthetic polymers to artificial nucleic acids or protein sequences produced by directed evolution methods. Nevertheless, they all belong to a common effort to elicit the properties of biopolymers in artificial systems. It is worth stressing here the usefulness of a well defined term ("foldamer") in uniting approaches rooted in different fields of chemistry.[2]

A number of factors have contributed to the current momentum of foldamer

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research. The first is the desire to eventually achieve chemical functions matching those of nature. Other factors came with technical developments, for example the increasing popularity of molecular biology tools in chemistry laboratories and the fact that biopolymers are a level of complexity that chemists can now routinely address. Another important factor is the understanding that chemical backbones prepared by stepwise synthesis and remote from those of biopolymers also adopt well-defined folded conformations. Over the last fifteen years, the field has rapidly expanded away from early efforts in peptidomimetics and nucleic acid analogues towards a systematic exploration of folding in a diverse range of structures. This highlight focuses on these "synthetic foldamers"—a large open ground for chemists' creativity. The various sections below present snapshots of important developments, emphasize concepts, and evoke perspectives throughout the text.

Diverse backbones and less diverse structures

Synthetic foldamers are far too numerous for them all to be presented or even simply mentioned here.[3] Before the term "foldamer" was coined, many nucleic acid analogues and peptide analogues had already been successfully designed to mimic the structures and, potentially, the biological properties of their natural counterparts. Typical examples are peptide nucleic acids (PNAs)[4] and *N*-substituted oligoglycines (peptoids, Fig. 1a).[5] Seminal contributions by Seebach and Gellman *et al.* in 1996 reported the unanticipated ability of β-peptides to adopt helical conformations that are more stable than those of α-peptides (Fig. 1c).[6] This triggered a comprehensive exploration of β-peptides having one, two or even more cyclic or non-cyclic side chains, placed on the α or the β carbon, with various absolute and relative stereochemical arrangements. A large collection of β-amino acids are now commercially available. There followed investigations of the higher γ and δ homologues, and of the replacement of the amide bonds by, for example, ureas, hydrazide or hydroxyamide functions.[7]

The design and development of these "biotic" foldamers has been guided by analogy to biopolymers with which they share comparable folding principles. In contrast, "abiotic" foldamers with backbones and folding modes different from those of biopolymers have also emerged. Many of them are aromatic rich sequences: oligo-phenylene-ethynylenes;[8] sequences of alternating aromatic electron donors and acceptors;[9] aryl-oligomers in particular those based on aza-heterocycles (pyridines, pyrimidines, pyridazines, *etc.*);[10] aromatic tertiary amide, imide or urea oligomers; and aromatic oligoamides (Fig. 1).[11] The latter have been rapidly growing as an important class of foldamers due to a number of remarkable properties, including the high stability of their folded structures, the predictability of their folding modes, their propensity to crystallize (giving access to structural data at atomic resolution), and their relative ease of synthesis. In parallel, a vast ensemble of helical polymers[12] has emerged over the years and shed new light on the rules of handedness control in organic helices. Polyisocyanates, polyacetylenes, polyguanidines, polymethacrylates, polyisocyanides, polysilanes and poly(quinoxalin-2,3-diyl)s are some of the major classes of helical polymers. Altogether, this variety of backbones has shifted our perception of proteins and nucleic acids, which now stand as a few families of folding polymers among many others. There is no doubt that foldamer diversity will further increase even though designing, synthesising, and structurally characterizing a new foldamer can all prove very challenging.

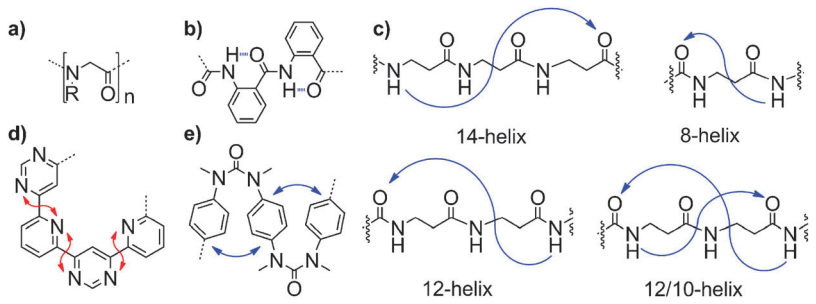

Fig. 1 Examples of foldamer backbones. (a) Peptoids. (b) Aromatic oligoamides. (c) β-Peptides. (d) Aza-aromatic oligomers. (e) Tertiary aromatic ureas. Red and blue arrows represent intramolecular repulsive and attractive interactions, respectively.

That such diverse backbones have a propensity to fold reflects the fact that folding may be governed by many internal or external parameters. Internal factors consist of the overall shape and rigidity of the molecule and its ability to establish attractive or repulsive intramolecular non-covalent interactions. These factors depend on monomer size and shape, linkage orientation, rotational restrictions, local intramolecular interactions, and interactions between monomers remote from each other in a sequence. A common feature to all foldamers is a certain degree of backbone rigidity that limits the entropic cost of adopting an organized conformation. External factors include solvent effects such as hydrophobic effects, aggregation (dimerization-induced folding), host–guest complexation (guest-induced folding), and contacts with interfaces (folding on surfaces).

The folded secondary structures of foldamers, however, are much less diverse than the variety of backbones would allow one to expect. The main motifs found in biopolymers (helices, linear strands, turns and sheets) appear to be ubiquitous and prevail in most foldamer families, as theoretical investigations predict.[13] The helix in particular is by far the most frequently characterized object. A possible explanation for the abundance of helices and the apparent rareness of sheet-like structures is that the latter tend to aggregate and precipitate when isolated, and require stabilization within a tertiary fold to remain in solution.[14] Therefore, it could be that sheets are not less common, but less tractable and still awaiting to be discovered.

Nevertheless, foldamers that display folding motifs unknown or uncommon in biopolymers do exist. These include pillar-like architectures (stacks of aromatic rings),[9] knots,[15] spiral like-objects ('tail-biters'),[16] or non-canonical helices.[17] It is worth noting that almost all backbones at the origin of these peculiar folds consist of monomers comprised of both aromatic and aliphatic elements, a combination

that is worth exploring further. Another appealing line of investigation for the future is the folding of oligomers having non-linear topologies such as cyclic[18] and branched structures. Folding dendrons have been reported,[19] but high-generation dendritic foldamers have yet to be seen.

Hybrid sequences combine different monomers

To a large extent, the foldamers discussed in the previous section consist of homogeneous backbones, *i.e.* oligomers assembled exclusively from monomers of a single class. In contrast to biopolymers, however, foldamer synthesis is not limited to homogenous oligomers. Unsuspected sectors of the structural and functional space may be reached in the foldamer world by creating heterogeneous backbones that combine more than one type of constituent units. This concept has been pioneered for aliphatic oligoamides.[20] Hybrid oligomers composed of two different aliphatic ω-amino acids have been investigated in a systematic way and found to adopt new secondary structures akin to those formed by the corresponding homogeneous sequences. A large ensemble of helical conformations has been characterized at atomic resolution for heterogeneous peptides having periodic motifs at the dimer level (αβ, αγ, βγ repeats), trimer level (ααβ, αββ repeats), tetramer level (αααβ repeats) or heptamer level (ααβαααβ, ααβαβαβ repeats).[21] Like 3_{10}- and α-helices, these heterogeneous helices (Fig. 2) are stabilized by 1 ← 4 or 1 ← 5 H-bonding patterns and display similar overall shapes. However, they may subtly differ in their residue distribution, thus allowing the arrangement of functional groups at the helix surface to be finely tuned from one scaffold to another. Another level of structural diversity may be added by considering heterochiral sequences.[22] Alternatively, distinct isosteric monomers sometimes give rise to almost identical secondary structures. Such monomers can be combined to generate heterogeneous backbones, isostructural to cognate homogeneous sequences, yet endowed with different physicochemical properties (*e.g.* water solubility, overall polarity). Representative examples include hybrid analogues of helical β- and γ-peptides incorporating hydrazido and urea elements, respectively.[23]

By analogy to block copolymers, a heterogeneous backbone is also produced when two oligomeric segments made of distinct constituent units are covalently joined (*e.g.* helical chimeric (αβ + α) peptides, Fig. 4c).[25] Intrinsic structural and functional properties of individual foldamer segments are then locally conserved. The regular alternation of different segments may give rise to non-periodic motifs. For example, sheets can be formed upon alternating turn and strand segments made of distinct backbones (*e.g.* nucleation of an α-peptide hairpin structure by a β-peptide reverse turn).[26] As presented in the next section, a promising extension of this concept is to combine segments of different nature in a single tertiary structure, *e.g.* a protein.[27,28]

The availability of 'biotic' and 'abiotic' building blocks, endowed with completely different folding principles, has allowed the preparation of hybrid foldamers distinct both from known synthetic homooligomers and from biopolymers. Several examples of hybrid oligoamides made of alternating aliphatic (α-amino acid residues) and aromatic amino acid units and showing unconventional periodic structures have been disclosed.[29] A high degree of sequence sophistication has been achieved with heterogeneous aromatic oligoamides coding for complex structural information and leading to unprecedented topologies. The helical capsule shown in Fig. 5, assembled from four different constituent units, is a representative achievement.[30] Whereas central residues code for a large helix diameter, the terminal ones serve as caps for the cavity. Judicious design of these elements allows the volume and the shape of the internal cavity to be modulated at will. Overall, approaches based on heterogeneous backbones reflect the many chemical solutions available to expand the diversity of folded systems with a finite number of monomeric units. The remarkable arrays of complementary and divergent folds uncovered by combining two (or more) monomeric units are now gradually making their way through applications.

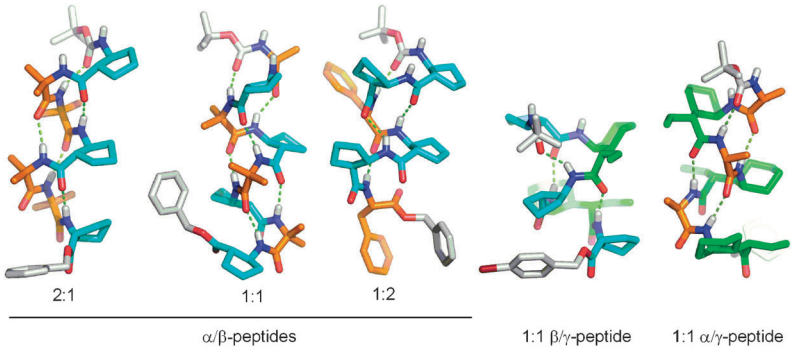

Fig. 2 Representative crystal structures of helical heterogeneous peptide backbones composed of various ratios of α-, β- and/or γ-amino acid residues. Carbon atoms of α-, β- and γ-amino acid residues are shown in orange, cyan and green, respectively.[20,24]

Towards synthetic foldamer proteins

As the two previous sections summarize, foldamer research has produced a vast and varied number of artificial backbones able to adopt well-defined folded secondary structures. In contrast, progress towards artificial tertiary and quaternary folds has been much slower: they are more difficult to synthesize, more difficult to characterize and, above all, there are not many obvious design rules to arrange several secondary folded modules in space. Nevertheless, biopolymers require the size and complexity of tertiary and quaternary structures to carry out most of their functions. Little can be achieved with an isolated helix. This line of development thus constitutes a major challenge and an essential objective for the years to come.

Among artificial tertiary (unimolecular) and quaternary (multi-molecular) structures characterized until now, the helix bundle emerges as a dominant motif. It is a rare pattern of protein folding that has been understood to such an extent that it can be engineered with good predictability. The relative ease of crystallization of

helix bundles and the subsequent availability of structural information at atomic resolution greatly contributed to this development. Thus, a number of examples of artificial α-peptidic helix bundles have been reported,[31] some of them equipped with metal centres or cofactors (*e.g.* quinones, porphyrins) for catalysis and light harvesting. This previous knowledge of α-peptidic helix bundles served to design the first bundles comprised of β-amino acids. Gellman *et al.* described three- and four-helix bundles based on 33-residue long sequences of αβ-peptides (Fig. 3a).[32] Schepartz *et al.* reported an eight-helix bundle based on a 12-residue β-peptide (Fig. 3b), which paves the way to the design of fully β-proteins.[33] Bundle-like structures of helical aromatic oligoamide foldamers have also been constructed (Fig. 3f).[34] In this case, a covalent tether imposing a short distance between two helical modules allowed structural information to be gathered about contacts between helices even before strong interactions between them were designed.

Besides helix bundles, a variety of multi-stranded structures more remote from biopolymers have been described. These include β-sheet structures and double stranded tapes combining both aromatic and aliphatic units.[14,35] Important progress has also been made in the design of organic (*i.e.* metal free) artificial multiple helices[36] as, for example, duplexes based on amidine–carboxylate recognition (Fig. 3d),[37a] and triple (Fig. 3c)[37b] and quadruple (Fig. 3e)[37c] helices of aromatic oligoamides.

Efforts toward artificial protein-like folding are also made in polymer chemistry. For example, "sticky" monomers have been used to promote the collapse of soluble individual polymer chains into discrete nanoparticles.[38] In such an approach, monomers remain randomly arranged in the polymer sequence as a result of a co-polymerization process. Nevertheless, the concept is promising and appears to be amenable to great sophistication.

The examples above illustrate the dichotomy between biotic and abiotic foldamers. The merits of the latter lie in their ability to display original structures that are often beyond the reach of natural polymers. In contrast, the benefits of the former arise from their resemblance of, and compatibility with, biopolymers. For example, the high degree of similitude between α- and β-peptide helices and the possibility to transpose design concepts from one series to its homologue are illustrated by the replacement of an α-helix by a similar β-peptide helix within a tertiary chemokine structure without loss of activity. This is despite the fact that the β-peptide helix has a different handedness and dipole orientation than its α-helix model.[27] A related example is the introduction of a β-amino acid based β-turn in the structure of ribonuclease A.[28] These two reports amount to a top-down approach to protein-sized foldamers. Their starting point is a known protein structure in which artificial modules ("molecular prostheses"[28]) are introduced. They combine both synthetic efforts to deliver non-natural sequences and molecular biology methods to produce protein fragments. In this respect, they bridge synthetic foldamers with bio-foldamers produced exclusively by molecular biology tools, *e.g.* using directed evolution, protein shuffling and protein design technologies. Other bridges between synthetic and bio-foldamers are expected in the future as molecular biology tools become increasingly compatible with non-natural building blocks. Indeed, the genetic encoding of non-natural α-amino acids and their introduction into protein sequences is rapidly expanding: α-hydroxy-acids, peptoids, and β-amino acids have also been successfully subjected to ribosomal synthesis.[39] A genetically encoded β-protein may thus be foreseen.

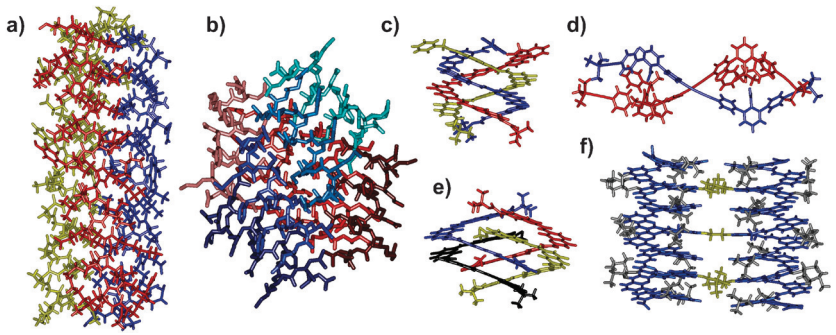

Fig. 3 Crystal structures (all shown at the same scale) of: (a) a three-helix bundle of a helical αβ-peptide.[32] (b) An eight-helix bundle of a dodecameric β-peptide.[33] (c) An aromatic oligoamide triple helix.[37b] (d) A double helical duplex based on carboxylate–amidine recognition.[37a] (e) An aromatic oligoamide quadruple helix.[37c] (f) Two covalently bound aromatic oligoamide single helices.[34]

Biological applications

Advances in synthetic folded architectures together with the finding that oligomeric backbones may retain folding in water have opened avenues toward selective foldamer–biomolecule interactions and foldamers that interfere with biological functions. Foldamers combine features that make them good candidates to target biopolymers: a medium size (M_w = 500–5000 g mol^{-1}, see Fig. 3) with large contact areas well suited to bind the extended surfaces buried at protein–protein interfaces; folding predictability, tunability and diversity (in size, shape, side chain appendages); and an expected resistance to proteolysis. Because they are structurally well-defined, foldamers can be used as scaffolds to precisely project binding motifs in space (Fig. 4a).

Early work focused on the design of cationic amphipathic foldamers which mimicked host-defense peptides and were capable of selectively disrupting bacterial membranes. Potent antimicrobials based on β-peptide 14-, 12- and 10,12-helical folds,[40] peptoid polyproline type I-like helix,[41] oligourea and oligo(urea/amide) helices[23b] have been described. In many cases, amphipathic sequences have been designed assuming idealized helical structures, by sequestration of cationic residues on one face of the helix.

An emerging and challenging foldamer application is to mimic folded peptide segments found in proteins, in particular the α-helix. Indeed, the use of short α-peptide fragments to target biomacromolecules (*e.g.* proteins) is limited because they generally do not maintain their secondary structure once extracted from the protein context. This leads to an

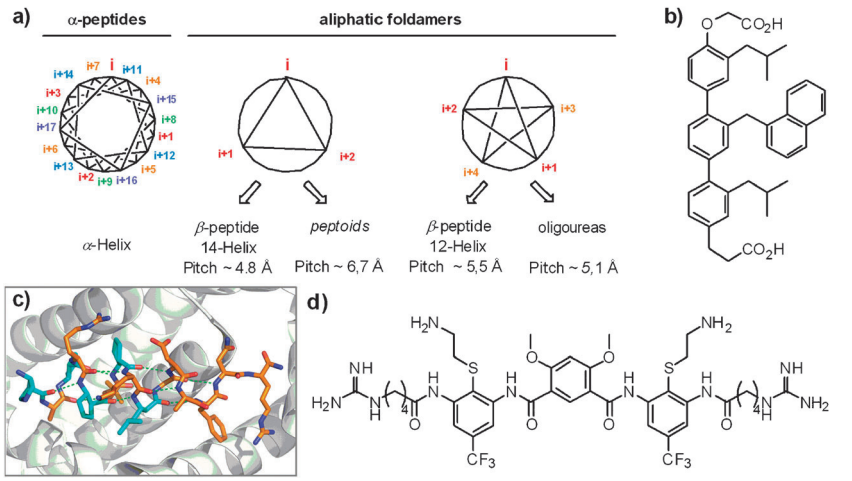

Fig. 4 (a) Helical wheel representation of various foldamer helices illustrating the spatial orientation of side chains in comparison to the α-helix. (b) Terphenyl-based antagonists of Bcl-xL. (c) Crystal structure of a chimeric (α/β + α) peptide foldamer bound to the BH3 domain of the proapoptotic Bcl-xL protein.[46] Carbon atoms of β-amino acid residues are shown in cyan. (d) A conformationally restrained arylamide foldamer showing antibacterial activity *in vivo*.[49]

increased susceptibility to degradation by circulating enzymes and to the loss of biological function. Stable mimics of protein fragments may thus succeed where peptides often fail. Recently, optimized helical sequences consisting of a judicious combination of α- and β-amino acids, namely the mixed αα βαααβ heptad, have been shown to effectively recapitulate the binding surface of a known α-peptide HIV inhibitor targeting the gp41 central trimeric coiled coil.[42] It is noteworthy that these foldamers were equipotent to the parent α-peptide in cell–cell fusion inhibition assays and in inhibition of HIV-1 infectivity. In addition, they displayed largely improved proteolytic stability. Crystallographic analysis confirmed the formation of the expected six-helix bundle between the α/β-peptide hybrid and the gp41 fragment. This strategy is particularly attractive because the six-helix bundle fusion mechanism is common to a large family of viruses and represents a general target to develop new antiviral agents. Concurrently, significant efforts have been engaged against intracellular targets known to be important in human cancer such as the p53/hDM2 (MDM2) interaction or anti-apoptotic protein Bcl-xL. Salt bridge-stabilized 14-helical β-peptides bearing MDM2 binding residues on one face of the helix have been developed as potent p53 mimetics. Importantly, the cell permeability of these β-peptides was significantly improved, at no cost to MDM2 binding, by installation of diether or hydrocarbon bridges between positions *i* and *i* + 3.[43] The issue of cell permeability and cell internalization of foldamers has been addressed in specific studies.[44]

Bioactivity is by no means restricted to foldamer backbones showing similarity to biopolymers. Aromatic scaffolds such as terphenyls, benzoyl aromatic oligoureas, and oligobenzamides have been introduced and developed as potent inhibitors of protein–protein interactions (Fig. 4b).[45] Side chains appended to these scaffolds can mimic peripheral functionalities of a protein surface as, for example the *i*, *i* + 4, and *i* + 7 residues of an α-helix.

A hurdle when using foldamers as protein secondary structure mimetics resides in faithfully reproducing the spatial arrangement of the side chains found at a protein surface. As an illustration, early attempts to mimic an α-helix of the BH3 domains of BCL-2 proteins using 12- and 14-helical β-peptides or 11-helical αβ-peptides resulted in disappointingly weak binding to Bcl-xL. Much tighter binding was finally achieved after fine tuning using chimeric peptide foldamers consisting of an N-terminal α/β segment and a C-terminal α-peptide segment.[25] The crystal structure of the complex with Bcl-xL reveals that the helical foldamer has the same orientation as the natural BH3 domains. The α/β-segment adopts a 14/15-helical structure with some cyclic β-amino acid residues making contacts with the protein surface (Fig. 4c).[46] Alternatively, screening collections of foldamers without *a priori* structural considerations may represent a viable approach to conciliate biopolymer and foldamer backbones and identify new recognition schemes. This has been achieved for β-peptide combinatorial libraries prepared by the split-and-mix method to optimize MDM2 binders.[47] Similarly, aromatic oligoamide helices that bind to G-quadruplexes have been identified through serendipitous screening.[48]

In light of these promising developments and by virtue of their unique properties, foldamers certainly represent innovative tools in pharmacology. However, it remains to be seen whether foldamers are endowed with necessary features such as favourable pharmacokinetics, low immunogenicity, cell permeability and activities in animal models. In this respect, the finding that facially amphiphilic aromatic oligoamides developed as antibacterial agents were active in an animal model of *S. aureus* infection (Fig. 4d) raises hopes for the development of foldamers as medium sized therapeutics.[49]

Molecular recognition and catalysis

Molecular recognition exploits the spatial organization of arrays of functional groups converging towards a binding site. Early designs of synthetic receptors depended on pre-organizing these functionalities onto rigid molecules such as macro-polycycles. In the last two decades, self-assembly has emerged as a very efficient method to produce large supramolecular containers endowed with molecular recognition properties. Such containers may be based on remarkably simple building blocks and often feature high levels of symmetry. In contrast, nature uses the self-organized folded structures of biopolymers to achieve recognition. By analogy, foldamers have opened new avenues in receptor design.

Recognition may occur at the surface of a foldamer, as illustrated in the previous section, and also within a cavity of its folded structure.[50] An important class of foldamer receptors thus consists of wide helices possessing a cavity (Fig. 5). Pioneering work by Moore *et al.* demonstrated the binding of hydrophobic guests within the cavities of oligo-phenylene-ethynylenes.[51] Contributions by Li and

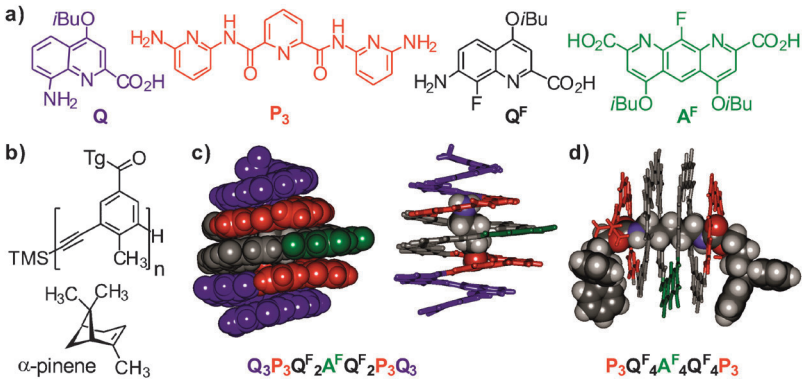

Fig. 5 (a) Examples of aromatic oligoamide foldamer units. (b) Formula of *m*-phenylene ethynylene helical hosts that bind to chiral lipophilic guests such as α-pinene.[51] (c) Color coded crystal structure of a helical capsule based on a sequence of the monomers shown in (a) surrounding a 4-amino-1-butanol guest.[30] (d) Color coded crystal structure of a helix wound around a dumbbell rod-like guest based on a sequence of the monomers shown in (a).[53]

Inouye *et al*. showed that saccharides can be bound into aromatic oligomers.[52] These helical receptors are inherently chiral, which eventually results in efficient discrimination between enantiomeric guests.

The design of binding sites within secondary folded structures—helices—illustrates the fact that foldamers may sometimes go beyond the abilities of biopolymers. Indeed, in proteins and nucleic acids, cavities are formed in tertiary folded structures between helices and sheets, and not within a simple helix. Another foldamer design beyond the reach of biopolymers is a helical capsule in which the helix diameter is larger in the centre than at the ends (Fig. 5c).[30] Such systems illustrate the emergence of new rational codes between the primary sequence, the folded three-dimensional structure, and its properties. Each monomer in a capsule sequence codes for a given helix diameter and carries defined recognition groups that converge towards the cavity. A recent extension of this design concerns helices that wrap around rod-like guests and can slide along them much faster than they dissociate (Fig. 5d), providing an entry to self-assembled molecular machines.[53]

Among the advantages of a receptor based on an oligomeric sequence are the modularity and the lack of, or low, symmetry. Each monomer in a sequence may be replaced by another which is better suited to recognize a particular guest with minimal perturbation to the overall folding. This allows a type of "guided evolution" of a sequence without having to revise the whole synthetic plan after each modification. In the footsteps of α-peptide and oligonucleotide syntheses, methods to design and prepare foldamers are being improved and will eventually give access to longer sequences and to selective receptors for increasingly large and complex guests.

In biopolymers, guest binding often causes a conformational change of the host. A number of foldamers also possess this feature, sometimes to the extent that folding does not occur in the absence of a guest. For example, metal ion-[54] and anion-induced[50] folding generates helicates. Neutral organic molecules or lipid bilayer membranes may also elicit helical folding in otherwise relatively flexible oligomers. The large conformation changes that occur in guest induced folding result in important changes of spectroscopic properties which make these systems suitable candidates to be used as sensors.[55] This perspective has brought "foldamer switching" into the spotlight: controlled transitions between folded and unfolded or differently folded states have been reported,[56] as well as the communication of structural information through organized backbones.[57]

Other perspectives of development of foldamer-based recognition include transport, controlled guest release and, ultimately, enzyme-like catalysis. The latter is of course a long term objective. Nevertheless, a few examples of foldamer-catalysts have been described.[58] Related to this are several reports showing that folding results in remarkable enhancements of foldamer backbone reactivity.[59] Examples of folding-enhanced self-assembly,[60] or the self-selection of foldamer precursors from mixtures[61] may also pave the way towards new generations of self-replicating systems.

Foldamer-based materials

Recent years have witnessed first forays of foldamers into the field of material sciences. The wide range of topologies, and physicochemical properties exhibited by known synthetic foldamers makes exploratory work and possible developments extremely diverse. One focus is the creation, through controlled molecular self-assembly, of materials with morphological features on the nano- or microscale. Several aliphatic and aromatic foldamers have been reported that spontaneously associate into nanofibers and nanospheres.[62] For example, hydrazide-based aromatic foldamers bearing long aliphatic side chains display a dual mode of assembly that leads to vesicles of narrow size distribution in polar solvents and to entangled fibres and gelation in hydrocarbons.[62d] Several 14-helical β-decapeptides consisting of different arrangements of lipophilic and hydrophilic side chains (including non-globally amphiphilic structures) self-assemble into fibres to form lyotropic liquid crystal phases in aqueous solution (Fig. 6a).[62c] Their application as alignment media for extraction of residual dipolar couplings (RDCs) by NMR spectroscopy has been described.[63] Although these early examples do not yet match self-assembled biopolymer nanomaterials in terms of sophistication and programmability, they certainly bring new capabilities. For example, unprecedented molecular architectures at the microscale have been reported for a 12-helical β-peptide composed exclusively of *trans*-(*S*,*S*)-2-aminocyclopentantecarboxylic acid residues.[64] Homogeneous microsized windmill shapes are formed upon peptide exposure to an aqueous environment (Fig. 6b). Remarkably, this self-assembly process is altered at an early stage in the presence of P123 ((ethylene glycol)$_{20}$–(propylene glycol)$_{70}$–ethylene glycol)$_{20}$) micelles, and leads to a dramatic morphological change with the formation of well-defined squared rods. The analogy between the role of P123 in guiding the self-assembly process of the β-peptide and molecular chaperones in protein folding is striking.

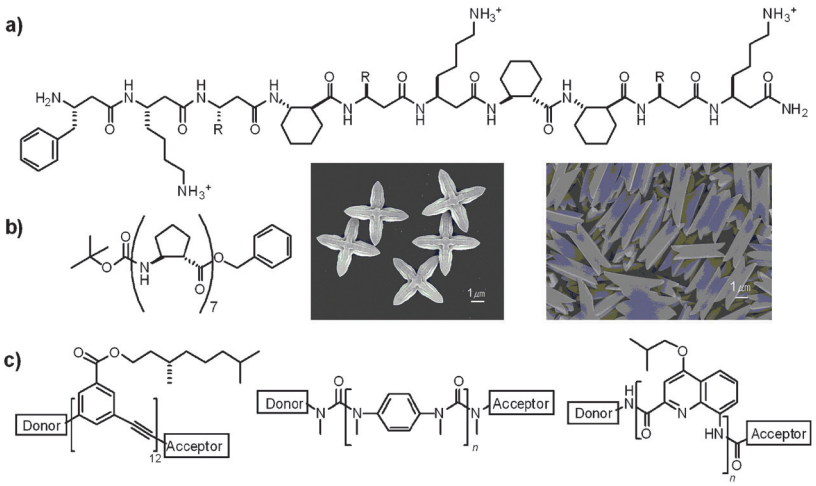

Fig. 6 (a) A 14-helical β-peptide forming lyotropic liquid crystals.[62c] (b) Microscale architectures formed by a 12-helical β-peptide in the presence of water (left view) and/or an aqueous solution of non-anionic surfactant P123 (right view).[64] (c) Examples of donor-bridge-acceptor molecules for photoinduced charge transfer with foldamer bridges.[68]

The control over the positioning of foldamers and their nanostructures relative to a surface is conditional to developing functional materials (*e.g.* photoelectronic active assemblies). Direct deposition onto surfaces essentially relies on non-covalent forces. Analysis by atomic force microscopy of drop-cast films of aromatic rich helical foldamers on mica is consistent with the persistence of superhelical structures at the interface.[62a] More robust covalent grafting of foldamers to surfaces has also been investigated. *m*-Phenylene-ethynylene oligomers covalently attached to high surface area and porous oxides by Rh-catalyzed hydrosilylation were found to retain solvophobically-driven folding properties.[65] The predictability and robustness of secondary structures formed by many foldameric backbones suggest that they can compare favourably with other materials (*e.g.* α-peptides) for the formation of ordered self-assembled monolayers (SAMs). Indeed, globally amphiphilic helical β-peptides bearing an N-terminal thiol group have been shown to form well-organized SAMs on gold surfaces.[66] Interactions between designed foldamers and crystal surfaces have also been studied. An extended aromatic oligoamide projecting an array of parallel carboxylic acid functions has been found to modulate the growth of calcite crystals and to induce new crystal morphologies.[67]

Concurrently, progress has been made in developing and characterizing foldamer-based systems with photoelectronic properties in solution. As opposed to α-peptides which have long been used as models to study charge transfer reactions in proteins, foldamer helices (provided that they are robust enough) give better control over the distance separating the donor and acceptor and over their relative orientation in space. Thus, donor-bridge-acceptor systems featuring *m*-phenylene ethynylene oligomers, oligo(arylureas), and aromatic oligoamides as helical bridges of various lengths have been reported (Fig. 6).[68] In the case of oligo(*m*-phenylene ethynylene) the extent of photoinduced charge separation was found to be dependent on the nature of the solvent which controls the degree of folding of the bridge.

Conclusions

Folding is the approach nature has selected to organize nano-sized molecules in space with atomic precision. Chemists have fully appreciated the value of this lesson. As the number of accomplishments in foldamer chemistry increases, the perspectives and expectations also increase. Foldamers not only promise to eventually match the capabilities of biopolymers, but also pave the way to structures and functions beyond the reach of biopolymers. Molecules consisting of long sequences of diverse monomers offer unsurpassed modularity; monomers may be varied at will without having to reconsider the whole synthetic scheme. The guided evolution of a sequence allows properties to be improved in an iterative and rational fashion; sequences are also amenable to parallel synthesis and screening. Having the optimized automated chemical synthesis of long peptide and nucleotide sequences as a background, there is no doubt that some foldamer families will soon enter a regime of routine engineering and fabrication.

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