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Bioinspired Chemistry Based on Minimalistic Pseudopeptides

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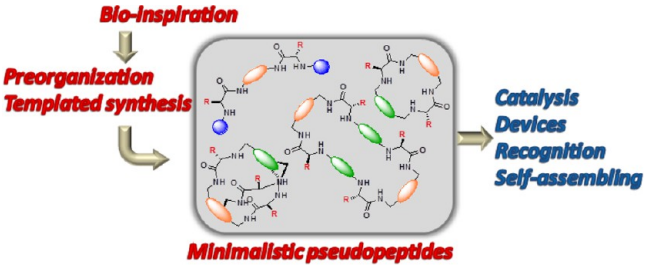
CONSPECTUS



For years researchers have tried to understand the molecular behavior of complex biomolecules through the development of small molecules that can partially mimic their function. Now researchers are implementing the reverse approach: using the structural and mechanistic knowledge obtained from those complex systems to design small molecules with defined properties and for specific applications. One successful strategy for constructing bioinspired, minimalistic molecules is to combine natural building blocks that provide functional elements with abiotic fragments that serve as structural scaffolds. Therefore pseudopeptidic compounds, most of them based on C_2 symmetric structures, represent a unique opportunity to explore and evaluate this approach. Some of these molecules are as simple as two amino acids connected by a diamino spacer.

The results in this Account show how bioinspired minimalistic pseudopeptides can form ordered structures, participate in the recognition and transcription of information events in molecular devices, and catalyze reactions. This strategy allows researchers to design and prepare a variety of open-chain and macrocyclic compounds leading to systems that can self-aggregate to form hierarchically ordered micro- and nanostructures. In addition, small changes in the molecule or external stimuli can regulate the self-aggregation pattern. In the same way, researchers can also tune the molecular movements of simple pseudopeptides through environmental factors, providing a means to control new molecular devices. In addition, some of the prepared model compounds have shown interesting properties in molecular recognition and even as sensors for several targets of interest. Finally we have observed remarkable catalytic activities from these types of molecules, although those results are still far from the efficiency shown by natural peptides. This family of pseudopeptidic compounds offers the opportunity for the more elaborate design of relatively simple abiotic but bioinspired systems that display specific properties. In addition, the results can provide additional information that will increase the molecular understanding of the basic principles that underlie the extraordinary behavior of natural systems.

Introduction

Nature uses a limited number of structural units for constructing complex systems. Noncovalent interactions, selective recognition, self-assembly, and self-association are central for this and for achieving their astonishing functionalities. Not surprisingly, amino acids are one such basic element, having a large functional density and the side chain providing structural variability and information for conformational preferences. Although a limited number of amino acids are used, their combination forming long peptidic chains allows building of an infinite number of structures.[1]

Natural peptides and proteins play different roles as (i) structural elements, (ii) catalytic systems, and (iii) molecular devices for energy, matter, and information transport. To achieve this, natural evolution followed a combinational approach using the unlimited number of amino acid combinations (Figure 1). Some specific arrangements provide an explicit function. Those providing advantages for survival are selected and preserved. Thus, the generation of a precise functional structure usually requires large individual macromolecules, for which, however, activity can be associated with a small specific peptidic fragment.

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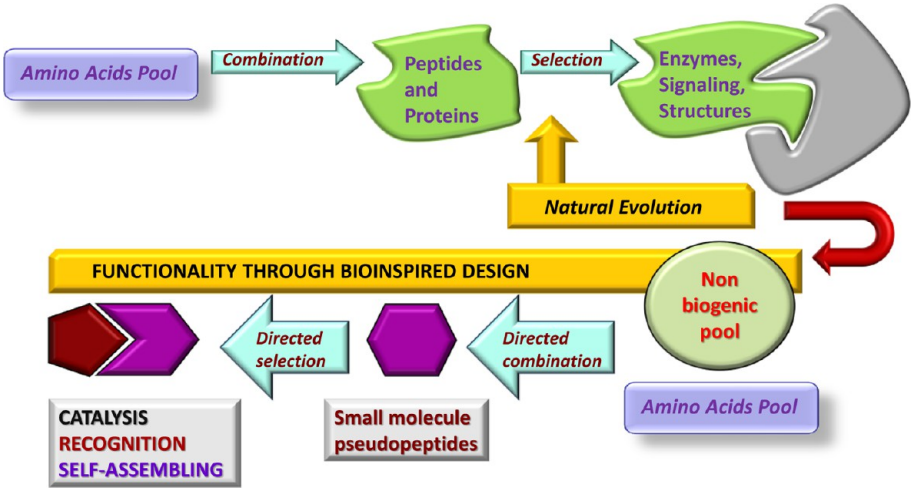


FIGURE 1. Biological and abiotic approaches to functionality.

The building of small model compounds has been used for the understanding of the structural parameters and factors determining the properties of interest in proteins and peptides.[2] Ideally, however, the combination of natural and non-natural components, properly designed using the knowledge gathered from natural systems, could achieve a desired functionality with low molecular weight molecules. The results here presented show how bioinspired minimalistic pseudopeptides are able to form ordered structures, participate in recognition and transcription of information events in molecular devices and display catalytic activity, opening the way for developing abiotic compounds efficiently mimicking properties of natural systems.

C_2 Symmetric Minimalistic Pseudopeptides

Some of the simplest pseudopeptides to be envisaged involve two amino acids attached to a diamino spacer (**I** in Figure 2). Despite their simplicity, changing the spacer, changing the amino acid (R), or functionalizing the amino terminal groups (Y) provides a high level of molecular diversity and sites for supramolecular interactions. Amine and amide functionalities allow for electrostatic and H-bonding interactions, while the spacer, the side chains, and groups attached to the amino functions can be involved in hydrophobic and $\pi-\pi$ interactions or in introducing additional functionalities. The C_2 symmetry facilitates the convergence of functional groups, while their synthetic accessibility enables construction of more elaborated structures (**II**–**V**), including related C_3 systems. Initial reports in the 1990s on the supramolecular chemistry of simple C_2 pseudopeptides reported by Burrows,[3] Kilburn,[4] Hamilton,[5] and others[6] involved in most cases the use of aromatic diamine spacers.[4,6–10] However, we initially focused

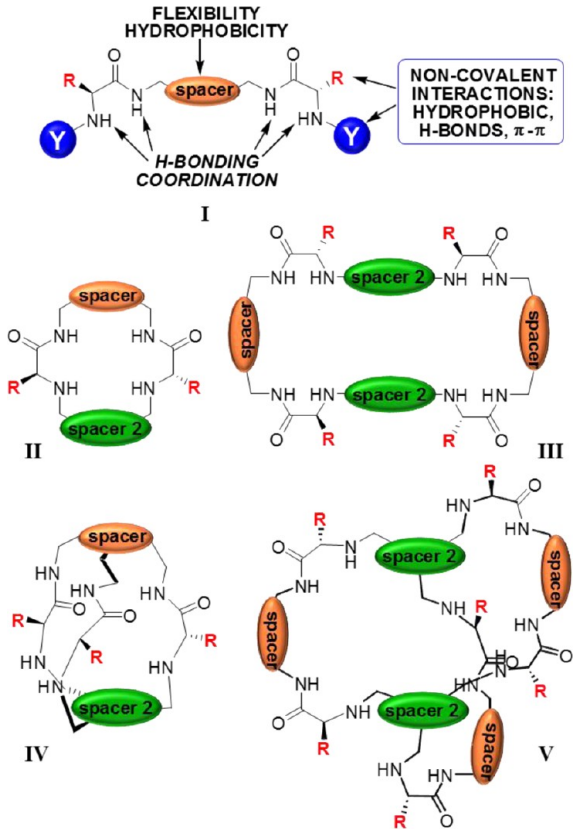


FIGURE 2. Schematic representation of pseudopeptidic structures.

on systems derived from α,ω-alkyldiamines (H_2N-$(CH_2)_n$-NH_2), in order to exploit their conformational flexibility.[11,12]

Open Chain and Macrocyclic Pseudopeptides: The Role of Preorganization

Open-chain C_2 pseudopeptides are efficiently obtained through standard methodologies.[12] Preparation of macrocyclic structures is, however, of particular interest.[13,14] Their

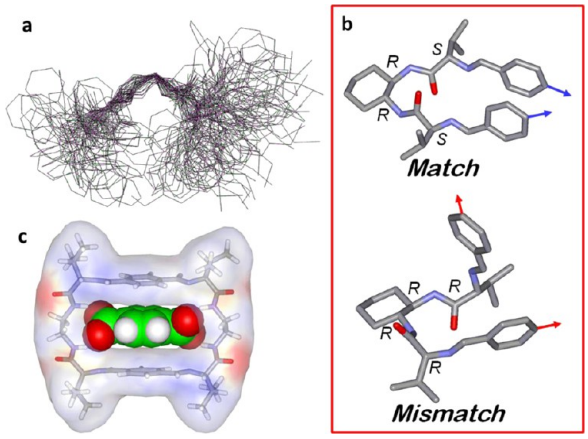


FIGURE 3. Preorganization favoring the cyclization of open-chain C_2 pseudopeptides: (a) conformational; (b) configurational; (c) anion-templated.

decreased conformational freedom can provide a significant level of organization, combining high functional density and directionality. Although macrocyclizations can be complex processes, an appropriate preorganization of the precursors, favoring the approach of both reactive ends, can afford significant improvements.[15] Different preorganization mechanisms have been used for synthetizing macrocycles **II**–**V**. The first one can be defined as *conformational preorganization*. Reaction of open-chain pseudopeptides derived from α,ω-alkyldiamines with *meta*- or *para*-bis(bromomethyl)benzene afforded the corresponding [1 + 1] macrocycles **II** in high yields (60–70%), based on a U-turn preorganization favored by intramolecular H-bonding and solvophobic effects (Figure 3a).[12,16] The combination of chiral centers of appropriate configuration can render a *configurational preorganization*. The synthesis of [2 + 2] macrocycles (**III**) was approached via the reductive amination of an aromatic dialdehyde with an open-chain pseudopeptide (Table 1). The *matched* combination of configurations at the chiral centers afforded excellent results (55–70% isolated yields, Figure 3b), while the *mismatched* combination or the absence of chirality in the spacer hampered the cyclization.[17,18]

Template induced preorganization represents an alternative and successful approach.[19–21] For open-chain intermediates not properly preorganized, preparation of [2 + 2] macrocycles was achieved using anionic templates (Table 1). Tetrabutyl ammonium terephthalate was selected because it perfectly fits inside the macrocyclic cavity of the tetraiminic intermediate (Figure 3c).[22,23] Thus, even macrocycles from systems having a *mismatched* configuration were efficiently prepared,[24] as well as related C_3 pseudopeptidic cages.[25] The participation of kinetic effects is also important,[26,27] and the preparation of different pyridine-derived macrocycles can be favored with the appropriate anion (bromide or chloride).[28]

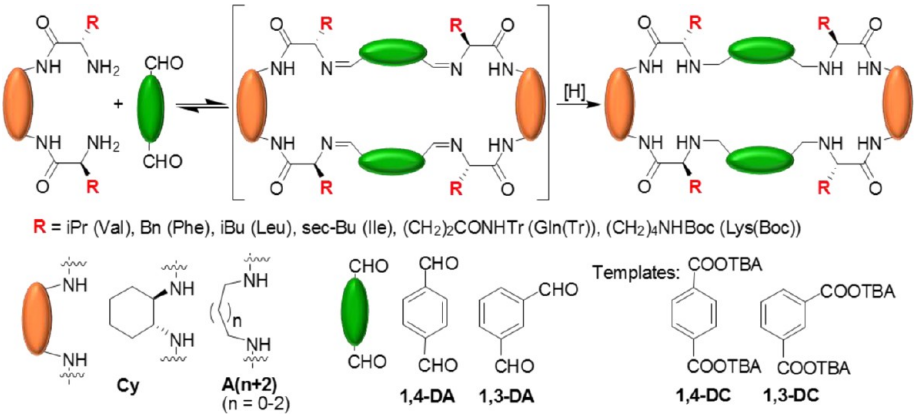
Minimalistic Pseudopeptides for Structured and Stimuli-Responsive Materials

Self-assembly of peptides, proteins, and pseudopeptides is of great biological relevance, abnormal processes being associated with important diseases.[29] In this regard, the proper design of low molecular weight peptides and pseudopeptides has allowed their self-assembling under physiological conditions to form hydrogels with important applications in tissue engineering.[30] Small pseudopeptides can also be organogelators at concentrations below 1%. An amphiphilic design combining polar amino acid derived moieties with long aliphatic chains is excellent for this purpose, lysine-based derivatives being an illustrative example (i.e., **1**, Figure 4).[31] This can be achieved in **I** using long central spacers or attaching long aliphatic tails to the amino groups (gemini amphiphilic pseudopeptides, GAPs).[32] Thus, compound **2** gelates *in situ* in different alcohol/water mixtures: addition of water to a solution of **2** in ethanol instantly forms the gel.[33] Substitution of amine by urea linkages for the tails provides stronger H-bonds, producing organogels with high thermal stability for a variety of solvents that can often be distilled at ambient pressure preserving the gel structure.[34] The gelation behavior of pseudopeptidic gelators can frequently be regulated by external stimuli, that is, devising a selective gel–sol response to Ag^+ or Li^+.[35]

Meta-substituted [1 + 1] macrocyclic derivatives like **3** are excellent organogelators for aromatic solvents and esters, providing complex networks of fibrillar structures. Sometimes, their intrinsic molecular chirality was transferred to the fibers: each enantiomer of **3** provided fibers with the opposite helicity.[36–38]

The morphology and properties of self-assembled structures obtained in the solid state depend on structural parameters but can also be modulated through external stimuli, according to the delicate balance of structural and environmental factors.[39] For [2 + 2] macrocycles **III**, the exact combination of the spacer and the side chain of the amino acid is essential. In **4**, containing a short aliphatic spacer ($-(CH_2)_2-$) and a *meta*-substituted aromatic subunit, the valine derivative ($R = CH(CH_3)_2$) self-assembles into a fibrillar structure, while the phenylalanine derivative ($R = CH_2Ph$) forms vesicles (Figure 5).[40] A dramatic change occurs when acidic instead of neutral conditions are used: only amorphous

TABLE 1. Synthesis of [2 + 2] Macrocycles



pseudopeptide	dialdehyde	template	yield (%)
CyVal	1,4-DA	no	67
CyPhe	1,4-DA	no	55
CyPhe	1,3-DA	no	35
CyLeu	1,4-DA	no	58
CyIle	1,4-DA	no	41
CyGln(Tr)	1,4-DA	no	17
A2Val	1,4-DA	1,4-DC	60
A2Phe	1,4-DA	1,4-DC	65
A3Val	1,4-DA	1,4-DC	30
A3Phe	1,4-DA	1,4-DC	36
A4Val	1,4-DA	1,4-DC	26
A4Phe	1,4-DA	1,4-DC	33
A2Val	1,3-DA	1,3-DC	36
A2Phe	1,3-DA	1,3-DC	30
A2Gln(Tr)	1,4-DA	1,4-DC	31
A2Lys(Boc)	1,4-DA	1,4-DC	40
A2Leu	1,4-DA	1,4-DC	50
A2Ile	1,4-DA	1,4-DC	35
A2Ile	1,3-DA	1,3-DC	26
A3Ile	1,4-DA	1,4-DC	27
Cy(D)Phe	1,4-DA	1,4-DC	50 [2 + 2], 15 [3 + 3]
Cy(D)Val	1,4-DA	1,4-DC	40 [3 + 3], 20 [4 + 4]

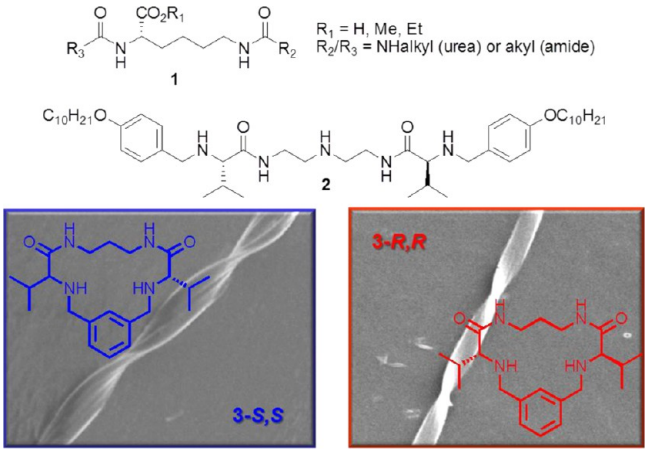


FIGURE 4. Some pseudopeptidic low molecular weight gelators.

materials are produced. However, when the aromatic spacer is *para*-substituted (**5**) only amorphous materials are formed under neutral conditions, but well-defined structures are obtained in acidic media: crystalline for the valine derivative and fibrillar for the phenylalanine derivative (Figure 5).

The modular structure of GAPs allows observation of a broad spectrum of self-assembly (Figure 6).[32] Compounds containing long alkoxyphenyl tails preferentially afford amorphous materials in $CHCl_3$, but fibrillar structures predominate in MeOH/H_2O under neutral or basic conditions. At low pH, the formation of well-defined spherical structures is associated with valine derivatives having three to five methylene groups at the central spacer, which is associated with the need to adopt a perfectly folded structure.

X-ray single crystal analyses provide interesting data, in particular regarding the role of the side chains (Figure 7). The crystal structure for the open-chain compound **6** confirms the presence of a U-turn conformation,[41] and the packing

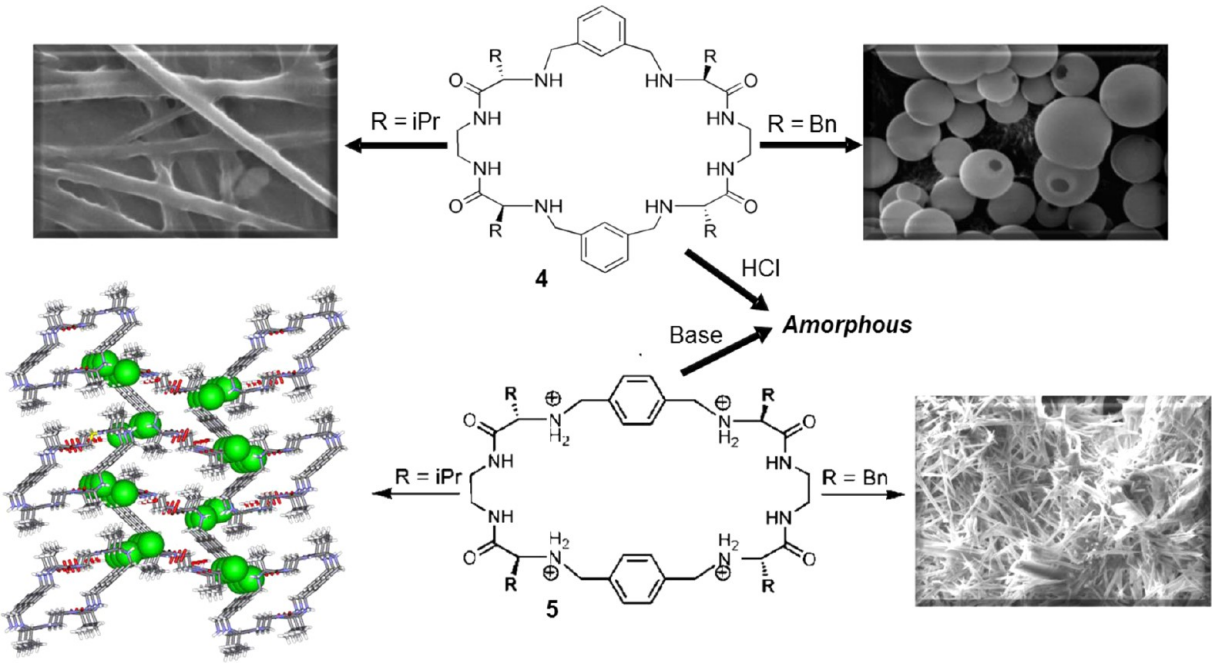


FIGURE 5. Solid state self-assembly of [2 + 2] pseudopeptides.

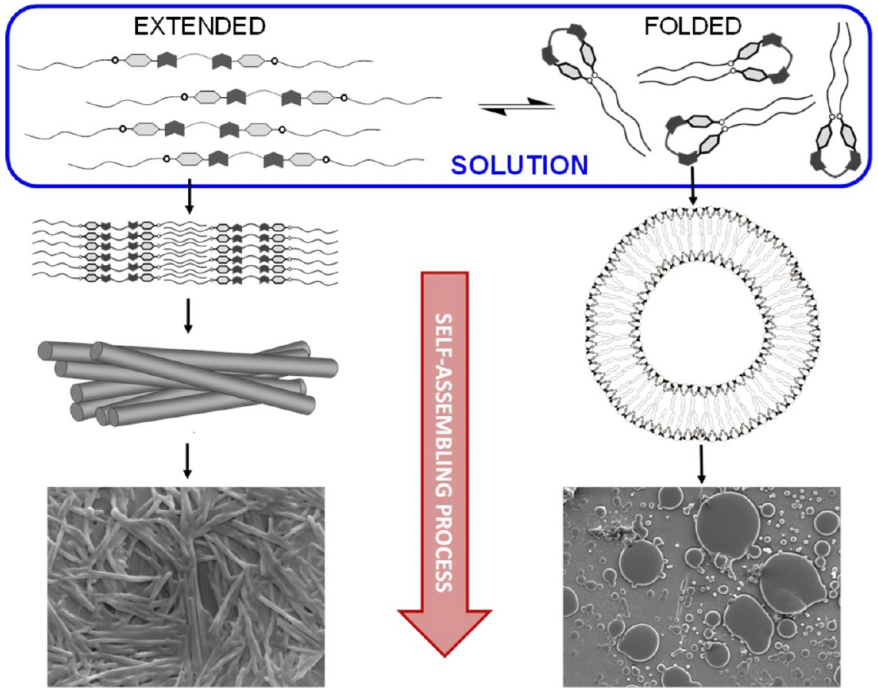


FIGURE 6. Diversity in the self-assembly of GAPs.

reveals intermolecular edge-to-face π–π interactions arranged in such a way that six different molecules, each participating with a single aromatic ring, complete a helical turn, generating well-defined chiral π-nanochannels (Figure 7A). The [2 + 2] macrocycles **5** associate in columnar arrangements through hydrogen bonding,[42] with the intercolumn assembly defined by a *knobs-into-holes* motif between side chains (Figure 7B).

Molecular Devices

Anion Recognition and Transport. Amide and protonated amine groups are appropriate for the interaction with

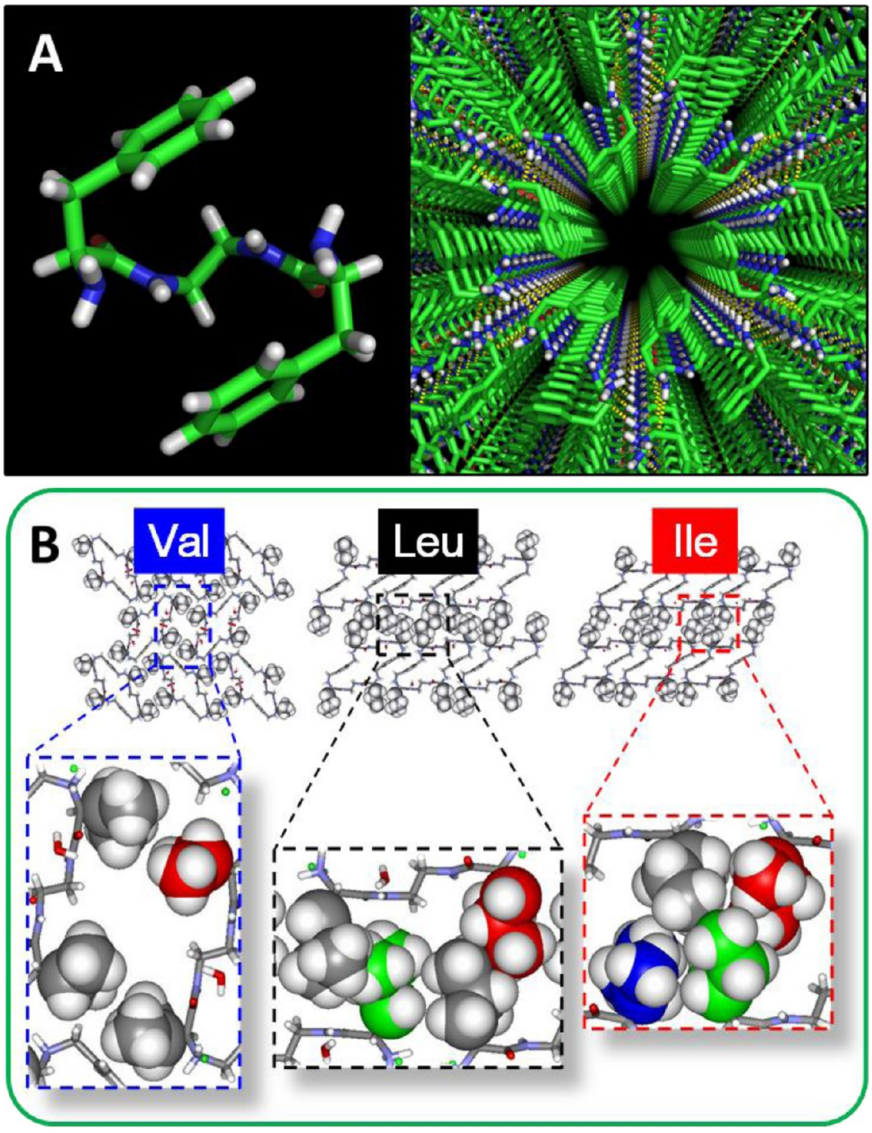


FIGURE 7. Crystallographic structure for (A) pseudopeptide **6** involving the formation of π-channels and (B) pseudopeptide **5** displaying *knobs-into-holes* motifs.

anions. Among halides, chloride is of high biological interest, and pseudopeptidic cages exert selective recognition of chloride.[43] Crystallographic structures show two different patterns displaying strong NH···Cl^- hydrogen bonds. In the first one, each protonated cage interacts with two chloride anions located outside or at the entrance of the cage (Figure 8A). In the second, one chloride anion is located within the cage cavity (Figure 8B). Encapsulation only takes place for phenylalanine derivatives with hexasubstituted aromatic units at the bottom of the cage. These complexes can act as Cl^- transporters through biomembrane models.

Recognition of phosphate-related species and developing artificial RNases and DNases are important targets.[44,45] Efficient interaction with double-stranded DNA was observed using open-chain pseudopeptides containing terminal guanidiniocarbonylpyrrole moieties, and their ratiometric sensing could be achieved using a pyrene-functionalized cationic oligopeptide,[46] allowing their intracellular imaging.[47] In this regard, acridine-derived pseudopeptides **7** and **8** allow the selective recognition and sensing of anions (Figure 9).[48] Protonation of the heterocyclic nitrogen atom contributes to complex formation and is accompanied by an increase in the fluorescence response, with the observed wavelength changing from 420 to 510 nm. Changes upon addition of H_3PO_4 were larger than for other acids. This sensing was selective in the presence of HSO_4^-, acetate, trifluoroacetate or halides, particularly for the macrocyclic derivative.

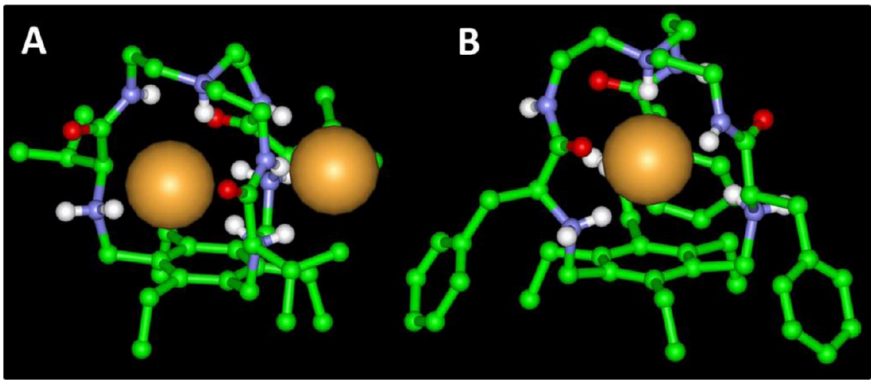


FIGURE 8. Crystal structures of chloride complexes of pseudopeptidic cages.

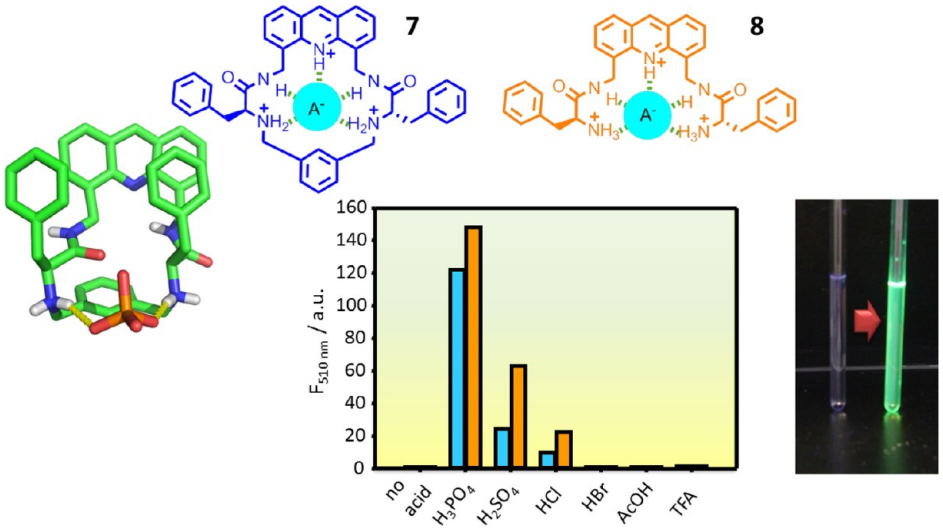


FIGURE 9. Selective sensing of $H_2PO_4^-$ by acridine derivatives. Graph shows the normalized fluorescence intensity at 510 nm for **7** and **8** (10 μM) upon addition of 25 equiv of each acid in $CHCl_3$, $\lambda_{ex} = 357$ nm.

Amino Acid and Peptide Recognition. The incorporation of naphthalene subunits in macrocyclic pseudopeptides like **9** facilitates developing selective fluorescent sensors.[49] This compound interacts selectively with N-Cbz protected amino acids bearing aromatic side chains. NMR and MS studies showed a very dynamic system. Besides the expected electrostatic and H-bonding interactions, the naphthalene ring of the receptor strongly interacts with the aromatic rings at the side chain or the Cbz group of the guest.[50] Both 1:1 and 1:2 host–guest complexes were detected (Figure 10). A small enantiodifferentiation in favor of the amino acid having identical configuration as the receptor was also observed for phenylalanine. Amino acid compositions related to diseases such as PKU (excess of aromatic amino acids) or MUSD (defect of those amino acids) can thus be detected. Larger [2 + 2] macrocycles are able to selectively interact with N-CBz protected dipeptides.[51] Regarding recognition of other organic anions, some pseudopeptides were able to enantiodifferentiate carboxylates by ^{1}H NMR.[52] Other groups have shown how related receptors containing 1,4-diamino-anthracene-9,10-dione fragments can colorimetrically enantiodifferentiate aspartate and malate anions.[53]

Acidity Markers. High sensitivity acidity markers are important targets for biomedical studies, according to the importance of this parameter in normal and abnormal metabolic processes, and fluorescent sensors are ideally suited for this purpose.[54] Compounds like **10** are interesting fluorescent pH sensors as protonation of the amine nitrogen atoms switches on their fluorescence (Figure 11). Structural changes like the length of the spacer modulate the pH value at which switching takes place, allowing a fine-tuning of the pH to be measured. These compounds can be efficiently used as intracellular pH sensors[55] and as fluorescent pH markers in flow cytometry.[56]

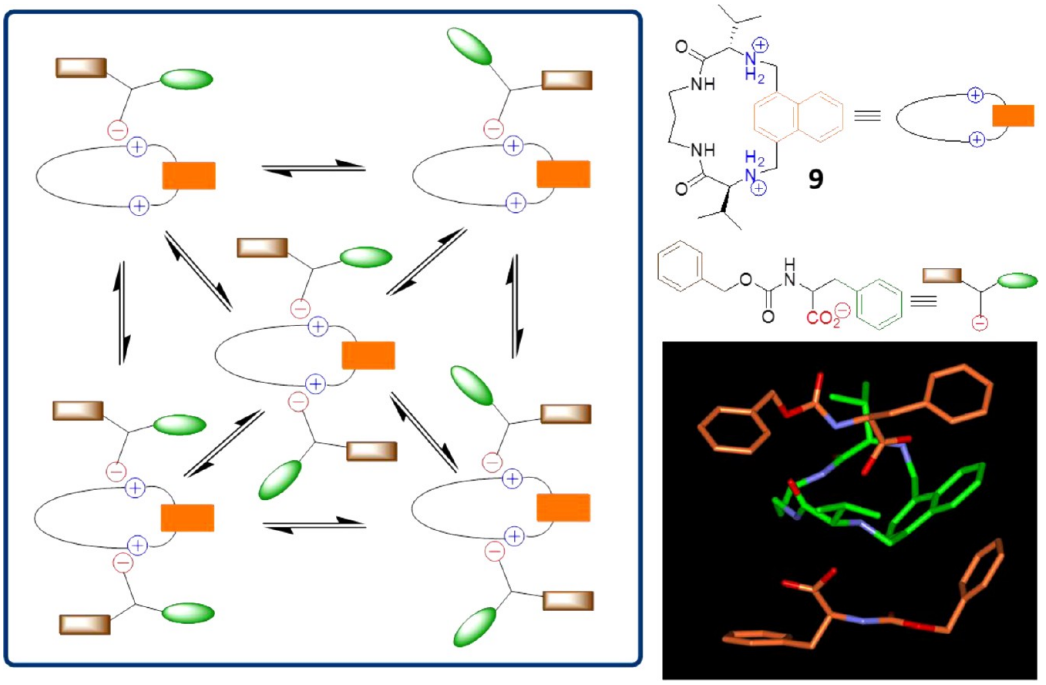


FIGURE 10. Proposed model for the interaction of Cbz protected amino acids with macrocyclic naphthalene pseudopeptides based on NMR data along with the optimized structure for the 2:1 complex.

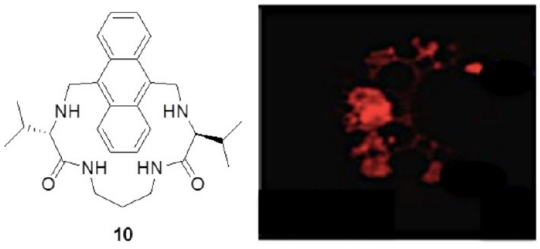


FIGURE 11. Confocal fluorescence image in Raw 264.7 cells obtained using **10** as pH sensor.

Inorganic Cations As Guests. Like in peptides, amino and amido functionalities in pseudopeptides can participate in metal complexation. For compounds **II**, the cavity size seems too small to accommodate coordinated metal cations, except for Ag(I) in some pyridine-derived [1 + 1] macrocycles.[57] However, open-chain precursors **I** are well suited for this purpose, and three different general arrangements can be expected for $(1:1)_n$ stoichiometric complexes (Figure 12), as demonstrated by X-ray crystallographic studies. Compounds with a propylene spacer form, when bisdeprotonated, 1:1 complexes involving three stable chelating rings and an excellent square planar arrangement for metals like Cu(II) or Ni(II) (Figure 12a).[58] For the monodeprotonated ligand derived from valine and an ethylenic spacer, a 2:2 complex with Cu(II) could be isolated (Figure 12b), showing one square planar and one square pyramidal Cu(II) atom. Ligands with longer aliphatic or 1,4-bisamino benzene spacers favor polymeric $(1:1)_x$ structures, as illustrated by the Zn(II) complex shown in Figure 12c.[59]

The side chain of the constituent amino acid also plays an important role.[60] In general, compounds containing aliphatic side chains and lower steric hindrance display higher stability constants, proline derivatives providing the most stable complexes.

Quantum Dots (QDs) as Guests. Because QDs are stabilized in organic media with the help of organic ligands containing long aliphatic chains, GAPs are very appropriate for interacting with them through an interdigitation mechanism of the alkyl chains (Figure 13). This has provided an efficient transfer of QDs from toluene to aqueous solutions.[61] Incorporation of QDs in organogels formed by pseudopeptides represents an interesting mechanism for their stabilization and practical applicability allowing the development of gel-phase NO sensors.[62] With noncommercial core QDs, a clear synergistic effect was observed. The interdigitation mechanism acts as a nucleating mechanism to facilitate gelation, affording fluorescent gels at lower concentrations, providing an increase in the fluorescence intensity of the QD (up to 528%) and its average lifetime (up to 1.7 times).[63] Pseudopeptidic gels containing long aliphatic tails have also been used to control the synthesis of gold nanoparticles.[64]

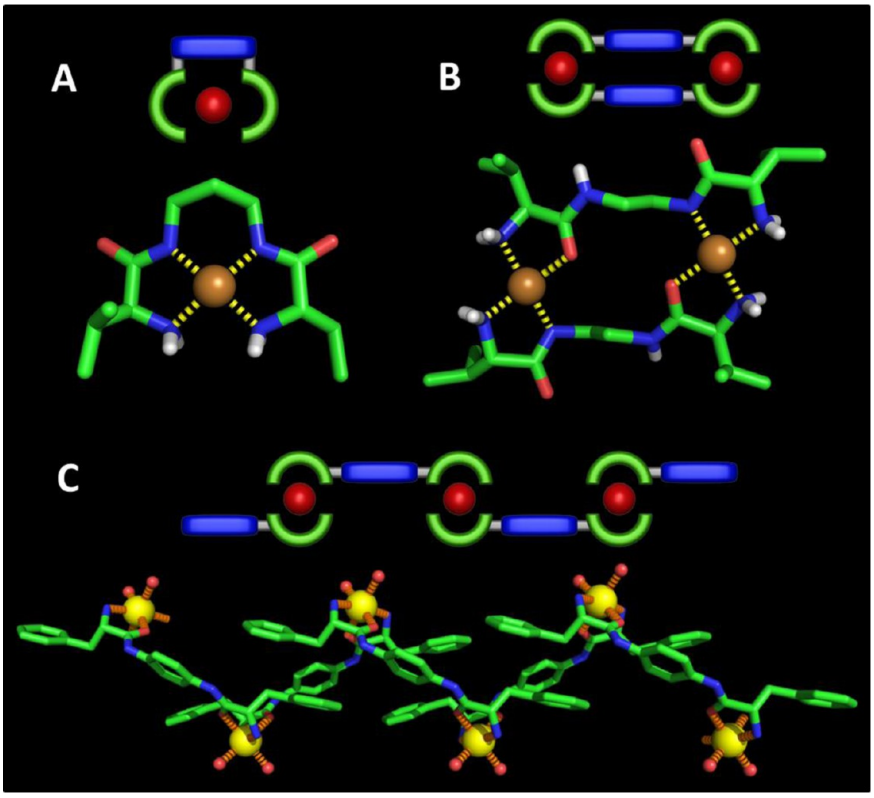


FIGURE 12. Cartoon and crystal structures for complexes involving $(1{:}1)_x$ metal/ligand stoichiometries: (a) 1:1 Cu complex; (b) 2:2 Cu complex; (c) polymeric $(2{:}2)_n$ Zn complex.

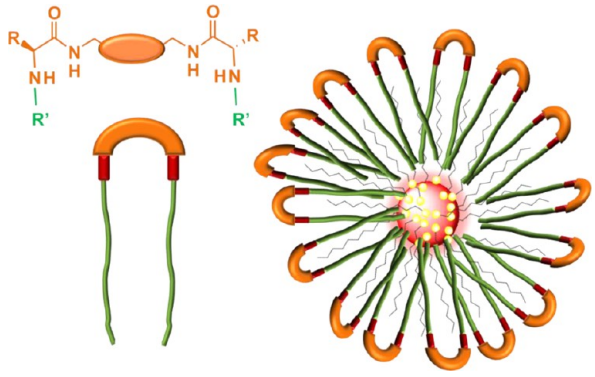


FIGURE 13. Proposed interdigitation mechanism between Gemini amphiphiles and QDs. The QD is represented by the red sphere with a shell of protecting ligands.

Dynamic Properties of Macrocyclic Pseudopeptides. The [1 + 1] macrocyclic pseudopeptides have interesting dynamic properties based on the movement of the aromatic moiety with respect to the macrocyclic main plane (Figure 14a). The time scale of those processes allows, in many cases, their detailed NMR study. For macrocycles containing 1,4-phenylene or 1,4-naphthalene aromatic subunits, the rotational barrier decreases with the ring size, but intramolecular hydrogen bonds represent a critical contribution to this barrier. Macrocycles with different amino acids at each side allowed how H-bonded amide N−H$\cdots\pi$ interactions play an essential role in the conformational behavior for peptides and peptide-like molecules to be highlighted. The solvation of the transition state is a fundamental parameter, affording favorable enthalpic and unfavorable entropic contributions compensating the disruption of intramolecular interactions. Thus, the flipping movement is solvent dependent, making it possible to devise a stimuli responsive minimalistic molecular rotor. The intramolecular interactions act as a *brake*, while the addition of a polar solvent (methanol) acts as a *fuel* providing the system with the energy required to accelerate the molecular rotation. The removal of the *fuel* restores the efficiency of the *brakes* and the rotation movement slows back to the initial rate.[65,66] Although these systems are still far from molecular machines reported by other groups,[67] including some containing pseudopeptidic fragments,[68] their high simplicity facilitates a deep understanding of the different factors affecting this dynamic behavior and their design as appropriate components for more complex systems.

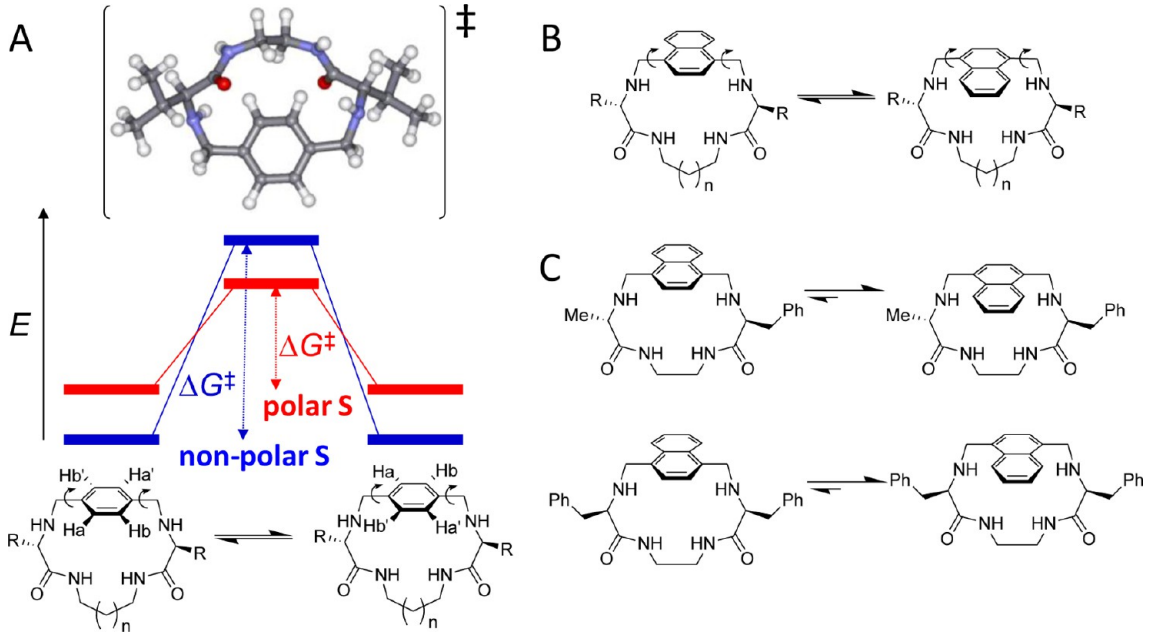


FIGURE 14. (A) Effect of the polarity of the solvent (S) on the rotation of the aromatic ring in pseudopeptidic *para*-cyclophanes. (B,C) Flipping of the aromatic ring in symmetric (B) and asymmetric (C) pseudopeptidic naphthalenophanes.

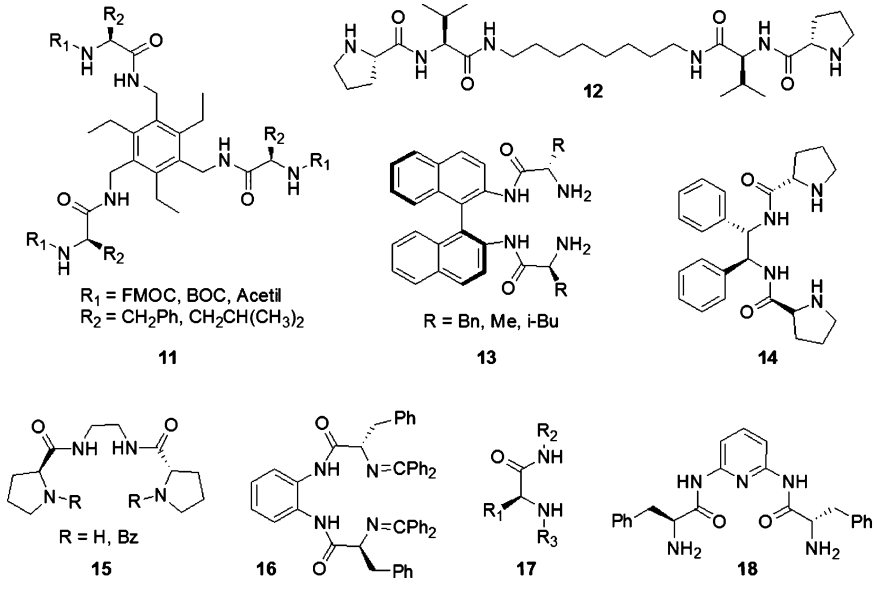


FIGURE 15. Structures of pseudopeptides studied for catalytic applications.

Catalytic Processes Based on Minimalistic Pseudopeptides

Although pseudopeptides seem to be excellent candidates to develop organocatalyts, only a limited number of reports have been presented. Asymmetric enolate alkylation was achieved by C_3 pseudopeptides **11** (Figure 15),[69] and the proline-derived organogelator **12** acts as catalyst for the Henry reaction but only in the gel phase, which was associated with a boost in the basicity of the proline residues upon aggregation.[70] Compound **13** with a BINAM spacer catalyzes the 1,3-dipolar cycloaddition of nitrones to *E*-crotonaldehyde; the presence of chirality at both the central spacer and the amino acid fragments is required for high enantioselectivities.[71] Recently, an enantioselective aldol reaction in water was developed using a pseudopeptide containing proline residues and chiral elements in the central spacer (**14**) as well as by the corresponding Zn(II) complex.[72] Initial studies by Burrows and Hamilton revealed

soon the potential of metal complexes of pseudopeptides as biomimetic metalloenzymes,[3,5] due to their capacity to activate unusual oxidation states of the metal, a usual requisite for biocatalysis. This is also illustrated when copper complexes of compounds **I** are used as catalysts for cyclopropanation reactions.[73] The actual catalysts are Cu(I) species, initial Cu(II) complexes being reduced *in situ* by the diazo reagent. The system displayed good activity and selectivity, although low-moderate enantioselectivity. Interestingly, supported catalysts were much more active than the homogeneous ones. Also low enantioselectivities (<36%) were observed for the iridium complexes of proline-derived ligands **15** as hydrogenation catalysts.[74] More successful are the applications reported for the addition of diethylzinc to aldehydes.[75] The use of compound **16** containing an *ortho*-substituted aromatic spacer and the terminal nitrogens substituted by bulky imino groups afforded excellent enantioselectivities. Simple ligands **I** also catalyze the addition of different dialkylzinc reagents,[76] and their Ni(II) complexes efficiently catalyzed the conjugated addition of dialkyl zinc derivatives to enones.[77] An even more interesting system was the one involving Ni(II) complexes of amino amides **17**, containing just one amino acid fragment.[78] A reversal in the topicity of the major product was observed for 1:1 or 1:2 (metal/ligand) stoichiometries. Pseudopeptides provide easy access to bifunctional catalysts: the Cu complexes of **18** behave as primary amine−metal Lewis acid catalysts for asymmetric direct aldol reactions, like efficient type II aldolase systems.[79] The titanium complex of **14** has also been described as a bifunctional catalyst for the enantioselective cyanosilylation of ketones (up to 94% ee).[80] More elaborated pseudopeptidic tripodal scaffolds have been reported for the enantioselective Cu(II)-catalyzed Diels−Alder and Michael addition reactions in water, achieving enantioselectivities of up to 55%.[81]

Conclusions and Prospective

Simple pseudopeptides can be properly designed as promising bioinspired molecules displaying functionalities related to those of peptides and proteins. Their structural simplicity and a rational selection of the abiotic and natural components facilitate their preparation. Macrocyclic and macrobicyclic compounds can be efficiently accessed through the conformational and configurational preorganization of the corresponding intermediates or with the use of anionic templates.

Most of the pseudopetides have shown interesting self-assembly abilities. Many examples of organogelating structures have been observed, some of them with relevant properties, including the transcription of their intrinsic chirality into the helical morphology of the fibers, their applicability for a broad range of solvents at very low concentrations, or high gel−sol transition temperatures. They can also form interesting nano- and microstructures in the solid state, being responsive to external stimuli. Their high level of modularity allows easy optimization of these self-assembling properties. Finally, the crystalline structures obtained have displayed features of great interest, for instance, for understanding the importance of side chain−side chain interactions for the assembling of protein structures.

These pseudopeptides have also shown interesting host−guest properties. The selective recognition of inorganic cations and anions, amino acid derivatives, and small peptides has been achieved. The introduction of fluorescent units has led to selective fluorescent sensors promising for potential biomedical applications, for instance, as intracellular acidity fluorescent markers. Interestingly, some macrocycles behave as models for controlled molecular rotors. Finally, some useful catalytic applications, mainly based on their metal complexes, have been reported, in particular for enantioselective transformations.

Taking into account the former results, developing practical applications can be expected in the near future. These could expand from the biomedical area to the preparation of materials responsive to external stimuli, to the development of new molecular devices, or to the accomplishment of new efficient enantioselective catalysts.

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FOOTNOTES

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