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The Use of Peptidic Frameworks for the Construction of Molecular Receptors and Devices

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Contents

1. INTRODUCTION

Through million of years of evolution, Nature has developed incredibly sophisticated and efficient molecular systems essential for the survival and the reproduction of living organisms. Among others, these include assemblies that store and transmit genetic information (DNA), control and regulate physiological responses (proteic receptors), convert of light into chemical energy (photosynthetic centers), and efficiently catalyze chemical reactions (enzymes). All these molecular systems have served as wonderful sources of inspiration for researchers in diverse fields. One of the major endeavours of modern organic chemistry has been the development of small synthetic molecular systems that can mimic some of the properties of natural ones. Considering the short amount of time invested by chemists compared to Nature, one can say that they have been quite successful in synthesizing molecular entities that imitate some aspects certain biological systems. For example, selective recognition of nucleotides,[1] amino acids,[2] carbohydrates,[3] and ions[4] has been achieved as well as the catalytic hydrolysis of amides,[5] esters,[6] and phosphates.[7] In addition, chemists have not only focused on the development of systems that mimic Nature's own, but also on novel entirely man-made ones such as fluorescent probes,[8] self-replicators,[9] molecular containers,[10] trains,[11] and shuttles.[12] However, even with these synthetic systems, researchers still have a long way to go to attain efficiencies that rival the biological ones. So, efforts are currently devoted to the development of new and efficient synthetic catalysts, selective and chiral receptors, as well as novel molecular materials.

In contrast with biological systems, most of the molecular receptors developed so far have used cyclic structures to maintain functional groups and binding sites in a proper manner for them to recognize and to complex a specific guest— the concept of preorganization.[13] On the other hand, only a few acyclic receptors have been developed.[14] One reason for this trend is the loss of preorganization inherent to the switch from a more rigid to a more flexible scaffold. However, flexibility has very important roles in natural systems, including regulation and control.[15] Therefore, the development of well defined but flexible acyclic molecular systems could have some intrinsic advantages and should be regarded as a complement to the rigid ones. In other words, whereas rigid receptors are based on the *lock-and-key*[16] concept, flexible receptors are inspired by the *induced fit*[17] concept.

Another striking aspect of biological systems is that, with evolution, polypeptides have emerged as the molecular material for the construction of most of the functional systems. This selection is by no means accidental. Indeed, polypeptides possess several important features that make them ideal for construction of efficient molecular systems. First, there are 20 amino acids (monomers) as constituents of the

proteins. Thus, Nature can choose among 20 different functional groups (acidic, neutral, basic, nucleophilic, hydrogen bonding, etc) on the side chains of these building blocks. In addition, amino acids have electrophilic and nucleophilic sites well suited for their sequential condensation to give linear polymers. Secondly and most importantly, a linear polypeptide of several amino acids is in a conformational equilibrium between an unordered form (random coil) and a specific ordered structure (folded form). In general, with long polypeptide chains (100 amino acids or more) the equilibrium lies towards the folded, globular-like form that constitutes the

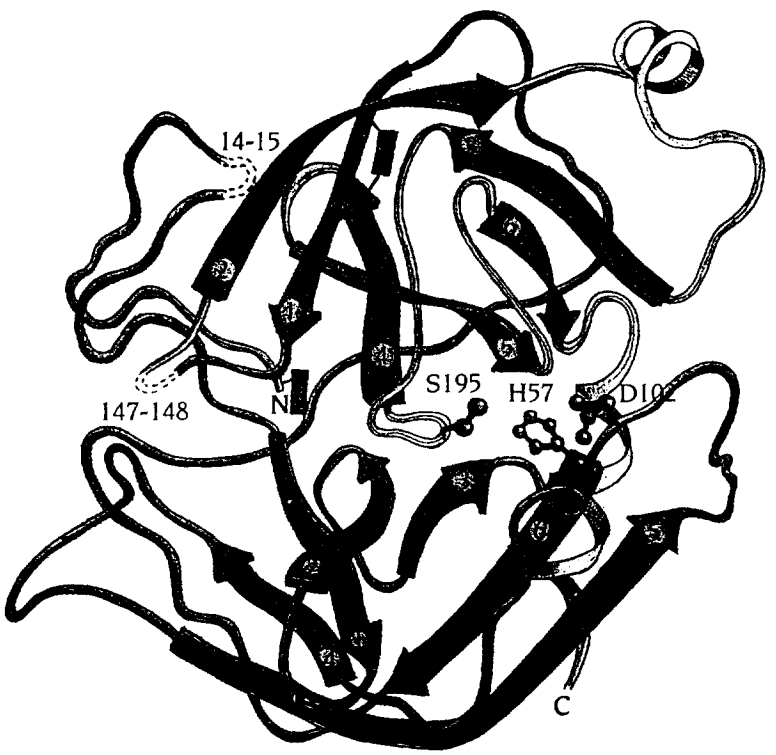


Figure 1. An example of Nature's use of polypeptide frameworks. Schematic representation of α-chymotrypsin where the polypeptide scaffold maintains in a perfect relationship the three functional groups involved in the catalytic hydrolysis of amides, namely the carboxylate of aspartic acid 102, the imidazole of histidine 57, and the primary alcohol of serine 195. Reproduced with permission from ref. 18.

active geometry of all enzymes and proteic receptors.[19] Therefore the polypeptide backbone serves as a molecular framework that assembles and holds together, in a

well defined spatial orientation, several distant functional groups (side chains) involved in the biological function (Figure 1). The well organized array of functional groups thus forms the active site of an enzyme or the binding site of a proteic receptor.

Even though polypeptides have been the molecular scaffold of choice for Nature for millions of years, they have not been used widely by chemists for the development of artificial systems. This situation is surprising in light of the arguments presented above. However, there have been an increasing number of reports recently in which polypeptides were used as frameworks. It is the objective of this Report not only to summarize recent developments in the preparation of molecular receptors and devices based on peptidic frameworks, but also to illustrate their advantages and future opportunities. We restrict our coverage to molecular systems that utilize polypeptide scaffolds to orient unnatural functional groups or effectors.[20]

2. WHY PEPTIDES AND POLYPEPTIDES AS FRAMEWORKS?

Because of their biological activity and significance, peptides and polypeptides have been studied extensively in many aspects. Based on these studies, we can summarize why peptides are ideally suited to serve as frameworks in the construction of molecular receptors and devices.

2.1 Availability

The first advantage of peptides is the commercial availability at reasonable price of numerous pure N-protected amino acids in both optically active forms. In addition to the proteogenic amino acids, several non-proteogenic amino acids as well as some unnatural aminoacids (such as dialkylglycines) are also commercially available. Furthermore, several efficient synthetic methods have been developed in the past few years that allow the enantioselective preparation of a great number of miscellaneous amino acids.[21] In this regard, chemists have an advantage over Nature, since they are not restricted to the 20 proteogenic amino acids.

2.2 Chirality

Peptides are composed of optically active amino acids and are intrinsically chiral. This chirality is an advantage for systems designed to perform chiral recognition and catalysis. Since both enantiomers of precursors are available, it is conceivable that both "enantiomers" of a synthetic receptor could be prepared since L amino acids form right-handed α-helical structures whereas the D analogs form left-handed ones. An elegant demonstration of this possibility has been reported recently

by Kent and his co-workers.[22] They synthesized the "enantiomer" of the HIV-1 protease using D-amino acids and showed that its specificity was reversed.

2.3 Predictability and monitoring of the solution conformation

In contrast to the situation for synthetic polymers, an important feature of polypeptides is the possibility of predicting their solution conformations from their primary structure, i.e. from the linear sequence of amino acids. Even though it is not currently possible to predict the tertiary structure of a given polypeptide from its linear sequence, one can predict quite accurately its secondary structure. Indeed, several empirical scales have been developed that evaluate the propensity of a given amino acid to force the backbone of a peptide to adopt a specific secondary structure, namely the α-helix, the ß-sheet, or the ß-turn.[23] Thus, it is possible to predict the most favorable conformation of a given peptide in solution and, hence, the relative orientation of its side chains, thereby allowing an efficient design (Figure 2). However, this predictability of the solution conformation of peptides holds only for

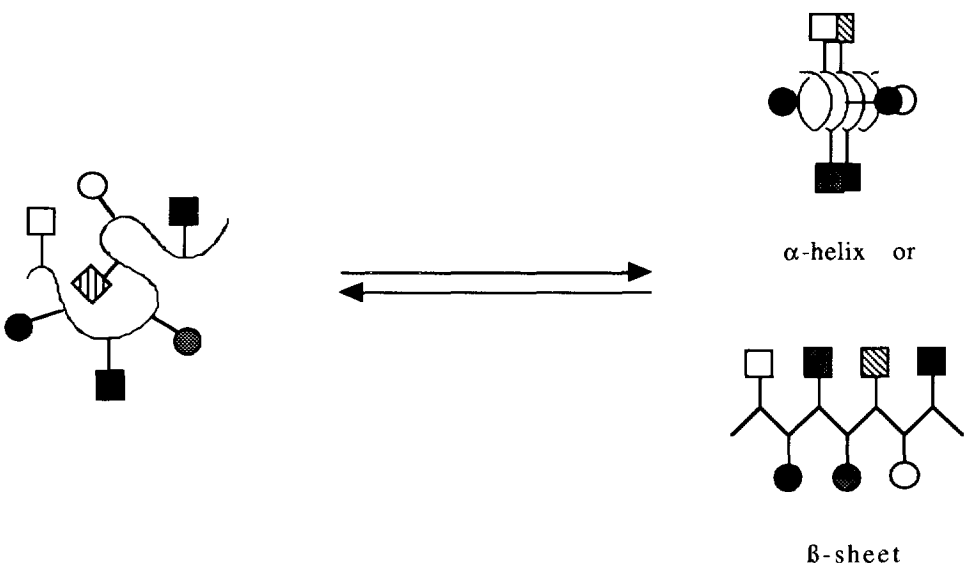


Figure 2. The folding of a linear peptidic chain into a ß-sheet or an α-helix allows prediction of the relative orientation of side chain functional groups.

chains having the minimum number of amino acids required to form a stable secondary structure, usually six or seven for a ß-sheet and around 12-13 for an α-helix. For shorter peptides, the conformational equilibrium is displaced towards the unordered form, and so the design of a receptor becomes more difficult. But the external control of this conformational equilibrium could eventually be used

advantageously to control recognition phenomena or molecular processes of peptide based molecular systems.

2.4 Synthesis

One criterion quite often neglected in the design of a functional molecular system is a versatile and flexible synthetic strategy. The strategy should allow easy modification of the position, the orientation, and the chemical composition of the functional groups involved in the binding and in the catalytic processes, etc. The use of peptides as scaffold units offers this possibility. Since the development of solid phase peptide methodology[24] more than 25 years ago, peptide synthesis has evolved to an extremely well developed area of science. Important progress has been made in coupling reagents that give high yields and low racemization, in more efficient protecting groups, and in novel solid supports that allow the rapid preparation of quite long peptides (up to 25 amino acids routinely) in a relatively large scale.[25] Furthermore, several resins now conveniently use photochemical reactions, trifluoroacetic acid, or nucleophilic displacements to remove the peptides from the solid support therefore avoiding the cumbersome use of HF. It is now also possible to obtain fully- or partially-protected peptides,[26] which can be useful for preparation of molecular systems designed to operate in apolar environments such as organic solvents and lipid membranes. Another important development in this area is the possible preparation of even longer peptides by use of solution or solid phase segment condensation strategies.[27] Finally, the possibility of simultaneous multiple peptide synthesis increases the flexibility and allows preparation of several peptides at the same time. Therefore, peptide based molecular receptors and systems with subtle variations can be synthesized concurrently.

2.5 Purification

All the advantages outline above would not be worthwhile if purification of the peptide based molecular devices were not achievable. However, purification of peptidic molecules has also developed dramatically in the past 20 years with the great improvements in high performance liquid chromatography.[28] This powerful technique available in almost every organic chemistry laboratory, offers the possibility of purifying tiny to large quantities of peptides in a reasonably short period of time. Technological improvements in this area are also expected in the future, hence purification of peptides will be even more efficient.

2.6 Characterization

Several different techniques can be used to characterize peptidic molecules. The most important ones are mass spectrometry and NMR spectroscopy. The use of these two techniques for characterization of peptides has been reviewed recently.[29,30] With

various mass spectrometry techniques, it is now possible not only to study very high molecular masses (even larger than 10,000), but also to sort out the sequence of the amino acid constituents. Furthermore, the study of molecular recognition phenomena through sophisticated mass spectrometry techniques is currently an active research area.[31]

Structural and conformational studies of peptide based molecules by use of NMR spectroscopy have also improved dramatically with the advent of 2- and even 3-dimensional techniques and the availability of stronger magnetic fields. It is now possible to determine the 3-dimensional structure of a rigid peptide in a matter of days. In fact, the use of NMR to elucidate the detailed structures of proteins is now a research area on its own.[32]

In addition to these techniques, and to classic amino acid analysis and sequencing, several other methods can be used to characterize peptides. For instance, FTIR[33] and Raman[34] spectroscopy can provide important details on secondary structures, especially in the case of ß-sheet peptides where information can be obtained on the nature of the string arrangement, parallel or antiparallel.[35] Finally, one other technique extremely useful in conformational studies of peptide based molecules is circular dichroism spectropolarimetry (hereafter CD).[36] Indeed, this technique requires only tiny amounts of material (< 1mg) and gives information on the secondary structure of peptides. Even though it is not the best method for studies of detailed solution structure, it is surely the simplest way to determine rapidly the gross secondary structure of a peptide chain and to follow its conformational changes.

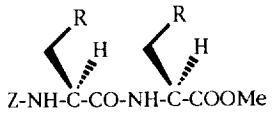
The advantages of peptidic frameworks now having been outlined, let us illustrate their potential usefulness with some examples reported in the literature.

3. MOLECULAR RECEPTORS FOR SPECIFIC GUESTS

3.1 Alkali metal ions

Since Pedersen's discovery of the ability of crown ethers to complex alkali metal ions,[37] the development of ion selective electrodes and molecular devices has been a major area of current research in molecular recognition.[38] In order to develop receptors selective to different ions, our research group and others decided to use bis-crown ethers. Indeed, it is known that ions larger than the cavity size of a crown ether form sandwich complexes with one ion trapped between two crown moities.[39] Several rigid and flexible bis-crown compounds[40] as well as polymeric crown compounds[41] reported in the literature showed some selectivity. Of particular interest, four articles describe the use of peptidic frameworks for the preparation of ion selective molecular receptors. Sonveaux and Berthet[42] reported the synthesis and the binding ability of a linear and a cyclic dipeptide, **1** and **2**, bearing two 15-crown-5 units as well as two poly(crown) phenylalanines, **3** and **4**. These compounds

complexed well K^+, NH_4^+, and the ammonium salts of leucine and glycine methyl esters.



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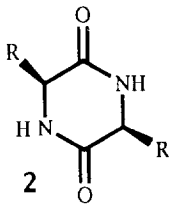

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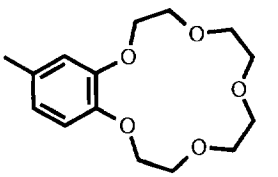
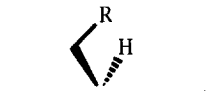
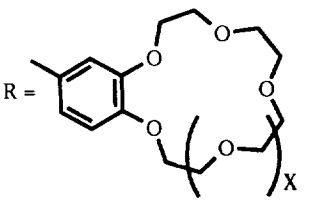
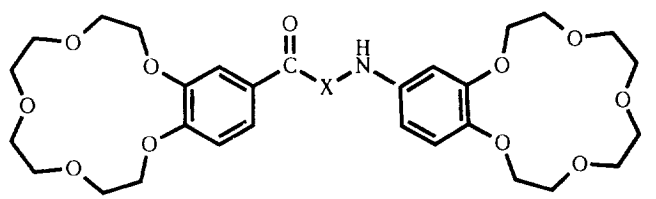
R= 



3 X=1 **4** X=2

R = 

Interestingly, the rigid cyclic receptor **2** did not form "sandwich" complexes, demonstrating the need for some flexibility for efficient complexation. Following this observation, the same authors[43] prepared several more flexible bis-crown receptors **5** with two binding sites (benzo-15-crown-5) attached at the ends of the peptidic frameworks. The best K^+ binders were those with ala-ala-ala and ala-pro-ala spacers, which evidently allow enough flexibility so the chain can adopt the required

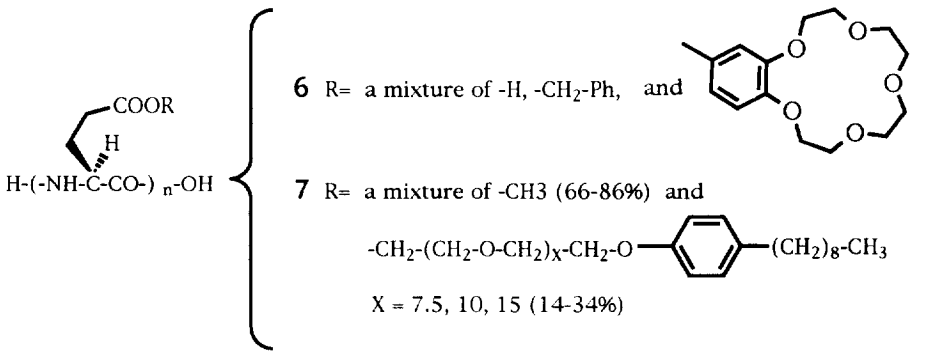


5 X= Ala; Pro; Pro-Ala; Ala_3; Ala-Pro-Ala; $-NH-(CH_2)_7-$ CO-

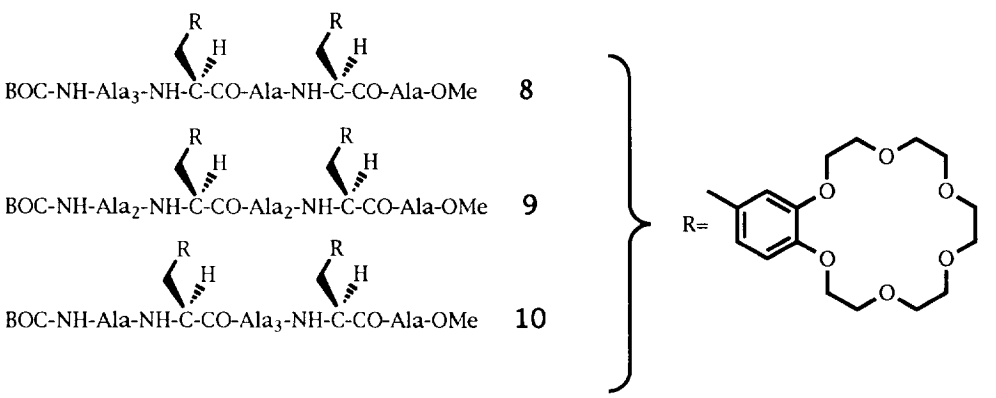
conformation that orients the two crowns suitably for a cooperative complexation of K^+. They also observed that the receptor with the more rigid pro-ala spacer is a poorer K^+ binder, thus confirming the conclusion about the need for some flexibility. Finally, they reported that the poly(crown) phenylalanines **3** and **4** were better phase transfer agents for ammonium ions than the monomeric analogs. However, they could not achieve the selective complexation of one enantiomer of leucine.[42]

Osa and Ueno and their coworkers used the rigid α-helical framework of poly-L- and poly-D-glutamates to develop selective receptors for ions. In the poly-L-series,[44] they used benzo-15-crown-5 appendages **6**, whereas in the D-series[45] the

binding sites were oligoethylene oxides of different lengths **7**. In the latter case, no side chain binding cooperativity was observed. In addition, they could not obtain



chiral discrimination with tryptophane and phenylalanine methyl esters. They also noted that no conformational change occurred during the complexation phenomena studied. On the other hand, using benzo-15-crown-5 with the poly-L-glutamate framework, they observed an important ion binding enhancement for Rb^+ and especially K^+, suggesting a good binding cooperativity between two crown moities.[44] Also in this case, the backbone conformation of the framework remained unchanged during all the complexation processes.



While working on the conformational modulation of peptidic molecules using remote molecular recognition interactions, our group[46,47] discovered the unusual ion binding selectivity of bis-crown ether peptides **8-10**. Our approach was to design model peptides having two distant benzo-18-crown-6 binding sites at different positions in the sequences. Depending on the distance between the two residues bearing the crown moities, the latter would be organized to complex cooperatively

difunctional guests only under specific conformations as illustrated schematically in Figure 3. Peptide **8** can have the crown side chain oriented correctly for cooperative

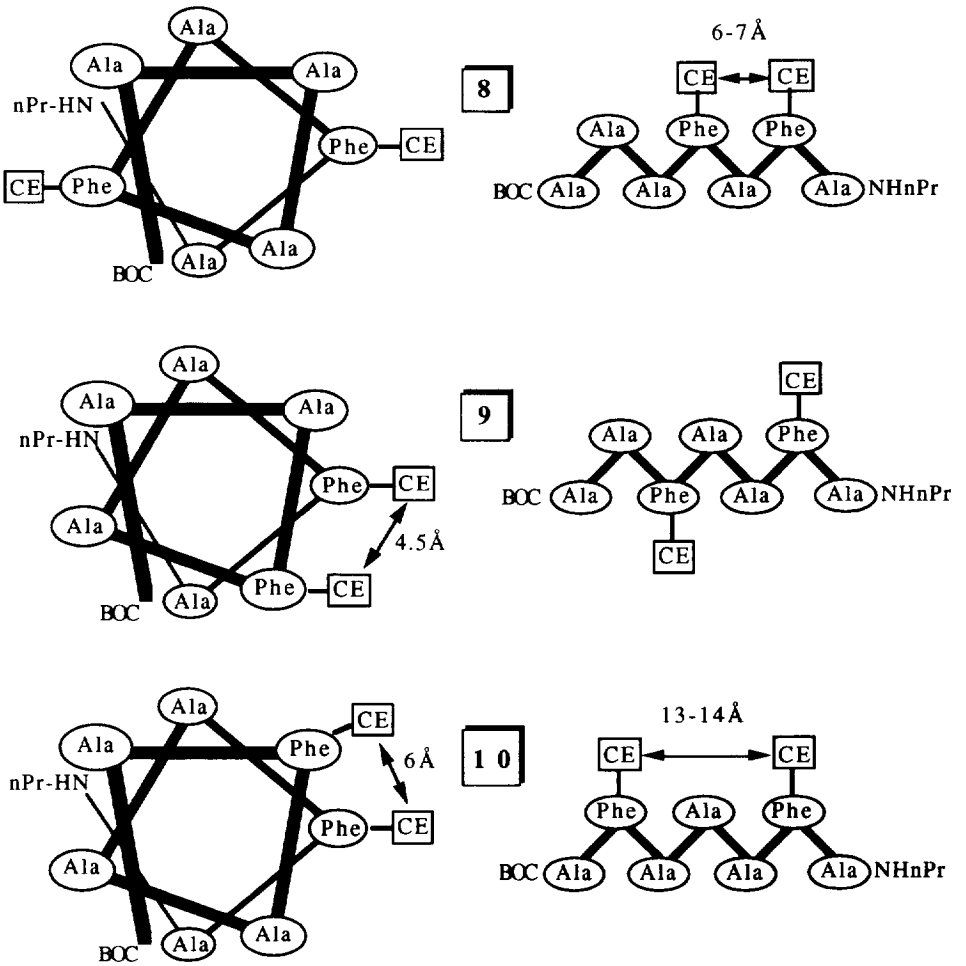


Figure 3. Schematic representations of peptidic receptors **8-10** in their α-helix (axial projections) and ß-sheet (side view) conformations. Ala= L-alanine, Phe-CE= 3,4-(18-crown-6)-L-phenylalanine.[46,47]

complexation only in a ß-sheet conformation, whereas the same opportunity prevails obtained with **9** only in an α-helix conformation. Peptidic receptor **10**, however, can

orient the ligand side chains in a cooperative fashion in either an α-helix or a ß-sheet conformation, but the distance between the two ligands varies from 6 Å to 13-14 Å respectively. Investigation of the ion binding ability of the bis-crown peptides **8-10** demonstrated a strong binding selectivity toward Cs^+ for all three peptides suggesting important cooperativity between the two distant crown side chains. Indeed, Cs^+ is known to bind as a sandwich complex between two 18-crown-6 ligands.[48] Among the three peptidic receptors, peptide **9**, which has two alanines between the crown ether residues, is the best Cs^+ ligand. This outcome is noteworthy since conformational studies demonstrated that only peptidic receptor **9** undergoes conformational change upon binding Cs^+.[47] Therefore, the ion selectivity observed in this case is a good example of an *induced fit* recognition process and demonstrates that flexible receptors can be quite selective. The Cs^+ binding selectivity can be explained by the highly favorable framework conformation required to organize the two binding sites in a cooperative fashion to form a stable sandwich complex with Cs^+. From CD conformational studies, it was demonstrated that the backbone of receptor **9** switched from a ß-sheet to a ß-turn type structure upon binding Cs^+. This result is somewhat contradicts the original prediction of an α-helical conformation for a cooperative complex with **9**. It is possible that the peptidic framework of **9** is too short to adopt the predicted helical conformation and that instead a stable ß-turn structure correctly orients the two ligands and thereby competes with the helical conformation. Nevertheless, the bis-crown ether peptides **8-10** are effective Cs^+ binders that could be useful in different applications such as in ion selective electrodes, in chiral recognition systems, and in the separation and recovery of Cs^+. In addition, peptidic receptor **9** can be considered as a functional molecular switch,[49] since its conformation is modulated by the complexation of Cs^+.

3.2 Diammoniums and diamines

Diamines and polyamines are important biological compounds and their selective complexation is therefore of interest.[50] Since the bis-crown ether peptides **8-10** demonstrated a strong side chain cooperativity in the binding of Cs^+, we were interested to see: (a) if they could perform the selective binding of α,ω-aliphatic diammoniums, and if so, (b) whether the peptidic framework conformation could be modulated by complexation of different difunctional ligands.[51] The binding ability of receptors **8-10** with aliphatic diammoniums is displayed in Figure 4 which reveals that the three peptidic receptors were more selective towards the longer diammonium guests. This tendency has also been observed with other bis-crown compounds and can be explained in terms of the greater adaptability of the longer guests as compared with the shorter ones.[52] However, even though the diammonium guests are very flexible and quite similar in shape, it is noteworthy that peptidic receptor **9** showed some selectivity toward the shortest diammonium over the ones

having three and four methylene groups. It is possible that this property of **9** can be attributed to two different and favorable conformations of the peptidic framework that orient the binding sites complementary to the short and the long difunctional guests, respectively. However, technical problems have so far precluded conformational studies of these complexation phenomena by CD, and therefore the latter hypothesis has yet to be confirmed.[47] Nonetheless, these bis-crown ether systems could eventually be used for selective recognition, detection, and separation of di- and polyamines and proteins of biological and environmental interest.

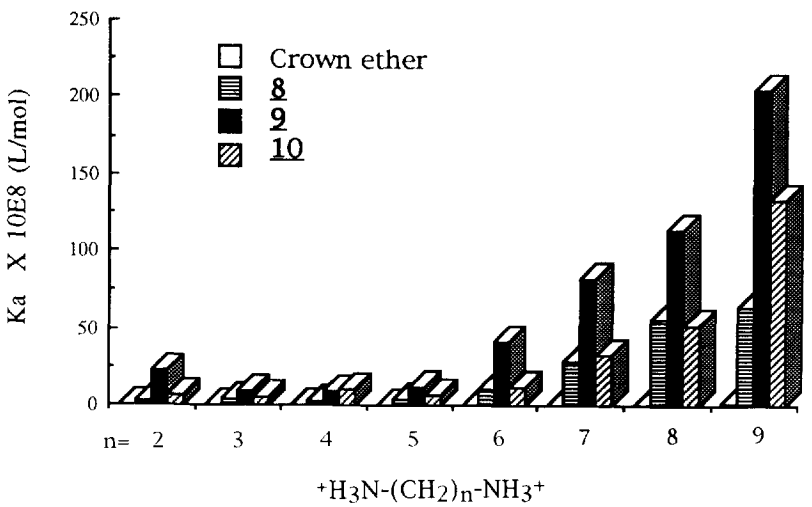


Figure 4. Binding ability of peptidic receptors **8-10** and the crown ether amino acid towards linear diammonium guests.

In another approach to the selective recognition of neutral diamines, our group designed several peptidic receptors **11-13** incorporating two zinc porphyrins attached to the side chain of glutamic acids.[53,54] The fundamental idea is the same: Use the peptidic framework to favorably orient the metalloporphyrin binding sites to form cooperative complexes with difunctional substrates (Figure 5). Since the zinc porphyrins have the ability to form well defined complexes with one axial ligand, we predicted that the peptidic receptors **11-13** should be more selective than their bis-crown analogs. After several attemps using conventional solution phase or solid phase strategies, we synthesized the bis-porphyrin peptidic receptors **11-13** quite conveniently by a combination of these synthetic methods.[55] Indeed, the synthesis and purification of the key tripeptide **14** was achieved in good yield by solution phase synthesis (Figure 6). Then the tripeptide acid **15** was attached to the oxime resin[26] and coupled with the required amino acids or peptide segments to obtain the

desired peptidic receptors after cleavage with DBU and methanol[58] (Figure 6). Preliminary binding studies were performed with the bisporphyrin hexapeptide **11** and several flexible mono- and diamines (Figure 7). The results demonstrated that **11** forms very stable complexes with diamines as compared to amines. This enhanced stability was again due to the highly favorable cooperative action of the two zinc porphyrin side chains to complex the diamines. In addition to the large binding constants, the formation of intramolecular complexes was further supported by (i) an isosbestic point in the titration curves, (ii) the formation of stoichiometric complexes with the diamines, and (iii) the observation of exciton couplings between the two porphyrins.[59]

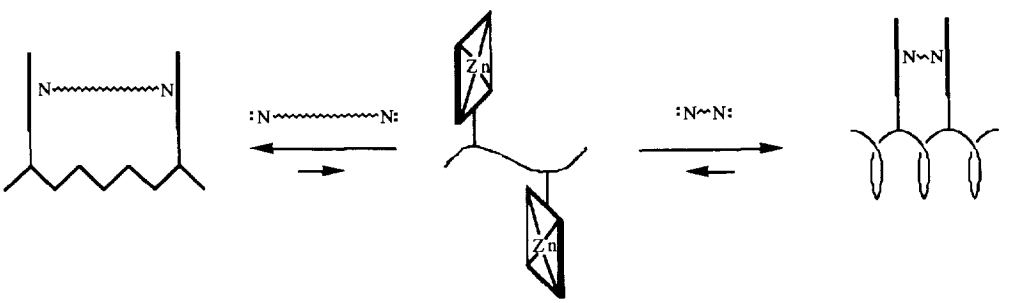
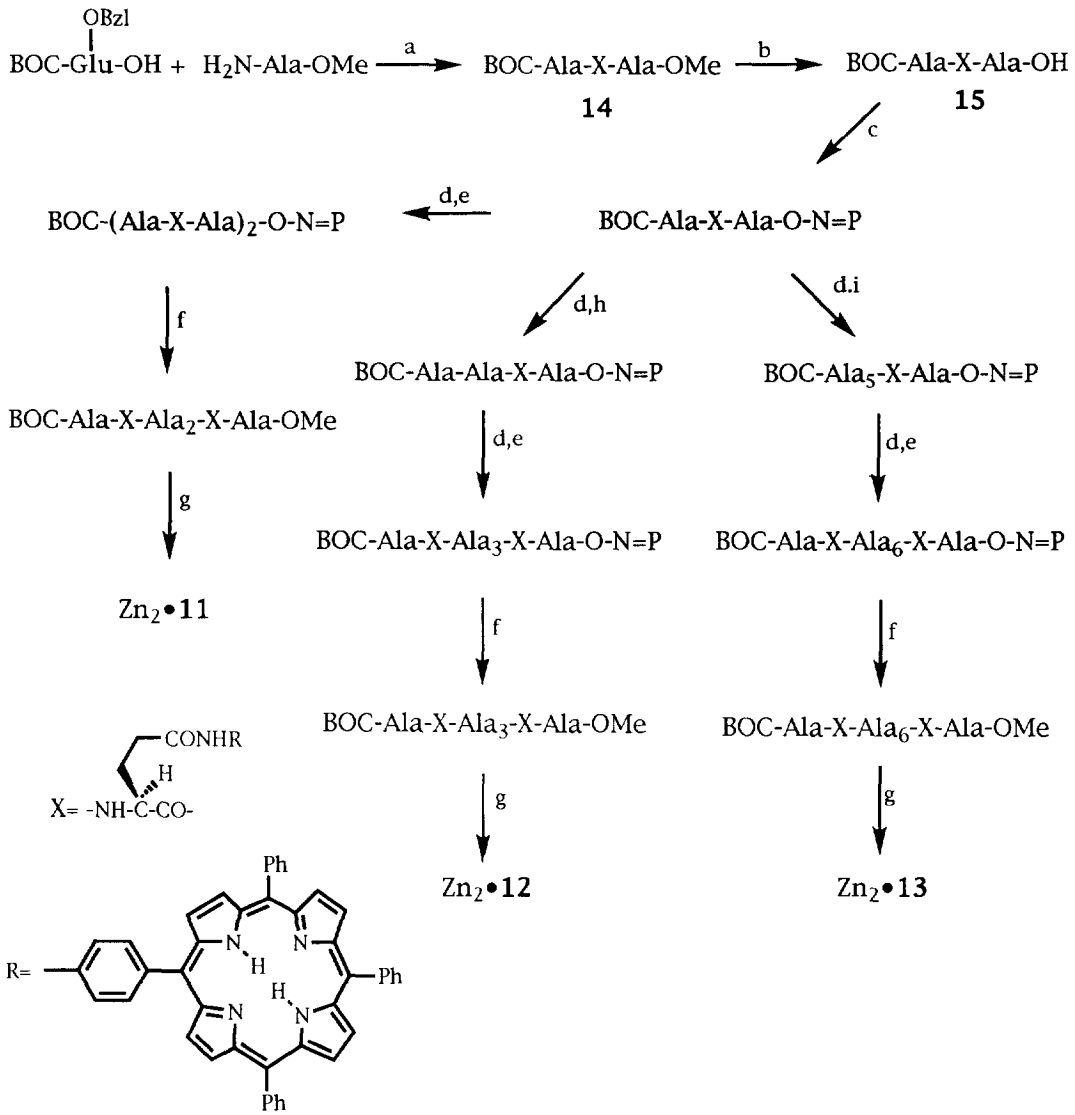


Figure 5. The selective complexation of diamines of different geometry by a bis-metalloporphyrin peptidic receptor adopting the required conformation to orient the binding sites complementary to the guest's shape.

Two phenomena are noteworthy with these bis-porphyrin peptidic receptors. First, the acyclic receptor **11** showed a high binding selectivity with the flexible linear diamines, even better than rigid cyclic bisporphyrin receptors.[50,54a] The unusally strong selectivity for 1,5-diaminopentane over the guests having one more or one less methylene unit can be explained by two factors. On the one hand, the conformation of the framework required to orient the binding sites complementary to the guest is extremely favorable. On the other hand, in its most stable extended conformation, 1,5-diaminopentane has the two nitrogen lone pairs pointing properly towards the zinc porphyrins in a convergent fashion, in contrast to a divergent manner for 1,4-diaminobutane and 1,6-diaminohexane.[54a] So the binding selectivity of receptor **11** is probably the outcome of these two factors acting in concert. Again, these results demonstrate that flexible receptors can effect selective binding if the stability of the resulting complex overcomes the loss in entropy associated with



Reagents: a) conventional solution phase synthesis, 5 steps, 16% overall yield; b) 1N NaOH, MeOH, 4h, 38%; c) Diisopropylcarbodiimide/hydroxybenzotriazole (DIC/HOBT), HO-N=P(oxime resin),[26]12h; d) 25% TFA/CH_2Cl_2, 1h; e) **15**,[56] DIC/HOBT, CH_2Cl_2/DMF, 4h; f) DBU/MeOH, 1h; $Zn(OAc)_2$, CH_2Cl_2, ultrasound,[57] 99%; h) BOC-Ala, DIC/HOBT, CH_2Cl_2/DMF, 2h; i) $BOC\text{-}Ala_4$, DIC/HOBT, CH_2Cl_2/DMF, 4h.

Figure 6. Synthesis of the bis-porphyrin peptide receptors **11-13**.

the recognition process, a situation encountered frequently with natural receptors (induce fit mechanism).

Another noteworthy characteristic of bis-porphyrin receptor **11** is the possibility of fine-tuning its spectral properties. Indeed, during the investigation of its binding ability by UV-visible spectroscopy, it was noted[53] that the position of the Soret band shifted depending on the guest used (Figure 8). When a monoamine was used to titrate **11**, the Soret absorption moved from 420 nm to 430 nm, as is observed normally for zinc tetraphenyl porphyrin. However, when diamines were used the absorption maximum shifted reliably from the 430 nm position. More importantly, the magnitude of the shifts depended on the guest sizes—the longer ones induced larger shifts than the shorter ones. This phenomenon is attributed to the exciton coupling between the two porphyrinic chromophores held in close proximity

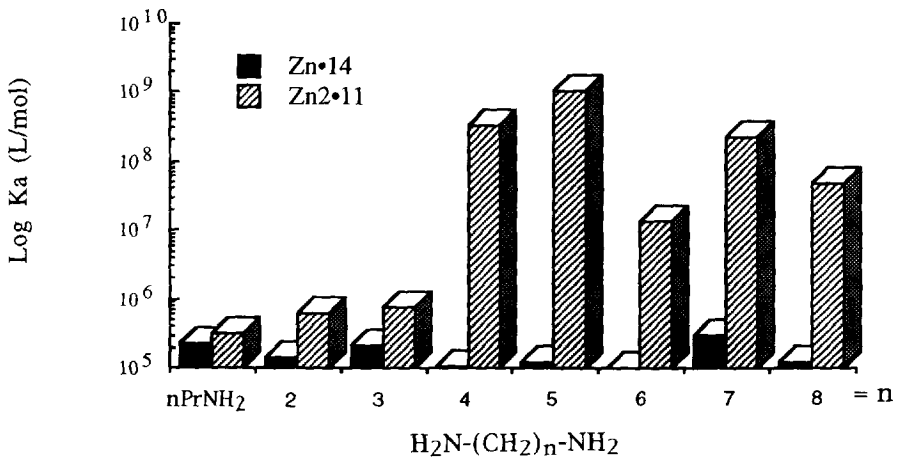


Figure 7. Binding ability of the bis-porphyrin peptide receptor **11** and the porphyrin peptide **14** towards n-propylamine and α,ω-linear diamines. The K_a in the case **Zn$_2$•11** and diaminopentane (n=5) is larger than 10^9 M^{-1}, which is the maximum observable value under the conditions used.[53]

to each other, a situation that results in bathochromic or hypsochromic shifts.[59] The magnitude of these shifts has been demonstrated to depend also on the distance separating the two chromophores and on their relative orientation.[59] Thus, the absorption properties of peptidic receptor **11** (and possibly of **12** and **13**) can be fine-tuned at the nanometer scale; and it is likely that its other spectral properties, such as fluorescence, could be tuned over an even wider margin. It is also possible that the spectral properties could be modulated by reversible or competitive

complexation processes therefore allowing applications in molecular electronics[60] and molecular sensors.[13]

3.3 Aromatic ammoniums

The biogenic amines and all the related neuroactive aromatic amines (dopamine, serotonine, etc.) are of great pharmacological interest. The development of selective sensors and transport systems for these compounds is therefore of importance. In addition, fundamental studies of the forces involved in binding these aromatic amines, in either their free or protonated forms, are needed since the three dimensional structure of their biological receptors is not known,[61] as is often the case with membrane proteins.

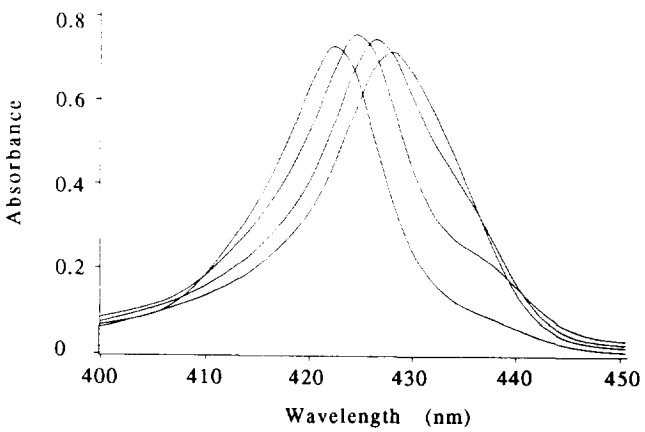
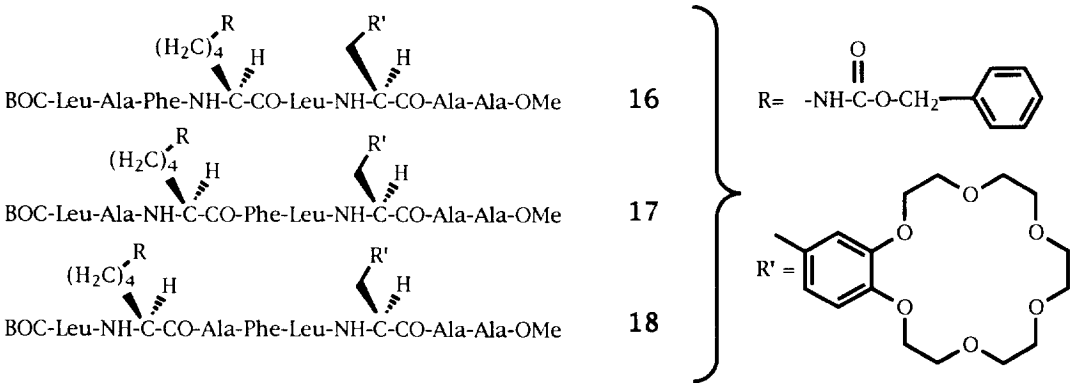


Figure 8. Selected UV/Visible spectra in the Soret region of **Zn_2•11** complexes with linear diamines having 2,4,6, and 8 methylene groups (from left to right respectively).

Inspired by the models of the receptor sites of dopamine, serotonine, and tryptamine,[61] we sought to develop molecular receptors that could bind selectively aromatic ammoniums through a combination of aromatic-aromatic, H-bonding, and electrostatic interactions.[62] To do so, we designed and synthesized the receptors **16-18**, which possess several features. First, they are fully protected and hydrophobic, so they should be soluble in low polarity media where they should operate just like their natural counterparts. Second, the length of the peptidic frameworks and the amino acids were chosen to favor a ß-sheet conformation. Also, two binding sites were incorporated at specific positions: a crown ether for H-bonding and electrostatic interactions and a benzyloxycarbonyl protected lysine for aromatic-aromatic

interactions (Figure 9). The distance between the two binding side chains was varied systematically to verify the effect of the relative positions of the binding amino acids on the complexation ability. Note that the crown binding site is close to the framework and does not move easily, whereas the aromatic binding sites is quite



flexible due to the lysine side chain methylenes. As with the peptidic receptors **8-10**, we prepared **16-18** by solid phase peptide synthesis using the oxime resin.[62,26] CD studies in 1,2-dichloroethane demonstrated that the free peptidic receptors **16-18** adopted a ß-sheet conformation in a low polarity environment as predicted. With these data in hand, it was predicted that, in contrast to **16** and **18**, receptor **17** would not bind aromatic ammoniums cooperatively since its binding side chains are on

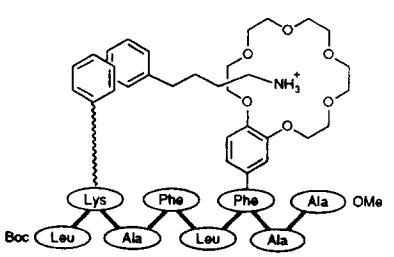


Figure 9. Proposed binding mode between an aromatic ammonium guest and peptidic receptor **18**. Reproduced with permission from ref. 62.

opposite sides of the framework (Figure 10). Complexation studies showed that receptors **16** and **18** indeed bind aromatic ammoniums much better than aliphatic ammoniums, whereas receptor **17** binds all ammoniums with the same strength and equal to that of the monomeric crown ether amino acid. These results suggest that

aromatic-aromatic interactions are important in the binding of aromatic amines. The participation of the lysine aromatic protecting group in the stabilization of the complexes with aromatic amines was further proven by control experiments.[62] In addition, CD studies showed that the backbone of receptor **18** undergoes an important conformational change upon complexing phenethyl ammonium, namely switching from a ß-sheet to a ß-turn structure. Detailed NMR and molecular modeling studies demonstrated that the framework of **18** adopts a type-I ß-turn structure

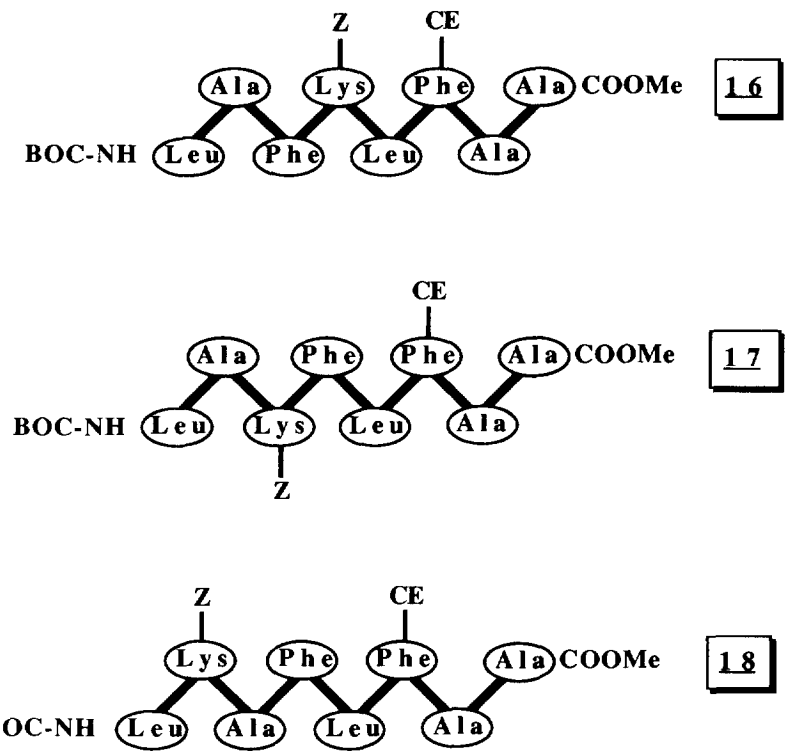
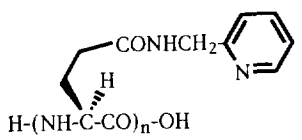


Figure 10. Schematic representations of peptidic receptors **16-18** in their ß-sheet conformations. Phe-CE= 3,4(18-crown-6)-L-phenylalanine; Z-Lys= benzyloxycarbonyl protected L-lysine; Ala= L-alanine; Leu= L-leucine.

upon complexation and that both edge-to-face and face-to-face aromatic-aromatic interactions are involved in the binding of phenethyl ammonium.[63] These investigations thus confirmed experimentally the importance of aromatic-aromatic, electrostatic, and hydrogen bonding interactions for the strong and selective complexation of important neuroactive aromatic amines. This work can be regarded

as the groundwork for the development of molecular probes, chiral separation, and catalysis systems for this type of compounds.

Another interesting recognition system for aromatic amines, **19**, has been developed by Kinoshita and coworkers[64] by use of an α-helical framework. The side chains of the poly-L-glutamic acid was modified with a pyridine derivative. They showed that the polypeptide **19** was capable of selectively binding tryptophane over tryptamine through the formation of a ternary complex with copper, as illustrated in Figure 11. In addition, they also observed some chiral discrimination between the D and L enantiomers of tryptophane, which lead to the conclusion that **19** could be used in the chiral separation of that amino acid.



19

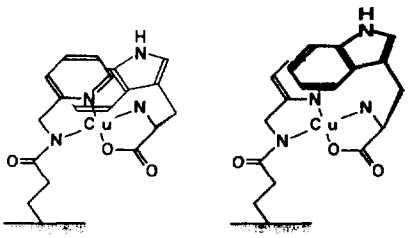


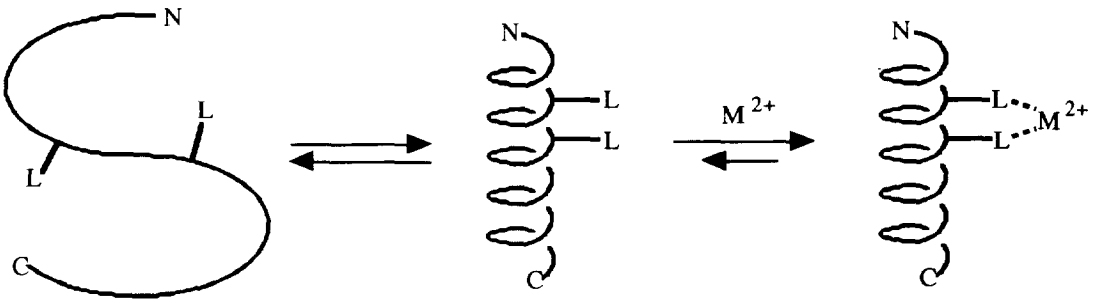
Figure 11. Binding mode proposed by Kinoshita and coworkers[64] for the selective complexation of tryptophane methyl ester by the pyridine modified poly-L-glutamic acid **19**. Reproduced with permission from ref. 64.

3.4 Transition metals

Transition metals such as Fe, Zn, and Cu are involved in the catalytic functions of several enzymes and in several biomimetic systems. Despite their possible uses in asymmetric catalysis, reports on the use of peptidic frameworks designed to complex transition metals using peptidic frameworks are scarce.

The selective complexation of a transition metal by two distant side chain binding sites of a peptidic structure was reported recently by two independent groups. The concept was to incorporate into an α-helical peptide two amino acids bearing a metal binding site two or three residues apart. Subsequently, the formation of a transition metal complex by the cooperative action of the two binding sites was meant to enhance and stabilize the helical structure (Figure 12). Interesting results were obtained, and the complexation indeed stabilized the helical conformation in the two different systems. In the work of Ghadiri and coworkers,[65] the complexation involved the formation of an inert Ru complex with the imidazoles of two histidine side chains of designed peptide **20**. On the other hand, Hopkins and coworkers[66] used the complexation of several metals in EDTA-like complexes using two bis-carboxylate,

side-chain modified amino acids in a peptidic structure, **21**. In this case, results were particularly impressive with Cd^{2+}, which enhanced importantly (0 to 80%) the helical content of peptide **21**. It is noteworthy that these peptidic systems offer adjustable and predictable chiral environments for transition metals and are therefore attractive for the development of molecular devices for chiral recognition and catalysis.

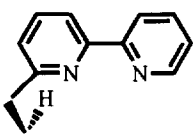


L= Ligand M^{2+} = Transition metal

Figure 12. Enhancement of the helical content of a peptide structure by selective complexation of a transition metal to two side chains.

Ac-Ala-Glu-Ala_2-Lys-**His**-Ala_3-**His**-Glu-Ala_3-Lys-Ala-NH_2 **20**

21 R= $-N(CH_2COOH)_2$



Ac-**Bpa**-Thr-Pro-D-Ala-Val-**Bpa**-NH_2 Bpa= -NH-C-CO-

22

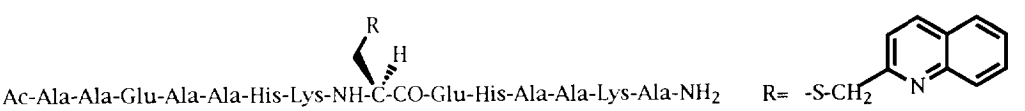
Towards that goal, Imperiali and Fisher[67] used another approach that invoked a stable ß-turn structure of type II (**22**). The ß-turn orients two bipyridine side chains suitably to form stable chiral complexes with certain transition metals. The selective and intramolecular binding of Cu^{2+} was demonstrated, and the complexation induced a CD signal for the bipyridine moities showing that the metal is bound in a chiral environment.

In addition to the development of enantioselective catalytic systems inspired by the active sites of natural metalloproteins, their work could also lead to the

stabilization and nucleation of regular peptide structures for the preparation of *de novo* designed proteins.

3.5 DNA and nucleotides

The biological recognition and transcription of DNA is one of the most complex and fundamental process of life. Because of the involvement of DNA in numerous genetic diseases and the desire to map the entire human genome, the development of artificial systems that can detect and complex nucleotides, oligonucleotides, and DNA itself have attracted much attention in the past 10 years. Several synthetic recognition and cleavage systems for DNA have been developed based on proteins,[68] oligonucleotides,[69] natural[70] and sequential peptides,[71] and metal complexes.[72] In addition, the complexation of nucleotides,[73] nucleobases,[74] and RNA[75] by artificial receptors is well documented. However, in almost all of the DNA binding proteins, the sequence specific recognition is effected through many selective electrostatic interactions of basic side chains (lysine, arginine) or hydrogen bonding side chains (asparagine, glutamine) that are held in the desired spatial orientation by large and relatively rigid polypeptidic frameworks.[76] Therefore, the use of peptidic scaffolds for the development of highly specific synthetic DNA recognition systems is attractive.



23

In this area, an interesting idea has been recently reported. The concept is to use an α-helix framework, as in DNA binding proteins, to orient favorably an intercalator.[77] The peptide **23** was designed to form a stable α-helix structure in water, and an intercalator was attached on the side chain of a cysteine by an S_N2 reaction. The helical stability was to be ensured by two electrostatic (salt bridges) interactions between two pairs of lysine and glutamic acid (Figure 13). In an α-helical conformation, the intercalator points out from the helix axis on its sterically less hindered side, thereby facilitating the approach to DNA. A noteworthy feature of the design is the addition of two histidines, at positions 5 and 9, which are well located to form a possible metal complex on the opposite side of the intercalator. This could enhance eventually the helical stability (Figure 13). NMR and CD studies demonstrated that the peptidic framework in this case adopted a nascent helical structure and that the helicity was enhanced in the presence of a low amount of a double strand of DNA.

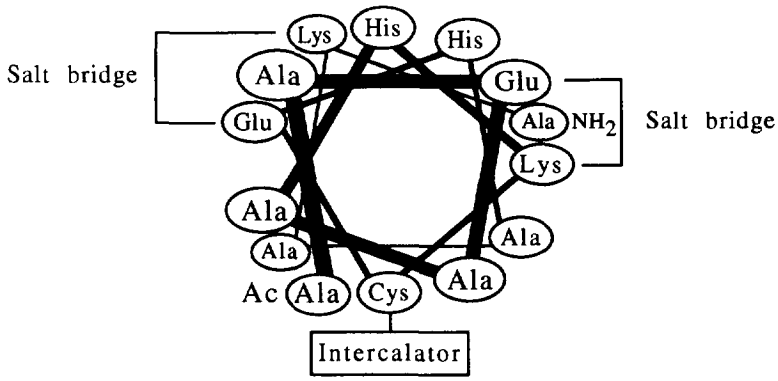
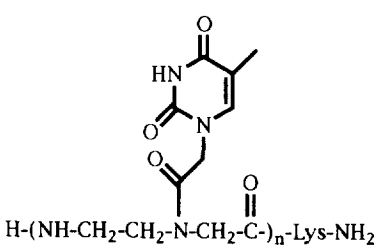


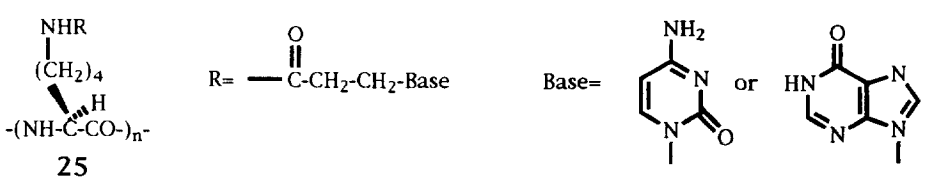
Figure 13. View of peptide **23** in an α-helical conformation sited down the helix axis.

Another approach towards selective recognition of DNA involves peptide nucleic acid (PNA) hybrid molecules.[78] These molecules have a peptide backbone modified on the side chains by nucleobases. Most of the work in this area has been done with



24

modified polyglycine scaffolds, such as **24**, that are achiral and flexible. Impressive and selective DNA binding using these hybrid molecules have already been observed and demonstrates their potential as selective cleavage agents, molecular sensors,



25

and even therapeutic agents. In the same vein, helical polylysine frameworks bearing adenines, uracils, thymines, and cytosines covalently linked to the side chains (general structure **25**) have been synthesized for use as selective DNA binding

molecules.[79] The polylysine carrying cytosine was also reported to form a 1:1 complex with the complementary nucleic acid strand, polythymine.

These results illustrate the potential of polypeptide frameworks for molecular devices that could serve not only in the detection, complexation, and separation of nucleotides and DNA, but also as therapeutic agents able to control and regulate gene transcription.

4. MOLECULAR ELECTRONIC, PHOTONIC, AND IONIC DEVICES

The development of molecular electronics and molecular data storage is one of the most rapidly developing areas of macromolecular science.[80-82] To prepare these "smart" materials, one has to control perfectly the three dimensional structure of large molecules. Therefore, peptidic frameworks are ideally suited for the development of these types of devices.

4.1 Molecular electronic and photonic devices

Several studies have been conducted to develop molecular electronic and photonic devices using polypeptides as frameworks. Three design strategies are common and will be presented separately.

4.1.1. Devices with a donor and an acceptor at both ends

The first strategy is to attach to one end of a polypeptide framework an electron rich donor, and at the other end an electron-deficient acceptor (Figure 14). Upon specific irradiation, either an electron or some energy can be transferred from

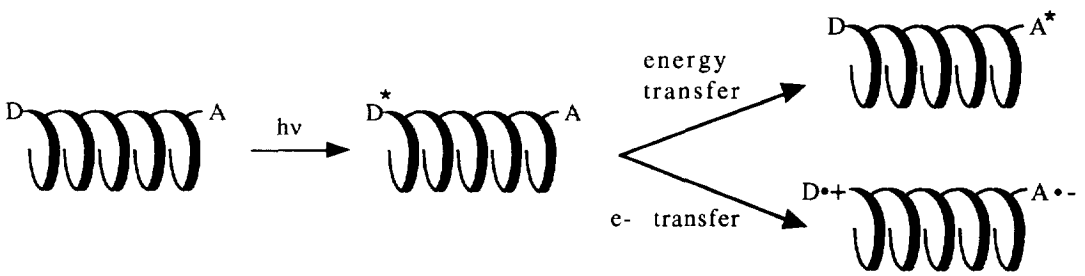
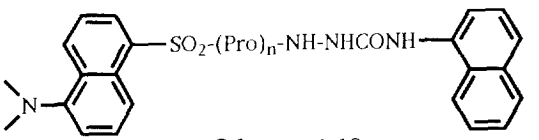


Figure 14. Schematic illustration of a photoactivated molecular device with a donor (D) and an acceptor (A) group at each end.

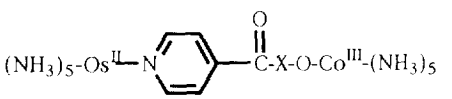
the donor to the acceptor groups (Figure 14). Photoinduced electron transfer can be triggerred by excitation of either the donor or the acceptor groups. Since these processes strongly depend on the relative distance and orientation of the two groups,

it is possible to prepare molecular devices with different characteristics by variation of the distance between the chromophores, i.e. the length of the polypeptide scaffold. Most of the chemists working in this area used α-helical or 3_1-helical (polyproline) frameworks. An important fundamental contribution was made by Stryer and Haughland,[83] who synthesized oligoprolines having a dansyl group and a naphthyl group at the N- and C-terminal positions, respectively **26**. Using fluorescence spectroscopy, they confirmed experimentally that energy transfer depends on the distance between the two groups, in accord with the Förster equation.[84]



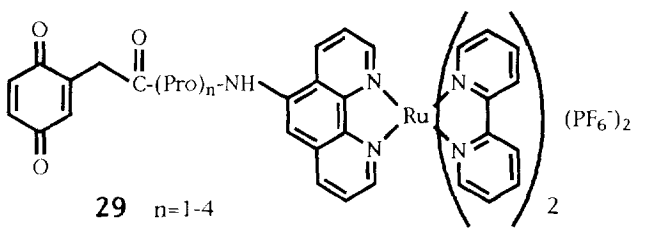
26 n=1-12

Along the same lines, Isied and coworkers[85] studied electron transfer between two different metal complexes separated by flexible dipeptide frameworks **27** and also by more rigid oligoproline spacers **28**. They demonstrated with **28** that, in contrast to the Ru(II) analogs, electron transfer from Os(II) to Co(III) was faster than cis-trans proline isomerization. They also observed significant differences in the photophysical properties according to the peptidic framework used.



27 X=Gly-Gly, Phe-Phe

28 X=$(Pro)_n$, n=1-4

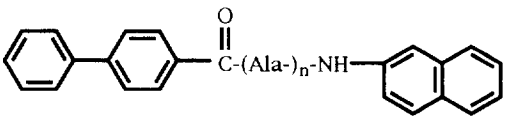


29 n=1-4

Another related system was reported by Schanze and Sauer.[86] They linked a ruthenium (II) bipyridyl complex to a reducible quinone through oligoproline frameworks **29**. Although they observed a decay in the electron transfer rates upon increasing the number of prolines in the framework, they could not determine

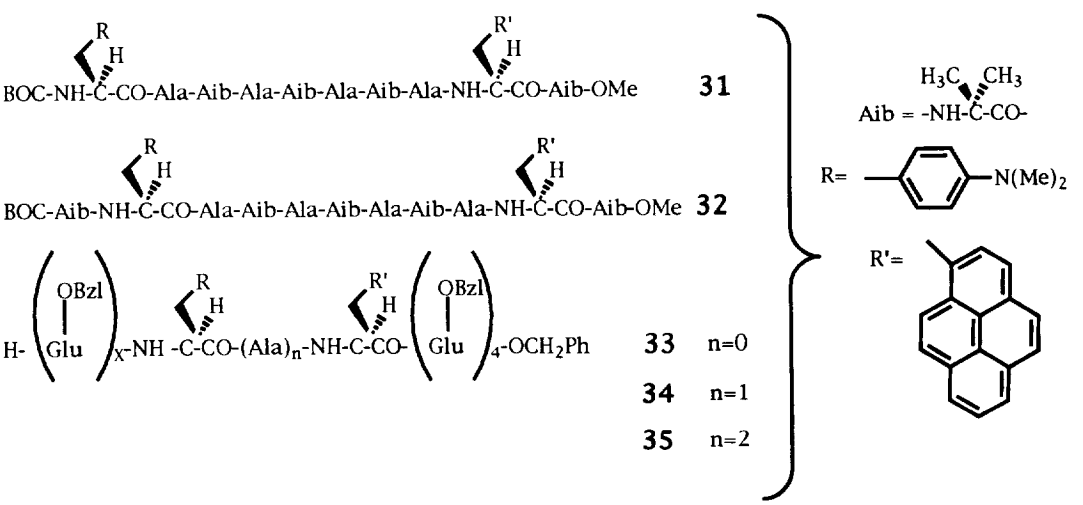
quantitavely the distance dependence because of the existence of at least two different conformations. This last result points out that scaffolds with a single and rigid conformation will be required for the development of efficient and reliable molecular electronic and photonic devices by this approach.

The use of an α-helical framework has also been attempted by Fox and coworkers.[87] They prepared oligoalanines with a naphthyl and a biphenyl group at both ends **30**. Unfortunately, the compounds having more than four alanines (the ones that could form α-helical structures) were too insoluble to be studied in detail. To avoid this problem, they adopted another strategy, which is discussed in the following section.



30 n= 0-4

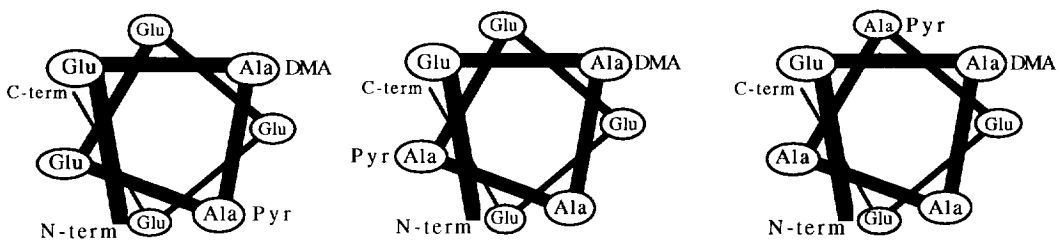
From these examples, it is obvious that the major advantage of this approach for the preparation of molecular devices is that it does not required the synthesis of unnatural amino acids bearing the chromophoric moieties since the two groups are attached at the C- and N-terminal ends. However, it suffers the important limitation that only the distance can be modified and not the relative orientation. Therefore, fine tuning of the physical properties is more difficult. Also, the peptidic frameworks need to be quite rigid.



4.1.2 Devices with a donor and an acceptor on the side chains

A more attractive but yet less developed strategy is to incorporate two chromophore-modified amino acids at a specific site such that in a particular conformation (helix, sheet, turn) the peptidic unit holds donor and acceptor groups at a fixed distance and orientation. The major advantage here is the possibility of designing and preparing a variety of photoactive devices with specific properties and characteristics that could be fine tuned and tailored for desired applications. This strategy has been used by Fox and coworkers[81] for the preparation of **31** and **32**. In

	Distances (Å)		k (1/s)
	center-to-center	edge-to-edge	
33	9.1	5.4	4.8×10^7
34	13.2	9.4	1.1×10^6
35	9.0	5.5	7.2×10^7



33 **34** **35**

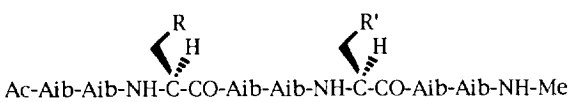
DMA = 4-N,N-Dimethylaniline Pyr = Pyrene

Figure 15. Calculated distances and electron-transfer rates between the donor and acceptor chromophores of molecular devices **33-35** along with their α-helix axial projections.[88]

these systems the several aminoisobutyric acid units enhanced the solubility and forced the peptidic framework to adopt a rigid 3_{10} helical conformation. In that conformation, the two chromophores are rigidly held at a fixed distance. This prediction was confirmed by the absence of an exciplex emission in **32**, as compared to the analog **31**, which is too short to form a stable 3_{10} helix in solution. From these results, we can conclude that molecular devices for directed electron transfer could

be prepared using this type of framework only if it has the required number (>9) of residues to adopt a stable helical conformation in solution.

On the other hand, Sisido and coworkers[88] used the same chromophoric amino acids inserted into an α-helical peptidic framework of poly-L-benzylglutamate (**33-35**). Interestingly, they found that when the electron transfer groups are separated by two alanines or by none, efficient fluorescence quenching was observed. This was predicted from the interchromophore distance that was calculated for an α-helix framework (Figure 15). However, when the two chromophores are separated by one alanine unit they are on opposite sides of the helical framework and further apart. Somewhat similar results have also been reported by the group of Kuki[89] using a shorter peptidic framework. They used an octapeptide composed of two unnatural amino acids, naphthylalanine and p-bromophenylalanine, inserted at specific positions. In addition, six aminoisobutyric acids were used to enforce a rigid 3_{10} helical conformation. They also found that energy transfer between the two chromophores was highly dependent on their spatial relationship.



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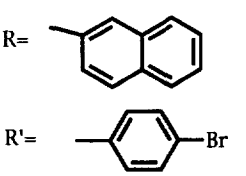


From the above studies, Sisido proposed[82] that electron (or energy) transfer can be efficient when the donor and acceptor groups are separated by 6Å or less, but is virtually negligible when separated by more than 10Å. These results constitute an important guideline for the development of functional peptide based molecular devices.

4.1.3. Devices with multiple donor and acceptor groups[82]

Another important strategy for development of photonic and electronic devices involves large polypeptides with several units of unnatural aminoacid bearing a chromophore on the side chain. Generally the polypeptides are prepared by the polymerization of a peptide fragment containing a mixture of natural and unnatural amino acids (Figure 16). The most commonly used natural amino acids are side chain protected glutamic acid and lysine, as well as modified alanines. All of these amino acids have a strong propensity to induce an α-helix conformation to the backbone. Depending on the sequence of the amino acids, it is possible to organize the chromophores at specific distances from each other and thus gain access to large and

regular molecular systems. After irradiation at a specific wavelength, either one (or more) electron transfer from a donor to an acceptor, or simple relay of energy

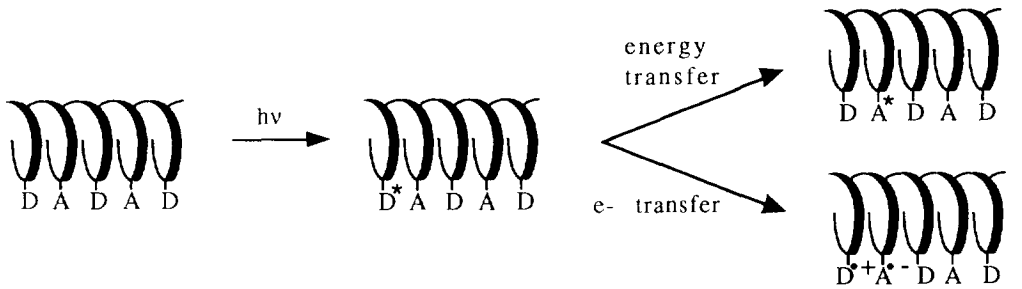


Figure 16. Schematic illustration of a photoactive molecular device with several donor (D) and acceptor (A) groups on the side chains of an helical peptide framework.

through several identical chromophores, can be observed (Figure 17). In the latter case, this process constitutes a molecular "wire." Several interesting molecular devices have been prepared by this strategy and are illustrated by examples **37**-**41**.[82] In particular, Sisido's team demonstrated that photoexcitation of system **41** results in efficient electron transfer and exciplex formation.[90]

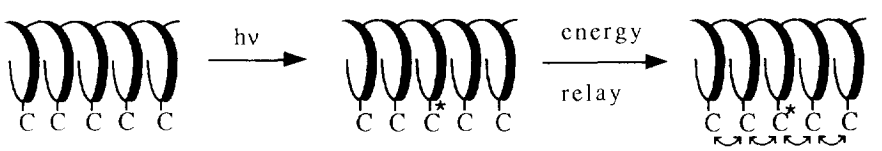
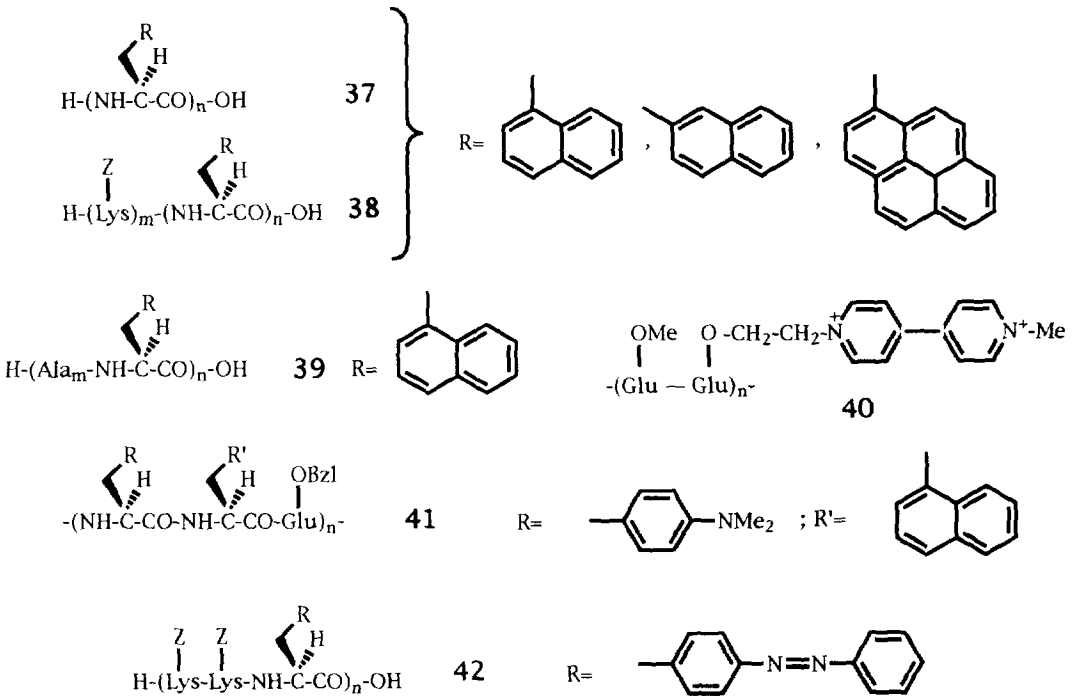


Figure 17. Schematic illustration of a photoactive molecular wire with several identical chromophores (C) on the side chains of a helical peptide framework.

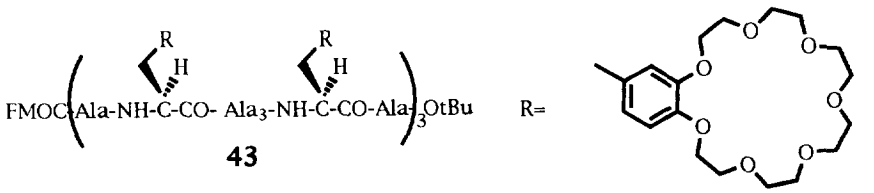
This approach offers to quite large linear molecules having several molecular effectors in a well defined spatial relationship has a disadvantage: the compounds obtained through polymerization of the repeating sequential peptides are unseparable mixtures of multiple oligomers with different molecular weights (hence different optical and physical properties). Nevertheless, the approach is flexible, rapid, and convenient, and will surely be used often in the future. Indeed, studies are currently under way to take advantage of the strong and photochemically reversible CD spectra of polypeptide-based assemblies for the development of photorecording devices.[91] For instance, polypeptide **42** was designed to adopt an α-helix

conformation that could be modulated by irradiation of the azobenzene side chains. It was synthesized and its CD spectrum was shown to change reversibly with the cis-trans isomerization of the diazo groups.[91] Even the helix sense can be photoregulated in some cases through the same type of cis-trans photoisomerization process.[92]



4.2 Molecular ionics

Molecular ionics[93,8d] is another relatively new area with promising applications. It is inspired by natural ion channel proteins that control the transport of ions across cell membranes. As stated earlier, one advantage of peptidic frameworks is the synthetic feasibility of relatively large molecules of nanometer scale. Coupled with the possibility of predicting the secondary structure and the side chain orientation from the primary sequence of amino acids, polypeptides are attractive scaffolds for the development of unimolecular weight artificial ion channels. To demonstrate this possibility, we designed[94] a 21 amino acid peptide (**43**) composed of L-alanines and six 21-crown-7 derivatives of L-phenylalanine. In an α-helix conformation, **43** forms a potential artificial ion channel by aligning the crown ethers on top of each other (Figure 18).



43

That hydrophobic entity has a length of about 3 nm, which is enough to span a lipid bilayer. The approach to **43** was to synthesize a suitably protected segment, the heptapeptide **44**, by solid phase peptide synthesis, then, after selective deprotections, to trimerize it in solution (Figure 19). Even though this approach worked and we obtained pure **43** after size-exclusion chromatography and HPLC, the segment coupling yields were very low owing to the insolubility of the seven residue segments. An improved strategy that gives higher overall yields of hexa-crown ether peptides involved coupling the segments on a solid support.[95]

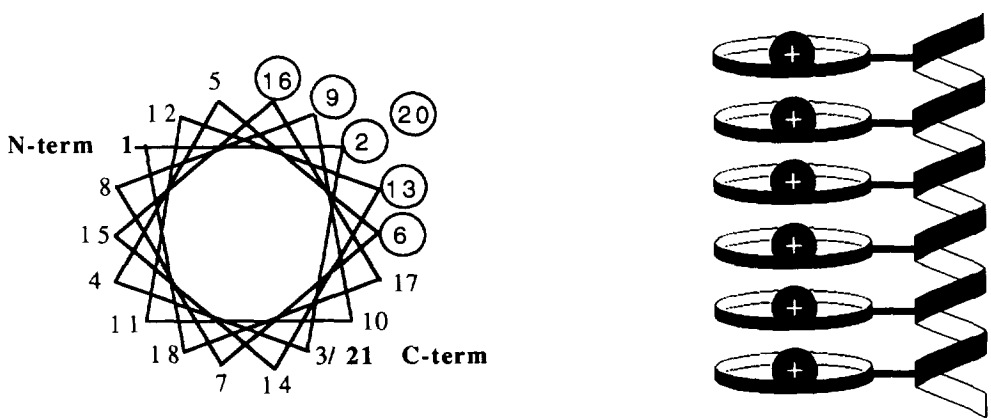
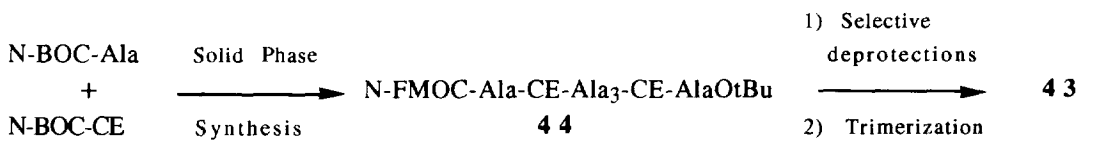


Figure 18. Left) Schematic representation of the α-helix of **43** looking down the helix axis. The position of the crown ether residues is noted by circles; right) proposed functional state of **43** in a lipid membrane.

Circular dichroism studies demonstrated that **43** adopts a largely α-helical conformation in 2,2,2-trifluoroethanol, and attested the ability of CD to predict the solution conformation. On the other hand, the supramolecular stacking arrangement of the crown ether side chains was supported by fluorescence spectroscopy.
Preliminary results in planar lipid bilayers demonstrated that **43** indeed acts as an artificial ion channel for Na^+, K^+, and Cs^+, although it is less proficient than natural ion

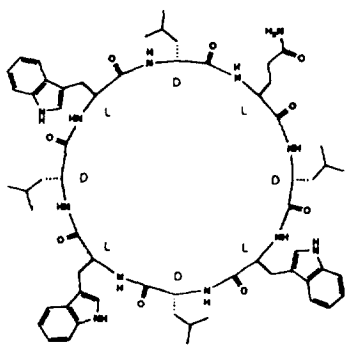
channels. In addition, we recently demonstrated in vesicle studies that a more lipophilic leucine version of **43** acts as an ion channel for Cs^+ and is as efficient as the natural channel Gramicidin A.[95]



CE = N-BOC-(21-crown-7) L-Phe

Figure 19. Synthetic strategy for the preparation of **43**.[94]

Another elegant approach to artificial ion channels has been reported by Ghadiri and coworkers.[96] They designed a cyclic octapeptide (**45**) that self-assembles to form nanotubes hydrophobic enough to incorporate into lipid bilayers. They have observed ion channel activity after incorporating **45** in a bilayer, and proposed that the channel is formed by the assemblage of eight macrocycles in the membrane as illustrated in Figure 20. They have also extended their work to the development of an artificial glucose transport system using the same self-assembling nanotubes.[97]



45 cyclo[-(Trp-D-Leu-)$_3$-Gln-D-Leu]

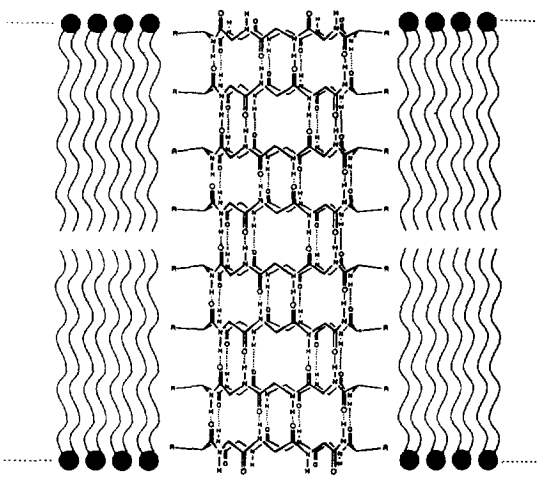


Figure 20. Schematic representation of the transmembrane channel formed by the self-assemblage of eight cyclic octapeptides **45**. Reproduced with permission from ref.96.

Even though it is too early to speculate on possible applications of these artificial channels, they clearly represent a new class of nanometer size materials

with novel and interesting properties potentially valuable for preparation of ion selective microelectrodes, molecular sensors, and drug-delivery systems.

5. LARGER MOLECULAR SYSTEMS

5.1 Enzyme and protein models

The development of artificial miniature enzymes and proteins has also been attempted with peptidic frameworks. Benner's group[98] has designed a simple synthetic decarboxylase (**46**) which takes advantage of an α-helical structure to correctly organize five primary amines of lysine side chains (Figure 21). Exhaustive structural and kinetic studies showed that the framework adopts an α-helical conformation and that the system indeed catalyzes the decarboxylation of a dianionic compound **47**. Although the rate enhancement obtained (roughly 10^2 compared to the spontaneous reaction) is far from the enhancement imparted by the natural enzyme (10^8), the work shows that even a simple molecular device with properly oriented functional groups can catalyze a difficult reaction without having a substrate binding site. It also points out that all of the reaction steps, not just the rate limiting one, will probably need to be catalyzed to achieve the rate enhancement observed with natural enzymes.[98c]

RNH-Leu-Ala-Lys-Leu-Leu-Lys-Ala-Leu-Ala-Lys-Leu-Lys-Lys-$CONH_2$

46 R= H or Ac

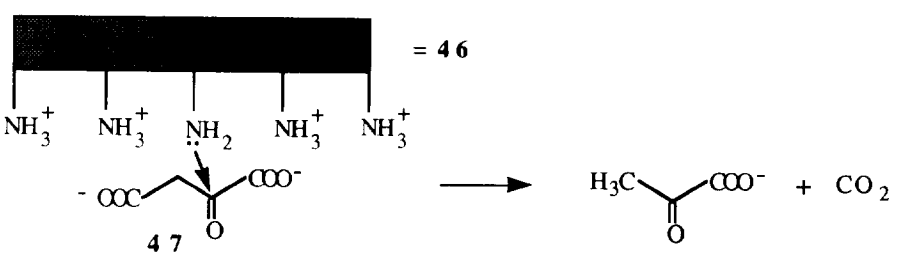


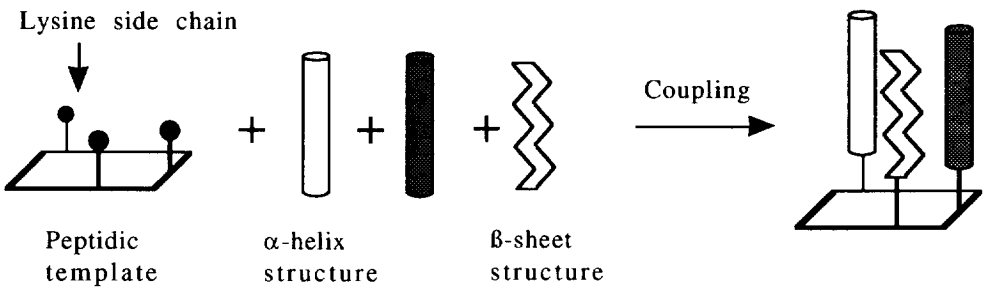
Figure 21. Schematic illustration of the synthetic decarboxylase **46** developed by Benner and coworkers using a helical peptidic framework.[98]

A different approach has been taken by Mutter and coworkers[99] to prepare artificial proteins. Their TASP (template assembly of synthetic proteins) concept is based on the attachment of peptide segments onto peptidic frameworks of defined three-dimensional structure to construct *de novo* designed proteins (Figure 22). Many peptidic frameworks (for example **48**) incorporating suitably γ-protected lysine were designed, synthesized, and characterized. The selective deprotection of the side chains

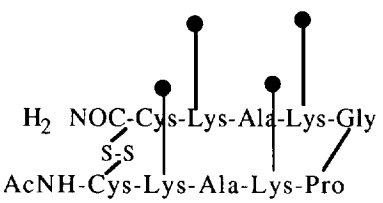
allow the synthesis of four or more different or identical peptidic structures. Several artificial proteins have been prepared and characterized by this strategy.[99] Even though no catalytic function has been successfully incorporated into these novel structures so far, the preparation of a functional artificial ion channel by this approach has been reported.[100]

Towards the preparation of artificial photosynthetic devices, DeGrado and coworkers[101] recently reported the preparation of helical peptidic scaffolds **49** and **50** designed to selectively bind one or four metalloporphyrins held at specific distances (Figure 23). The metalloporphyrins are bound selectively through the axial coordination of two imidazoles of histidines located in a hydrophobic pocket created when the peptidic frameworks aggregate to form four α-helix bundle structures.

These remarkable examples demonstrate not only the versatility of polypeptide frameworks but also their potential for use in engineerable electron-transfer, energy storage, and catalytic systems.



4 8



● = peptide structure

Figure 22. The template assembly of synthetic proteins (TASP) concept through peptidic frameworks developed by Mutter and coworkers.[99]

5.2 Peptide dendrimers

The preparation of large dendritic molecules has attracted considerable attention in the recent years,[102] and there is no doubt they will have useful properties and applications in the future. In this area, polypeptides are highly

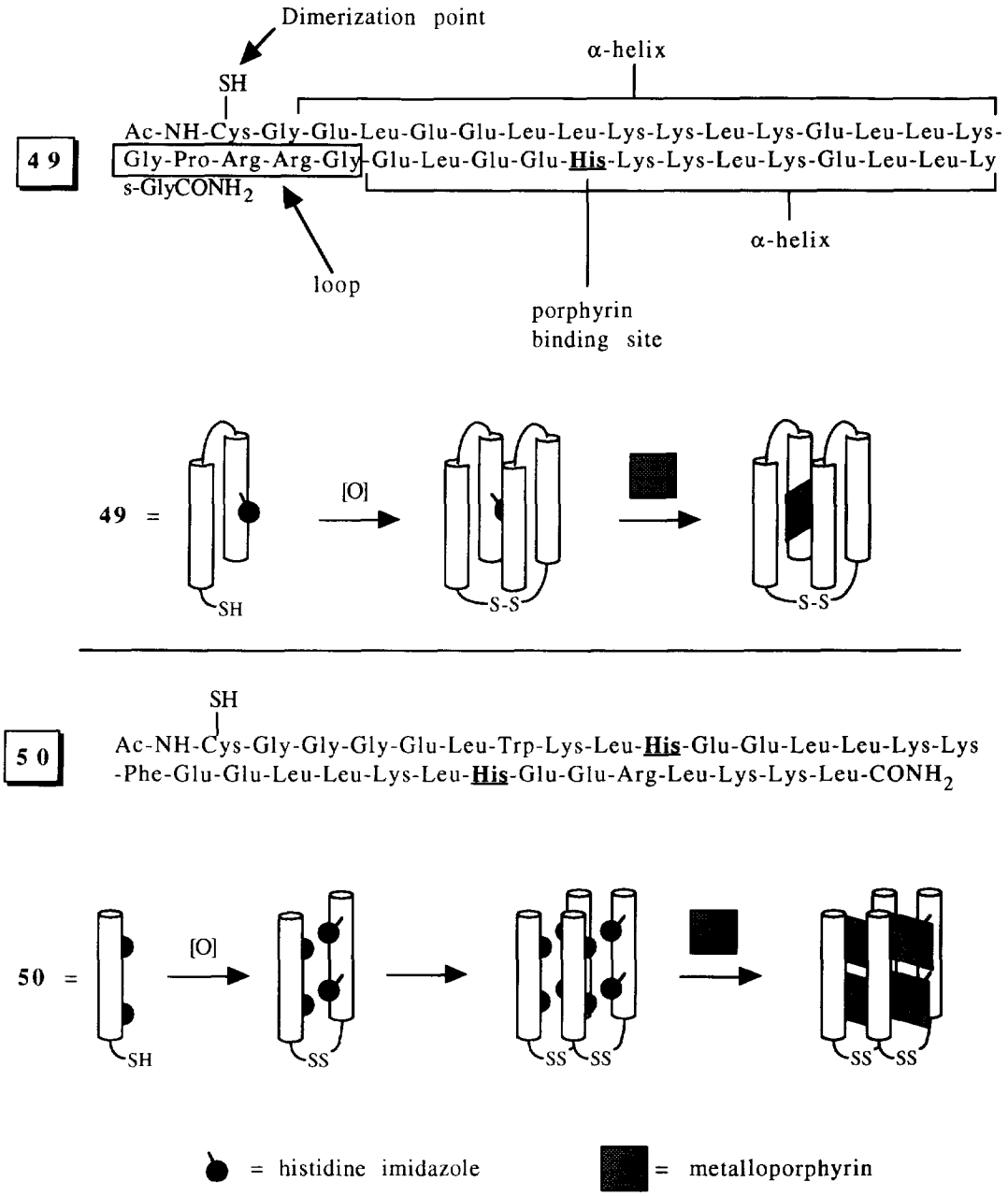
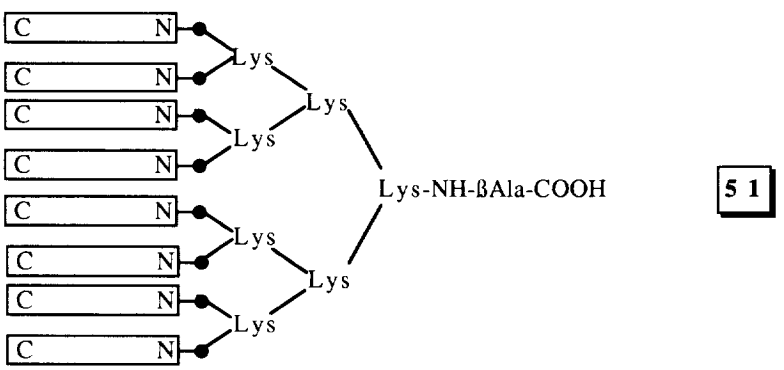


Figure 23. The development of self-assembling artificial proteins designed to bind metalloporphyrins.[101]

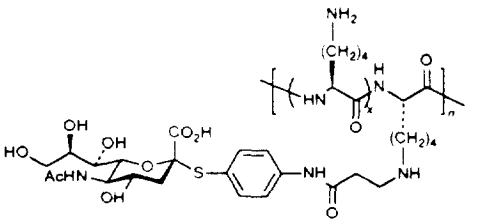
suitable for the preparation of such hyperbranched molecules, especially because of the possibility of synthesizing chiral dendrimers by solid phase procedures that do not require the isolation of (sometimes) quite insoluble intermediates. In particular, due to their trifunctional structure, lysine[103-105] and glutamic acid[106] can be considered as versatile building blocks for the synthesis of chiral dendrimers.

Tam and coworkers[103] have reported the use of lysine dendrimers to construct useful molecular systems. For instance, the attachment of an antigenic peptide to several amino groups of the outer shell of lysine dendrimers has already led to the development of diagnostic reagents and vaccines.[103] Indeed, the clustering of several antigenic peptides has been shown to favor a higher immune response than does the isolated peptide itself. This approach to produce vaccines has been coined MAP (multiple antigene peptides) by Tam and coworkers.[105] In order to develop an AIDS vaccine, the same group also recently reported the preparation of **51**. Compound **51** is formed by the simultaneous coupling of a peptide corresponding to a neutralizing determinant of the surface protein gP120 of HIV-1 to a lysine dendrimer of eight units.[105]

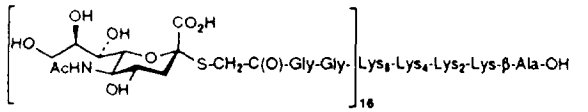


In a related but more linear approach, Roy and coworkers[107] have used an α-helical polylysine framework for the development of a vaccine for the Influenza A virus and for one kind of meningitis. Sialic acid derivatives were attached to the amino group of the lysine side chains via a Michael addition to give the desired glycoconjugate, such as **52**. Studies demonstrated that the glycoconjugate effectively generated antibodies in mouse. An advantage of this strategy is the ability to orient

several antigenic sites perpendicular to the helical scaffold, which is biodegradable and normally not immunogenic. However, a rigourous control of the incorporation of the sialic acid derivatives is not possible. The same research group reported recently the use of a lysine dendrimer/sialic acid conjugate **53** for the same goals.[108]



52



53

The examples presented above show the potential of polypeptides for the construction of large chiral structures with some macromolecular order. The preparation of peptide dendrimers will surely be an area of active research in the future that will lead to novel molecular systems with useful applications.

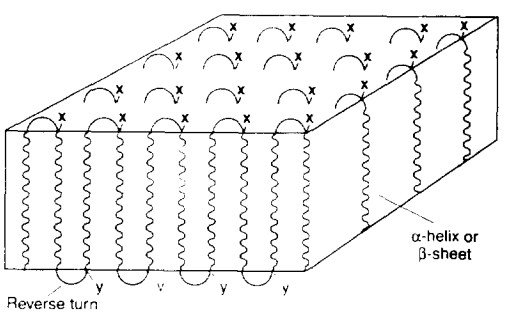


Figure 24. The correct folding of polypeptides having a repeating sequence can be used to prepare lamellar molecular "crystals" bearing specific functional groups (X and Y) in well defined structural relationships. Reproduced with permission from ref.109.

5.3 Molecular materials

One field where designed polypeptides will likely have an important impact is in preparation of novel "smart" materials and surfaces.[82,109] An illustrative example has been reported by Tirrell and coworkers.[110] They used genetically engineered bacteria to synthesize polypeptides with repeating sequences, for example -((Gly-

Ala)$_3$-Gly-Selenomethionine)$_9$-. These polypeptides were designed to fold into lamellar molecular "crystals" that orient functional groups or atoms (X and Y) on surfaces in a well defined relationship (Figure 24). Furthermore, the relationships could eventually be fine-tuned to obtain the desired properties by modification of the structure and the sequences of the polypeptidic frameworks. Such molecular materials could be useful in development of tailor-made surfaces for photographic applications and molecular electronic devices.

6. CONCLUSIONS AND PROSPECTS

A primary objective of this review article was to present an up-to-date account of the reported molecular devices and receptors being built using peptidic frameworks, as well as their potential applications. A second objective was to stimulate research in this area. The availability of the building blocks and their intrinsic chirality, the ease of synthesis, purification, and characterization, and the predictable solution conformation from the primary amino acid sequence make polypeptides the frameworks *par excellence* for the design and the development of smart molecules tailored for specific functions at the molecular level. However, we are still far off from understanding and predicting reliably the behavior and the properties of peptide based molecular systems. In fact, accurate prediction of the solution conformation (secondary *and* tertiary structures) and the side chain orientations of a peptidic molecule made from its linear sequence will require a great deal more of fundamental work. The same is true for the characterization of the newly designed molecular devices. Here, the recent and important developments in multidimensional NMR, imaging techniques, and surface science should be of great help to designer chemists. From the observed developments of the past 10 or 15 years, and the important potential uses, it is legitimate to foresee that the construction of molecular systems using peptidic frameworks will be an active area of research in the future.[111]

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