TUTORIAL REVIEW

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Highly ordered structures of peptides by using molecular scaffolds

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Protein secondary structures such as α-helices, β-sheets, and β-turns are important in inducing the three-dimensional structure and biological activity of proteins. Designing secondary structure mimics composed of short peptides has attracted much attention not only to gain fundamental insight into the factors affecting protein folding but also to develop pharmacologically useful compounds, artificial receptors, asymmetric catalysts, and new materials. In this *tutorial review*, we focus on molecular scaffolds employed to induce β-sheet-like structure in attached peptide chains, thereby creating highly ordered molecular structures, and discuss the versatility of these molecular scaffolds to regulate the attached peptide strands in the appropriate dimensions.

1 Introduction

Architectural control of molecular self-organization is of great importance for the development of functional materials.[1] Control of hydrogen bonding[2] attracts much attention in the design of various molecular assemblies by virtue of its directionality and specificity.[3] The reversibility and tuneability of hydrogen bonding is also of fundamental importance in the physical properties of molecular assemblies. The utilization of self-assembling properties of short peptides, which possess chiral centers and hydrogen bonding sites, is considered to be a relevant approach to highly ordered molecular assemblies.

Hydrogen bonds play a crucial role in regulating the three-dimensional structure and function of biological systems and the highly-ordered molecular assemblies constructed in proteins enable them to fulfil the unique functions, as observed in enzymes, receptors, *etc.* The regular secondary structure components of proteins such as α-helices, β-sheets, and β-turns are stabilized both by hydrogen bonding and hydrophobic interaction of side chains.[4] Highly specific patterns of complementary intra- and inter-molecular hydrogen bonds are created in such secondary structures; a series of 12-membered hydrogen-bonded rings are formed in parallel β-sheets, while an alternating series of 10- and 14-membered hydrogen-bonded rings are organized in antiparallel β-sheets. Although β-sheets are the key structural elements in the three-dimensional structure and biological activity of proteins, the structure and stability of β-sheets are still not as well understood as α-helices. It is difficult to predict the pattern of protein folding from the sequence of amino acids.

Considerable efforts have focused on designing secondary structure mimics composed of short peptides to gain fundamental insight into the factors affecting protein structure and stability, and to facilitate the rational design of pharmacologically useful compounds. Generally, preparation of chemical models of β-sheet is difficult due to the complexity of their folding and their propensity for self-association. Therefore, various molecular scaffolds have been employed to create the β-sheet-like structure of attached peptide chains and serve as substitute for the β-turn in the chemical models of protein secondary structures. This review sketches an outline of such molecular scaffolds, both organic and

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organometallic, which have been shown to induce β-sheet-like structure in attached peptide chains and highly ordered molecular structures.

2 Organic molecular scaffold

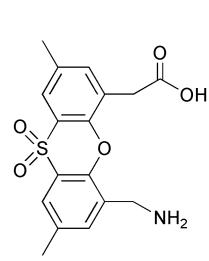
The utilization of molecular scaffolds is one strategy for organization of peptide structures, which allows control of intramolecular interaction of peptide or peptidomimetic strands. This section focuses on scaffolds that are purely organic in nature and the following section discusses organometallic scaffolds. It should be noted that the temperature-dependent NMR shifts of the NH protons, ϕ dihedral angles calculated by a Karplus analysis of $J_{C\alpha H-NH}$ coupling constants, and the proton magnetic resonance nuclear Overhauser effect (NOE) studies are a useful tool to determine the β-sheet structure.

Aromatic scaffolds have been demonstrated to induce β-sheet-like structure between two attached peptides.[5] The rigid aromatic spacer **1** forces a hydrogen bonding bridge in the cyclic peptide **2** consisting of the amino acid sequence Ile-Val-Gly. Although cyclic peptides may adopt several conformations in a solution, NOE studies and temperature-dependent NMR shifts of the NH protons indicate that the cyclic peptide **2** forms the β-type hydrogen bonding bridge in DMSO-d_6.[5a]

The biphenyl-containing pseudo-amino acid scaffold **3** is also incorporated into the backbone of cyclic peptides **4** to form antiparallel β-sheets.[5b] Three interconverting (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-diastereomers are observed in a solution due to the atropisomerism of the biphenyl units. NMR (^{1}H NMR, COSY, and ROESY) studies and molecular dynamics calculation suggest that the major diastereomer of **4** to adopt the antiparallel β-sheet conformation in DMSO-d_6 is the (*R*,*R*)-isomer.[5b] The chemical shift of the Me (Ala) resonance at high field supports the (*R*)-configuration of both biphenyl moieties. In the case of the scaffold **3**, the hydrogen bonding pattern is considered to depend on the chirality of the biphenyl moieties. For the cyclic peptide **5**, the NMR technique at pH 5.0 in 95 : 5 10 mM CD_3COOD/CD_3COONa aqueous buffer/D_2O and simulated-annealing protocols with ROE-derived distance restraints reveal the type V′ β-turn.[6] The semi-rigid biphenyl scaffold induces this unexpected turn type. Incorporation of this scaffold into the backbone of cyclic peptides appears to be a useful strategy for tuning conformational properties.

The epindolidione scaffold **6** is connected by L-Pro-D-Ala and a chain-reversing urea linking unit to the peptide chains, leading to the artificial antiparallel β-sheet **7**.[7] In contrast to the above-mentioned scaffold, the rigid epindolidione scaffold serves as a central strand of the β-sheet to orient the hydrogen-bonding functionality appropriately, although the strand-strand side chain interactions are not possible due to the planarity of the epindolidione strand mimic. The dipeptide L-Pro-D-Ala is incorporated into the turn region to favor the formation of a type II β-turn. The antiparallel β-sheet conformation of **7** in DMSO-d_6 is supported by NMR: the temperature dependence of the amide NH chemical shifts, ϕ dihedral angles calculated by a Karplus analysis of $J_{C\alpha H-NH}$ coupling constants, and NOE effects.[7a] The parallel β-sheet is also formed in the case of **8** in DMSO-d_6, in which the urea linking units are not present.[7b] In these systems, a pair of two-stranded β-sheets shares a β-strand mimic. The combination of the rigid epindolidione scaffold as a central strand with the dipeptide L-Pro-D-Ala as β-turn is important for β-sheet nucleation.

The dibenzofurans, in which the distance between C4 and C6 (4.9 Å) is close to that between the strands of an antiparallel β-sheet, are used as a backbone of the nucleating amino acid. Protein folding is driven not only by the hydrogen bonding but also the hydrophobic interaction. For stabilization of a β-sheet structure, the 4-(2-aminoethyl)-6-dibenzofuranpropionic acid scaffold **9** is designed to form a hydrophobic cluster composed of the dibenzofuran skeleton and the hydrophobic side chains of the flanking amino



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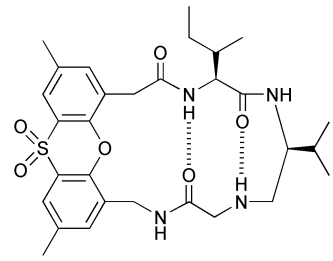

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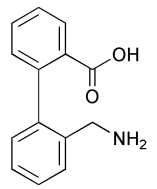

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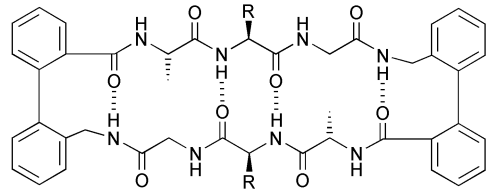
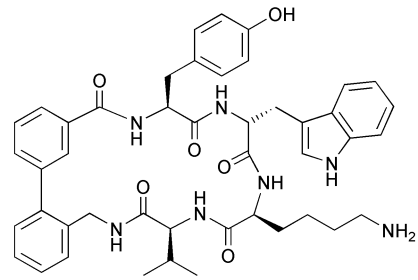


4: R = CH_2Ph, *i*-Pr



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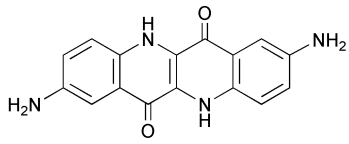
acids in addition to intramolecular hydrogen bonding between the attached amino acid residues.[8] The CD spectrum of heptapeptide **10** (R^1 = R^6 = Val, R^2 = R^7 = Lys, R^3 = R^8 = Leu) reveals both random coil and β-sheet structure at pH 2.9 in 10 mM phosphate buffer. Strong NOEs between the dibenzofuran protons and the methyl protons on the flanking R^3 Leu and R^6 Val residues confirm the formation of a hydrophobic cluster. The upfield shift of these methyl protons in ^{1}H NMR due to the ring current effect of the dibenzofuran skeleton also supports the hydrophobic cluster formation at pH 4.6 in 10 mM 9 : 1 H_2O/D_2O, 50 mM deuterated acetate buffer.[8a] The formation of a hydrophobic cluster plays a key role in β-sheet nucleation. Heptapeptides **10** are capable of forming an antiparallel β-sheet structure only when the side chains of the flanking amino acid residues are hydrophobic. Furthermore, the His residue is also demonstrated to nucleate a cluster through π-cation-like interactions with improvement of solubility.[8b]

Metal ions have been known to exhibit a variety of properties in proteins, the most important of which is the stabilization of the structures required for biological functions. The bipyridine-based molecular scaffolds **11** and **12** are incorporated into peptides to promote β-sheet folding upon the addition of Cu(II) ions.[9] Coordination to Cu(II) in a cisoid square planar conformation brings the attached peptide strands in an appropriate dimension. The peptide, Lys-Val-Thr-Val-Lys-**11**-Lys-Val-Thr-Val-Lys-NH_2 (**13**), adopts an antiparallel β-sheet structure through the coordination at pH 9.5 in 10 mM borate buffer although peptide **13** exists in a random coil conformation in the absence of Cu(II). On the other hand, the peptide, Lys-Val-Thr-Val-Lys–Val-**12**-Val-Lys-Val-Thr-Val-Lys-NH_2 (**14**), in which **11** is replaced by –Val-**12**-Val–, is capable of effecting β-sheet structure formation even in the absence of Cu(II) through hydrophobic cluster formation at pH 9.1 in 10 mM borate buffer. Hydrophobic cluster formation may stabilize the



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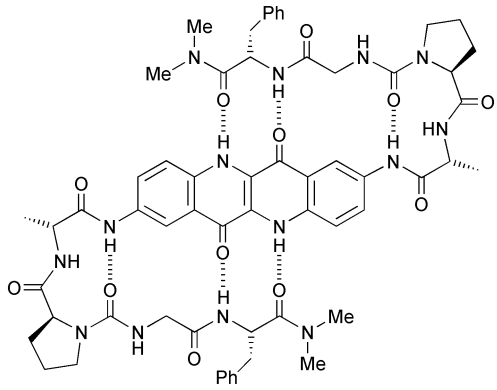

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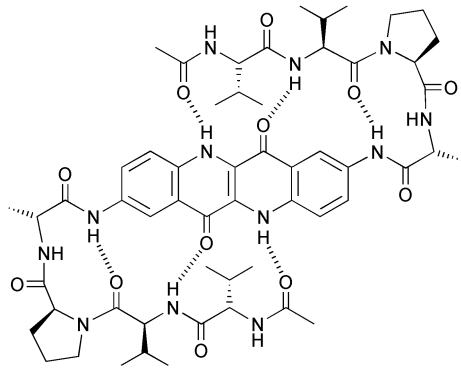

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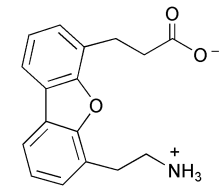

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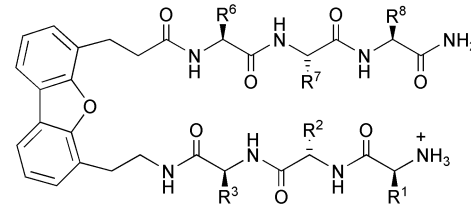

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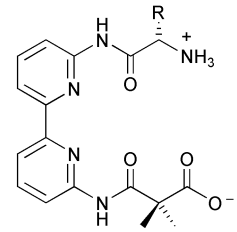

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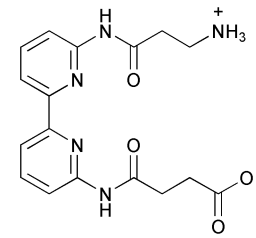

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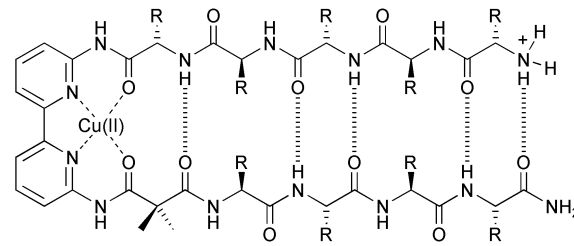

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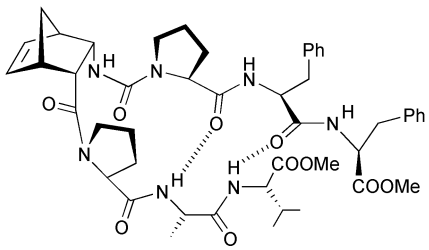
cisoid bipyridine conformation to afford a nucleation competent conformation. The addition of Cu(II) strengthens the β-sheet structure of **14**. The ligand substructure of the peptides would be stabilized in the cisoid conformation by Cu(II) binding, promoting β-sheet folding in the attached peptide strands. Hydrophobic cluster formation alone or hydrophobic cluster formation in combination with Cu(II) binding play a crucial role for β-sheet nucleation.

The *endo*-(2*S*,3*R*)-2-amino-3-carboxynorbornene represents a conformationally constrained β-amino acid scaffold, which is related to a turn-inducer proline and serves as a β-sheet inducer.[10] Pseudopeptide **15** containing a urea linkage is designed to offset the two peptide chains from one another so as to allow interchain hydrogen bonding. The $J_{C\alpha H-NH}$ coupling constants and NOEs suggest that pseudopeptide **15** adopts a parallel β-sheet conformation in $CDCl_3$. The parallel β-sheet is stabilized by two intramolecular hydrogen bonds involving the NHs of Ala and Val units. On the other hand, an antiparallel β-sheet conformation is formed in the case of the peptide **16** in $CDCl_3$. The CD spectra of **16** (in CH_2Cl_2 or CH_3CN) exhibit a maximum at 190 nm and a minimum at 225 nm, which are almost exactly those expected for a β-sheet conformation. The conformational constraint of the norbornene unit is necessary for the formation of these β-sheet conformations. The *endo*-(2*S*,3*R*)-norbornene dicarbonyl unit[11] of **17** is also demonstrated to be a reverse-turn molecular scaffold for nucleating the hydrogen-bonded parallel β-sheet structures in DMSO-d_6. The advantage of using norbornene derivatives as molecular scaffolds is that they have built-in U-architecture and that they are small and of low molecular weight.

An oligourea molecular scaffold is designed to hold multiple peptide or peptidomimetic strands in proximity.[12] Artificial parallel β-sheet **19**, in which a diurea molecular scaffold juxtaposes two peptide strands, is synthesized by treatment of diamine **18** with peptide isocyanates. ^{1}H NMR spectroscopy indicates that the peptide **19** adopts a parallel β-sheet conformation in $CDCl_3$.[12a] To stabilize a β-sheet conformation, 5-amino-2-methoxybenzamide β-strand mimic as a second structural template is introduced into the peptide **20**. The exceptional downfield shift of the "upper" urea NH and leucine NH resonances in the ^{1}H NMR and NOE studies suggests that **20** is hydrogen-bonded to form a small artificial β-sheet in $CDCl_3$. The combination of the diurea molecular scaffold and 5-amino-2-methoxybenzamide β-strand mimic stabilizes the formation of an antiparallel β-sheet effectively.[12b] Furthermore, well-defined β-sheet dimers **21**, in which tripeptides, the diurea molecular scaffold, and 5-amino-2-methoxybenzoic acid hydrazide β-strand mimic with an oxalamide linker are combined, is formed in $CDCl_3$ by this strategy.[12c] Oligoureas could orient different groups in a parallel fashion. The β-strand mimic helps reinforce and rigidify the β-sheets and prevent intermolecular association.

A urea molecular scaffold is introduced into peptides to induce hydrogen-bonded duplex formation.[13] The single-crystal X-ray structure determination of the dipeptidyl urea **22** composed of two dipeptide chains bearing the C-terminal pyridyl moiety (–L-Ala-L-Pro-NHPy) reveals that two molecules are held together by six intermolecular hydrogen bonds to form a hydrogen-bonded duplex. The NOE ($CDCl_3$) and FT-IR (CH_2Cl_2) studies indicate the preservation of the hydrogen-bonded duplex of **22** even in a



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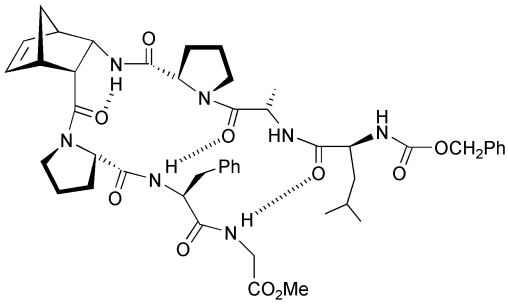

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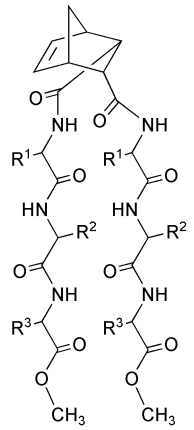

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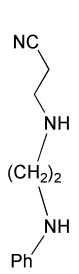

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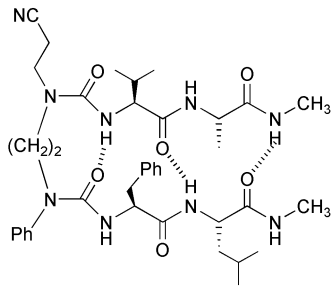

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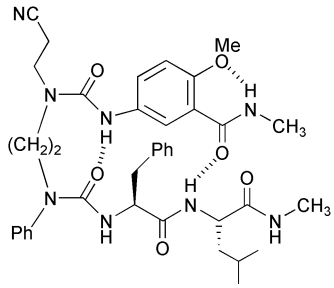

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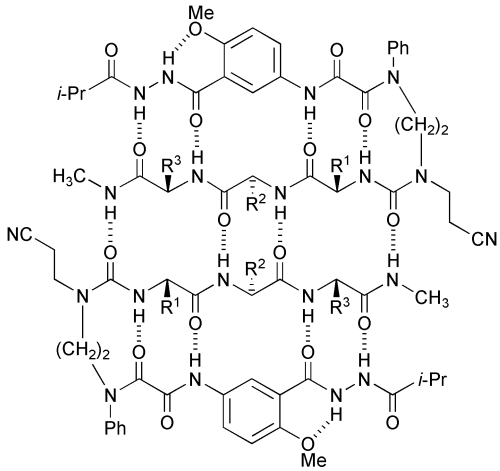

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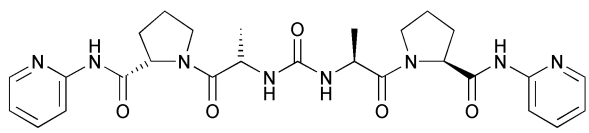
solution. Furthermore, a shuttle-like molecular dynamics based on the recombination of hydrogen bonds is observed as shown in Fig. 1. The activation energy of this process was calculated as 9.4 kcal mol^{-1} from the Arrhenius equation. The dipeptidyl urea **23** composed of two dipeptide chains bearing the C-terminal pyrenyl moiety (–L-Ala-L-Pro-$NHCH_2$Pyr) exhibits both monomer and eximer emissions in the fluorescence spectra in $CHCl_3$. On the other hand, only monomer emission was observed with the peptidyl urea composed of only one dipeptide chain. These results and the ESI-MS spectra support the duplex formation. A combination of the C-terminal amide NH function in each side and the designed sequence of hydrogen-bonding sites are considered to be a crucial factor for the duplex formation.

The quadruply hydrogen-bonded duplex **24·25**, which contains the unsymmetrical, complementary hydrogen-bonding sequences ADAA/DADD, serves as a noncovalent scaffold for the nucleation of β-sheet structure.[14] The hydrogen-bonded duplex is regarded as a two-stranded mimic. The attachment of four tripeptide chains to the same end of a hydrogen-bonded duplex **24·25** leads to the formation of four hybrid duplexes, **24a·25a**, **24a·25b**, **24b·25a**, and **24b·25b**. The formation of β-sheet conformation in $CDCl_3$ is revealed by the changes in H_α chemical shifts and the numerous inter- and intrastrand NOEs. The duplex scaffold prevents further aggregation in the peptide segment. The reversibility and tune-



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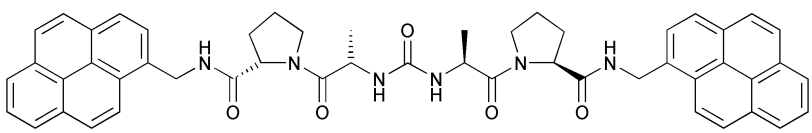

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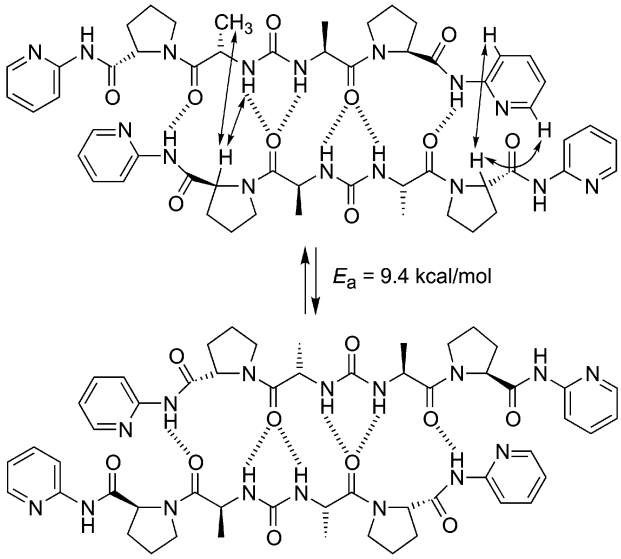


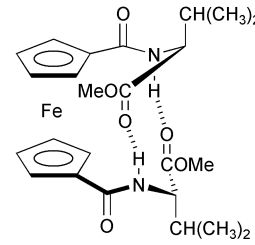
Fig. 1 The shuttle-like dynamic process of **22**. NOEs observed between the dipeptidyl ureas are shown with arrows.

ability of hydrogen bond formation would allow direct control of β-sheet nucleation.

3 Organometallic scaffold

Ferrocenes are recognized as an organometallic scaffold for molecular receptors possessing redox properties and two rotatory coplanar cyclopentadienyl (Cp) rings with *ca.* 3.3 Å separation.[15] The inter-ring spacing of ferrocenes is appropriate for hydrogen bonding of the attached peptide strands. The utilization of a ferrocene unit as a molecular scaffold is considered to be one strategy to study the hydrogen bonding ability of various peptide strands.[16]

The capability of ferrocenes as a molecular scaffold for an ordered conformation through intramolecular hydrogen bonds has been demonstrated in a preliminary study using a valine unit.[16a] Two identical intramolecular hydrogen bonds are formed between the ester carbonyl of each valine and the NH of another valine in $CDCl_3$ to give a 10-membered hydrogen-bonded ring in the ferrocene **26**, which resembles the hydrogen bonding pattern



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observed in an antiparallel β-sheet. Generally, an antiparallel β-sheet is characterized by alternating 10- and 14-membered hydrogen-bonded rings, while a parallel β-sheet is formed by a 12-membered hydrogen-bonded ring.

Conformational enantiomers based on the torsional twist about the Cp(centroid)–Fe–Cp(centroid) axis are possible in the case of the 1,1′-disubstituted ferrocene as shown in Fig. 2.[17] Conformational enantiomers can interconvert with ease due to the low barrier of Cp ring twisting. The introduction of peptide chains into a ferrocene scaffold is envisaged to induce conformational enantiomerization by restriction of the torsional twist through the intramolecular hydrogen bondings. In this context, we have focused on the introduction of dipeptide chains into the ferrocene scaffold to

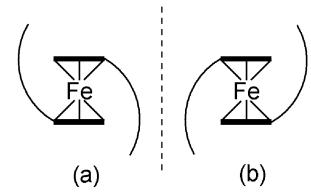
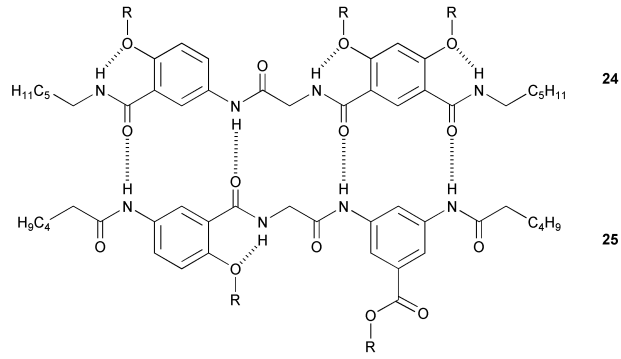
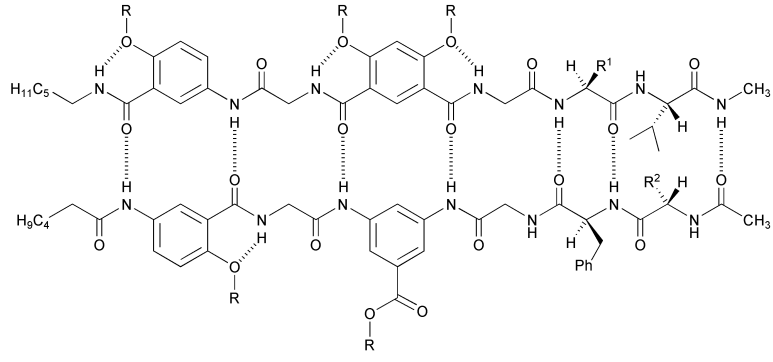


Fig. 2 Enantiomorphous conformations of the 1,1′-disubstituted ferrocene. The enantiomorphs are related by the mirror plane.



24 **25**

24•25



24a = **24**-Gly-Ala-Val-NHMe

24b = **24**-Gly-Leu-Val-NHMe

25a = **25**-Gly-Phe-Leu-Ac

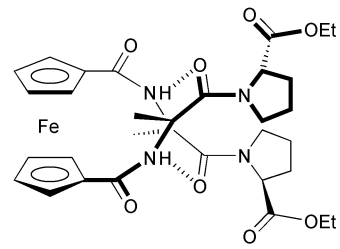
25b = **25**-Gly-Phe-Ala-Ac

24a/24b•25a/25b

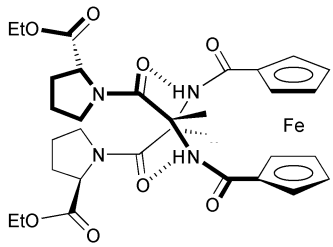
induce chirality organization through the intramolecular interchain hydrogen bonding.[18]

The crystal structure of **27** bearing the podand L-dipeptide chains, –L-Ala-L-Pro-OEt, reveals the formation of two C_2-symmetrical intramolecular hydrogen bondings between CO (Ala) and NH (another Ala) of each podand dipeptide chain to give a 10-membered hydrogen-bonded ring.[18a–b] The molecular structures of **27** and **28** composed of the enantiomeric dipeptide chains, –D-Ala-D-Pro-OEt, are in a good mirror image relationship as shown in Fig. 3, indicating that they are conformational enantiomers (Fig. 2). As a result, the introduction of the chiral dipeptide chains into ferrocene induces the chirality organization by restriction of the torsional twist through the intramolecular hydrogen bonds between podand peptide chains.[18b]

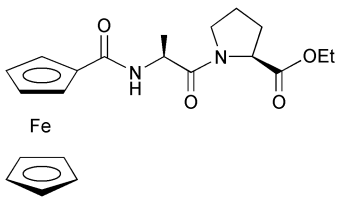
A good mirror image relationship of an intrinsic induced CD around the absorbance of the ferrocene function in CD spectra of **27**



27



28



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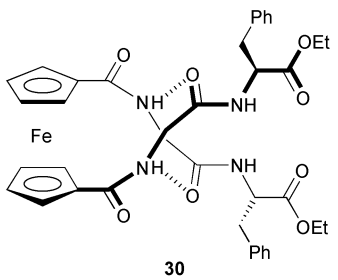

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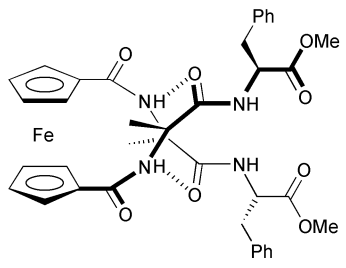

31

and **28** in MeCN indicates the presence of the chirality-organized structure *via* intramolecular hydrogen bondings even in solution. In contrast, such induced CD was not detected in the case of the ferrocene **29** bearing only one dipeptide chain, –L-Ala-L-Pro-OEt. Furthermore, two identical intramolecular hydrogen bonds between the podand dipeptide chains are supported by ^{1}H NMR ($CDCl_3$) and FT-IR (CH_2Cl_2) analyses.

Another noteworthy feature of the ferrocenes bearing podand dipeptide chains is their strong tendency to self-assemble through contribution of all available hydrogen bonding donors in a solid state. In the case of the ferrocene **30** bearing the podand dipeptide chains (–Gly-L-Phe-OEt), each chirality-organized molecule is bonded to two neighboring molecules. Each podand dipeptide chain forms a 14-membered intermolecularly hydrogen-bonded ring through two pairs of symmetrical intermolecular hydrogen bonds between the NH of the Phe residue and CO adjacent to the ferrocene unit.[18b] A similar organization is also observed in the case of the ferrocene **31** bearing the podand dipeptide chains (–L-Ala-L-Phe-OMe).[19] The ferrocene serves as a reliable organometallic scaffold for the construction of the chirality-organized structure *via* intramolecular hydrogen bondings. The architectural control of molecular assemblies utilizing peptide chains, which possess chiral centers and hydrogen bonding sites, is considered to be a useful approach to artificial highly-ordered systems.

Metal ions have been known to exhibit a variety of properties in proteins, one of which is structural stabilization for biological functions.[20] Metal ions also play a crucial role in the redox processes of proteins.[20] The incorporation of metal coordination sites into peptides has been investigated for the stabilization of secondary structures[21] and catalytic activities.[22] Phosphine-containing β-turn ligands are used in asymmetric catalysis.[22b]

The ferrocene **32** bearing the podand dipeptide chains, –L-Ala-L-Pro-NHPy, forms the palladium complex **33** with $PdCl_2(MeCN)_2$ to stabilize the chirality conformational regulation in both solution and solid states.[23] The greater downfield shifting of Ala N–H resonance is observed in the ^{1}H NMR spectrum of the palladium complex **33** in $CDCl_3$ as compared with that of **32**, indicating that complexation strengthens the intramolecular hydrogen bonding. The single-crystal X-ray structure determination of **33** confirms the pseudo-helical conformation through palladium binding and chirality organization as depicted in Fig. 4.

4 Conclusion and outlook

A variety of molecular scaffolds have been designed and incorporated into peptides to induce highly ordered structures of peptides. With molecular scaffolds, the attached peptide strands are regulated in the appropriate dimensions, for example, as observed in protein β-sheets. Introduction of additional hydrophobic interaction sites, β-strand mimics, and reverse-turn units into peptides permits further regulation. These chemical models of protein secondary structures afford fundamental insight into the factors affecting protein structure and stability. In addition to organic molecular scaffolds, ferrocenes serve as a reliable organometallic scaffold for the construction of chirality-organized structures *via* intramolecular hydrogen bonding. This bioorganometallic chemistry is envisioned to provide not only a peptidomimetic basis for protein folding, but also pharmacologically useful compounds, artificial receptors, asymmetric catalysts, and new materials with functional properties.[24] The architectural control of molecular assemblies utilizing peptide chains, which possess chiral centers and hydrogen bonding sites, is envisioned to be a useful approach to artificial highly-ordered systems.

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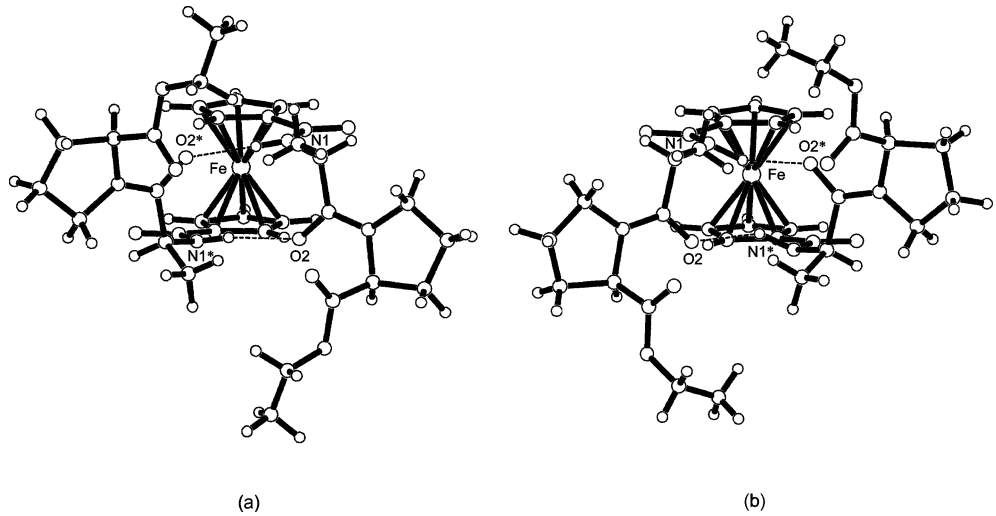


Fig. 3 (a) Molecular structures of **27** and (b) **28**.

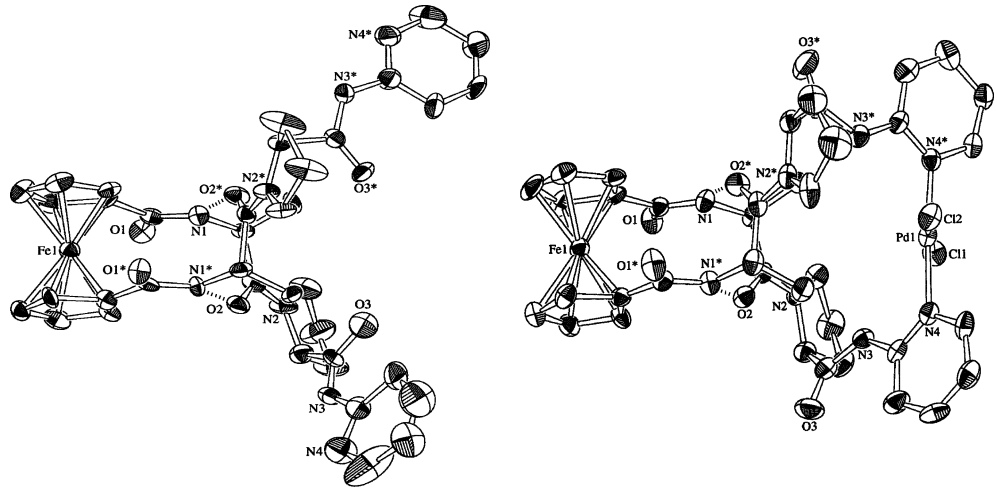
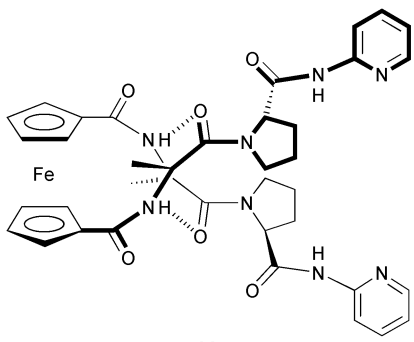


Fig. 4 (a) Molecular structures of **32** and (b) **33**.



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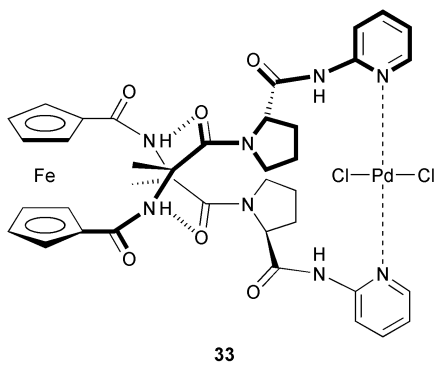

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