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REVIEW ARTICLE

Dipeptide-induced chirality organization

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Abstract This review describes an outline of dipeptide-induced chirality organization by using molecular scaffolds. A variety of ferrocene-dipeptide conjugates as bioorganometallics are designed to induce chirality-organized structures of peptides. The ferrocene serves as a reliable organometallic scaffold with a central reverse-turn unit for the construction of protein secondary structures via intramolecular hydrogen bondings, wherein the attached dipeptide strands are constrained within the appropriate dimensions. Another interesting feature of ferrocene-dipeptide conjugates is their strong tendency to self-assemble through contribution of available hydrogen bonding sites for helical architectures in solid states. Symmetrical introduction of two dipeptide chains into a urea molecular scaffold is performed to induce the formation of the chiral hydrogen-bonded duplex, wherein each hydrogen-bonded duplex is connected by continuous intermolecular hydrogen bonds to form a double helix-like arrangement.

Keywords Peptide · Amino acid · Ferrocene · Pyridine · Urea · Hydrogen bond · Chirality organization · Self-assembly · Bioorganometallic chemistry

Abbreviations

Ala	Alanine
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
i-Bu	Isobutyl
t-Bu	*tert*-Butyl
CA	(1*R*,3*S*)-Camphoric acid
CD	Circular dichroism
Cp	Cyclopentadienyl
CSA	Cysteamine
DNA	Deoxyribonucleic acid
Et	Ethyl
Fc	Ferrocene
Fc-aa	1,n′-Diaminoferrocene
Fc-ac	1′-Aminoferrocene-1-carboxylic acid
Fc-cc	Ferrocene-1,1′-dicarboxylic acid
FT-IR	Fourier transform infrared spectrometry
Gly	Glycine
Leu	Leucine
Me	Methyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Ph	Phenyl
Phe	Phenylalanine
Pr	Propyl
Pro	Proline
Val	Valine

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Introduction

Architectural control of molecular self-organization is of importance for the development of functional materials [1–3]. Highly-organized molecular assemblies are constructed in proteins to fulfill the unique functions as observed in enzymes, receptors, etc. Hydrogen bonding is a key factor in regulating the three-dimensional structure and function of biological systems. Secondary structures of proteins such as α-helices, β-sheets, and β-turns play an important role in protein folding, which is mostly stabilized by hydrogen bonding and hydrophobic interaction of side chains [4, 5].

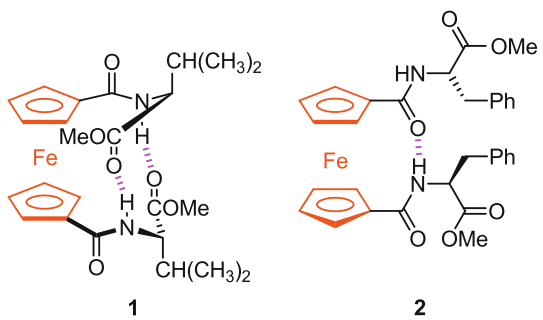
Although β-sheets are the key structural elements in proteins to fulfill the biological activity, the structure and stability of β-sheets are less understood as compared with those of α-helices. A series of 12-membered hydrogen-bonded rings are formed in parallel β-sheets, while an alternating series of 10- and 14-membered hydrogen-bonded rings are organized in antiparallel β-sheets. It is difficult to predict the pattern of protein folding from the sequence of amino acids. Considerable efforts have focused on to design secondary structure mimics composed of short peptides for fundamental insight into the factors affecting the protein structure and stability, and for rational design of pharmacologically useful compounds. Highly specific patterns of complementary intra- and intermolecular hydrogen bonds are formed in such secondary structures. Control of hydrogen bonding [6] attracts much attention in the design of molecular assemblies by virtue of its directionality and specificity [7–9]. The tuneability and reversibility 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 hydrogen bonding sites possess and chiral centers, is considered to be a relevant approach to highly ordered molecular assemblies. This review describes an outline of dipeptide-induced chirality organization by using molecular scaffolds. Especially, the hydrogen bonding properties of peptide conjugates to create chirality organization is focused on.

Chirality organization of ferrocene-dipeptide conjugates

Recently, the research field of bioorganometallic chemistry, which is a hybrid area between biology and organometallic chemistry, has attracted much attention. Conjugation of organometallic compounds with biomolecules such as amino acids, peptides, and DNA is envisioned to provide novel systems depending on both properties. In these conjugates, the organometallic moiety can serve as a molecular scaffold, a chromophore, a sensitive probe, a biological marker, a redox-active site, a catalytic active site, etc. Considerable efforts have focused on designing conjugates composed of organometallic compounds and biomolecules [10–14]. Ferrocene (Fc), which is one of the most stable organometallic compounds and the most useful one among metallocenes, has drawn much attention in their application to materials due to a reversible redox couple and two rotatory coplanar cyclopentadienyl (Cp) rings [15]. The inter-ring spacing of about 3.3 Å is appropriate for hydrogen bonding interaction between introduced peptide strands on the two Cp rings as observed in β-sheets. The utilization of a ferrocene unit as an organometallic scaffold with a central reverse-turn unit is considered to be one strategy to study the hydrogen bonding ability of various peptide strands. Ferrocenylalanine, which is the first example of a ferrocene-amino acid conjugate, was synthesized in 1957 [16–18]. After its discovery, a variety of ferrocene-amino acid or peptide conjugates have been designed to obtain a peptidomimetic basis for protein folding and to construct highly-ordered molecular assemblies [19–25].

The capability of ferrocene-1,1′-dicarboxylic acid (Fc-cc) as a molecular scaffold for a regulated conformation through intramolecular hydrogen bonds was demonstrated in the ferrocene-amino acid conjugate using a valine unit by Herrick et al. [26]. Two identical intramolecular interchain hydrogen bonds are formed between CO (Val) and NH (Val of another chain) in $CDCl_3$ to give a 10-membered hydrogen-bonded ring in the case of the ferrocene **1** bearing amino acid chains (-L-Val-OMe), which resemble the hydrogen bonding pattern observed in an antiparallel β-sheet. The regulated conformation of **1** is confirmed by the single-crystal X-ray structure determination [27]. On the other hand, the ferrocene **2** bearing amino acid chains (-L-Phe-OMe) is characterized by only one intramolecular interchain hydrogen bond between CO adjacent to the ferrocene unit and the NH of another strand [28]. The molecules of **2** arrange in a helical fashion, wherein the molecules are linked together via intermolecular hydrogen bonds (Chart 1).

Conformational enantiomers, *P*- and *M*-helical arrangements, 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 depicted in Fig. 1 [15, 29]. Conformational enantiomers can interconvert with ease due to the low barrier of Cp ring twisting. The introduction of peptides into a ferrocene scaffold is envisaged to induce conformational enantiomerization by restriction of the torsional twist through intramolecular interchain hydrogen bonding. The single-crystal X-ray structure determination of the ferrocene **3a** bearing L-dipeptide chains (-L-Ala-L-Pro-OEt) confirms "Herrick" pattern of interchain intramolecular antiparallel β-sheet-like hydrogen bonding between CO (Ala) and NH (Ala of another chain) of each dipeptide chain to induce the chirality-organized structure



1 2

Chart 1 Ferrocenes **1**–**2** bearing amino acid chains

(Fig. 2a) [30–32]. The ferrocenoyl moiety of **3a** adopts a *P*-helical arrangement. The introduction of the dipeptide chains into the ferrocene scaffold induces the chirality-organized structure based on two rigid intramolecular interchain hydrogen bonds, although a wide range of relative orientations are possible depending on two rotatory Cp rings. The crystal structure of **4** composed of the corresponding D-dipeptide chains (-D-Ala-D-Pro-OEt) reveals an *M*-helical arrangement of the ferrocenoyl moiety (Fig. 2b). The molecular structures of **3a** and **4** are in an excellent mirror image relationship as shown in Fig. 2, indicating conformational enantiomers present (Fig. 1). As a result, the introduction of the chiral dipeptide chains into the ferrocene induces the chirality organization by restriction of the torsional twist through the intramolecular interchain hydrogen bonds [32]. X-ray crystallographic analyses of **3b–d** bearing the methoxycarbonyl, propoxycarbonyl, and benzyloxycarbonyl groups, respectively, show the chirality-organized structure as observed in **3a** based on the similar hydrogen bondings (Chart 2) [31].

The ferrocene **3a** shows a positive Cotton effect at the absorbance region of the ferrocenoyl moiety in acetonitrile, which indicates a *P*-helical arrangement of the ferrocenoyl moiety (Fig. 3). The mirror image of the signals is observed in the CD spectrum of **4**, indicating the chiral molecular arrangement based on the chirality-organized structure via intramolecular interchain hydrogen bondings is formed even in solution [32].

The crystal structure of the ferrocene **5a** bearing dipeptide chains (-Gly-L-Leu-OEt) is characterized by two intramolecular interchain hydrogen bondings between CO (Gly) and NH (Gly of another strand) of each dipeptide chain to induce the chirality-organized structure, which adopts the same conformation as observed with **3a** (Fig. 4a). The NH of the Leu in this conformation is available for participating in intermolecular hydrogen bonding with CO adjacent to the ferrocene unit, creating the highly organized self-assembly in the crystal packing, wherein each molecule is bonded to four neighboring molecules [32] as shown in Fig. 4b. The kind and grouping of amino acid side chains is known to affect protein secondary structures. The crystal structure of the ferrocene **5b** bearing dipeptide chains (-Gly-L-Phe-OEt) exhibits the same chirality-organized structure based on the "Herrick" pattern of hydrogen bondings (Fig. 5a). However, the ferrocene **5b** shows a different molecular arrangement in the crystal. Each molecule is connected to two neighboring molecules, wherein each dipeptide chain forms a 14-membered intermolecularly hydrogen-bonded ring with the dipeptide chain of the neighboring molecule through two

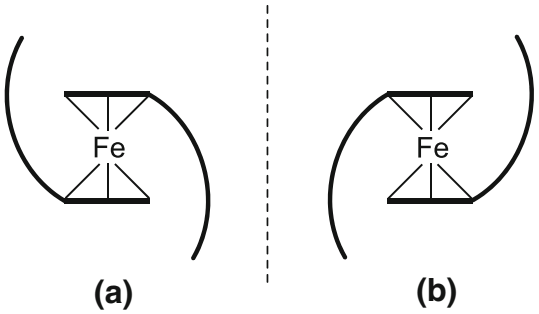


Fig. 1 Enantiomorphous conformations of 1,1′-disubstituted ferrocene

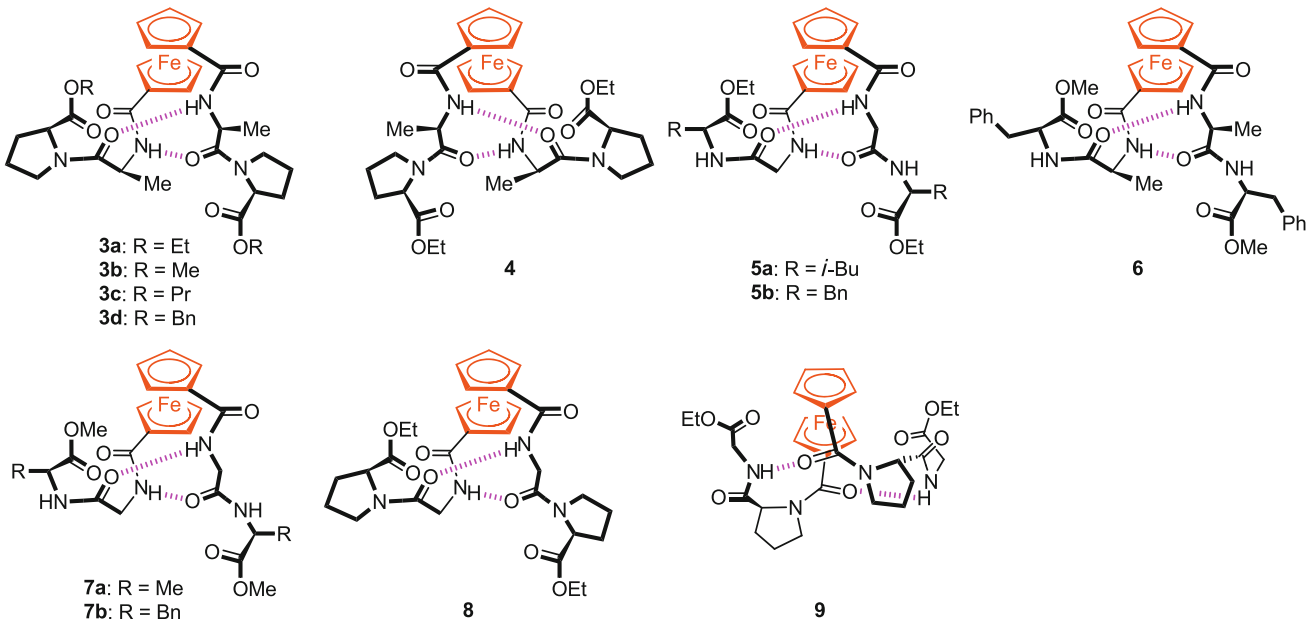


Chart 2 Ferrocenes **3–9** bearing dipeptide chains

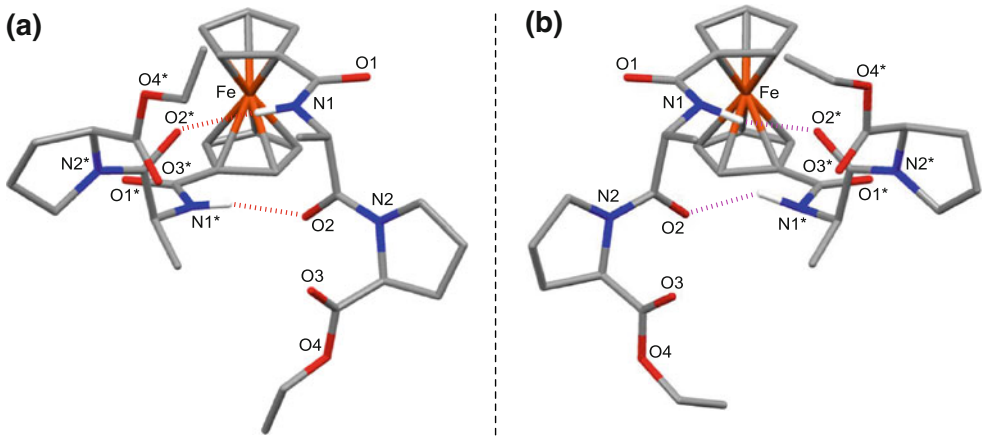
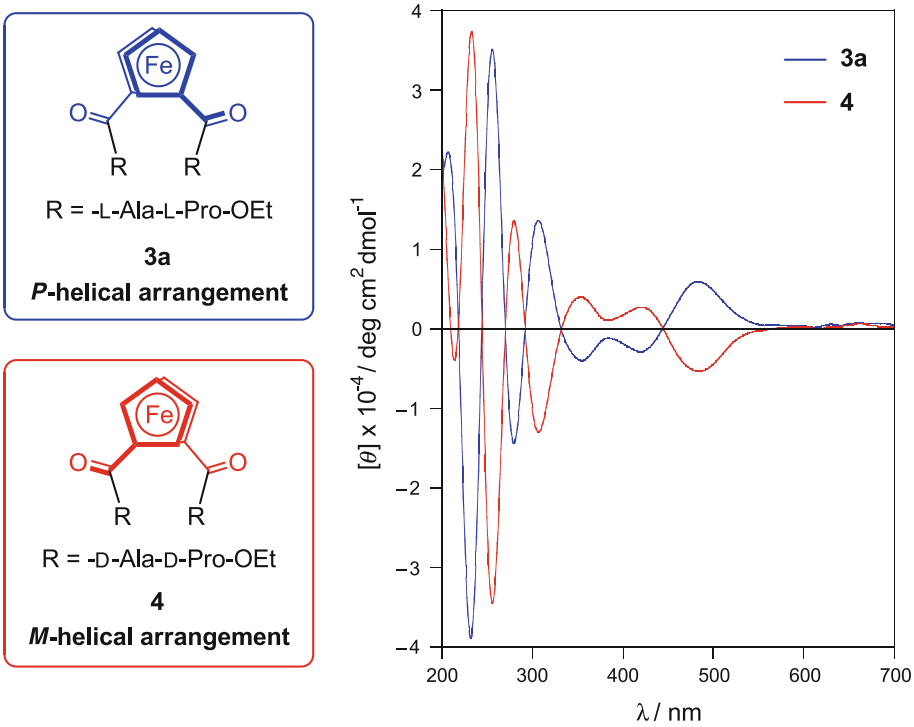


Fig. 2 Crystal structures of **a 3a** and **b 4**. The *purple dotted line* represents the hydrogen bond

Fig. 3 CD spectra of **3a** and **4** in MeCN (1.0×10^{-4} M)



pairs of symmetrical intermolecular hydrogen bonds [32] as shown in Fig. 5b. A similar organization is observed in the case of the ferrocene **6** bearing dipeptide chains (-L-Ala-L-Phe-OMe) although the unit cell of **6** contains two crystallographically independent molecules [28]. An ordered structure via intramolecular hydrogen bondings is also formed in the case of the ferrocenes **7a**–**b** [33]. The ferrocene **8** composed of the -Gly-L-Pro-OEt dipeptide chains forms a 10-membered hydrogen-bonded ring to induce the chirality-organized structure as observed with **3a**. On the contrary, a 14-membered hydrogen-bonded ring is assumed to be formed in the case of the ferrocene **9** composed of the -L-Pro-Gly-OEt dipeptide chains [34].

Configuration and sequence of amino acids are considered to be a key factor for constructing chirality-organized bio-inspired systems with highly ordered structures. The single-crystal X-ray structure determination of the ferrocene **10** bearing dipeptide chains of the heterochiral sequence (-L-Ala-D-Pro-NH-2-Py) reveals the formation of the interchain intramolecular antiparallel β-sheet-like hydrogen bonds as observed in **3a** to induce the chirality-organized structure, in which a *P*-helical arrangement of the ferrocenoyl moiety is formed (Fig. 6a) [35]. The *P*-helical arrangement of the ferrocenoyl moiety appears to be controlled by the configuration of the alanyl α-carbon atom [36, 37], because a similar type of the chiral

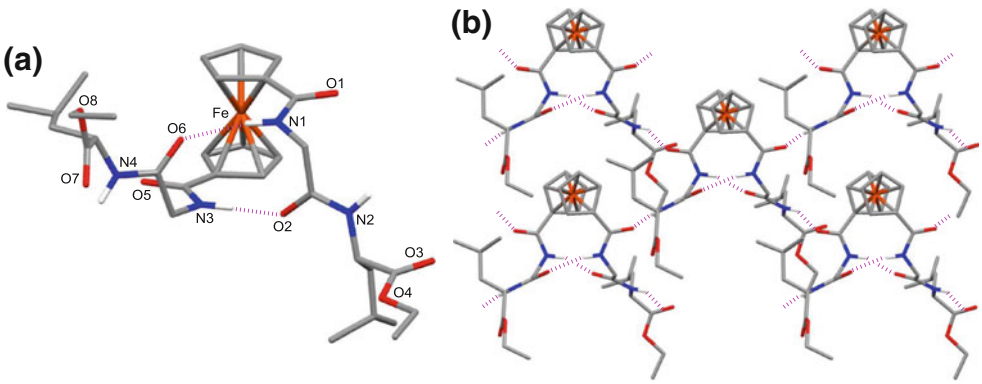


Fig. 4 **a** Crystal structure of **5a** and **b** a self-assembly of **5a** through intermolecular hydrogen bonding in the crystal packing. The *purple dotted line* represents the hydrogen bond

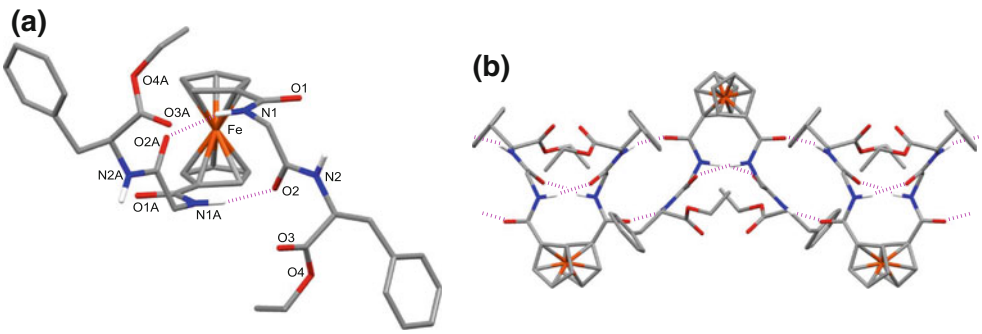


Fig. 5 **a** Crystal structure of **5b** and **b** a self-assembly of **5b** via the formation of a 14-membered intermolecularly hydrogen-bonded ring in the crystal packing. The *purple dotted line* represents the hydrogen bond

molecular conformation is observed with the ferrocene **3a** bearing -L-Ala-L-Pro-OEt dipeptide chains. Another interesting structural feature is that NH adjacent to the pyridyl moiety participates in the intramolecular hydrogen bonding with CO adjacent to the ferrocene unit of the same dipeptide chain, to nucleate a type II β-turn-like structure in each dipeptide chain. The combination of the ferrocene scaffold as a central reverse-turn unit with the L-Ala-D-Pro hetrochiral dipeptide sequence permits the formation of the artificially regulated antiparallel β-sheet-like and type II β-turn-like structures simultaneously. The crystal structure of **11** composed of the D-Ala-L-Pro-NH-2-Py dipeptide chains, in which an *M* helical arrangement of the ferrocenoyl moiety is formed (Fig. 6b), is in a mirror image relationship with **10** (Chart 3) [35].

A positive Cotton effect of the ferrocene **10** in dichloromethane indicates a *P*-helical arrangement of the ferrocenoyl moiety [35]. Proton magnetic resonance nuclear Overhauser effect (NOE) of **10** in $CDCl_3$ at 25 °C additionally provides diagnostic evidence for the type II β-turn-like structure. Irradiation of the Cp proton at the α position enhances NH (Ala), NH adjacent to the pyridyl moiety, and pyridyl proton at the 3-position.

The crystal structure of the ferrocene **12** bearing dipeptide chains of the homochiral sequence (-L-Pro-L-Ala-NH-2-Py) is characterized by the presence of the NH adjacent to the pyridyl moiety participating in an intramolecular hydrogen bond with CO (Pro) of the same dipeptide chain to nucleate an inverse γ-turn-like structure in each dipeptide chain, where the interchain intramolecular antiparallel β-sheet-like hydrogen bondings between CO adjacent to the ferrocene unit and the NH of the Ala attached to another dipeptide chain are formed (Fig. 7a) [38]. The combination of the ferrocene scaffold with the L-Pro-L-Ala homochiral sequence permits the simultaneous formation of the artificial inverse γ-turn-like and antiparallel β-sheet-like structures.

The diastereomeric dipeptide configurations induce different self-assembling properties. In the crystal structure of the ferrocene **13** bearing L-Pro-D-Ala-NH-2-Py dipeptide chains, the interchain intramolecular antiparallel β-sheet-like hydrogen bonds are observed between CO adjacent to the ferrocene unit and the NH of the Ala attached to another dipeptide chain (Fig. 7b) [38]. On the contrary to **12**, the NH adjacent to the pyridyl moiety participates in an intermolecular hydrogen bond with CO (Pro) of the neighboring molecule to form a 14-membered intermolecularly hydrogen-bonded ring as shown in Fig. 8.

The crystal structure of the ferrocene **14** bearing amino acid chains (-L-Pro-OMe) shows a 1,3′-conformation of two amino acid chains, which minimizes steric interaction of the amino acid chains [39]. The growing oligoproline chain of **15** adopts a stable polyproline-II helix in solution (Chart 4).

Cyclization of ferrocene-dipeptides is a useful strategy to form and stabilize a β-sheet structure based on the close

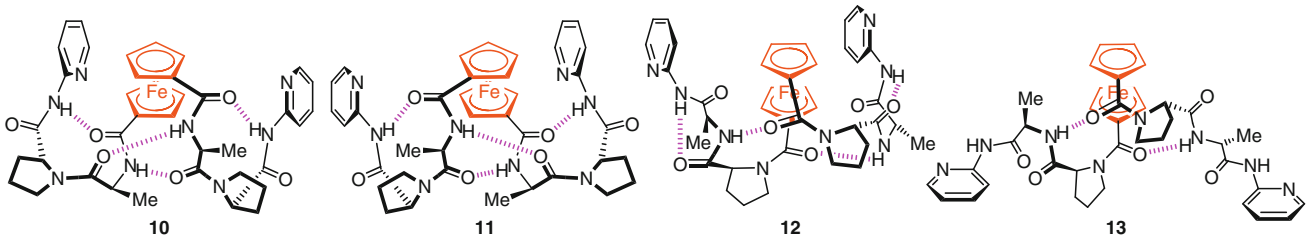


Chart 3 Ferrocenes **10–13** bearing dipeptide chains

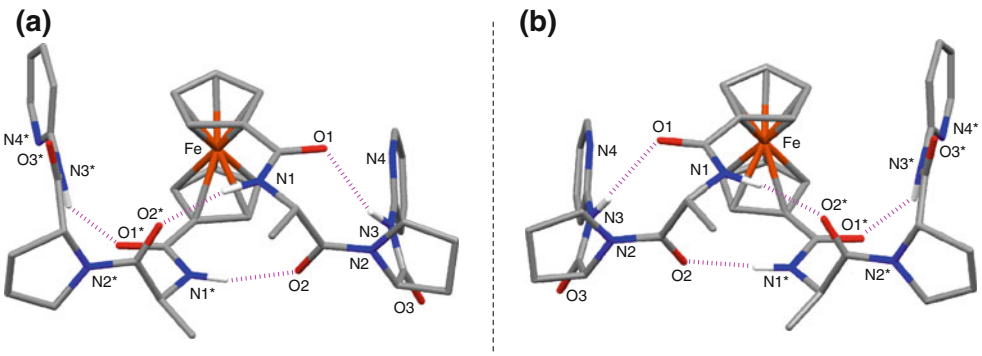


Fig. 6 Crystal structures of **a 10** and **b 11**. The *purple dotted line* represents the hydrogen bond

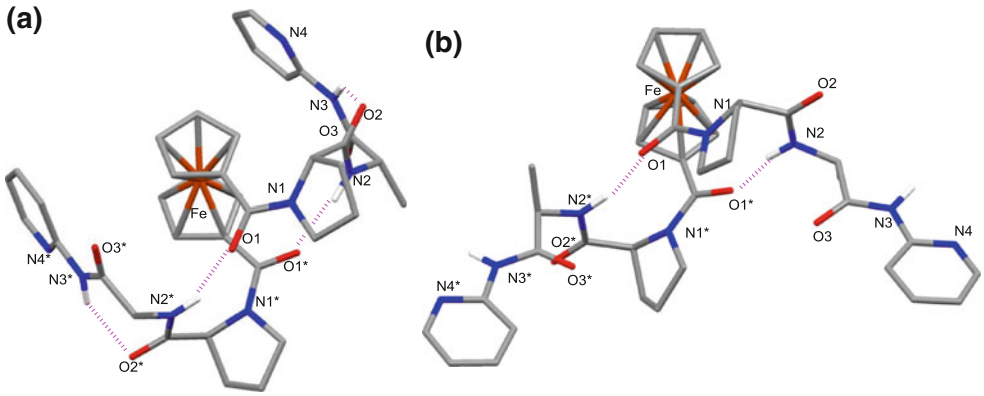


Fig. 7 Crystal structures of **a 12** and **b 13**. The purple dotted line represents the hydrogen bond

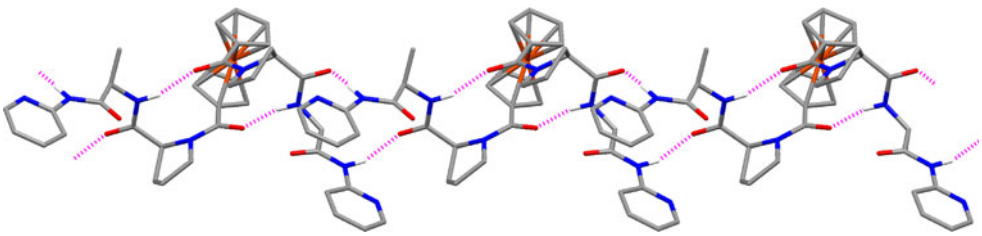
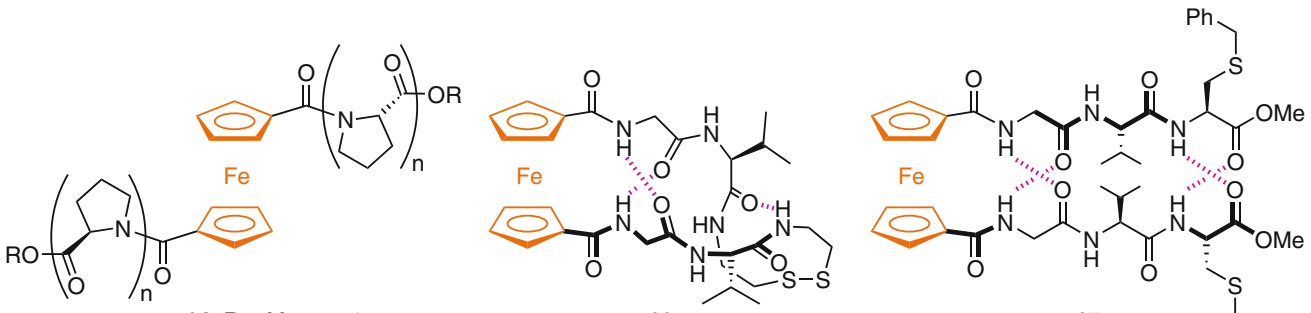


Fig. 8 A self-assembly of **13** via the formation of a 14-membered intermolecularly hydrogen-bonded ring in the crystal packing. The *purple dotted line* represents the hydrogen bond

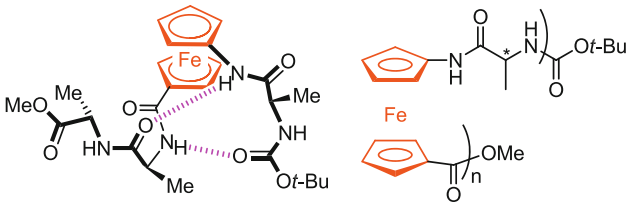
proximity of the two peptide strands. The crystal structure of the cyclic ferrocene **16** bearing the cyclic peptide (-Gly-L-Val-CSA)$_2$ reveals the formation of "Herrick" pattern of intramolecular hydrogen bonds and a *P*-helical arrangement of the ferrocenoyl moiety [40]. Furthermore, four molecules of **16** interact through intermolecular hydrogen bonding to form a β-barrel-like structure.

The extension of the β-sheet-like structure, in which the two peptide chains align and engage in interchain hydrogen bonding, is performed in the ferrocene **17** bearing tripeptide chains (-Gly-L-Val-Cys(Bn)-OMe)$_2$ [41]. The crystal structure of **17** shows that two peptide chains are in an extended conformation and are aligned with respect to each other allowing for the formation of hydrogen bonds between



14: R = Me, n = 1
15a: R = Bn, n = 1
15b: R = Bn, n = 2
15c: R = Bn, n = 3
15d: R = Bn, n = 4

Chart 4 Ferrocenes **14**–**17** bearing dipeptide chains



n = 1: **19a** (*S*); **19b** (*R*)
n = 2: **20a** (*S*); **20b** (*R*)
n = 3: **21a** (*S*); **21b** (*R*)
n = 4: **22a** (*S*); **22b** (*R*)

Chart 5 Ferrocenes **18**–**22** bearing dipeptide chains

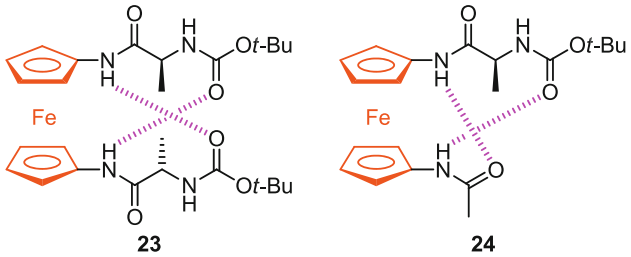
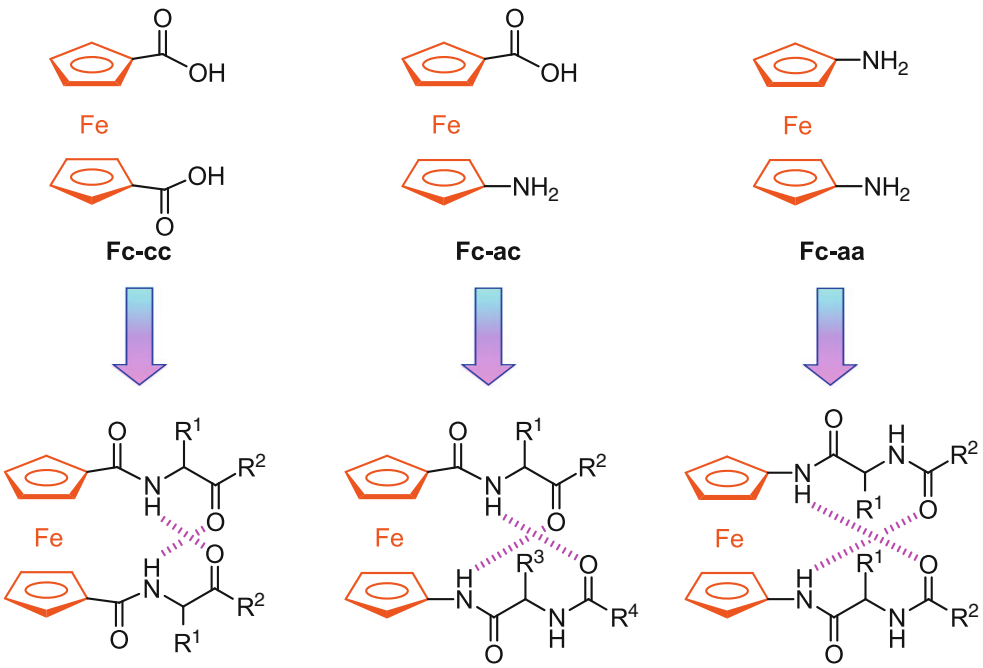


Chart 6 Ferrocenes **23**–**24** bearing dipeptide chains

the two peptide chains. In addition to the Herrick-type hydrogen bonds proximal to the ferrocene unit, a second cross-strand hydrogen bonding interaction exists between the two amino acids on the C-terminal side of the peptide.

The organometallic amino acid, 1′-aminoferrocene-1-carboxylic acid (Fc-ac), also serves as a reliable molecular scaffold to induce a turn structure. The crystal structure of the ferrocene **18** (Boc-L-Ala-Fc-ac-L-Ala-L-Ala-OMe) displays intramolecular hydrogen bonds to form a 12-membered hydrogen-bonded ring and a *P*-helical arrangement of

Scheme 1 Chirality-organized structures of ferrocene-peptide conjugates composed of Fc-dicarboxylic acid (Fc-cc), Fc-amino acid (Fc-ac), or Fc-diamine (Fc-aa) scaffold



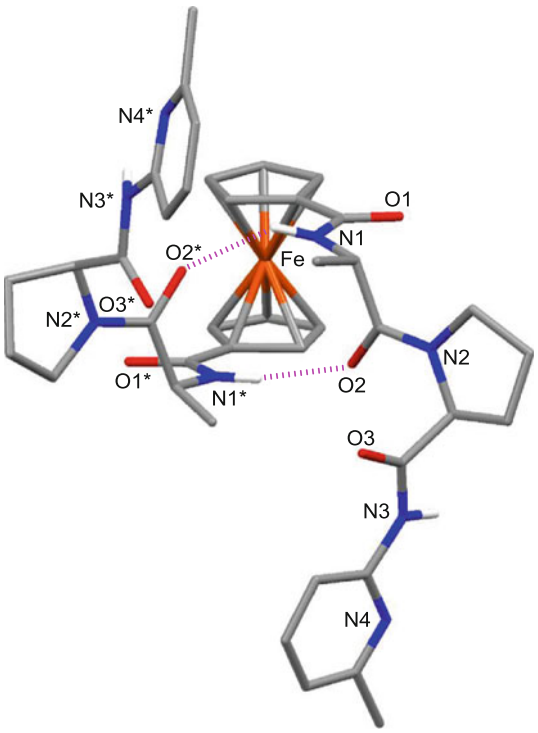


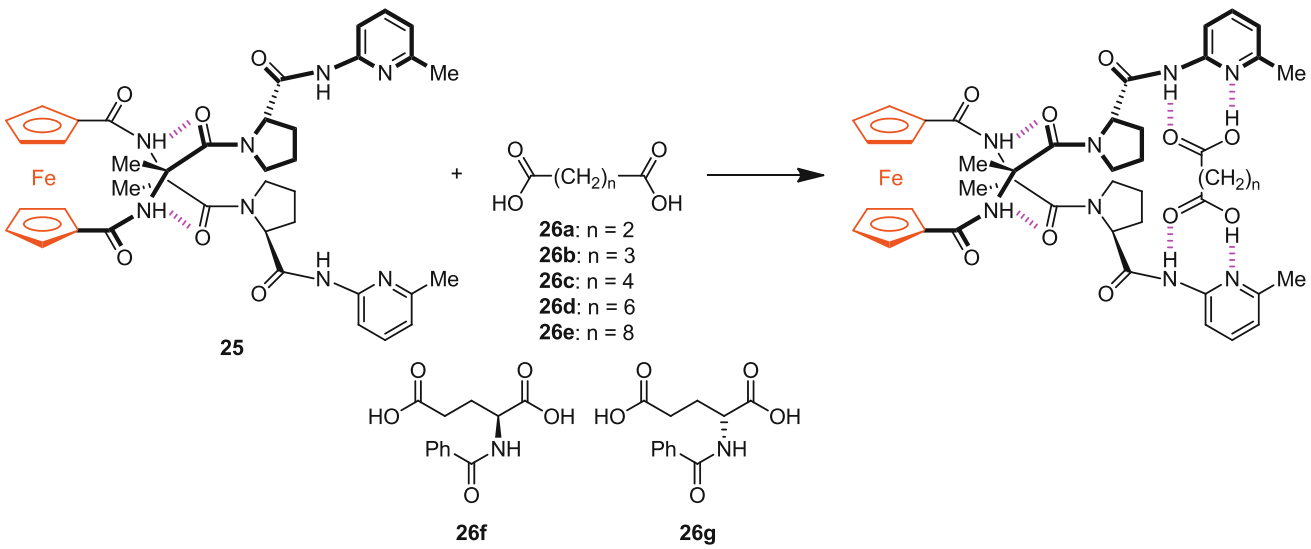
Fig. 9 Crystal structure of **25**. The *purple dotted line* represents the hydrogen bond

the Fc-ac moiety [42]. The structural rigidity of Fc-ac to induce a turn structure is exploited to design extended helical foldamers. The ferrocenes **19**–**22** with Fc-ac unit exhibit a *β*-helical-like structure in solution and solid states [43]. The helicity is not influenced by the size of the foldamer. All conjugates derived from L-Ala adopt a *P*-helical conformation, whereas D-Ala induces an *M*-helical conformation (Chart 5).

1,*n*′-Diaminoferrocene (Fc-aa) serves as a reliable molecular scaffold to allow the attachment of two peptide strands. The ferrocene **23** bearing amino acid chains (-L-Ala-Boc) forms an intramolecular 14-membered hydrogen-bonded ring to induce the chirality organization, wherein the Fc-diamine moiety adopts a *P*-helical arrangement [44]. The attachment of one amino acid substituent at the 1,1′-diaminoferrocene central unit is performed to induce chirality organization through intramolecular hydrogen bonds in the ferrocene **24** (Chart 6) [45].

Chirality-organized structures of ferrocene-peptide conjugates composed of Fc-dicarboxylic acid (Fc-cc), Fc-amino acid (Fc-ac), or Fc-diamine (Fc-aa) scaffold are summarized in Scheme 1. With ferrocene scaffolds, the introduced peptide strands are regulated in the appropriate dimensions. Fc-cc scaffold induces a 10-membered hydrogen-bonded ring. A 12-membered hydrogen-bonded ring is formed in the case of Fc-ac scaffold. Fc-aa favors a 14-membered hydrogen-bonded ring.

The self-assembling organization of host molecules is a useful strategy to form active receptors [46]. Utilization of self-assembling properties of amino acids as observed in proteins, which are organized into well-organized three-dimensional structures, is considered to be a convenient approach to the desired receptors. Ferrocenes have been focused on as an organometallic scaffold for molecular receptors [47–51]. Ferrocene-peptide conjugates are demonstrated to recognize anions [52, 53] and biomolecules [54–58]. In the ferrocene **25** bearing dipeptide chains (-L-Ala-L-Pro-NH-2-PyMe), the two amido pyridyl moieties as hydrogen bonding sites are well arranged for binding of dicarboxylic acids by the chirality organization through two intramolecular hydrogen bondings as observed



Scheme 2 Binding of dicarboxylic acid to the ferrocene **25**

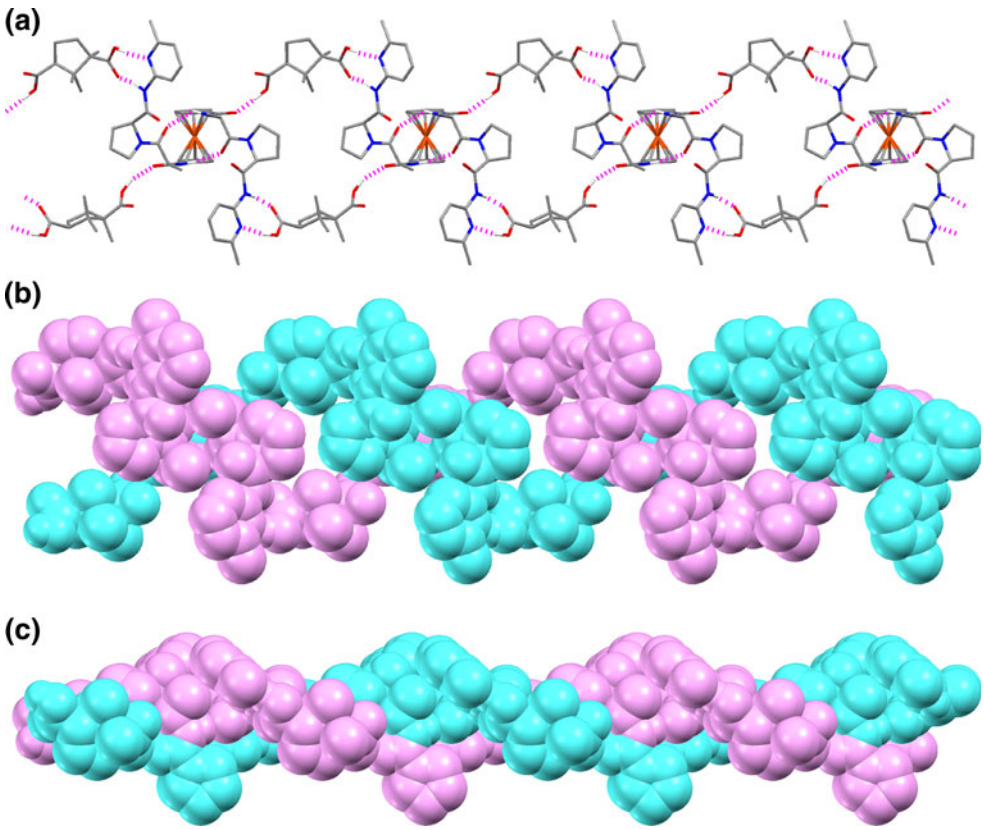


Fig. 10 **a** A portion of a layer containing the double-helical-like hydrogen-bonded molecular assembly in the crystal packing of **25**·$(\mathbf{CA})_2$, **b** space-filling representations of a top view, and **c** a side view. The *purple dotted line* represents the hydrogen bond

with **3a** (Fig. 9) [59]. In fact, the size-selective and chiral recognition of dicarboxylic acids is performed by multi-point hydrogen bondings of the binding sites of **25**. The ferrocene **25** forms a 1:1 complex with a series of dicarboxylic acids **26**, wherein a most highest association constant is observed with adipic acid (**26c**, $K_a = 2.1 \times 10^4$ M^{-1}, Scheme 2). The binding sites of **25** can discriminate the size of dicarboxylic acids. Noteworthy is that benzoyl-L-glutamic acid (**26f**, $K_a = 5.5 \times 10^3$ M^{-1}) is bound approximately fifteen times more tightly to **25** than benzoyl-D-glutamic acid (**26g**, $K_a = 3.7 \times 10^2$ M^{-1}). The chirality-organized binding sites of **25** is capable of discriminating the chirality of guest molecules.

Crystallization of a 1:2 mixture of **25** and (1*R*,3*S*)-camphoric acid (**CA**) gives the 1:2 complex **25**·$(\mathbf{CA})_2$ [60]. The single-crystal X-ray structure determination of **25**·$(\mathbf{CA})_2$ reveals a cocrystal composed of alternating units of **25** and two molecules of **CA**, which are connected by continuous intermolecular hydrogen bonds to form the double-helical-like hydrogen-bonded molecular arrangement (Fig. 10). Each molecule of **CA** serves as a hydrogen bonding bridge. One carboxyl group of **CA** binds to the amide pyridyl binding site of **25** while another carboxyl moiety of **CA** interacts with CO adjacent to the ferrocene unit of another molecule of **25**. Another noteworthy feature is that the chirality-organized structure of **25** is preserved in spite of complexation with **CA**.

Generally, an organized structure through intramolecular interchain hydrogen bondings is not formed in the case of ferrocenes bearing only one peptide chain, and an intermolecular hydrogen bonding network is created in a solid state. The ferrocene **27** bearing one amino acid chain (-L-Glu-$(OBn)_2$) exhibits a linear chain-like structure of molecules linking through intermolecular hydrogen bonding in a crystal structure [61]. Each molecule of the ferrocene **28** bearing one amino acid chain (-L-Cys(SBn)-OMe) is also linked by intermolecular hydrogen bonding as observed in **27** [61]. The hydrogen bonding interactions of CO adjacent to the ferrocene unit with OHs of the α-carboxyl group and the Asp acid side chain of two adjacent molecules, which form a bifurcated hydrogen bond, are observed in the crystal structure of the ferrocene **29** bearing one amino acid chain (-L-Asp-OH) (Chart 7) [62].

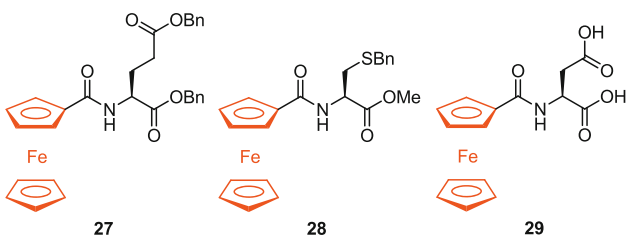


Chart 7 Ferrocenes **27**–**29** bearing one dipeptide chain

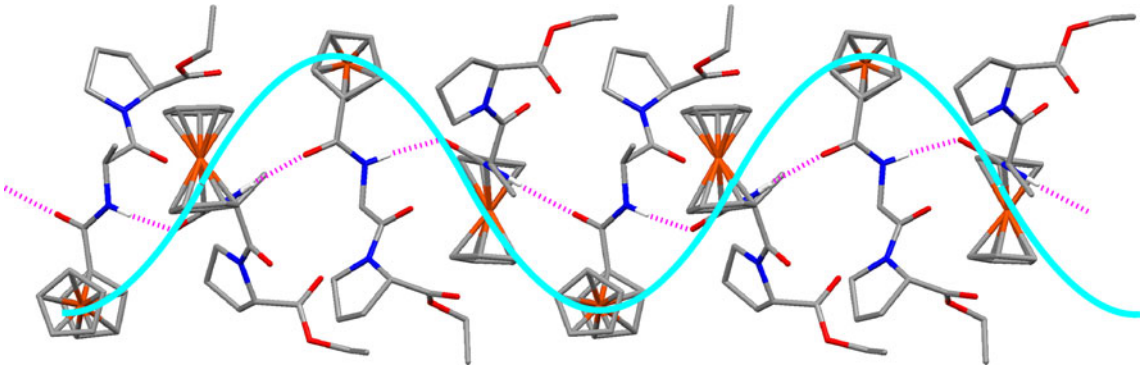


Fig. 11 A portion of a layer containing the helical assembly of crystal packing of **30a**. The *purple dotted line* represents the hydrogen bond

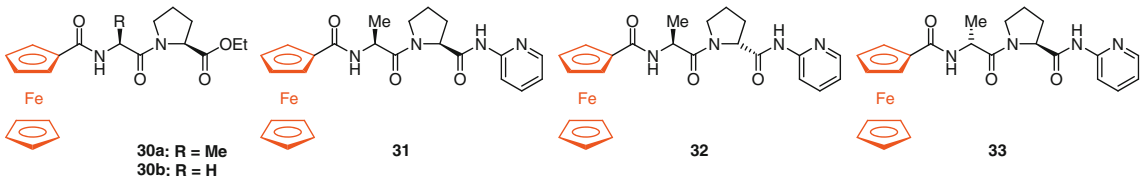


Chart 8 Ferrocenes **30**–**33** bearing one dipeptide chain

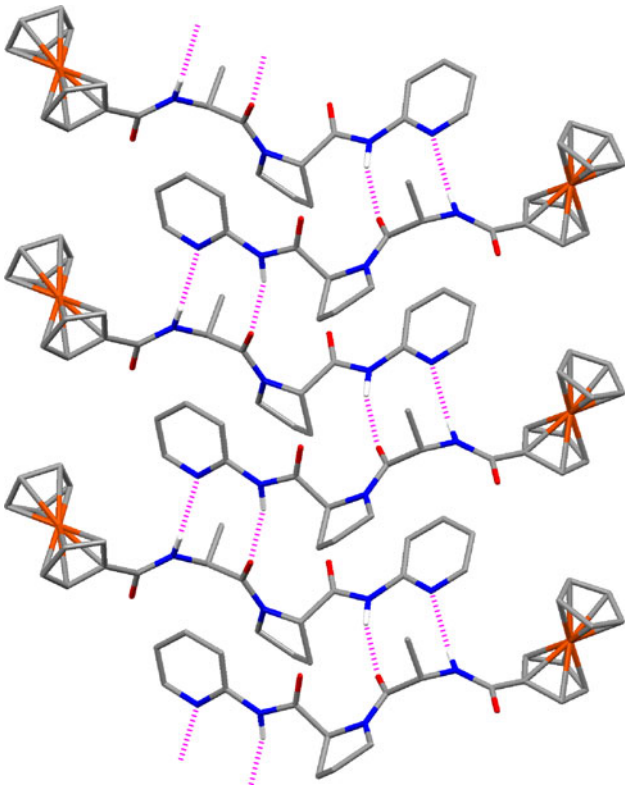


Fig. 12 A portion of a layer containing the antiparallel arrangement of crystal packing of **31**. The *purple dotted line* represents the hydrogen bond

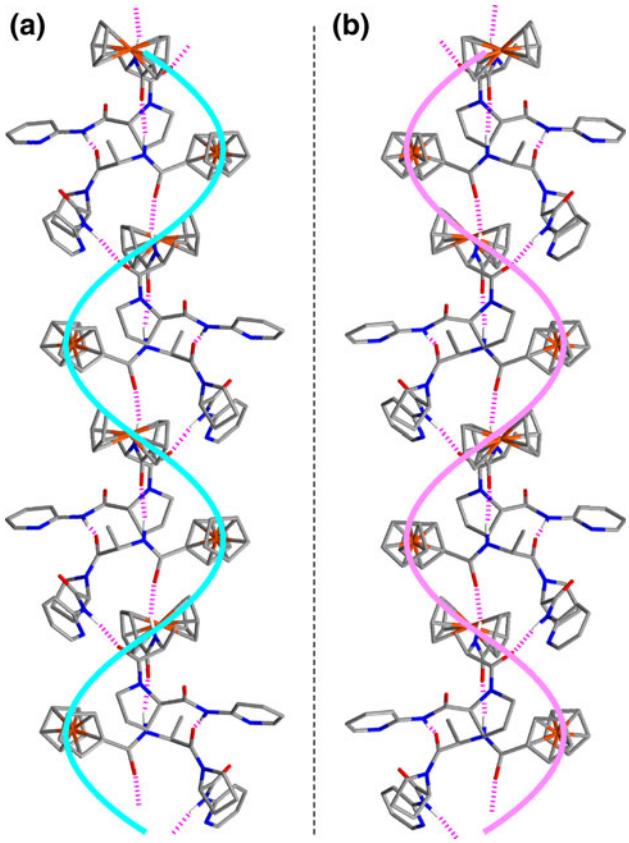


Fig. 13 A portion of a layer containing the helical assembly of crystal packing of **a 32** or **b 33**. The *purple dotted line* represents the hydrogen bond

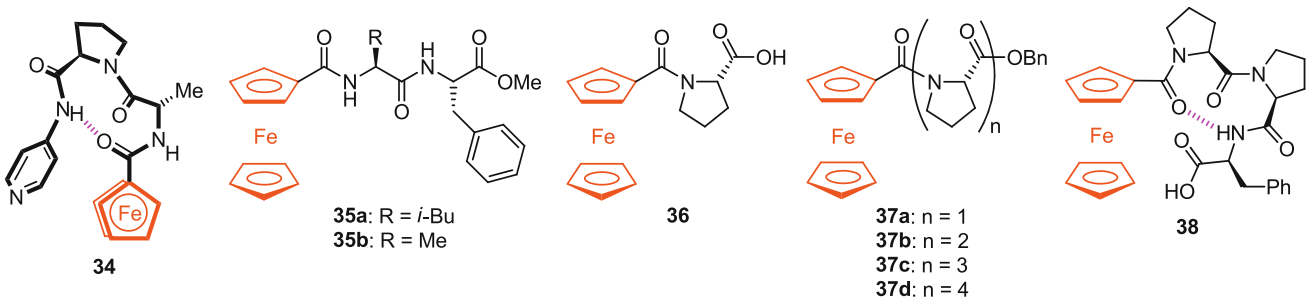


Chart 9 Ferrocenes **34**–**38** bearing one dipeptide chain

The ferrocene **30a** bearing one dipeptide chain of the homochiral sequence (-L-Ala-L-Pro-OEt) shows intermolecular hydrogen bondings between CO (Ala) and the NH of the Ala attached to another molecule, wherein two independent molecules exist in an asymmetric unit and are connected alternately to form an intermolecular hydrogen bonding network, resulting in a left-handed helically ordered molecular arrangement (Fig. 11) [31]. A similar left-handed helically ordered molecular arrangement is also observed in the ferrocene **30b** bearing one dipeptide chain (-Gly-L-Pro-OEt) (Chart 8) [34].

An antiparallel hydrogen bonding network is formed in a solid state of the ferrocene **31** bearing one dipeptide chain of the homochiral sequence (-L-Ala-L-Pro-NH-2-Py) to create a highly organized assembly, wherein each molecule is connected to two neighboring molecules by NH (Ala)/N (pyridine of another molecule) and NH (adjacent to pyridine unit of another molecule)/O (Ala) intermolecular hydrogen bonds forming a 9-membered intermolecularly hydrogen-bonded ring (Fig. 12) [63]. In contrast, the ferrocene **32** bearing one dipeptide chain of the heterochiral sequence (-L-Ala-D-Pro-NH-2-Py) exhibits intermolecular hydrogen bonds, wherein two independent molecules exist in the asymmetric unit and are connected alternately to be packed in a left-handed helically ordered molecular arrangement through a network of intermolecular hydrogen bonds, as shown in Fig. 13a [35]. An opposite helically ordered molecular assembly, a right-handed helically ordered molecular arrangement, is created in the crystal packing of the ferrocene **33** bearing one dipeptide chain of the heterochiral sequence (-D-Ala-L-Pro-NH-2-Py) (Fig. 13b) [35].

The creation of the β-turn mimic is achieved by utilizing the minimum-sized peptide chain. The crystal structure of the ferrocene **34** bearing one dipeptide chain of the heterochiral sequence (-L-Ala-D-Pro-NH-4-Py) reveals that NH adjacent to the pyridyl moiety participates in an intramolecular hydrogen bonding with CO adjacent to the ferrocene unit of the same dipeptide chain to nucleate a type II β-turn-like structure (Fig. 14) [64]. This chirality-organized structure is in sharp contrast to the crystal structure of

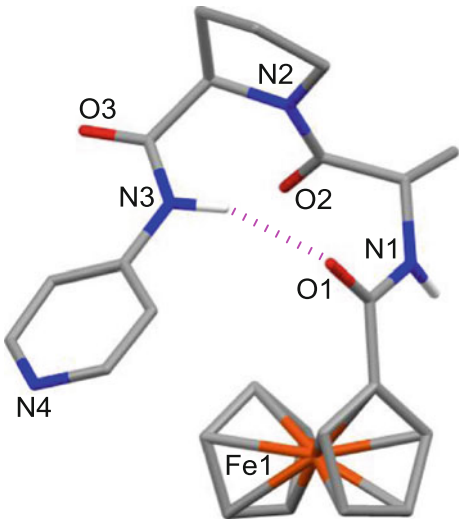


Fig. 14 Crystal structure of **34**. The *purple dotted line* represents the hydrogen bond

32. The position of the pyridyl nitrogen is found to control the self-organization (Chart 9).

The intermolecular hydrogen bonding interactions of the ferrocene **35a** bearing one dipeptide chain (-L-Leu-L-Phe-OMe) forms the helicate with the ferrocene groups on the outside of the helix and the isobutyl groups on the inside of the helix [65]. A helical molecular arrangement by intermolecular hydrogen bonding interactions is also observed in the ferrocene **35b** bearing one dipeptide chain (-L-Ala-L-Phe-OMe) [28]. X-ray crystallographic analyses of the ferrocenes **36** and **37b**–**d** bearing one oligoprolyl chain show that these ferrocene-peptide conjugates adopt a left-handed polyproline II helix with all prolines in a mutually *trans*-conformation [66]. On the other hand, ferrocene **38** bearing one tripeptide chain (-L-Pro-L-Pro-L-Phe-OH) forms a strong intramolecular hydrogen bond between CO adjacent to the ferrocene unit and NH (Phe) to create a β-turn structural motif [66].

Metal ions are known to show a variety of properties in proteins, one of which is structural stabilization for biological function [67, 68]. Incorporation of metal

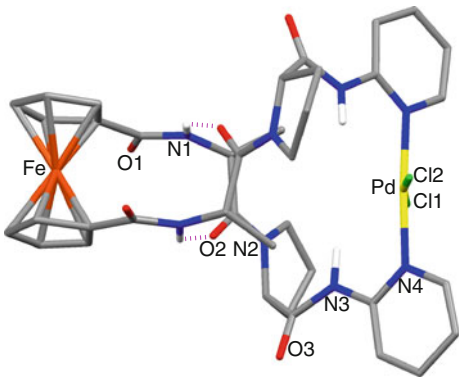


Fig. 15 Crystal structure of **40**. The *purple dotted line* represents the hydrogen bond

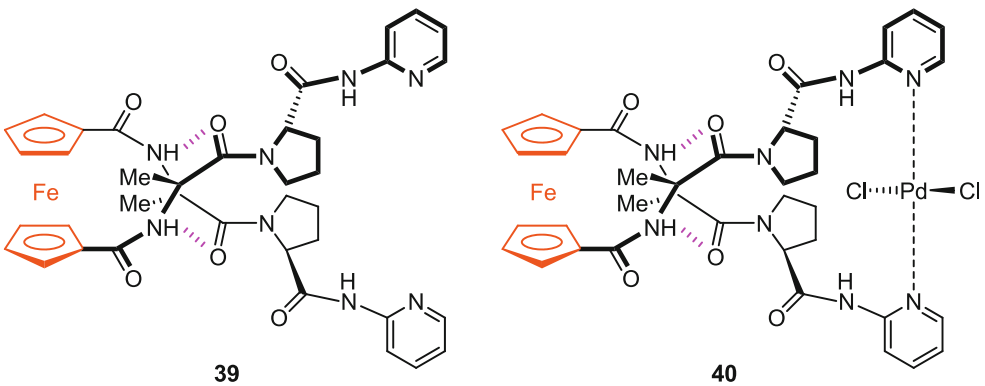
coordination sites into peptides has been investigated on the stabilization of secondary structures [69–73] and catalytic activities [74–76]. The complexation with metal ion is expected to stabilize and/or regulate secondary structures of peptide chains. The ferrocene **39** bearing dipeptide chains of the homochiral sequence (-L-Ala-L-Pro-NH-2-Py), which is characterized by the chirality-organized structure through two intramolecular interchain hydrogen bondings as observed with **3a**, forms the 1:1 *trans*-palladium complex **40** with $PdCl_2(MeCN)_2$ to stabilize the conformational regulation in both solution and solid states (Fig. 15) [77]. The more downfield shifting of Ala N–H resonance in the ^1H NMR spectrum of **40** in $CDCl_3$ as compared with that of **39** indicates that the complexation strengthens the intramolecular hydrogen bondings. The single-crystal X-ray structure determination of **40** reveals the pseudo-helical conformation through palladium coordination and chirality organization based on the preservation of the intramolecular interchain hydrogen bonds as shown in Fig. 15 (Chart 10) [77].

The ferrocene **32** bearing one dipeptide chain of the heterochiral sequence (-L-Ala-D-Pro-NH-2-Py) forms the 2:1 *trans*-palladium complex **41** [78]. The crystal structure of **41** shows a pseudo-helical conformation through coordination to palladium and chirality organization through NH (Ala)/Cl, NH (adjacent to pyridine unit)/O (Ala), and NH (adjacent to pyridine unit of another molecule)/O (Ala) intramolecular hydrogen bonds, in which two ferrocene-dipeptide conjugates coordinate to a palladium center unsymmetrically (Fig. 16a). Noteworthy is that NH adjacent to the pyridyl moiety of one dipeptide chain participates in the intramolecular hydrogen bonding with CO (Ala) of the same dipeptide chain to nucleate a γ-turn-like structure. This chirality-organized structure is in sharp contrast to the crystal structure of **32**, in which intermolecular hydrogen bonds are formed instead of the intramolecular hydrogen bonds to induce a helically ordered molecular assembly (Fig. 13a) [35]. These findings indicate that the complexation with $PdCl_2(MeCN)_2$ induces the γ-turn-like structural regulation of the dipeptide chain through intramolecular hydrogen bonding in the crystal structure (Chart 11).

Transition metal-directed assembly is regarded as a useful strategy to form a highly ordered molecular assembly. To assemble the ferrocene-dipeptide conjugates, a metal-directed strategy is embarked upon by using $[Pd(MeCN)_4](BF_4)_2$ which has four binding sites as a metal binder. The ferrocene **34** forms the 4:1 palladium complex **42** with 0.25 equiv of $[Pd(MeCN)_4](BF_4)_2$ in acetonitrile [64]. The crystal structure of **42** reveals that the four ferrocene-dipeptide conjugates are assembled around a palladium center in the same direction to form a chiral pocket surrounded by the dipeptide chains, wherein one BF_4^- counter anion is accommodated (Fig. 16b). Another interesting feature of the palladium complex **42** is that a β-turn-like structure through the intramolecular hydrogen bonding is preserved in each ferrocene-dipeptide conjugate despite of complexation, wherein a type II β-turn-like structure of one ferrocene-dipeptide conjugate changes to an intermediate between a type I' and type III' β-turn-like structures.

Self-assembled monolayers (SAM) of helical ferrocene contained peptides have been focused on to investigate the electron transfer (ET) reaction. The well-ordered SAMs are formed from helical peptides **43** and **44** having a ferrocene moiety at the N- or C-terminal end [79]. Electrochemical

Chart 10 Ferrocene **39** and the 1:1 *trans*-palladium complex **40**



39 **40**

Chart 11 The 2:1 *trans*-palladium complex **41** and the 4:1 palladium complex **42**

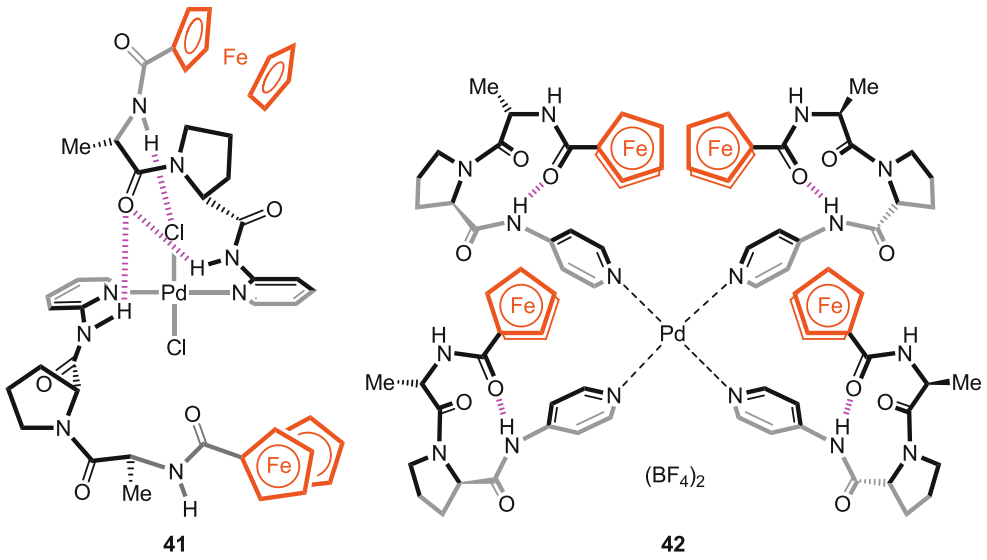
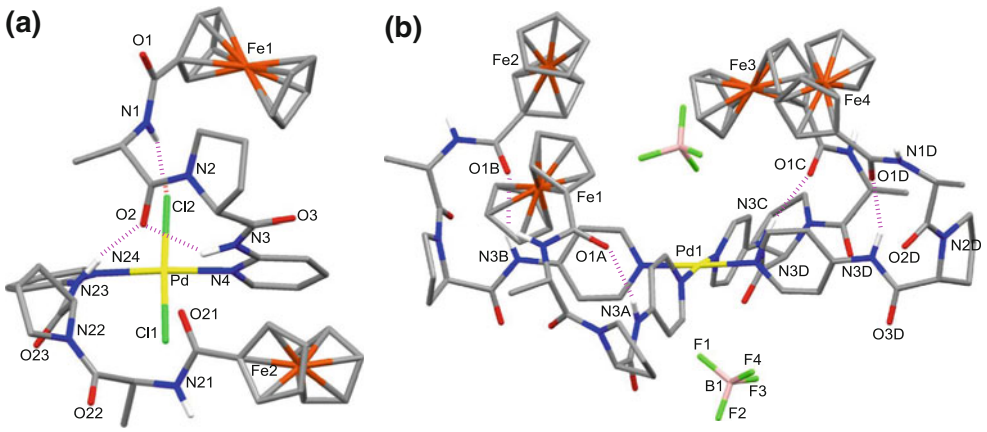
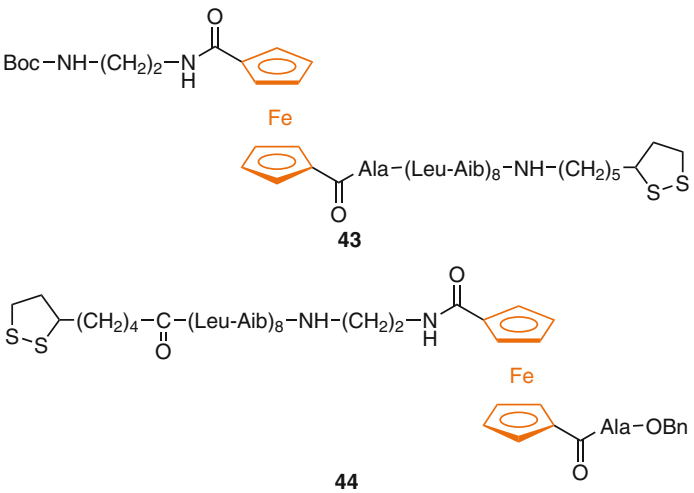
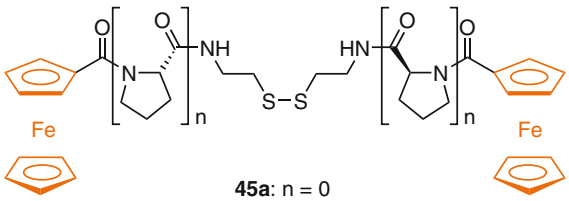


Fig. 16 Crystal structures of **a 41** and **b 42**. The *purple dotted line* represents the hydrogen bond



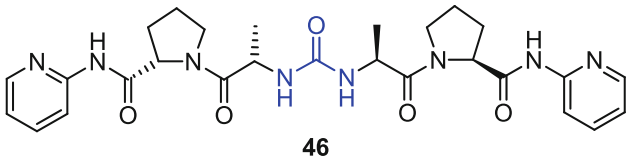




45a: n = 0
45b: n = 1
45c: n = 2
45d: n = 3
45e: n = 4
45f: n = 5
45g: n = 6

Chart 12 Ferrocenes **43**–**45** bearing peptide chains

measurements suggest that a long-range ET reaction over 4 nm occurs with the inelastic hopping mechanism over the superexchange mechanism in the SAMs. The accelerating effect of the helix dipole on the ET rate is observed probably due to the lowering of the barrier height between the gold surface and the peptide layer. The



46

Chart 13 The dipeptidyl urea **46** composed of two dipeptide chains (-L-Ala-L-Pro-NH-2-Py)

N-ferrocenoyl-labeled oligoproline cystamines **45** form stable monolayers on gold, in which the formation of hydrogen bond between adjacent molecules is considered to be a key factor in packing and stability of the monolayers [80]. The ferrocenes **45e–g** adopt the helical all-*trans* polyproline II conformation in solution although **45b–c** show higher flexibility and potential to undergo *cis–trans* isomerization in solution. The ferrocene moiety of **45** becomes easier to be oxidized with increasing length of the oligoproline chain. The significant deviation from Marcus-type behavior indicates a through-bond mechanism in the ET process between the ferrocenyl redox probe and the gold microelectrode surface across the oligoproline spacer although the k_{ET} is distance-dependent (Chart 12).

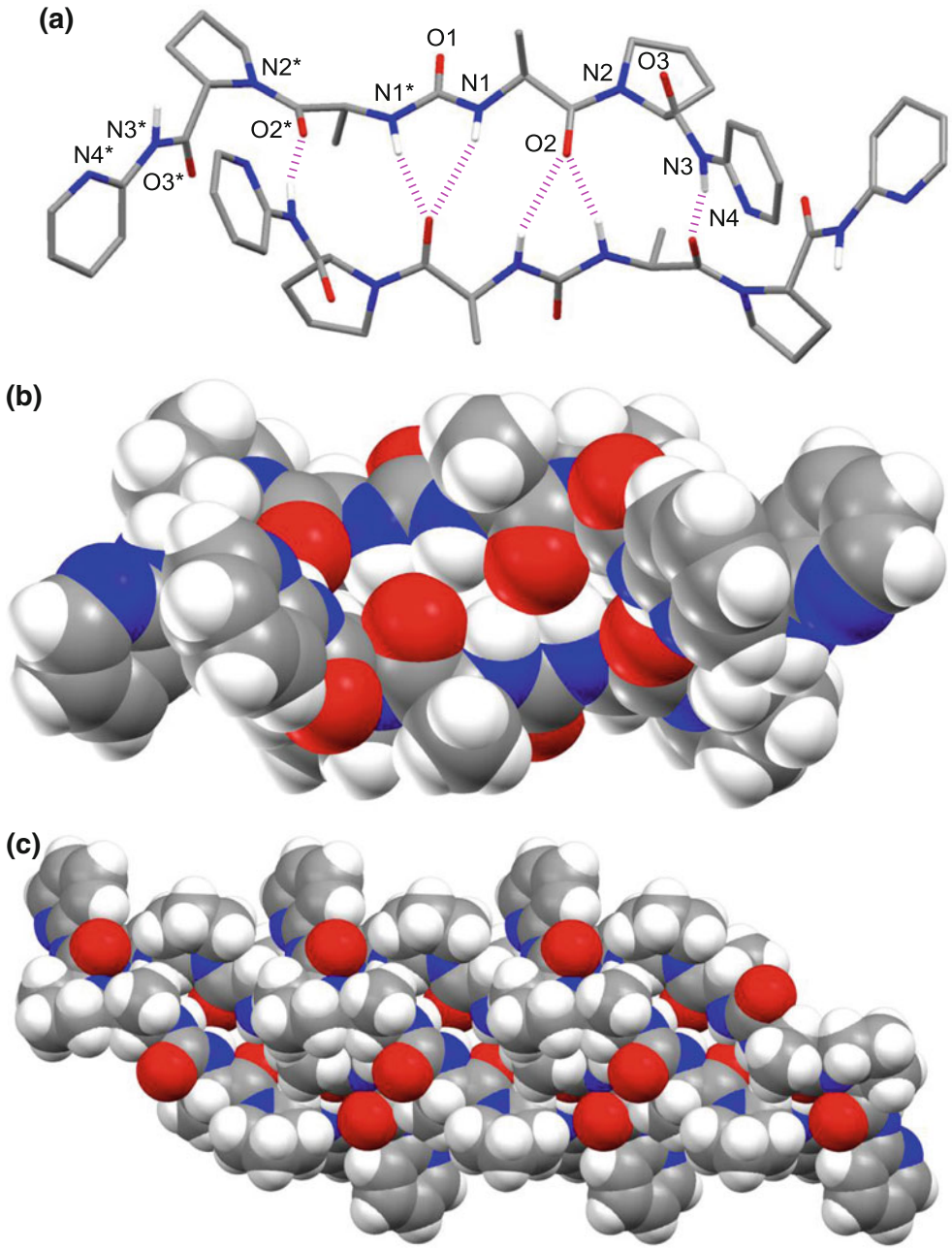
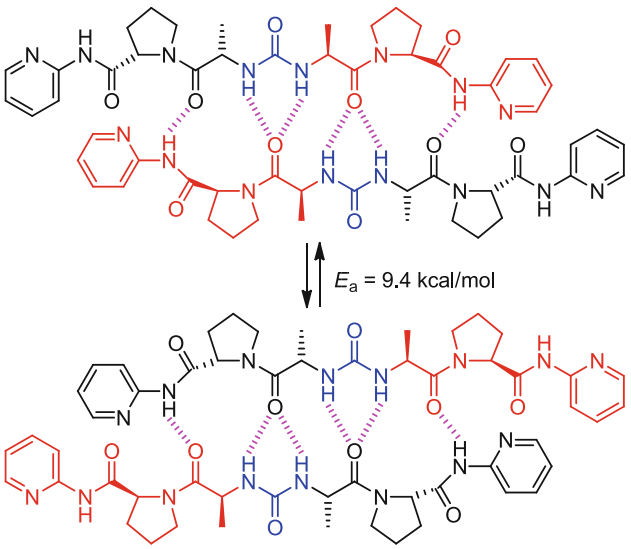


Fig. 17 **a** Stick, **b** space-filling representations of a hydrogen-bonded duplex of **46**, and **c** space-filling representation of a portion of a layer containing the double helix-like arrangement of the crystal packing of **46**. The *purple dotted line* represents the hydrogen bond



Scheme 3 A shuttle-like dynamic process of the dipeptidyl urea **46**

Chirality organization of dipeptidyl urea

Urea functionality has been utilized to create highly organized molecular assemblies through hydrogen bonding [81–90]. Combination of a urea and peptide unit is expected to provide stable hydrogen-bonded molecular assemblies [91–94]. Among the numerous artificial self-assembly systems through hydrogen bonding, formation of stable hydrogen-bonded molecular duplexes is one of the important targets of current research [95–102]. The crystal structure of the dipeptidyl urea **46** composed of two dipeptide chains (-L-Ala-L-Pro-NH-2-Py) reveals that two molecules of **46** are held together by six intermolecular hydrogen bonds to form a hydrogen-bonded duplex, which adopts a right-handed helical conformation (Fig. 17a–b) [103]. The propensity to form the chiral helicity is considered to be induced by the chirality of the peptide chains. Interestingly, each hydrogen-bonded duplex is connected by continuous intermolecular hydrogen bonds between urea CO and C-terminal amide NH to form a double helix-like arrangement as depicted in Fig. 17c. This hydrogen-bonded duplex shows a shuttle-like dynamic process based on the recombination of hydrogen bonds in a solution state (Scheme 3) [103]. The activation energy of this process is calculated as 9.4 kcal/mol (Chart 13).

Conclusion

A variety of dipeptide-induced chirality-organized structures are designed by the incorporation of dipeptides into molecular scaffolds. With molecular scaffolds, the introduced peptide strands are regulated in the appropriate dimensions. The utilization of molecular scaffolds is a useful strategy for organization of peptide structures, which allows the control of intramolecular interaction of peptides or peptidomimetic strands. The configuration and sequence of the amino acids are key factors in the construction of the chirality-organized bio-inspired systems under controlled hydrogen bonding. The chemical models of protein secondary structures provide fundamental insight into the factors affecting protein structure and stability. A further interesting feature of the peptide conjugates is their strong tendency to self-assemble through contribution of all available hydrogen bonding donors in a solid state. An assembling of the chirality-organized bioconjugates is also performed by metal-directed assembly. The architectural control of molecular assemblies utilizing biomolecules, which possess hydrogen bonding sites and chiral centers, is envisioned to be a useful approach to artificial highly-organized systems.

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