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Citation	European Journal of Inorganic Chemistry. 2022(5); e202100902
Issue Date	2022-02-16
Version of Record	2021-12-14
Type	Journal Article
Textversion	Author
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DOI	10.1002/ejic.202100902

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Moriuchi, T. (2021). Helical Chirality of Ferrocene Moieties in Cyclic Ferrocene - Peptide Conjugates. *European Journal of Inorganic Chemistry*. 2022. https://doi.org/10.1002/ejic.202100902

Helical Chirality of Ferrocene Moieties in Cyclic Ferrocene-Peptide Conjugates

Toshiyuki Moriuchi*[a]

Abstract: Ferrocene has been utilized as an organometallic scaffold for more than 25 years, serving as a central reverse-turn unit with the inter-ring spacing of about 3.3 Å. A variety of ferrocene-peptide conjugates have been designed to construct protein secondary structures and demonstrate the chirality organization via hydrogen bonding. In general, the helical chirality of ferrocene moieties in acyclic ferrocene-peptide conjugates is induced by the absolute configuration of the α-carbon atom of an amino acid adjacent to the ferrocene unit. Cyclization regulations restrict conformational flexibility of the peptide chains, inducing inversion of the helical chirality based on the reordering of the hydrogen bonding interactions. In this Minireview article, the helical chirality of ferrocene moieties in cyclic ferrocene-peptide conjugates is focused on. Controlled helical chirality of ferrocene moieties in a series of ferrocene-peptide conjugates by adjusting conformational flexibility of the peptide chains through cyclization regulations is introduced.

1. Introduction

Ferrocene (Fc), which was discovered in 1951,[1] is one of the most stable organometallic compounds. The interesting characteristic features of ferrocenes depend on reversible redox properties and a sandwich-shaped structure with two rotatory coplanar cyclopentadienyl (Cp) rings. Since its discovery, ferrocene has received extensive interest.[2] The ferrocenium cation is known to show an antiproliferative effect on a variety of cancer cell lines although ferrocene by itself is not toxic.[3] After the reports of hydroxyferrocifens **1**-**3**[4] as anticancer drug candidates and ferroquine **4**[5] as an antimalarial drug candidate (Figure 1), ferrocenes, as an organometallic moiety, have attracted increasing attention in organometallic medicinal chemistry,[6] a part of bioorganometallic chemistry which is a hybrid research field between biology and organometallic chemistry.[7]

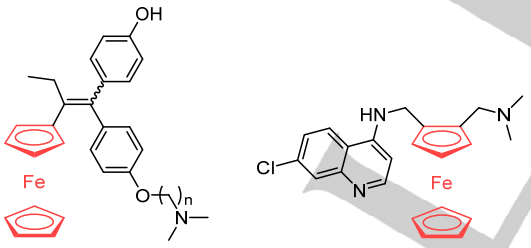

Figure 1. Hydroxyferrocifens **1**-**3** and ferroquine **4**.

Another Intriguing structural feature of ferrocene is that the inter-ring distance between the two rotatory Cp rings is about 3.3 Å, which is appropriate for hydrogen bonding between attached peptide chains on two Cp rings. Secondary structures such as α-helices, β-sheets, and β-turns are formed depending on the hydrogen bonds, which play key factors in protein foldings to fulfill unique functions as observed in enzymes, receptors, etc.[8] In general, construction of chemical models of protein secondary structure is difficult due to the complexity and aggregation tendencies of peptides. Various molecular scaffolds consist of organic compounds have been focused on to induce the β-sheet-like structure of introduced peptide chains[9] until the report of the acyclic ferrocene-amino acid conjugate **5**, in which L-Val-OMe is introduced (Figure 2).[10] The intramolecular antiparallel β-sheet-like hydrogen bonds are suggested to be formed in **5**. The acyclic ferrocene-amino acid conjugate **5** demonstrated the capability of ferrocene-1,1′-dicarboxylic acid (Fc-cc) as an organometallic scaffold, which serves as a central reverse-turn unit, to study the hydrogen bonding ability of introduced peptide chains.

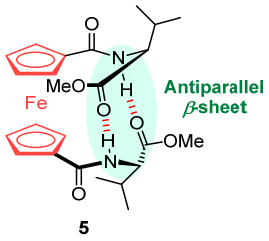

Figure 2. Acyclic ferrocene-amino acid conjugate **5**.

Toshiyuki Moriuchi received his bachelor's degree in 1991 and his doctoral degree in 1995 under the supervision of Professor Toshikazu Hirao, both from Osaka University. He became Assistant Professor at Osaka University and was a postdoctoral fellow at California Institute of Technology with Professor Jacqueline K. Barton (1996–1997). Dr. Moriuchi was promoted to Lecturer in 2004 and Associate Professor in 2008. He was promoted to Professor at Osaka City University in 2018. His current research interests focus on the development of functional bioorganometallic systems and the construction of hybrid molecular systems for functionalized catalysts and materials. He is a member of the International Advisory Board of the International Symposium on Bioorganometallic Chemistry and the International Vanadium Symposium. He received the Inoue Research Award for Young Scientists in 1997, HGCS Japan Award of Excellence 2011 in 2012, the 15th Kansai Branch Award of the Society of Synthetic Organic Chemistry, Japan in 2017, and Nagase Foundation Award 2018 in 2018.

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After the study of the acyclic ferrocene-amino acid conjugate **5** by Herrick and co-workers, a variety of ferrocene-peptide conjugates have been designed to shed light on the factors affecting the formation and stability of protein secondary structures.[11] In addition to Fc-cc, 1′-aminoferrocene-1-carboxylic acid (Fc-ac) and 1,1′-diaminoferrocene (Fc-aa) have also been utilized as organometallic scaffolds as shown in Figure 3. In acyclic Fc-cc-peptide conjugates, "Herrick",[10] "van Staveren",[12] and "Xu"[13] patterns with different orientations of the peptide chains are known (Figure 4). DFT calculations by Heinze and Rapić showed that the "Herrick" pattern is stable than the "van Staveren" or "Xu" patterns.[14]

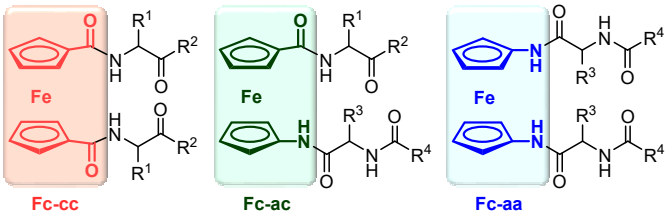

Figure 3. Ferrocene-1,1'-dicarboxylic acid (Fc-cc), 1'-aminoferrocene-1-carboxylic acid (Fc-ac), and 1,1'-diaminoferrocene (Fc-aa) organometallic scaffolds.

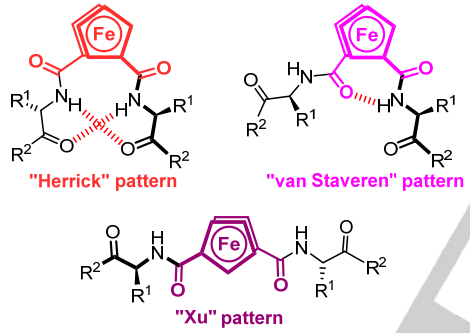

Figure 4. "Herrick", "van Staveren", and "Xu" patterns in Fc-cc-peptide conjugates.

P- and *M*-Helical conformations, which are interconvertible, based on a torsional twist about the Cp(centroid)-Fe-Cp(centroid) axis are present in the 1,*n*′-disubstituted ferrocene (Figure 5).[2] The introduction of the peptide chains, which have hydrogen bonding sites and chiral centers, into the ferrocene organometallic scaffold is expected to induce the helical chirality of the 1,*n*′-disubstituted ferrocene moiety by restriction of the torsional twist through the formation of intramolecular hydrogen bonds between the introduced chiral peptide chains. In fact, the acyclic ferrocene-peptide conjugate **6**, wherein the L-Ala-L-Pro-OEt homochiral dipeptide chains are introduced into the Fc-cc scaffold, shows *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety through the formation of intramolecular antiparallel *β*-sheet-like hydrogen bonds ("Herrick" pattern) as depicted in Figure 6.[15] In acyclic Fc-cc-peptide conjugates, the induced helical chirality of the ferrocenoyl moiety depends on the chirality of an amino acid adjacent to the ferrocene core.[11a, 16] In other words, when L-Ala is introduced as the adjacent amino acid, *P*-helical chirality is induced, irrespective of the chirality of the remote amino acid. For example, the acyclic ferrocene-peptide conjugate **7** composed of the L-Ala-D-Pro-NH-2-Py heterochiral dipeptide chains exhibits the formation of intramolecular antiparallel *β*-sheet-like hydrogen bonds to induce *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety (Figure 6).[17]

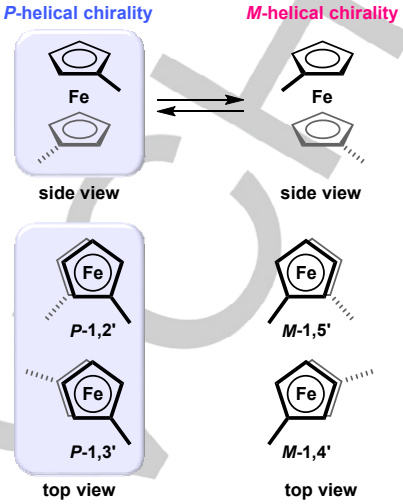

Figure 5. Side and top views of *P*- and *M*-helical chirality of the ferrocene moiety of 1,*n*′-disubstituted ferrocenes.

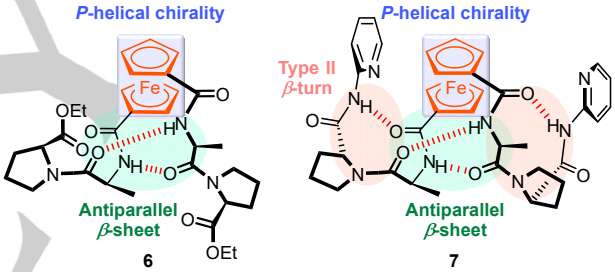

Figure 6. Acyclic ferrocene-peptide conjugates **6** and **7**.

One simple strategy to realize the control of the helical chirality of the 1,*n*′-disubstituted ferrocene moiety without changing the chirality of the adjacent amino acid is the conformational restriction of the peptide chains. Cyclization regulations, which act as a clamp to tie the terminals of the peptide chains together, is envisioned to restrict conformational flexibility of the peptide chains, resulting in the reordering of the hydrogen bonding interactions to switch the helical chirality of the ferrocene moiety. Recently, switching of the helical chirality of the ferrocene moiety in the double-stranded ferrocene pseudopeptide has been performed by solvent exchange or addition of acid.[18] In this Minireview article, the helical chirality of ferrocene moieties in cyclic ferrocene-peptide conjugates is described (Figure 7).

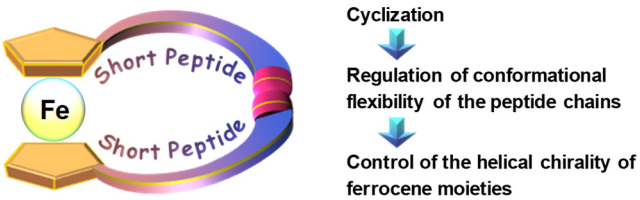

Figure 7. Strategy for controlling the helical chirality of ferrocene moieties in ferrocene-peptide conjugates.

2. Cyclic Ferrocene-Peptide Conjugates

Lactamization of 1,1′-ferrocenylbis(alanine) derivative (*S*,*S*)-**8** with the coupling reagent, PyAOP ((7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate), was reported to afford not only the cyclic ferrocene-peptide conjugate **9** but also the cyclic ferrocene-peptide conjugates **10** and **11** (Figure 8).[19] From ^{1}H NMR studies, the cyclic ferrocene-peptide conjugates **10** and **11** are indicated to be C_2 and C_3 symmetric, respectively. However, the helical chirality of the ferrocene moiety is not mentioned.

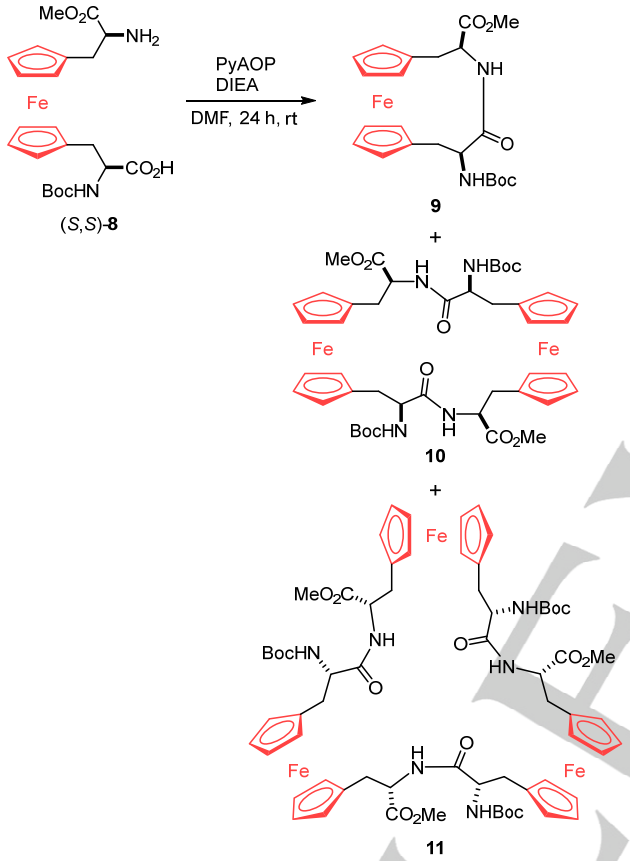

Figure 8. Cyclic ferrocene-peptide conjugates **9**-**11**.

A series of cyclic ferrocene-peptide conjugates **12**-**21** composed of Fc-cc organometallic scaffolds were reported by Cheng and co-workers (Figure 9).[20] In these cyclic ferrocene-peptide conjugates, disulfide linkage of L-cystine, which is composed of two cysteines connected by a disulfide bond, is utilized to cyclize two peptide chains as the conformational restriction of the peptide chains. The cyclic ferrocene-peptide conjugates **12**-**14** show a positive Cotton effect at the absorbance region of the ferrocene moiety in the CD spectra, indicating *P*-helical chirality of the ferrocenoyl moiety.[11] The results of CD spectra showing a positive Cotton effect of the cyclic ferrocene-peptide conjugates **15** (-L-Ala-L-cystine- L-Ala-), **16** (-L-Leu-L-cystine- L-Leu-), **17** (-L-Met-L-cystine- L-Met-) and **18** (-L-Pro-L-cystine-L-Pro-) suggest that *P*-helical chirality might be induced. In these cyclic conjugates, despite the conformational restriction of the peptide chains by cyclization, the induced helical chirality of the ferrocenoyl moiety depends on the chirality of an amino acid adjacent to the ferrocene core. On the contrary, *M*-helical chirality of the ferrocenoyl moiety is indicated to be induced in the cyclic ferrocene-peptide conjugates **19** composed of the cyclic peptide (-Gly-L-cystine-Gly-) and **20** composed of the cyclic peptide (-β-Ala-L-cystine- β-Ala-), wherein an amino acid adjacent to the ferrocene core is achiral, from the result of a negative Cotton effect in the CD spectra. This is in contrast to the report that *P*-helical chirality is induced in the acyclic ferrocene-peptide conjugate composed of the Gly-L-Pro-OEt dipeptide chains.[21] It might be due to the conformational restriction of the peptide chains by cyclization, but the reasons for this chirality induction are unclear because no structural discussion has been made. The cyclic ferrocene-peptide conjugate **21** composed of the cyclic peptide (-L-Ala-L-Pro-L-cystine-L-Pro-L-Ala-) also exhibits a positive Cotton effect based on *P*-helical chirality.

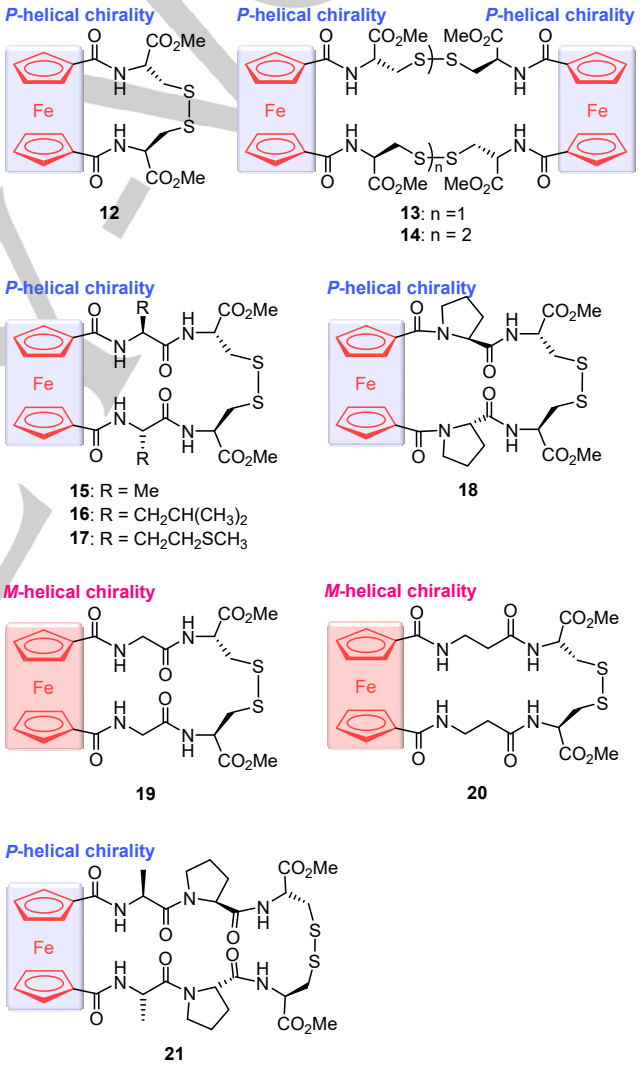

Figure 9. Cyclic ferrocene-peptide conjugates **12**-**21**.

Kraatz and co-workers designed the cyclic ferrocene-peptide conjugates **22**-**25** by using disulfide containing cystamine ($H_2NCH_2CH_2S$-$SCH_2CH_2NH_2$) linkages (Figure 10).[22] Cyclization of ferrocene-peptide conjugates leads the close proximity of the two peptide chains, allowing the formation of intramolecular

hydrogen bonds. Variable-temperature ^{1}H-NMR studies of **22-25** reveal the presence of hydrogen bonds involving the Fc-cc–amino acid NH, which are also supported by IR studies. In fact, single-crystal X-ray structure analysis of the cyclic ferrocene-peptide conjugate **22** confirms a 1,2′-conformation of the ferrocenoyl moiety through the formation of intramolecular antiparallel β-sheet-like hydrogen bonds. No further insights into the helical chirality of the ferrocenoyl moiety has been performed.

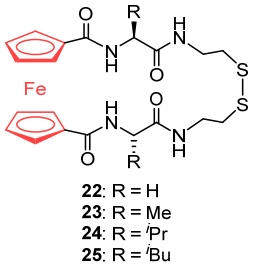

Figure 10. Cyclic ferrocene-peptide conjugates **22-25**.

The cystamine linked cyclic ferrocene-peptide conjugate **26** composed of the cyclic peptide (-Gly-L-Val-cystamine-L-Val-Gly-) shows *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety induced by the formation of intramolecular antiparallel β-sheet-like hydrogen bonds (Figure 11).[23] Despite the cyclization, this cyclic conjugate is able to form Herrick-type hydrogen bonds, inducing *P*-helical chirality. Another interesting feature of the cyclic ferrocene-peptide conjugate **26** lies in the formation of a pseudo-β-barrel-like structure.

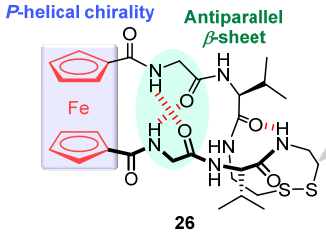

Figure 11. Cyclic ferrocene-peptide conjugate **26**.

In the crystal structure of the cyclic ferrocene-amino acid conjugate **27** composed of only one amino acid, both CO groups of the ferrocenoyl moiety align in a *syn* fashion, affording approximately *P*-1,1' helical conformation of the ferrocenoyl moiety (Figure 12).[24] The CD spectrum of the cyclic ferrocene-amino acid conjugate **27** suggests weak helical chirality in solution. Switching of the helical chirality of the ferrocenoyl moiety of **27** is possible by conformational regulation based on the binding to alkali metal ions. Complexation of **27** with Na^+ induces *M*-helical chirality probably due to the slight rotation of the Cp ring toward *M*-helical chirality by the coordination of the two *syn* CO groups.

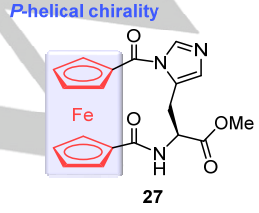

Figure 12. Cyclic ferrocene-amino acid conjugate **27**.

The diamine linked cyclic ferrocene-peptide conjugates **28-30** composed of two amino acids were also designed by Kraatz and co-workers (Figure 13).[25] A positive Cotton effect at the absorbance region of the ferrocene moiety in the CD spectra of **28-30** suggests the expected *P*-helical chirality. The diaminobutane linked cyclic ferrocene-peptide conjugate **28** shows a very weak CD signal at the absorbance region of the ferrocene moiety, indicating that the diamine linker affects the formation of a *P*-1,2′ helical conformer through the restriction of conformational flexibility of the peptide chains as observed in the cyclic ferrocene-amino acid conjugate **27**.

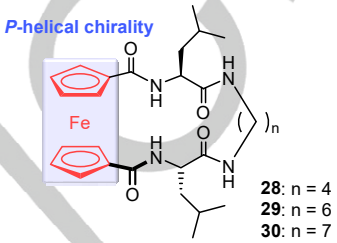

Figure 13. Cyclic ferrocene-peptide conjugates **28-30**.

In the utilization of cystamine as a linkage to cyclize two peptide chains attached to the ferrocene scaffold, the corresponding ring-opened conjugate can be readily accessed by the reductive cleavage of the disulfide bond to the thiols. Single-crystal X-ray structure analysis of the cystamine linked cyclic ferrocene-peptide conjugate **31** composed of the cyclic homochiral peptide (-L-Ala-L-Pro-cystamine-L-Pro-L-Ala-) reveals the formation of intramolecular antiparallel β-sheet-like hydrogen bonds to induce *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety (Figure 14).[26] This result indicates that the cystamine linker does not interfere with the formation of intramolecular antiparallel β-sheet-like hydrogen bonds. As an example to prove this, the acyclic ferrocene-peptide conjugate **32** bearing two L-Ala-L-Pro-NHCH$_2$CH$_2$SH dipeptide chains adopts *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety induced by the formation of intramolecular antiparallel β-sheet-like hydrogen bonds.

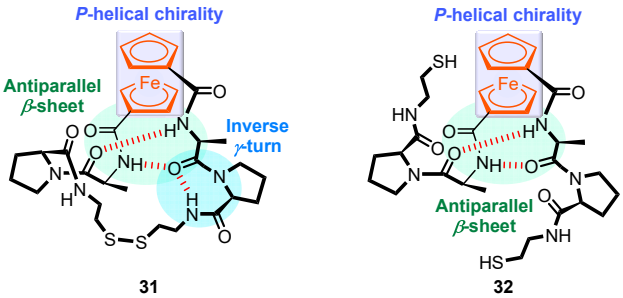

Figure 14. Cyclic ferrocene-peptide conjugate **31** and acyclic ferrocene-peptide conjugate **32**.

In the cyclic ferrocene-peptide conjugates where conformational flexibility of the peptide chains is restricted by cyclic linkages, the helical chirality of the ferrocenoyl moiety can be inverted without changing the chirality of the adjacent amino acids by changing an antiparallel β-sheet type structure to a different secondary structure through reorienting the hydrogen bonding interactions. A heterochiral sequence such as L-Pro-D-

Ala is known to create a reverse-turn structure in some oligopeptides.[27] The cystamine linked cyclic ferrocene-peptide conjugate **33** composed of the cyclic heterochiral peptide (-L-Ala-D-Pro-cystamine-D-Pro-L-Ala-) was designed to induce a reverse-turn structure (Figure 15).[26] Single-crystal X-ray structure analysis of **33** confirms *M*-helical chirality with an *M*-1,4' helical conformation of the ferrocenoyl moiety induced by the formation of a type II β-turn-like structure. The chirality of the remote amino acid regulates the induced chirality, and both *P*- and *M*-chirality can be induced without changing the chirality of the adjacent amino acid (i.e., **31** vs **33**). In contrast to the structure of **33**, the formation of intramolecular antiparallel β-sheet-like hydrogen bonds to induce *P*-helical chirality with *P*-1,2' helical conformation is observed in the acyclic ferrocene-peptide conjugate **34** bearing two L-Ala-D-Pro-NHCH$_2$CH$_2$SH dipeptide chains.

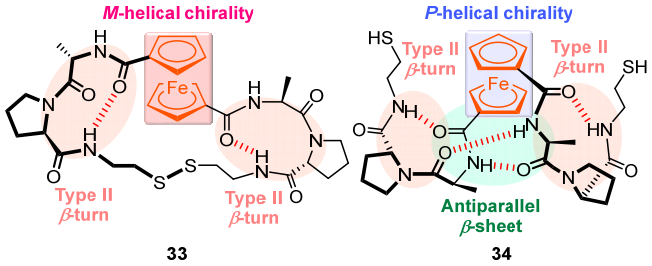

Figure 15. Cyclic ferrocene-peptide conjugate **33** and acyclic ferrocene-peptide conjugate **34**.

3. Cyclic Ferrocene-Peptide Conjugates Based on Complexation

Metal ions perform a variety of functions in proteins. One important role of metal ions is structural stabilization for biological function.[28] Complexation with metal ions is one of the simple strategies to tie and bind the peptide chains, which might induce conformational change by reorienting the hydrogen bonding interactions. The complexation of the acyclic ferrocene-peptide conjugate **35** bearing two homochiral L-Ala-L-Pro-NH-2-Py dipeptide chains, which shows *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety based on the formation of intramolecular antiparallel β-sheet-like hydrogen bonds, with $PdCl_2(MeCN)_2$ affords the 1:1 palladium complex **36** (Figure 16). X-ray crystal structure analysis of the 1:1 palladium complex **36** reveals the pseudohelical conformation through palladium coordination, wherein *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety is retained.[29] ^{1}H NMR studies in $CDCl_3$ indicate that complexation strengthens the intramolecular hydrogen bondings.

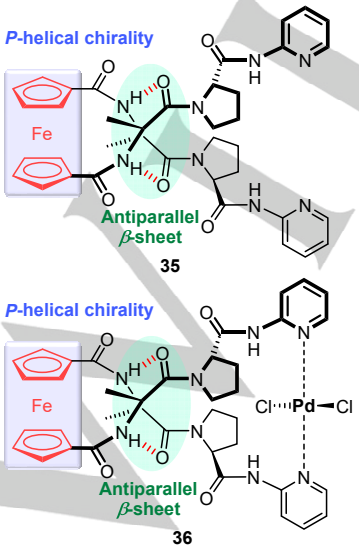

Figure 16. Acyclic ferrocene-peptide conjugate **35** and the 1:1 palladium complex **36**.

The cyclic ferrocene-peptide-[FeFe] complex **37**, which is the first peptide-coordinated iron hydrogenase active-site model complex, was reported by Metzler-Nolte and co-workers (Figure 17).[30] The cyclic ferrocene-peptide-[FeFe] complex **37** can be obtained by the reaction of the acyclic ferrocene-peptide conjugate bearing two L-Cys-OMe aminio acids with $Fe_3(CO)_{12}$. Single-crystal X-ray structure analysis of **37** confirms *M*-helical chirality with an *M*-1,5' helical conformation of the ferrocenoyl moiety. The cyclic ferrocene-peptide-[FeFe] complex **37** shows no strong negative band around 450 nm in the CD spectrum because it is flexible in solution due to the absence of intramolecular hydrogen bonds.

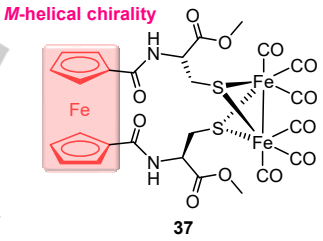

Figure 17. Cyclic ferrocene-peptide-[FeFe] complex **37**.

The ferrocene moieties of the acyclic Fc-aa-peptide conjugates **38** bearing two homochiral L-Pro-L-Ala-CO-2-Py dipeptide chains and **39** bearing two homochiral D-Pro-D-Ala-CO-2-Py dipeptide chains adopt *P*-helical and *M*-helical chirality, respectively, in solution (Figure 18).[31] These Fc-aa-peptide conjugates form 1:1 complexes with Zn^{2+}, Cd^{2+}, Cu^{2+}, or Fe^{2+}. Thus-obtained 1:1 complexes exhibit the Cotton effects of the same sign as the corresponding Fc-aa-peptide conjugates **38** and **39** at the absorbance region of the ferrocene moiety, indicating that the helical chirality is not changed by complexation with metal ions.

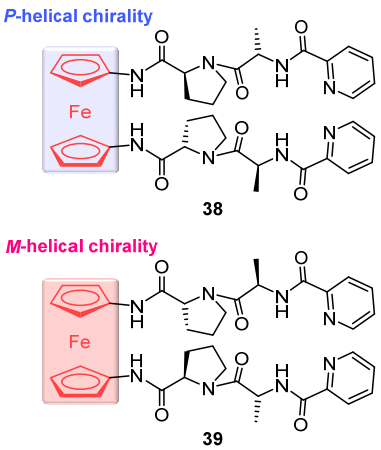

Figure 18. Acyclic ferrocene-peptide conjugates **38** and **39**.

The helical chirality of the ferrocenoyl moiety can be controlled by changing the introduced metal ions through the conformational change based on the difference in coordination mode. The CD spectrum of the acyclic ferrocene-peptide conjugate **40** bearing two L-His(DNP)-Gly-OMe dipeptide chains shows a positive Cotton effect at λ = 480 nm in the CD spectra, suggesting *P*-helical chirality of the ferrocenoyl moiety (Figure 19).[32] Spectroscopic and electrochemical studies indicate that the conjugate **40** forms a 1:1 complex with metal ion such as Mg^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, and Cu^{2+}. The CD signal with a positive Cotton effect upon addition of Mg^{2+}, Zn^{2+}, or Cd^{2+} suggests the preservation of *P*-helical chirality of the ferrocenoyl moiety. On the contrary, the addition of Fe^{2+} or Cu^{2+} causes the appearance of a negative Cotton effect at the absorbance region of the ferrocenoyl moiety, indicating the conversion of *P*-helical chirality into *M*-helical chirality based on the conformational change in the structure of the ferrocenoyl moiety.

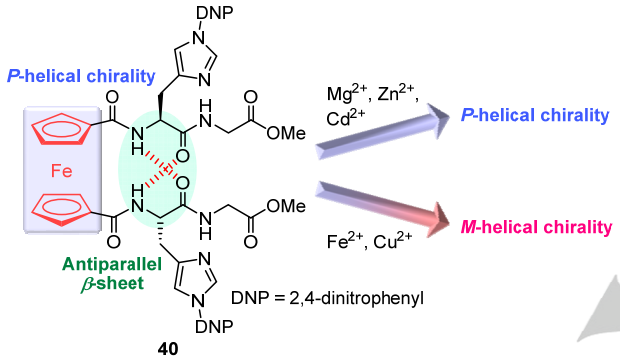

Figure 19. Switching of the helical chirality of the ferrocenoyl moiety of the acyclic ferrocene-peptide conjugate **40** by complexation.

The acyclic ferrocene-peptide conjugates **41** bearing two homochiral L-His(Trt)-L-His(Trt)-OMe dipeptide chains, **42** bearing two homochiral L-His(Trt)-L-Asp(OMe)-OMe dipeptide chains, and **43** bearing two homochiral L-His(Trt)-L-Glu(OMe)-OMe dipeptide chains were also reported to reveal chiral switching of the helical chirality of the ferrocenoyl moiety through the complexation (Figure 20).[33] Although L-amino acids adjacent to the ferrocene core generally induce *P*-helical chirality of the ferrocenoyl moiety in the case of acyclic Fc-cc-peptide conjugates, the steric bulk of the triphenylmethyl protecting groups of the acyclic ferrocene-peptide conjugate **41** bearing two homochiral L-His(Trt)-L-His(Trt)-OMe dipeptide chains causes *M*-helical chirality of the ferrocenoyl moiety, which is supported by the negative Cotton effect at the absorbance region of the ferrocenoyl moiety in the CD spectra in solution. Single-crystal X-ray structure analysis of **42** and **43** proves *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety through the formation of intramolecular antiparallel β-sheet-like hydrogen bonds of "Herrick" pattern. ^{1}H NMR and UV titration studies, electrochemical investigations, and ESI-MS experiments support that the binding of the conjugates **41**-**43** to metal ions (Mg^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, or Mn^{2+}) occurs in a stoichiometric ratio of 1:1 stoichiometric ratio. According to the CD spectra, the CD signals of **41** remain negative upon addition of Mg^{2+}, Cd^{2+}, Ni^{2+}, or Mn^{2+}, indicating the preservation of *M*-helical chirality of the ferrocenoyl moiety. Chiral switching from *M*-helical chirality to *P*-helical chirality of the ferrocenoyl moiety of **41** can be performed by binding of Zn^{2+} or Cu^{2+}. In the case of the conjugates **42** and **43**, *P*-helical chirality of the ferrocenoyl moiety is retained even in the addition of Mg^{2+} or Cd^{2+}. On the other hand, addition of Zn^{2+}, Cu^{2+}, Ni^{2+}, or Mn^{2+} induces chiral switching from *P*-helical chirality to *M*-helical chirality of the ferrocenoyl moieties of **42** and **43**.

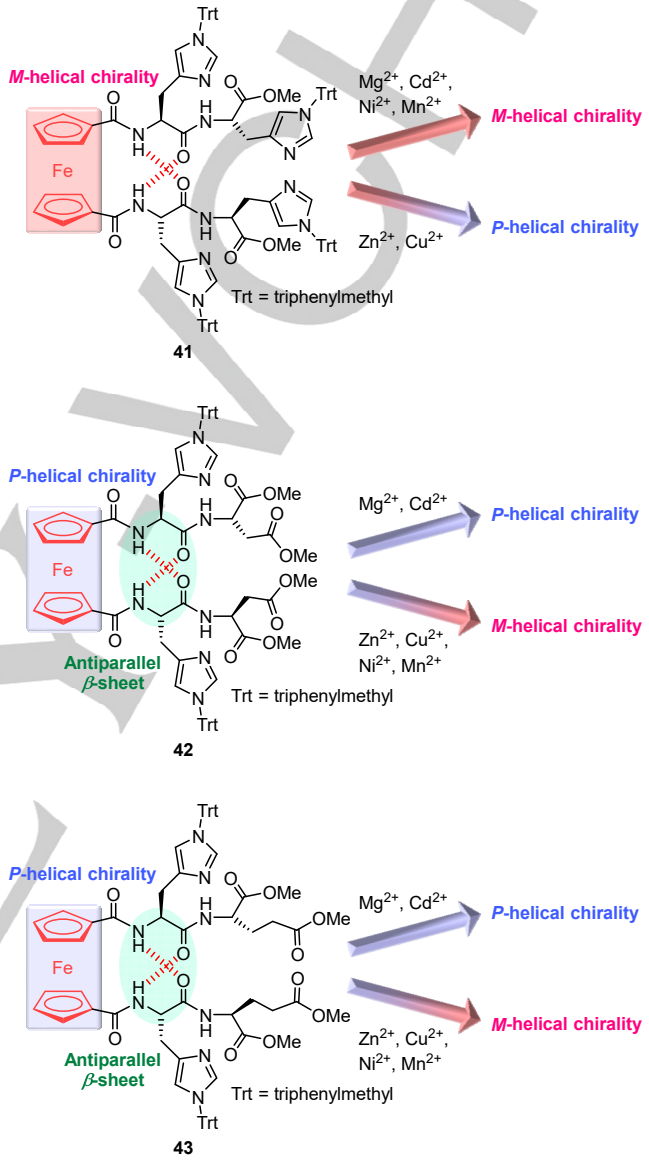

Figure 20. Switching of the helical chirality of the ferrocenoyl moiety of the acyclic ferrocene-peptide conjugates **41**-**43** by complexation.

Kraatz and co-workers designed the unsymmetric ferrocene-peptide conjugate **44** bearing the homochiral L-His(Trt)-Gly-L-His(Trt)-OMe and Gly-L-His(Trt)-OMe peptide chains (Figure 21).[34] The unsymmetric conjugate **44** forms a discrete complex with divalent metal ions Cd^{2+}, Zn^{2+}, or Co^{2+} through the coordination of three histidine residues to the metal center, and exhibit a switchable helical chirality of the ferrocenoyl moiety. Chiral switching from *P*-helical chirality to *M*-helical chirality of the ferrocenoyl moiety of the unsymmetric conjugate **44** is triggered upon the addition of either Cd^{2+}, Zn^{2+} or Co^{2+} divalent metal ions.

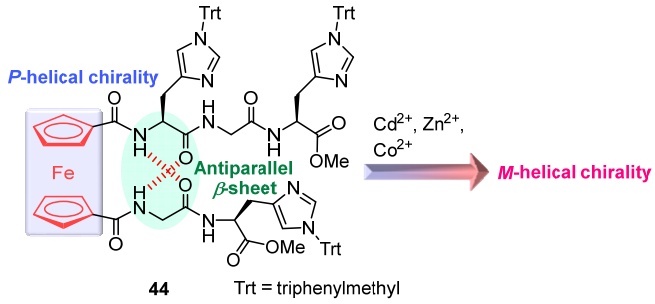

Figure 21. Switching of the helical chirality of the ferrocenoyl moiety of the unsymmetric ferrocene-peptide conjugate **44** by complexation.

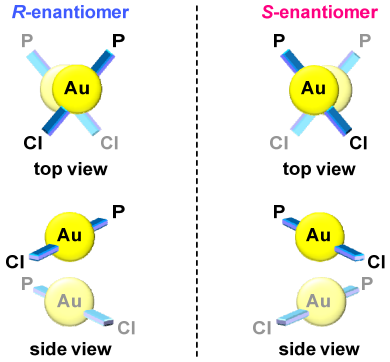

Figure 22. *R*- and *S*-enantiomers of the dinuclear gold(I) complexes.

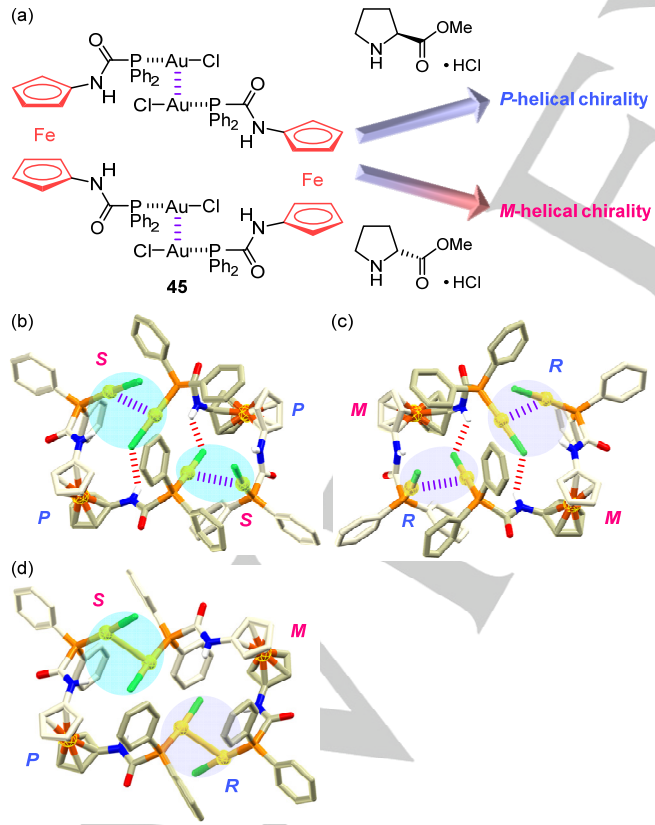

Figure 23. (a) Switching of the helical chirality of the ferrocene moieties of the macrocyclic dimer gold(I) complex **45** by the chirality of proline methyl ester hydrochloride, (b) homochiral *PP* macrocyclic dimer structure of **45**, (c) homochiral *MM* macrocyclic dimer structure of **45**, and (d) heterochiral *PM* macrocyclic dimer structure of **45**.

The conformational enantiomers, *R*- and *S*-enantiomers, based on a torsional twist about the Au(I)-Au(I) axis are present in the dinuclear gold(I) complexes as shown in Figure 22.[35] The axial chirality of the Au(I)–Au(I) axis is able to transmit the chirality to the ferrocene moiety. The macrocyclic dimer gold(I) complex **45**, induced by aurophilic Au(I)-Au(I) interactions, can be obtained by the reaction of 1,1'-bis(phosphinecarboxamidyl)ferrocene with chloro(tetrahydrothiophene)gold(I) (Figure 23).[36] In the macrocyclic dimer gold(I) complex **45**, homochiral *PP*, homochiral *MM*, and heterochiral *PM* macrocyclic dimers based on the helical chirality of the ferrocene moieties through intermolecular aurophilic Au(I)-Au(I) interactions are formed, wherein *S*- and *R*-conformational enantiomers based on axial chirality of the Au(I)-Au(I) axis induce *P*- and *M*-helical chirality of the ferrocene moieties, respectively. The hosphinecarboxamide binding sites of **45** can accommodate halide ion of ammonium salt. *P*-helical chirality of the ferrocene moiety is induced by the addition of L-proline methyl ester hydrochloride to the solution of **45**, and conversely, the addition of D-proline methyl ester hydrochloride induces *M*-helical chirality.

Host-guest binding through multipoint hydrogen bonds is another strategy to tie and bind the peptide chains. The acyclic ferrocene-peptide conjugate **46** bearing two homochiral L-Ala-L-Pro-NH-2-PyMe dipeptide chains adopts *P*-helical chirality with *P*-1,2' helical conformation of the ferrocenoyl moiety based on the formation of intramolecular antiparallel *β*-sheet-like hydrogen bonds (Figure 24).[37] In the ferrocene-peptide conjugate **46**, the chirality organization through two intramolecular hydrogen bonds allows the two amido pyridyl moieties as hydrogen bonding sites to be well arranged for binding dicarboxylic acids. In fact, the ferrocene-peptide conjugate **46** exhibits size-selective and chiral recognition of dicarboxylic acids, forming the 1:1 complex **47** by multipoint hydrogen bondings of the binding sites (Figure 24), wherein *P*-helical chirality of the ferrocenoyl moiety is preserved to provide a rigid binding site for the selective recognition.[37]

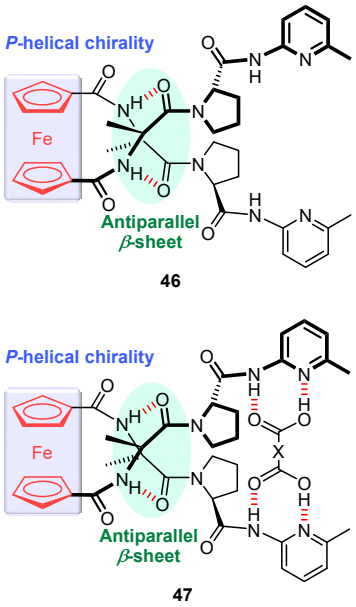

Figure 24. Acyclic ferrocene-peptide conjugate **46** and the 1:1 complex **47** with a series of dicarboxylic acids.

The ferrocene-peptide conjugate receptor **48** composed of the Fc-cc-L-Val core for binding dihydrogen phosphate ions ($H_2PO_4^-$) was designed by Sanders and co-workers (Figure 25).[38] The CD spectrum of the conjugate **48** shows a positive peak at 485 nm, indicating *P*-helical chirality of the ferrocenoyl moiety. The conjugate **48** can accommodate two molecules of $H_2PO_4^-$ cooperatively to form the 1:2 complex **49**, wherein helical binding of two $H_2PO_4^-$ is suggested by NOESY and NMR titration experiments. The presence of 2 equiv. of $H_2PO_4^-$ does not cause a significant change in the CD spectrum, suggesting that two $H_2PO_4^-$ are bound while maintaining *P*-helical chirality of the ferrocenoyl moiety.

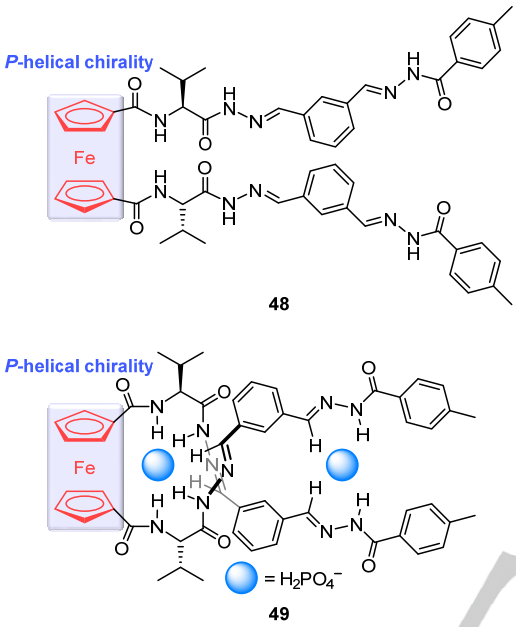

Figure 25. Acyclic ferrocene-peptide conjugate **48** and the 1:2 complex **49** with two dihydrogen phosphate ions.

4. Conclusions and Outlook

Ferrocene, one of the most stable organometallic compounds, has an exquisite structure with the iron atom sandwiched between two rotatory coplanar Cp rings. Two rotatory coplanar Cp rings with the inter-ring distance of about 3.3 Å allows ferrocene to serve as an organometallic scaffold with a central reverse-turn unit to construct protein secondary structure mimics composed of short peptides for fundamental insight into the factors affecting structure and stability of protein. A variety of ferrocene-peptide conjugates have been designed to construct chemical models of protein secondary structures and chirality-organized structures.

In this Minireview article, the helical chirality of the ferrocene moiety in cyclic ferrocene-peptide conjugates is outlined. Cyclization regulations, which act as a clamp to tie the terminals of the peptide chains together, is one simple strategy to restrict conformational flexibility of the peptide chains, resulting in the reordering of the hydrogen bonding interactions to switch the helical chirality of the ferrocene moiety. So, the helical chirality of the ferrocene moiety can be inverted without changing the chirality of the adjacent amino acids by changing the hydrogen bonding pattern exemplified by an antiparallel β-sheet type structure to a different secondary structure. Complexation with metal ions is another effective strategy to adjust conformational flexibility of the peptide chains for chiral switching of the helical chirality and stabilize the chirality-organized structures. Chiroptical switching has attracted much attention in applications in molecular electronics such as logic gates and memory devices.[39] The study of the chirality-organized ferrocene-peptide conjugates may provide not only the fundamental basis for the development of biologically useful compounds but also artificial chiral receptors, asymmetric catalysts, and functional materials.

Acknowledgements

The author thanks Prof. Toshikazu Hirao (Osaka University) for valuable discussion.

Keywords: Ferrocene • Peptide • Cyclic conjugate • Helical chirality • Protein secondary structure

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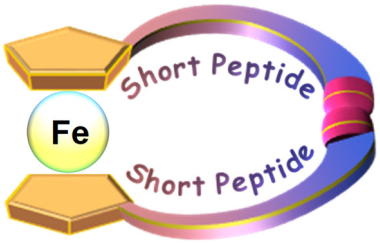

Helical chirality of ferrocene moieties in cyclic ferrocene-peptide conjugates is reviewed. Control of the helical chirality of ferrocene moieties in a series of ferrocene-peptide conjugates by regulation of conformational flexibility of the peptide chains through cyclization regulations is discussed.

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