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Designer Peptides: Attempt to Control Peptide Structure by Exploiting Ferrocene as a Scaffold

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The design of peptides that display a β-sheet-like secondary structure remains a challenge. Molecular scaffolds, such as ferrocene (Fc) can help to overcome some of these challenges. Monosubstituted Fc derivatives offer no control over the self-assembly of the conjugates, and the formation of supramolecular structures is entirely serendipitous. 1,*n*′-disubstituted Fc derivatives provide a significant level of control over the direction of the peptide, their relative orientation, and the intramolecular hydrogen-bonding patterns, which increases the rigidity of the molecule and in many cases, generates a new H-bonding interface for intermolecular assembly. In this Microreview, we explore the use of ferrocene as a scaffold in the design of structurally well-defined peptide conjugates.
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Introduction

Enormous efforts have been devoted to the design of structurally well-defined synthetic peptides – and with good reason. Understanding and controlling peptide secondary structures are of central importance and will help to unravel mechanisms of protein folding, of biochemical processes,[1] and will help to develop new molecules and materials with potential biological applications.[2,3] Various strategies have been employed to design and control the structure of peptides and to create synthetic foldamers that adopt specific secondary structures. Work by Kaiser, who formulated the basic principles for foldamer design, DeGrado and many others focused on helical peptides.[4] A careful choice of the amino acid sequence is critical for obtaining a stable helical conformation that ultimately allows the design of versatile foldamers with specific functions.[5] The helical foldamers are often stabilized by intra-helix hydrogen bonding. It is interesting to note that such helical foldamers can be used as building blocks for the construction of larger supramolecular structures. Two examples illustrate this point. Metal coordination was exploited by Ogawa to assemble a de novo metalloprotein from smaller peptide precursors. This approach is highly adaptive and enables the incorpora-

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Heinz-Bernhard Kraatz (centre) is a Professor of Chemistry at the University of Western Ontario. After studying at Heinrich-Heine Universität and the University of Kent, he received his Ph.D. from the University of Calgary in 1993. After postdoctoral work at the University of Maryland and at the Weizmann Institute of Science, he took a position at the Steacie Institute of Science and in 1998 joined the Department of Chemistry at the University of Saskatchewan for his first academic appointment. In his research, he combines synthetic peptide chemistry with surface-based electro-analytical methodology. His current research is focused on the design of surface-supported functional bioorganometallic conjugates and bio(nano)materials and their application as electrochemical biosensors for the detection of proteins, genetic material and small molecules. He is the recipient of the Petro-Canada Young Innovator Award (2001), the CSC Award for Pure and Applied Inorganic Chemistry (2006), the Florence Bucke Science Prize (2009) and held the Canada Research Chair in Biomaterials.

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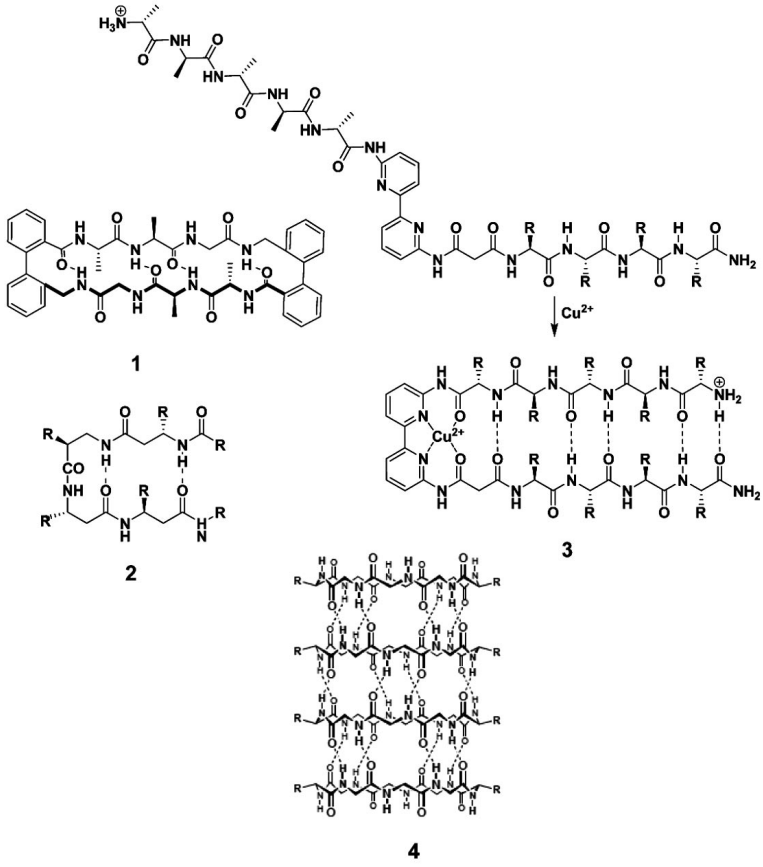
tion of functionality into the foldamer assembly and has provided insight into protein dynamics and protein–protein interactions.[6] This approach has been expanded recently by Texcan and co-workers who developed a highly adaptive and versatile assembly strategy that provides access to well-defined protein complexes by exploiting metal–ligand coordination.[7] Peptide foldamers that adopt β-sheet-like conformations are of interest and have tremendous potential as model systems in furthering our understanding of diseases, such as Alzheimer's and Huntington's. In contrast to helical peptide foldamers, the design of β-sheet foldamers is a more complex problem. Whereas it is possible to design peptide sequences consisting of amino acids with a high propensity for β-sheet formation, such peptide strands will quickly associate into larger aggregates that are insoluble and, in many cases, present an intractable problem. Controlling the assembly of peptide strands, their alignment in a parallel or antiparallel fashion and controlling interstrand H-bonding patterns remain a significant challenge. As illustrated in Scheme 1, at present one relies on strategies including cyclization of peptides,[8] the insertion of β-amino acids into the amino acid sequence,[9] the complexation of metal ions to the specific binding sites which might induce structural changes to the entire peptide conjugate enabling the interaction of individual peptide strands,[10] and the presence of alternating D- and L-amino acids into cyclopeptides leading to a flat building block that enables a more controlled aggregation.[11] Non-peptidic scaffolds have been particularly successful for obtaining foldamers with a defined stable β-sheet-like structure.[12] In this context, ferrocene (Fc) has recently been recognized as a suitable molecular scaffold for the design of β-sheet-like structures and turns. The separation of the two Cp rings is about 3.3 Å and is ideal for allowing H-bonding interaction between peptide substituents on the two Cp rings.

Fc-peptide conjugates are synthetically accessible molecules that often display hierarchical supramolecular structures in which the assembly is guided by intra- and intermolecular H-bonding interactions of the bio component. In this Microreview, we explore the use of Fc as a scaffold for the design of structures that are mimics for peptide turns and sheet-like foldamers and focus on some recent work that provides some insight into the design of such structures.



Scheme 1. Common approaches to control peptide aggregation and to design β-sheet models: (a) formation of antiparallel β-sheet-like conformation upon cycliaztion of biphenyl peptide conjugates (**1**); (b) hairpin turn of *N*-acyl-β-tetrapeptide (**2**); (c) β-sheet stabilization of bipyridine peptide conjugates with Cu^{2+}(**3**); (d) formation of cyclopeptides by using alternating D- and L-amino acids, the circular conformation adopt tubular architecture (**4**).

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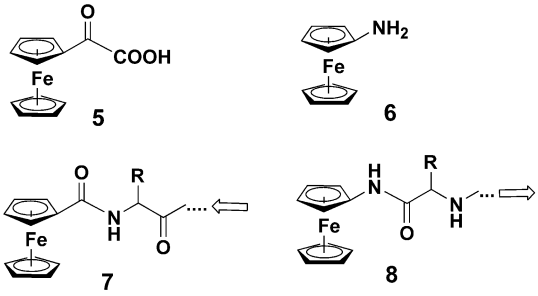
Monosubstituted Ferrocene-Peptide Conjugates

We would like to begin our discussion with monosubstituted Fc conjugates. Just as amino acids and peptides often assemble into extended supramolecular three-dimensional structures, monosubstituted Fc conjugates associate into larger aggregates. However, directing the self-assembly process is highly problematic and largely up to chance. Fc-carboxylic acid (**5**) and Fc-amine (**6**) serve as convenient starting materials for the synthesis of Fc-peptide conjugates **7** and **8** (Scheme 2), both of which provide control over the directionality of the peptide.



Scheme 2. Two ferrocene synthons, ferrocenylcarboxylic acid (**5**) and ferrocenylamine (**6**) have been used for the synthesis of a large variety of Fc-peptide conjugates. The two synthons provide control over the directionality of the peptide attachment and thereby enable the introduction of the Fc group to either side of the peptide dipole. Fc-carboxylic acid conjugate **7** shows the N-terminus side of a peptide attached to the Fc group, whereas the Fc-amine conjugate **8** has the C-terminus of the peptide attached to the Fc moiety. In both cases conjugation is achieved through an amide linkage.

In practical terms, orthogonal synthesis of these Fc conjugates is achieved by peptide-coupling strategies, involving the activation of the carboxylate (active ester or acid chloride), followed by coupling to the amino component. The Fc-active ester derivatives are readily accessible by using carbodiimides and uronium reagents.[13] The supramolecular assembly of such Fc conjugates by intermolecular H-bonding, while interesting and aesthetically pleasing, is essentially uncontrollable and left to serendipity. Self-assembly leads to chains or helical arrangements as is illustrated by the following examples.

Molecules of the Fc-amine conjugate Boc-Gly-NH-Fc (**9**) aggregate in the solid state in a side-on fashion resulting in the formation of linear chains that are connected by an intermolecular H-bonding framework that is reminiscent of that observed in parallel β-sheets. The 12-membered rings observed in Fc-CO-Gly$_2$OEt are similar to the H-bonding pattern observed in parallel β-sheets (Figure 1).[14] This is not too surprising since the donor–acceptor sites in both complexes are identical, and only the directionality of the peptide attachment is affected.

In contrast, the ferrocene-dipeptide conjugates (Fc-L-Ala-L-Pro-NHPy) (**10**) align in an antiparallel manner having molecules connected through intermolecular N–H···N and N–H···O H-bonds, forming a nine-membered H-bonded ring (Figure 2).[15] Palladium(II) ion coordination to the pyridyl moiety was unsuccessful to stabilize the β-sheet-like structure between the two ferrocenyl-dipeptides **10**, a rotational barrier of 42.3 kJ mol^{-1} is required to adopt a *syn* conformer of the dipeptides **10** in the *trans* Pd^{II} complex.

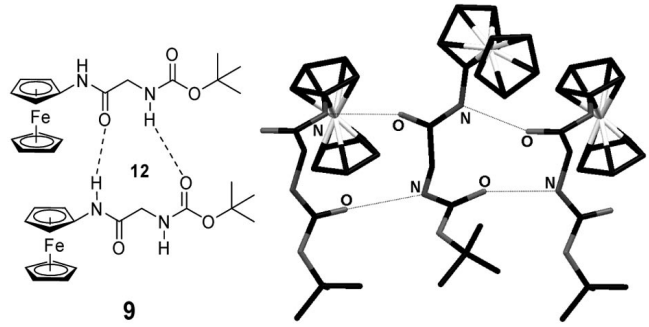


Figure 1. Chemical drawing and molecular structure of Boc-Gly-NH-Fc (**9**) show the H-bonding interactions leading to the formation of 12-membered H-bonded ring.

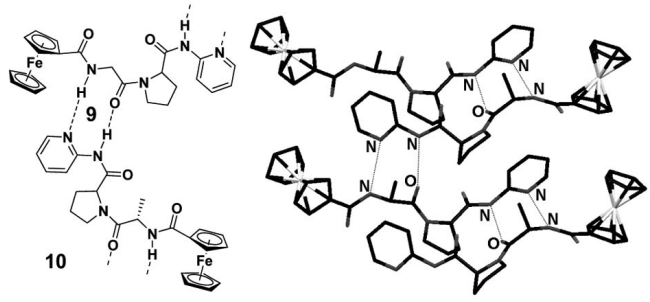


Figure 2. Layer of Fc-L-Ala-L-Pro-NHPy containing an antiparallel arrangement of conjugate **10**; H-bond lengths are *d*(N···N) = 3.153(7) Å and *d*(N···O) = 2.902(5) Å. As a result a nine-membered H-bonded ring is established between adjacent Fc-peptide conjugate units.

The Fc-glycyl-cystamine conjugate [Fc-Gly-CSA]$_2$ (**11**) possesses a number of H-bond donor and acceptor sites that are engaged in intermolecular H-bonding in the solid state.[16] The two parts of the molecule, while chemically identical, engage in significantly different interactions giving rise to two different helical supramolecular arrangements for each of the two parts of the molecule.

H-bonding through the Fc-amide and cystamine functions involved interactions with the identical portion of two neighbouring molecules. The two parts displays a distinct H-bonding pattern involving 12-membered rings. As indicated in Figure 3, one of the H-bonding interactions established involves a pair of H-bond acceptors/donors arranged in an unusual *syn* fashion resulting in a highly asymmetric H-bonding [O(3)···N(3*) = 2.976 (12) Å, O(4)···N(4*) = 2.789 (12) Å.]. The Fc groups decorate a central H-bonded peptide core. Small changes, such as the substitution of Ala for Gly, have a profound effect on the arrangement of the donor and acceptor sites, which guides the H-bonding ability and the supramolecular assembly. [Fc-Ala-CSA]$_2$ is sym-

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metrical and exhibits a proteinic H-bonding pattern only. The unusual H-bonding found in the Gly analogue is lost.[17]

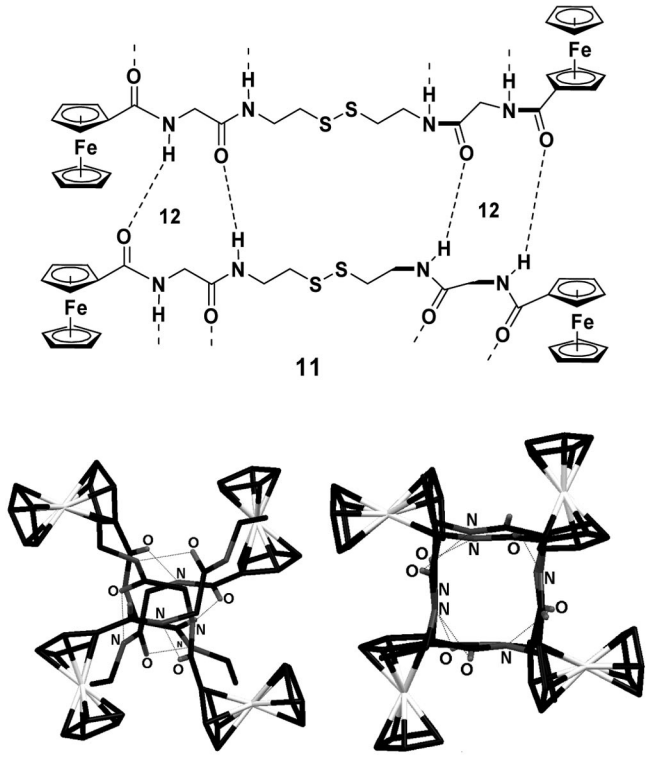

Figure 3. Chemical drawing of ferrocenoylglycylcystamine (**11**). The molecule displays two types of H-bonding interactions, one of them being a highly unusual involving a *syn* arrangement of the donor–acceptor sites. The figure shows a view along the two different helical arrangements. Note that 12-membered H-bonded rings are formed for the two different H-bonding motifs in the solid state.

Kenny has reported a series of structurally related peptide conjugates of ferrocenylbenzoic acid. Figure 4 shows the interactions between two molecules of *N*-[*meta*-(ferrocenyl)benzoyl]alanineglycine ethyl esters (**12**). It is interesting to note that the H-bonding pattern established by this compound is essentially identical to that of [Fc-CO-Gly-CSA]$_2$ (**11**) involving two *syn* NH groups, which interact with two CO groups from an adjacent conjugate forming a 12-membered H-bonded ring.[18] The molecules interact in a head-to-tail helical fashion resulting in the formation of a helical structure akin to that observed in compound **11**.

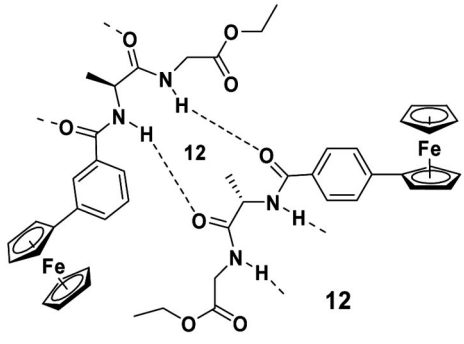

Figure 4. Two molecules of Fc conjugate *N*-[*meta*-(ferrocenyl)benzoyl]-L-alanineglycine ethyl ester (**12**) interacting. The arrangement of the amide provides a *syn* alignment leading to the formation of a 12-membered H-bonded ring.

The H-bonding distances in this structural arrangement with *syn* alignment of the amides is similar to that observed for **11** [d(O1···N3) = 2.828(2) Å and d(O2···N4) = 2.794(3) Å].

Disubstituted Ferrocene-Peptide Conjugates

Clearly, monosubstituted Fc derivatives do not provide any control over the self-assembly of peptides. In contrast, disubstituted Fc derivatives **13**–**15** provide much greater control. The separation between the two Cp rings in Fc is about 3.3 Å, and it is close to the N···O distance found in β-sheets. Fc-dicarboxylic acid **13**, Fc-amino acid (Fca) **14** and Fc-diamine **15** have been used as scaffolds for the synthesis of Fc-peptide conjugates. The particular choice of Fc scaffold dictates the directionality of the peptide strand and influences the rigidity of the molecule by controlling the inter-strand H-bonding. Different H-bonding patterns are possible. For example, amino acid or peptide conjugates of Fc-dicarboxylic acid (**13**) for the most part engage in H-bonding leading to a 10-membered H-bonded ring as indicated in Schemes 3 and 4. This structural motif is also known as the "Herrick motif".[19] Alternative arrangements shown as **20**, showing only a single H-bonding interaction and **21** showing no intramolecular H-bonding interactions, are less frequently observed. Calculations by Heinze and co-workers show that small energetic differences exist in the stability of the conformers, favouring the formation of the "Herrick" conformation over the "van Staveren" (**20**) or "Xu" (**21**) conformers.[20]

Other Fc derivatives favour different inter-strand H-bonding interactions, resulting in the formation of 12-membered rings in the case of Fca derivatives **17** and 14-membered rings in case of Fc-diamine derivatives **18**. It is important to point out at this point that the conformations provide a significant degree of rigidity that is maintained in solution, even at elevated temperatures, giving rise to isolable stereoisomers in which the Fc group displays axial chirality. A systematic nomenclature for these systems was developed and makes use of the relative orientation of the two Cp rings with respect to each other. The dihedral angle ω between the substituents on the two Cp rings defines any given positional isomer (Scheme 5).[19a] For example, a 1,1′-isomer is defined by ω = –36° and +36°, whereas a 1,2′-isomer is defined as $-36° < \omega < 108°$.

The element of axial chirality of the Fc core is defined by using the helical chirality descriptors *P* and *M* and by considering the relative orientation of the two peptide substituents on the 1,*n*′-Fc core. The *P* isomer has the higher priority substituent in position 1 on the top Cp ring, whereas the lower-priority substituent on the lower Cp ring are in positions 2′ or 3′ giving a clockwise when rotation applying the Khan–Ingold–Prelog rules.

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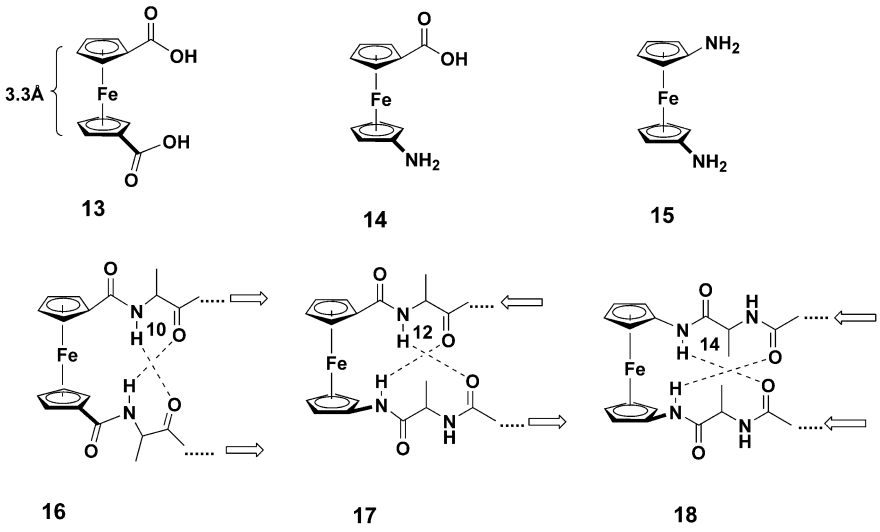
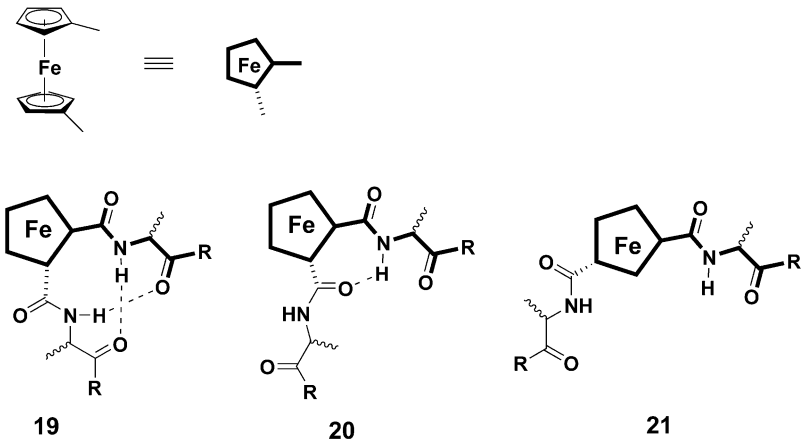
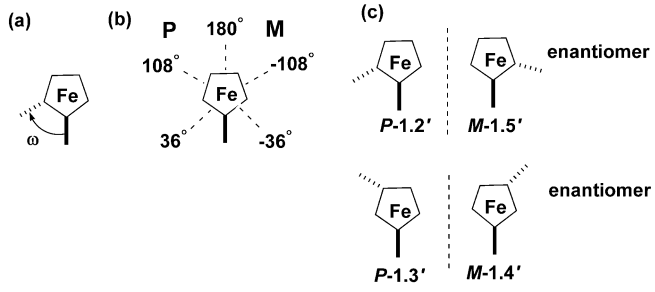


Scheme 3. Chemical structure of Fc-dicarboxylic acid (**13**), Fc-amino acid (Fca, **14**), Fc-diamine (**15**). Peptide conjugation to the Fc derivatives allows the formation of peptide conjugates with parallel (**16**, **18**) or antiparallel (**17**) alignment of the peptide substituents as is indicated by the arrows. As a consequence, different intramolecular H-bonding patterns are established ranging from a 10-membered H-bonded ring in conjugate **16** ("Herrick pattern"), to a 12-membered ring in the Fca derivative **17**, to an even larger 14-membered H-bonded ring in the Fc-diamine conjugate **18**. It is interesting to note that it appears possible to retain such structural motifs in larger Fc-peptide foldamers (vide infra).



Scheme 4. H-bonding patterns and orientation of the two peptide substituents observed in Fc-dicarboxylic acid peptide conjugates resulting in the formation of the "Herrick motif" (**19**), the "van Staveren motif" (**20**), and the "Xu motif" (**21**).



Scheme 5. (a) Schematic representation of the torsion angle ω in 1,*n*′-disubstituted Fc derivatives; (b) possible arrangements of the two susbstituents at the two different Cp rings; (c) examples of stereoisomers with a focus on the axial chirality and the orientation of the two substituents.

The *M* isomer has lower-priority substituents in positions 4′ or 5′ resulting in a counter-clockwise rotation. This gives rise to isomers *P*-1,1′, *P*-1,2′, *P*-1,3′, *M*-1,4′, and *M*-1,5′. The helicity is defined in terms of the orientation of the peptide substituents. Of the common amino acid, those with *s* stereogenicity of the α-C atom (most L-amino acids with exception of L-Cys) possess a *P*-helical conformation, whereas *r* stereogenicity (most D-amino acids with exception of D-Cys) possesses an *M*-helical conformation. This has profound spectroscopic consequences: the circular dichroism (CD) spectra of *P*-helical structures display a signal in the Fc region with a positive Cotton effect, whereas *M*-helical systems have a negative Cotton effect. This phenomenon is nicely demonstrated by the two

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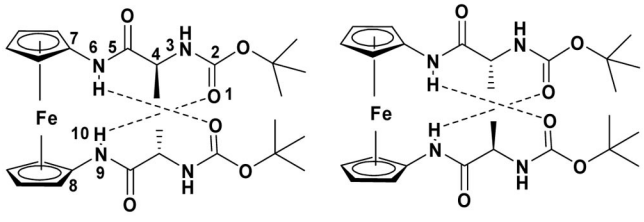

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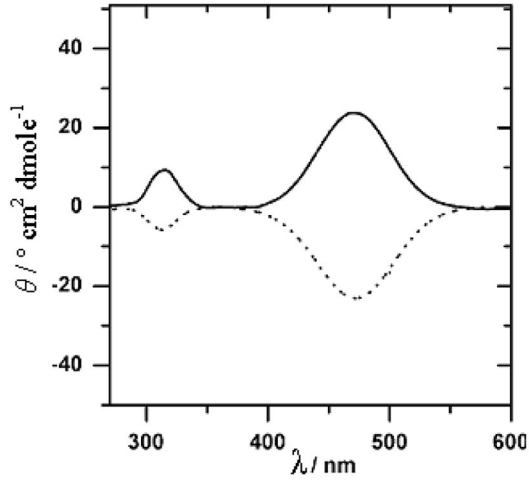


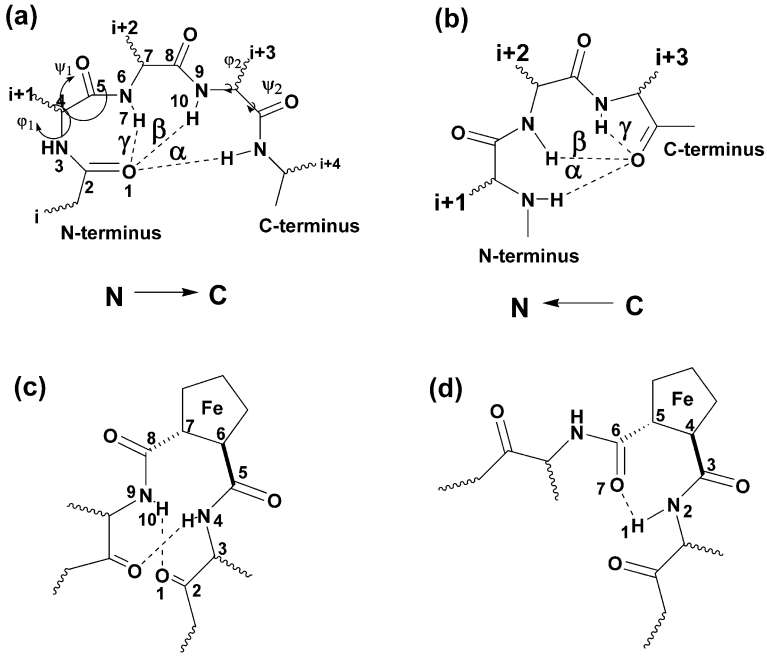
Figure 5. CD spectra of a 1 mM solution of Fc[NH-L-Ala-Boc]$_2$ (**22**, −) and Fc[NH-D-Ala-Boc]$_2$ (**23**, ···) in CH_2Cl_2. As expected, the two enantiomers are displaying CD spectra that are the mirror image of each other indicating the structural rigidity is maintained in solution. Modified and partially redrawn from ref.[21]

Fc-diamine conjugates Fc[NH-L-Ala-Boc]$_2$ (**22**) and its mirror image Fc[NH-D-Ala-Boc]$_2$ (**23**) shown in Figure 5 (vide infra).[21,36b]

Importantly, the intramolecular H-bonding present in 1,*n*′-disubstituted Fc-peptide conjugates exhibits structural features that enable us to classify them as turns, reverse turns, and sheets. In the following section, we briefly summarize the structural features observed in this class of conjugates.

Turn Structures

Turn structures are important secondary structural elements in proteins, which can be classified according to their H-bonding pattern and the associated peptide dihedral angles ϕ and ψ. The most common turns in peptides are γ-turns (7-membered ring) and β-turns (10-membered ring), whereas 13-membered rings are present in α-helices (Scheme 6). In reverse turns, the direction is defined as C→N and rvs-γ (5-membered ring), rvs-β (8-membered ring) and rvs-α (11-membered ring). Reverse turns are energetically disfavoured and rarely observed in protein structures; β-turns are usually defined by four amino acids with a distance ≤ 7Å between *i* and *i* + 3 amino acids that facilitate folding by reversing the direction of the polypeptide. Analogously, the β-turn in Fc-dicarboxylic acid conjugates is defined by a 10-membered ring formed by intramolecular H-bonding interactions between the carbonyl oxygen atom of one amino acid residue of one Cp ring and the amide



Scheme 6. Schematic representation of turns (a) and reverse turns (b); β-turns are derived from four amino acids forming a 10-membered ring. The characteristic β-turn motif in Fc-dicarboxylic acid conjugates is two 10-membered rings formed between the podant peptide strands (c); in Fc conjugates of Fc-dicarboylic acid, the γ-turn possesses a seven-membered ring formed by intramolecular H-bond between the two podant peptide strands (d).

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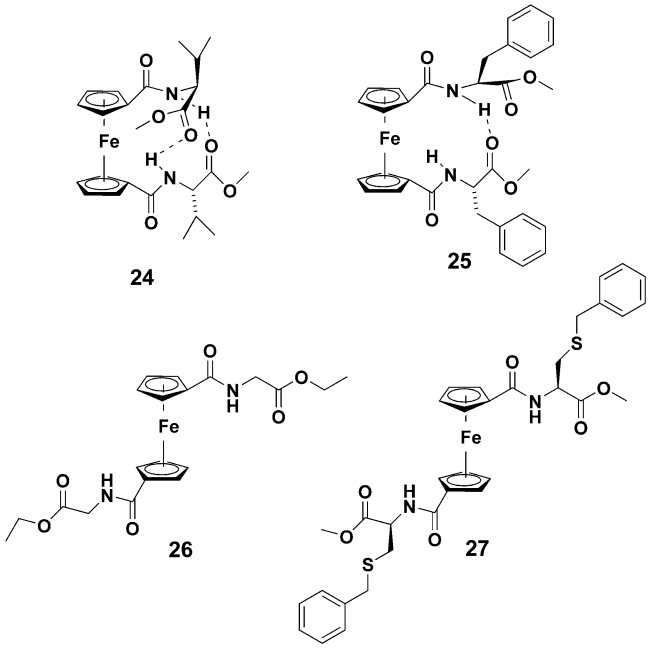
proton of the amino acid on the other Cp ring. Similarly, the γ-turn is defined by a seven-membered ring formed between the two podant peptide chains.[19a]

Ferrocene Derivatives and β-Turn Structures

Ferrocenedicarboxylic acid (**13**), aminoferrocenecarboxylic acid (**14**), and ferrocenediamine (**15**) have been exploited as turn-inducing scaffolds. They provide some level of control over the interaction between the two amino acid/peptide substituents and display different H-bonding motifs (**16**–**18**). Herrick and co-workers were the first who reported a series of Fc-dicarboxylic acid amino acid conjugates with the formula Fc[CO-Aaa-OMe]$_2$ (Aaa = Val, Phe, Pro).[19b] By using Fc[CO-Val-OMe]$_2$ (**24**) as a representative example of this group, two equivalent intramolecular H-bonds between the amide NH group of one strand and the carbonyl CO group of the opposite strand are formed resulting in the formation of a 10-membered H-bonded ring identical to that observed in a β-turn. Theoretical calculation by Heinze et al. demonstrate that the "Herrick" motif is energetically favored over the other conformations with an activation barrier for H-bond breaking and Cp-ring rotation of 13–18 kJ mol^{-1}.[22a,22b]



However, some conjugates display structures different from the common "Herrick" motif. Whereas calculations indicate that the "Herrick" motif is energetically favorable, steric factors appear to play an important role in controlling the energetic balance of intra- vs. intermolecular H-bonding interactions. For example, in disubstituted Fc-Glu dendrimers, sterics are the controlling factor. As the size of the dendrimer increases with increasing dendrimer generation, the conformation of the Fc core is shifted from a 1,2′- "Herrick" motif to the open "Xu" conformation in order to minimize steric congestion.[22c] For example, in Fc[CO-Phe-OMe]$_2$ (**25**) the relative orientation of the amide groups enables the formation of a single cross-strand H-bond only. And, no intramolecular H-bonds are formed in Fc[CO-Gly-OEt]$_2$ (Gly = glycine) (**26**) and Fc[CO-Cys(OBz)-OMe]$_2$ (**27**) (Cys = cysteine), which both adopt the "Xu" conformation.[23] In particular, the latter case is surprising since the Gly-OEt conjugate is the sterically least hindered conjugate. Upon ester deprotection, the structure changes from a 1,3′- to a 1,2′-H-bonded "Herrick" conformation.[23a] Clearly, sterics play an important role which cannot be underestimated but should be carefully explored in a systematic fashion.

Hirao and co-workers were the first who systematically explored Fc-dipeptide conjugates in an effort to prepare conjugates in which the podant peptide strands are aligned and able to interact in a β-sheet fashion. A series of compounds was synthesized with the general formula Fc[CO-Ala-Pro-OR]$_2$ where the ester protecting group was altered (R = Me, Et, Pr, CH_2Ph).[24] Fc[CO-Ala-Pro-OMe]$_2$ (**28**) (Figure 6) displays the typical "Herrick" conformation with the Fc core adopting a *P*-helical arrangement.

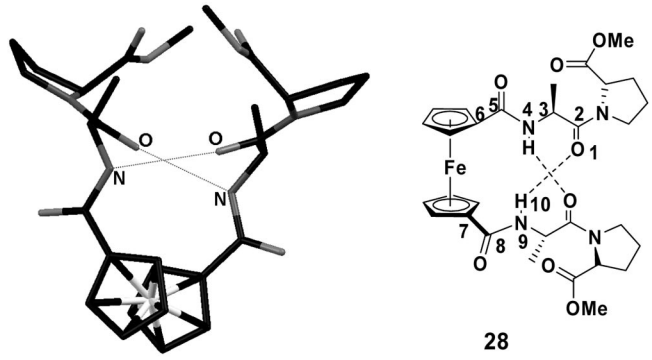


Figure 6. Molecular structure and chemical drawing of Fc[CO-L-Ala-L-Pro-OMe]$_2$ (**28**).

By using D-amino acids results in the formation of the enantiomer and the CD spectra of solutions of Fc[CO-Ala-Pro-OMe]$_2$ and Fc[CO-D-Ala-D-Pro-OMe]$_2$ are mirror images. In addition to the symmetrical Fc-peptide conjugates, Metzler-Nolte explored the unsymmetrical Fc-peptide conjugates having Phe and Ala on the two Cp rings.[25a] The CD spectra of Fc[CO-L-Phe-OMe][CO-L-Ala-OMe] (**29**) and Fc[CO-D-Phe-OMe][CO-L-Ala-OMe] (**30**) in CH_2Cl_2 are shown in Figure 7.

CD spectra of compound **29** with a strong positive band around 482 nm suggest a *P* helicity around the Fc core and formation of intramolecular hydrogen bonds. However, for compound **30**, having a D-Phe residue, only a weak negative band was observed at 476 nm, which may suggests the existence of two diastereomers (*M* and *P*) in solution. There is a slight excess of the *M*-helical diastereomer, which induces a weak negative band in the CD spectra suggesting that there are differences in the ability to induce a particular helicity.

As was described recently, for some asymmetric systems, "semi-Herrick" or even non-classical H-bonding patterns might be observed and in some cases represent the stable

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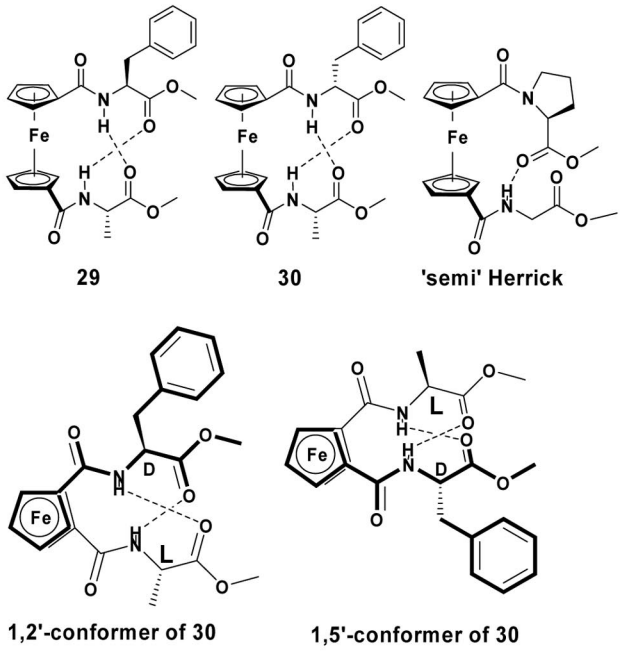


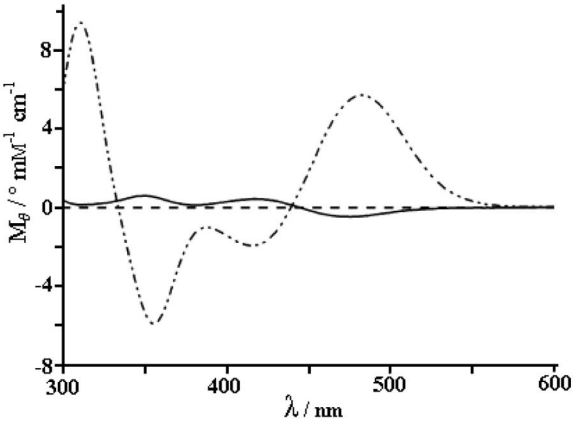
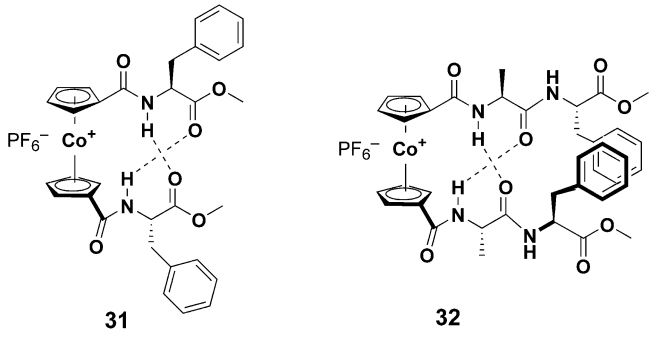


Figure 7. CD spectra of CH_2Cl_2 solutions of the Fc-peptide conjugates Fc[CO-L-Phe-OMe][CO-L-Ala-OMe] (**29**, −) and Fc[CO-D-Phe-OMe][CO-L-Ala-OMe] (**30**, ---). Modified and partly redrawn from ref.[25]

conformation.[25b] Whereas the cross-strand H-bonding interaction provides significant rigidity in the vicinity of the Fc core, the two C-termini are not aligned and are pointing away from each other. This initially begged the question if Fc conjugates can serve as models for extended β-sheets (vide infra).

It is interesting to note that the presence of a charge on the metallocene does not influence the β-turn structure, as was shown by Metzler-Nolte and co-workers, who investigated the cobaltocenium complexes [Co(CO-Phe-OMe)$_2$]-PF_6 (**31**) and [Co(CO-Ala-Phe-OMe)$_2$]PF_6 (**32**). Solution studies clearly show that the secondary structure is similar to the ferrocene analogue; the IR and NMR spectroscopic studies clearly show the engagement of the amide group proximal to the cobaltocene in intramolecular H-bonding interaction with the carbonyl oxygen atom on the opposite peptide strand.[26]



However, the effect of metal-ion coordination has been explored less thoroughly, and only two examples are known that provide some insight into its effects. The cyclic conjugate 1,1′-Fc-His (**33**) has both Fc-proximal carbonyl groups aligned in a *syn* fashion (see Figure 8).[27] In the absence of any metal ions, its structure can be described as approximately *P*-1,1′. However, coordination of alkali metal ions presumably to the two *syn* carbonyl groups causes subtle changes in the axial chirality of the Fc core. Moreover, the molecule is sensitive to the nature of the alkali metal ion, and significant changes in the oxidation behaviour are observed.

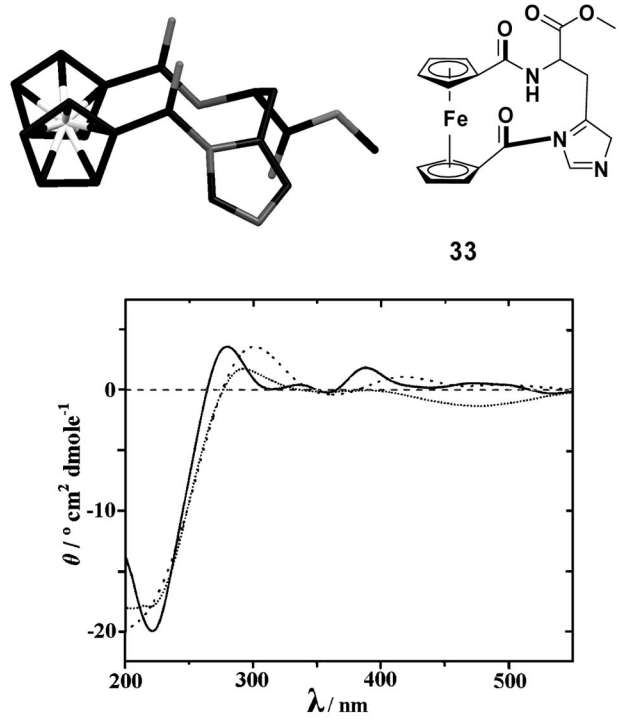


Figure 8. Molecular structure of the Fc-His conjugate **33** and its CD spectra in acetonitrile solution in the absence (−) and the presence of 10 equiv. of the alkali metal ion Li^+ (- - -) and Na^+ (···). Modified and partly redrawn from ref.[27]

A second example is Hirao's Fc[Ala-Pro-NHPy]$_2$ (**34**) system shown in Figure 9.[28] In the absence of Pd^{II}, the system adopts a "Herrick" structure. Coordination of Pd^{II} to the two pyridine groups in conjugate **34** strengthens the

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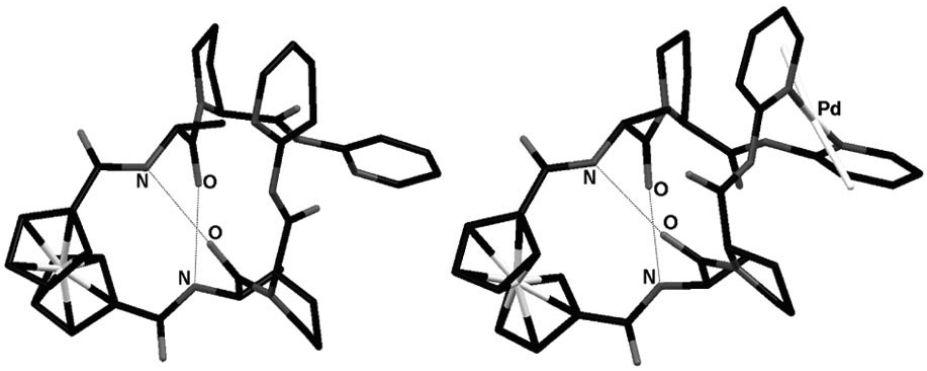

Figure 9. Molecular structure of conjugate **34** and its palladium complex. Please note the change in the alignment of the distal pyridine ring. Coordination to the Pd center causes changes in the orientation of the N-donor and forces a stronger alignment of the podant peptide chains. As a consequence, the H-bond lengths are reduced from *d*(N1···O2*) = 3.01(1) and *d*(N1*···O2) = 2.98(1) Å before Pd complexation to *d*(N1···O2*) = 2.88(1) and *d*(N1*···O2) = 2.97(1) Å after complexation of the Pd center to the two pyridine groups.

interaction between the two podant peptide chains. Structural consequences are not only the reorientation of the two py ligands but also a slight shortening of the H-bonding distances in the "Herrick" pattern.

Tighter H-bonding is maintained in solution resulting in a downfield shift of the Ala-NH protons by about 0.2 ppm. Despite some noticeable changes in the CD spectrum before and after metal complexation, indicating changes in the conformation of the podant peptides, the *P* helicity of the Fc core is maintained (Figure 10).

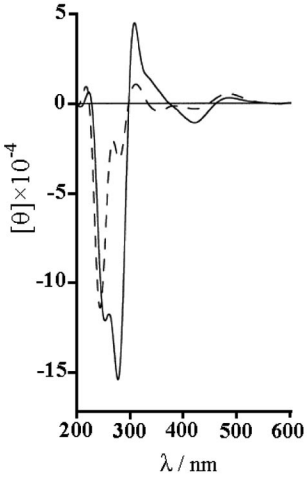

Figure 10. CD spectra in dichloromethane of conjugates **34** in the absence (- - -) and presence of Pd^{II} (—). Modified and partly redrawn from ref.[28]

1′-Aminoferrocene-1-carboxylic acid or aminoferrocencarboxylic acid derivatives of amino acids are an interesting class of peptide conjugates and enhance the structural arsenal available for structural design. Essentially, it allows peptide strands being attached to the Fca core in an antiparallel fashion. The first peptide conjugate of **14**, shown in Figure 11, was reported by Metzler-Nolte.[29] Contrasting Fc-dicarboxylic acid conjugates, the structure of Boc-L-Ala-Fca-L-Ala-L-Ala-OMe (**35**) (Figure 11) displays a 9- and 11-membered H-bonded ring, established by interactions involving the proximal Fc-NH and the OC-Ala groups.

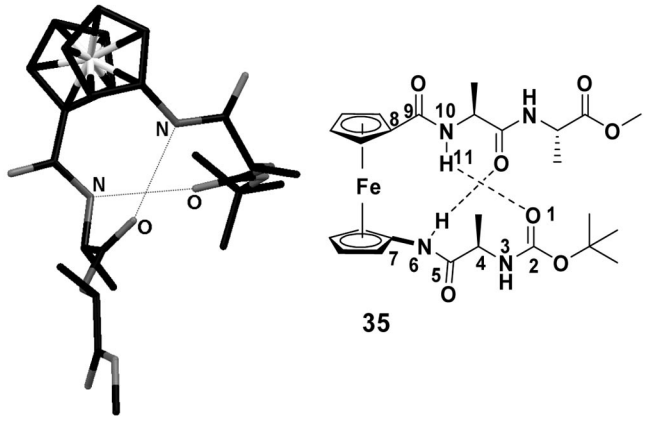

Figure 11. Molecular structure of Fca conjugate Boc-L-Ala-Fca-L-Ala-L-Ala-OMe (**35**) showing the expected interstrand H-bonding pattern. According to the nomenclature established in Scheme 4 this turn is an approximate β-turn.

It is interesting to note that the H-bonding interactions and therefore the axial chirality element of the Fc core are present also at elevated temperatures and in the presence of methanol. As we have mentioned earlier in Fc-dicarboxylic acid peptide conjugates, the amino acid proximal to the Fc group dictates the axial chirality of the Fc moiety. Presumably, the size of the amino acid side chain plays a role in the statistical distribution of one or more conformers in solution as indicated in Figure 7. In Fca amino acid conjugates, the amino acid can be attached to either the C- or the N-terminal of Fca (**14**), potentially leading to different stereoisomers. What will be the effect of amino acid attachment to Fca on the axial chirality of the resulting Fca conjugate? One might assume significant differences in between having a given amino acid attached to the amino or carboxylic acid group of Fca. Studies on Fca-peptide conjugates clearly demonstrate that the helicity of the Fca core is dependent on the nature of the first amino acid attached to the Fca-amino group.[30]

In solution and in the solid state, the enantiomeric dipeptides Boc-Fca-L-Ala-OMe (**36**) and Boc-Fca-D-Ala-OMe (**37**) adopt *M*- and *P*-helical conformations, respectively

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(Figures 12 and 13). In contrast, the conjugate **35**, which possesses L-Ala at both terminal groups, adopts a *P*-helical conformation both in the solid state and in solution.

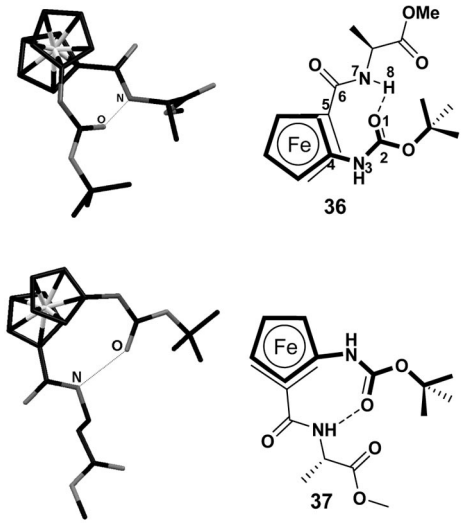


Figure 12. Molecular structure chemical drawing of Boc-Fca-L-Ala-OMe (**36**) and Boc-Fca-D-Ala-OMe (**37**) shows the formation of an eight-membered ring with L,*M* conformation for **36** and D,*P* conformation for **37**.

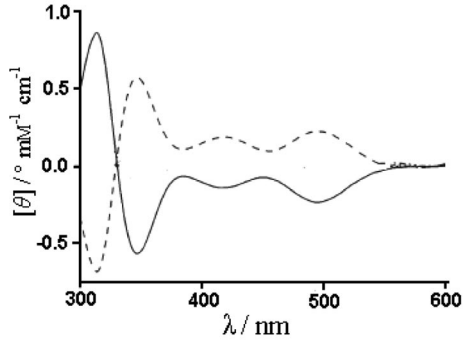
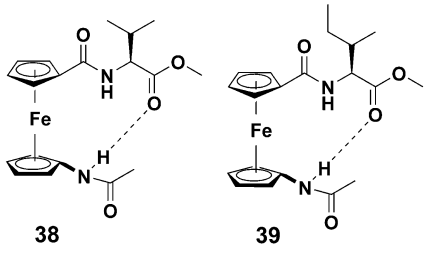


Figure 13. CD spectra of conjugates **36** (—) and **37** (- - -) modified and partly redrawn from ref.[30]

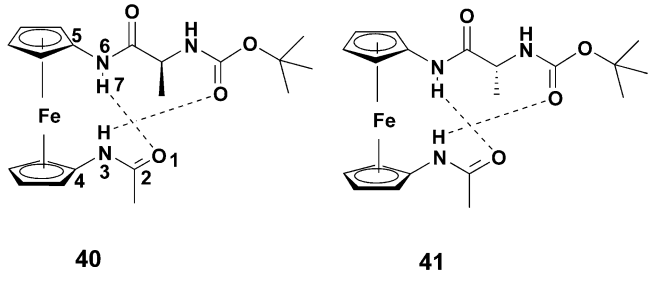
Heinze's work demonstrates that attachment of an L-Val/L-Ile to the C-terminal side of an *N*-acetylated Fca induces *P* helicity of the Fca core.[22] This is supported by calculations of the most stable conformation, which shows that both Fca conjugates (**38** and **39**) should exhibit a particular H-bonding pattern and *P* helicity.



As these calculations show, alternative H-bonding motifs are possible but they are less favourable. This raises the issue of steric bulk of the N-terminal substituent on Fca and its role in favouring a particular conformation. This issue remains an open question and will need to be addressed.

The ferrocenediamine scaffold allows the attachment of two parallel peptide strands. Its conjugates are providing a complementary peptide attachment to the Fc core to that of ferrocenedicarboxylic acid and provide access to a 14-membered ring (Scheme 3). The molecular structures of the enantiomeric L- and D-Ala conjugates **22** and **23** (vide supra) and the CD spectra of the two conjugates are shown in Figure 5 and as expected are mirror images of each other as is expected for enantiomers. The conjugates are conveniently prepared from the bis(Boc)-protected precursor.[21]

In a very recent study by Rapić and co-workers, who prepared a series of asymmetric 1,*n*′-diaminoferrocene conjugates of α-amino acids Ac-Fc-AA-Boc [AA = Gly, Ala (**40**), D-Ala (**41**) and Val], it was shown that such compounds form seven-membered H-bond rings involving the NH groups proximal to the Fc unit resulting in the formation of a γ-turn structure, which is stable under a variety of solvent conditions ranging from $CHCl_3$, MeOH, and even DMSO.[20b] Unfortunately no solid-state structure is available for a γ-turn structure based on Fc-diamines.



The helicity of the Fc core is similar to that observed for other symmetric Fc-diamine conjugates where L-amino acids induce *P* helicity and D-amino acids induce *M* helicity. DFT calculations on conjugate **40** show the presence of several stable H-bonded conformers. The majority of low-energy conformers possess a *P*-helical Fc moiety.

Ferrocene Derivatives and γ-Turns

The first example of a crystallographically characterized Fc-based γ-turn structure was provided by Hirao and co-workers.[31] This example represents an interesting application of our earlier discussions on the design of peptide turn structures involving Fc-peptide conjugates. Here a central Fc-based peptide turn acts as a rigid scaffold leading to the formation of a γ-turn.[31] In Fc[CO-L-Pro-L-Ala-NHPy]$_2$ (**42**) and in Fc[CO-D-Pro-D-Ala-NHPy]$_2$ (**43**), the central Fc-Pro core acts as a strong rigid turn motif, which enables the next amino acid Ala to backfold (Figure 14).

The aniline NH group provides an H-bond donor site that enables the formation of a γ-turn involving the CO group of Pro. Overall, the structure is supported by an additional H-bond between the podant peptide chains involving the Ala NH group. At present, this is the only example

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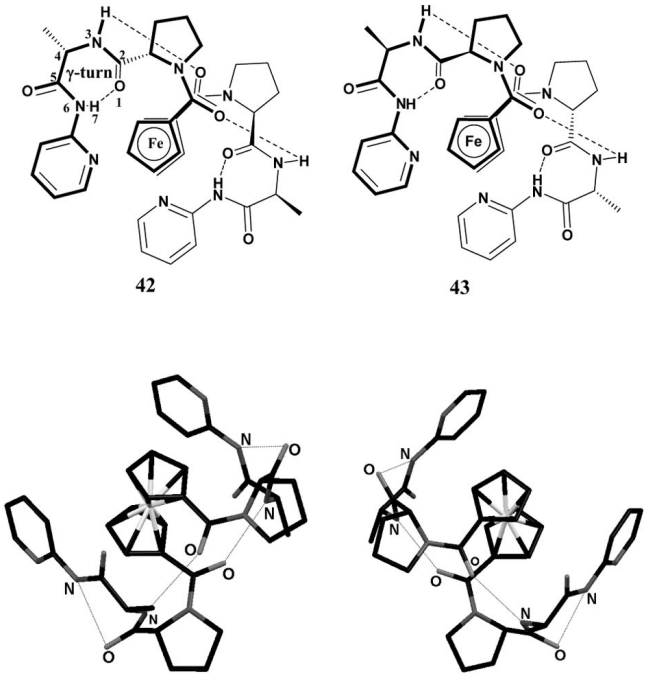

Figure 14. Induction of a γ-turn-like structure in Fc conjugates bearing dipeptide chains by conformational control: Fc[-L-Pro-L-Ala-NHPy]$_2$ (**42**, left), Fc[-D-Pro-D-Ala-NHPy]$_2$ (**43**, right).

of this structural motif observed in Fc-dicarboxylic acid conjugates, and it is not clear yet how general this approach is for the design of such γ-turns.

Formation of β-Sheets

Two basic methods are currently available enabling the formation of β-sheet-like structures. Cyclization of Fc-peptides is a useful method to form and stabilize a β-sheet conformation between peptides since it forces the two peptide strands into close proximity. This alignment of peptide strands and the resulting "Herrick" pattern of H-bonding jointly with the rigidity of the macrocycle set the conditions for intermolecular H-bonding. A series of cyclic Fc-peptide conjugates with the general formula Fc[CO-Aaa-CSA]$_2$ (Aaa = Gly, Ala, Val, Leu) and Fc[CO-Gly-Aaa-CSA]$_2$ (Aaa = Val, Ile) are now available.[32] The presence of the cystamine linker tying the two peptide strands significant adds to the rigidity provided by the "Herrick" cross-strand interactions and establishes an interface for intermolecular H-bonding.

However, the β-sheet-like interactions are established on an intermolecular level. In the solid state, molecules of Fc[CO-Gly-CSA]$_2$ (**44**) associate by intermolecular H-bonding (Figure 15). It is this H-bonding interface on the edge of the molecule that was exploited for the design of a β-sheet interface.

Extending the H-bonding interface within these molecules in a rational fashion is possible and favours the side-to-side interaction between the peptide strands leading to the formation of an antiparallel strand alignment. It is important to point out that Gly as an Fc-proximal amino acid is critical in providing the necessary flexibility in this conjugate. The solid-state structure of Fc[CO-Gly-Val-CSA]$_2$ (**45**) clearly shows the intermolecular H-bond interactions and the peptide alignment (Figure 16). However, the Fc core provides a curvature to the individual molecules that enables the formation of a β-barrel-like structure.[33] This β-barrel-like structure has eight peptide strands running parallel to the axis of the barrel with an internal pore diameter of 8 Å, which is similar to proteinic β-barrels.

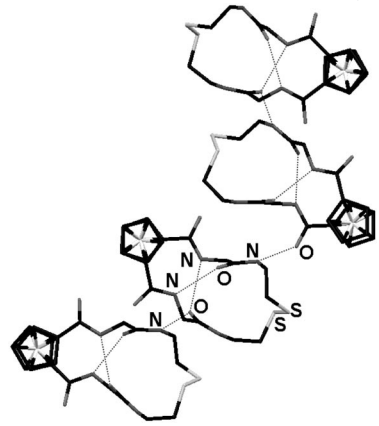

Figure 15. Molecular structure of Fc[CO-Gly-CSA]$_2$ (**44**), showing the interaction of individual molecules. It is noteworthy to point out that the H-bonding interface on the edge of the macrocycles is not of sufficient size to allow more extensive H-bonding interactions.

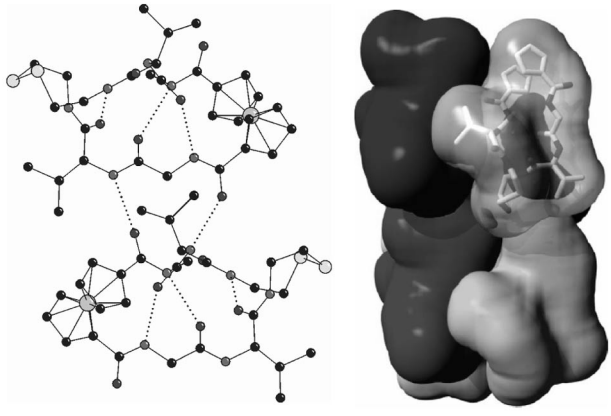

Figure 16. Molecular structure of Fc[CO-Gly-Val-CSA]$_2$ (**45**). Antiparallel alignment of the molecules leads to the formation of a β-sheet interface. The H-bond lengths are 2.898 Å and 3.036 Å. The H-bond interfaces are established on both sides of the molecule, ultimately leading to a cyclic arrangement of the Fc building blocks. It is important to point out that the individual supramolecular cyclic structures stack one on top of each other, forming a continuous tubular structure. In this structure, the peptide strands of stacked Fc conjugates align forming a "continuous" β-strand. The individual strands align into a pseudo-β-barrel-like structure with strand direction as indicated.

From our earlier discussion of peptide conjugates of Fc-dicarboxylic acids, we learned that, whereas these systems are rigid in proximity to the Fc core, they are highly flexible

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at the C-terminal ends of the conjugate. Whereas cyclization adds rigidity to the molecule, it limits the validity of the conjugate as a model for an extended β-sheet-like structure. Is it possible to generate conjugates that enable the parallel or antiparallel alignment of two peptide strands on an Fc core and the formation of H-bond-supported extended structures in the absence of additional steric constraints that force the strands into close proximity? Recently, examples were reported of extended β-sheet-like structures in which the two podant peptide chains align and engage in interstrand H-bonding. The solid-state structure of Fc[CO-Gly-Val-Cys(Bn)-OMe]$_2$ (**46**) is shown in Figure 17.[34]

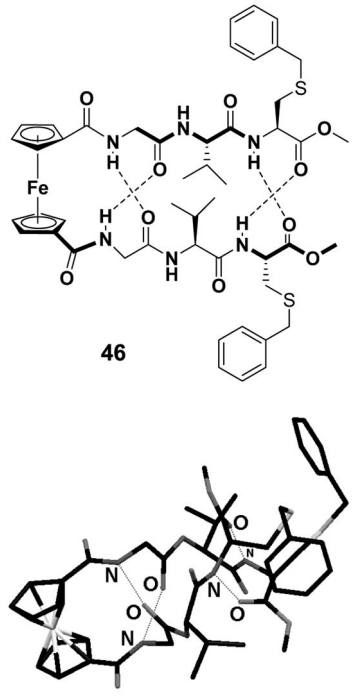

Figure 17. Chemical drawing and molecular structure of Fc[CO-Gly-Val-Cys(Bn)-OMe]$_2$ (**46**). The structure shows that the two podant peptide chains are in an extended conformation and are aligned with respect to each other allowing for H-bonding interactions between the two peptide chains. In addition to the "Herrick motif" proximal to the Fc group, a second cross-strand H-bonding interaction exists between the two amino acids on the C-terminal side of the peptide.

In contrast to earlier results on Fc-dipeptide derivatives, the peptide strands in these two conjugates are aligned in a parallel fashion. It is important to point out that, although the alignment of the strands is parallel, the H-bonding interactions are significantly different. At present there are only two examples of Fc conjugates displaying an extended β-sheet-like structure. Additional work will need to explore the versatility of this approach and examine the effects of amino acid sequence, asymmetric peptide substitution, and peptide extension.

Ferrocene and β-Helical Structures

As it was mentioned earlier, Fca has a specific structural rigidity to induce β-turns between the peptide strands. This property was exploited recently to design extended helical foldamers. Fca conjugates with the general formula Boc-[Fca-Ala]$_n$-OMe (n = 1–4) exhibit a β-helical-like structure in solution and in the solid state.[35] The solid-state structures of a series of molecules of this family were examined and exhibit molecular helicity as shown in Figure 18 for Boc-[Fca-L-Ala]$_3$-OMe (**47**) and Boc-[Fca-D-Ala]$_3$-OMe (**48**). The helicates of L-Ala and D-Ala are enantiomers and display opposite helicity that is preserved in solution and at elevated temperatures. Intramolecular and intermolecular hydrogen-bonding interactions between the peptide strands would adopt structures, which are similar to a β-helical structure. The H-bonding patterns observed in these foldamers are similar to that observed earlier for simple Fca-peptide conjugates. L-Ala gives rise to a *P*-helical structure, whereas D-Ala causes the formation of the *M*-helical enantiomer. In this case, Ala is attached to the NH and COOH groups of Fca. As would be expected from earlier results by Metzler-Nolte for the Fca conjugate **41**, the system adopts a *P*-helical conformation. Intramolecular H-bonding provides stability to the helicate having H-bond lengths d(N–O) between the NH group of Fca and the CO group of Ala that are in the range of 2.92–2.95 Å and slightly longer for the interaction with the next Fca unit above [NH of Ala and CO of Fca: d(N···O) = 2.97–2.99 Å]. Importantly the dihedral angles of the helicate are within the region established for β-sheet-like structures ($-79° < \phi < -67°$ and $155° < \psi < 138°$).

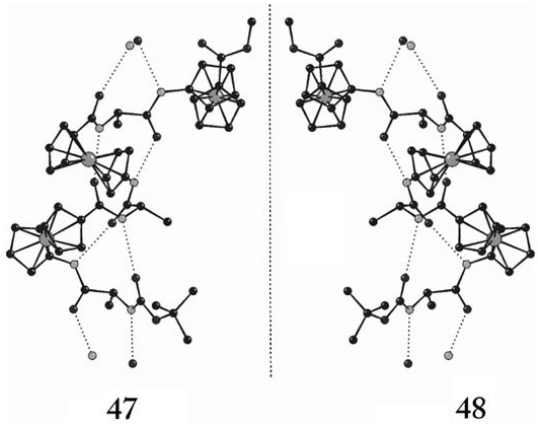

Figure 18. Molecular structure of Boc-[Fca-L-Ala]$_3$-OMe (**47**) and of Boc-[Fca-D-Ala]$_3$-OMe (**48**). These molecules adopt a molecular helicity in solution and the solid state that is related to a β-helical arrangement. The helix is stabilized by intramolecular H-bonding.

It is important to point out that the helicity is not influenced by the size of the foldamer. For all systems of Boc-[Fca-L-Ala]$_n$-OMe (n = 1–4), *P* helicity was observed, and for all L-Ala-containing foldamers *M* helicity was observed for D-Ala analogues. As would be expected for such a case, the CD spectra of the two enantiomeric helicates are displaying identical spectroscopic features with opposite ellipticity values (Figure 19). At present, this is the only set of foldamers of this type, and again questions are open as to the generality of this design principle.

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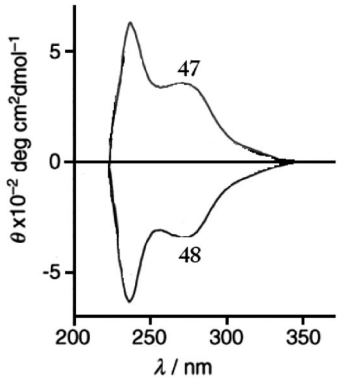

Figure 19. CD spectra of Boc-[Fca-L-Ala]$_3$-OMe (**47**) and Boc-[Fca-D-Ala]$_3$-OMe (**48**) in acetonitrile indicating the presence of rigid conformations in solution, which is supported by ROESY measurements. Redrawn from ref.[35]

Will it be possible to exploit this design principle for other Fca helicates involving other amino acids or even peptides resulting in more complex helicates? Such systems are of fundamental interest but can also serve as models for extended β-sheets and may serve as a more convenient model to study the interactions between such models and small molecules.

Recently, the first hydrogenase model involving an Fc-peptide conjugate Fc[CO-Cys-OMe]$_2$[Fe$_2$(CO)$_6$] (**49**) was reported (see Figure 20).[36] Coordination of the active site to cysteine and in close proximity of this site to the Fc unit as electrochemically active motif are two important characteristics of this compound as hydrogenase model; this has been achieved by the covalent attachment of the [Fe$_2$(CO)$_6$] core to two cysteine amino acids that are connected to Fc-dicarboxylic acid through a peptide bond, the molecular structure shows the formation of a macrocycle.

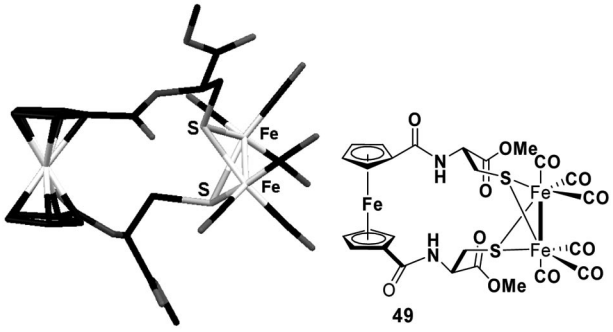

Figure 20. Molecular structure and chemical drawing of Fc[CO-Cys-OMe]$_2$[Fe$_2$(CO)$_6$] (**49**).

The substitution pattern of Fc is in a nearly perfect 1,2′ conformation with *M*-helical chirality. In contrast to earlier examples of an Fc-peptide conjugate, there is no intramolecular H-bond to stabilize the helicity in solution. Thus, there is the potential for interconversion between the two helical conformers. The CD spectrum of compound **49** exhibits only a weak negative Cotton effect in the Fc region from 400 to 500 nm.

Final Thoughts and Future Aspects

In this Microreview, we have demonstrated the tremendous promise that 1,*n*′-disubstituted Fc-peptide conjugates hold for the design of models for peptide turn and as β-sheet models. However, there are still a number of unsolved questions that need to be addressed for Fc-peptide conjugates to truly live up to their full potential as mimics for secondary structural peptide motifs.

The scarcity of examples in some cases is noticeable. For example, at present there are only two examples for Fc-based γ-turn motifs. In addition, the effects of amino acid sequence in Fca derivatives have not been explored fully. Although it is now clear that the C-terminal attachment appears to dominate the helicity of the Fc core, more work needs to be done to fill in the gaps. Helical foldamers need to be explored in more detail. At present such foldamers exist only for Fca derivatives. Metal chelation to the peptide or to attached ligating sites holds tremendous promise being able to reversibly alter peptide structures and switch between conformations. This has been explored already for larger helical peptide aggregates,[6,7] but remains largely unexplored for Fc-peptide conjugates.

The application of Fc-peptides as metallodrugs for the treatment of diseases or as antibacterial compounds are being explored.[37] Effects on cancer cells have already been recognized. However, more data is necessary to evaluate the efficacy of Fc conjugates for this application. In addition, Fc-peptide conjugates are being exploited as bioorganometallic sensors to detect protein-binding interactions[38] or even enzymatic activity.[39] Whereas this Microreview does not specifically address this interesting application of Fc-peptide conjugates, one has to recognize the importance of this class of compounds in biosensing. Briefly, the Fc group acts as the redox probe providing an electrochemical readout of a target analyte interacting with the peptide recognition sequence.[38] In this context, Fc-peptide nucleic acid conjugates can serve as suitable targets to recognize single-strand DNA sequences but also to probe essential biochemical processes.[40]

The design of new Fc-peptide conjugates has already opened up new areas of scientific inquiry. One can only speculate about future applications of this fascinating family of bioorganometallic conjugates.

Acknowledgments

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