Bisglycine-Substituted Ferrocene Conjugates

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Summary: The solid state structures of three bissubstituted glycine ferrocene conjugates are described allowing a direct comparison of the structural parameters. Whereas the fully protected glycine ester $Fc(Gly\text{-}OEt)_2$ adopts a 1,3'-conformation leading exclusively to intermolecular H-bond formation, the free acid $Fc(Gly\text{-}OH)_2$ adopts the more compact 1,3'-comformation with intramolecular H-bonding. The same intramolecular H-bonding pattern is adopted by the glycine ferrocenophane $Fc(Gly\text{-}CSA)_2$.

Keywords: ferrocene; hydrogen bonding peptide; supramolecular assembly

Introduction

Due to their inherent ability to engage in intermolecular interactions, such as hydrogen bonding or salt-bridge formation, amino acids and peptides are ideally suited as building blocks in the synthesis of supramolecular systems.[1] Recent efforts have been directed at equipping non-covalent supramolecular peptide assemblies with redox-active groups, such as ferrocenes[2] or cobaltocenes and give them specific electric properties that may be exploited for biosensing or may have potential for the design of bioelectronic materials.[3] In particular, 1,1'-disubstituted ferrocene peptide conjugates have proven useful to generate chiral helical supramolecular arrangements that do not rely on intermolecular H-bonding but are the result of chiral patterning. In most cases, this type of ferrocene-peptide conjugates display a rigid intramolecular cross-strand H-bonding interaction in solution and the solid state having the amino group proximal to the Fc group on one strand engages in H-bonding with the CO group of the same amino acid on the opposite peptide strand.[2] Intermolecular H-bonding is only observed if the second amino acid has available H-bonding donor sites, giving an indication of the interplay between inter- and intramolecular H-bonding. Futhermore, the intramolecular H-bonding is robust withstanding even the presence of other strongly H-bonding components that co-crystallize, showing the potential

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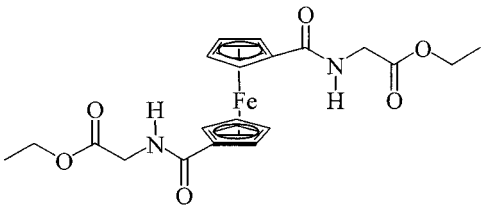
utility of these Fc-conjugates for the systematic supramolecular design of redox active assemblies. We recently reported the use of cystamine-linked Fc-peptide conjugates for the generation of Fc-peptide-modified surfaces. Furthermore, we explored the use of a cystine-linker to connect the podand peptide chains on the two Cp rings in 1,1'-bissubstituted ferrocenes, giving ferrocenophanes. In essence this should restrict the mobility even further providing more rigid building blocks. Recently, the synthesis of peptide ferrocenophanes and their metal chelating abilities was reported.[4] However, structural data are unavailable in the literature. Ferrocenophanes display a range of interesting properties, ranging from metallo-cryptants for the coordination of ions to starting materials for metallopolymers.[5] Our efforts have been guided by our desire to investigate the electron transfer properties in these systems, which should make two peptide-thiol linkages per Fc-peptide conjugate, on the gold surface and compare them to our growing library of simple Fc-peptides.[6] Here we compare the structural features of three bissubstituted ferrocene glycine conjugates: the bisglycine ethylester **1**, the free acid **2**, and the glycine ferrocenophane **3**.



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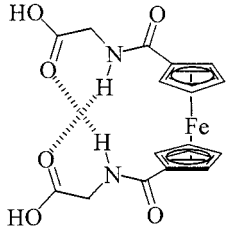

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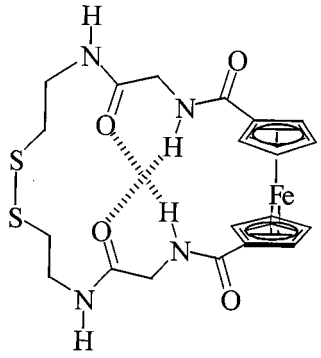


3

Molecular Structure

Single crystals of compounds **1**, **2**, and **3** were obtained by diffusion methods giving yellow to orange x-ray quality crystals. The structure of the glycine ethylester **1** is shown in Figure 1. The compound adopts the for this class of bisubstituted ferrocene conjugates unusual 1,3'-conformation, which allows it to engage in intermolecular H-bonding to neighbouring molecules via the amide O(1) and N(1) with a H-bond distance of 2.839(5) Å. The other podand amino acidester is not involved in any H-bonding. The result is a one dimensional H-bonded zig-zag chain shown in Figure 1 in which the molecules stack alternating with the non-H-bonding glycine ligand pointing up and down. These chains are packed into a layered structure, with an interlayer separation of 4 Å. Similar layer and double layer structures were observed before for Fc-Gly_2-Oet, which also form a 1-D H-bonded chain. This H-bonding pattern is reminiscent of that reported by Hirao and coworkers for the monosubstituted Fc-Ala-Pro-OEt with alternating up-down orientation of the molecules.[2a]

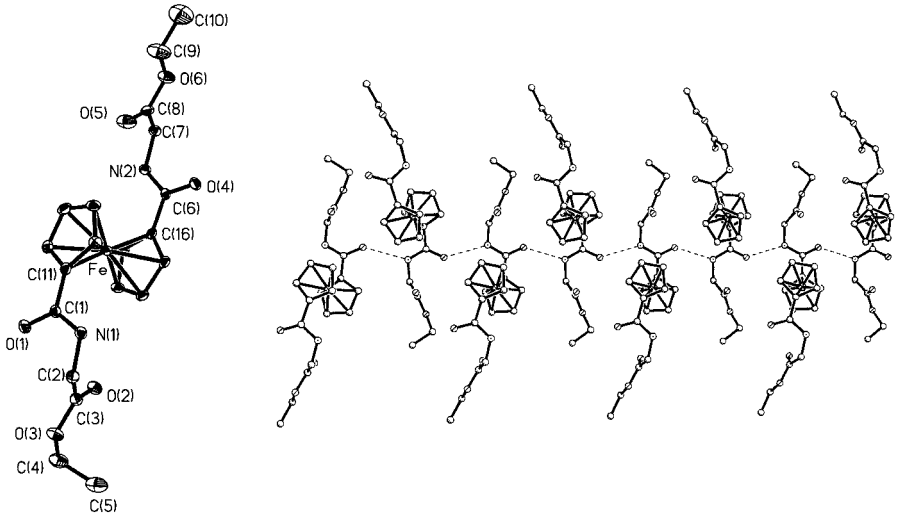


Figure 1. left: Structure of the ferrocenoyl bisglycine ethylester **1** showing the 1,3'-substitution of the ferrocene group. right: Interaction between neighbouring molecules via the interaction of the O(1) of one of the two amide groups with the N(1) of the same amide group of an adjacent molecule resulting in the formation of a 1-D H-bonded polymeric chain.

This creates some degree of asymmetry in the Fc-amide groups, allowing a direct comparison of the effect of H-bonding on the podand glycine ethyester. Althought the difference between the C=O distances of the two amides is small, the one involved in H-bonding is slightly elongated. The difference is clearer in the amide N-C=O distances, in which the H-bonded N(1)-C(1) is significantly shortened compared to the non-H-bonded N-C=O distance (d(N(1)-C(1)) =1.326(5) Å, d(C(6)-N(2)) = 1.344(5) Å). In sharp contrast to the structure of the ester, the free acid, the synthesis of which was reported earlier,[7] shows the now familiar 1,2'-conformations allowing the formation of the cross-strand intramolecular H-bonding interaction involving the two amide NH and the two acid C=O on opposite Cp rings (Figure 2). This interaction also provides the correct conformation for the acid OH and the Fc-C=O to allow additional intermolecular H-bonding giving a two-dimensional H-bonded network. In this network the Fc-C=O of one molecule interacts with the OH groups of an adjacent molecule (d(O(1)···O(3*) = 2.620(3) Å). Additional weak In O···H-C interactions between O(1) and H(12) are present in the solid state, which contribute to the stability of the network.

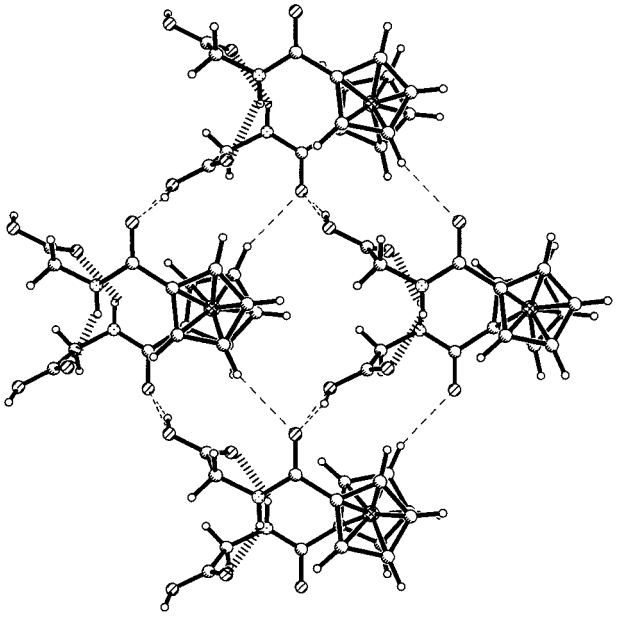


Figure 2. 2-D network formed by the interaction of adjacent molecules of **2**. H-bonding interactions between adjacent molecules involving the interaction of the Fc-C=O group with the acid OH (d(O(1)···O(3*) = 2.620(3) Å. Individual molecules display the familiar intramolecular H-bonding pattern with d(N-O(2A)) and d(N(A)-O(2)) = 2.875(3) Å.

Compound **3** displays the same basic structural features. The system adopts a 1,2'-configuration similar to the open chain Fc-conjugate **2**, having both Fc-C=O pointing outwards and are engaged in intermolecular H-bonding interactions. Both amide NH in the ferrocenophane **3** are engaged in strong intramolecular H-bonding to the opposite peptide C=O across the ring (see Figure 3), which has been observed in other open-chain ferrocene dipeptide conjugates reported by Hirao and Metzler-Nolte.[2] Importantly, the dihedral angles of the podand peptide chains are slightly influenced by these variations. In particular, the dihedral angle Φ_1 increases somewhat upon de-esterification and ring closure to form the macrocycle.

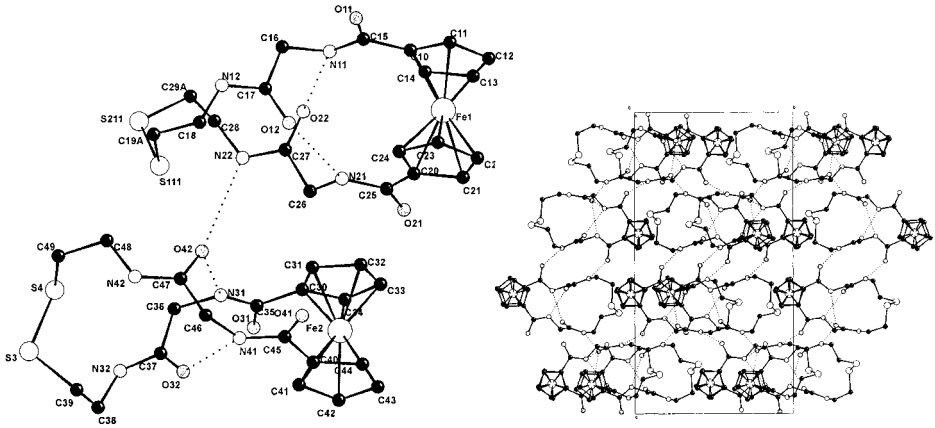
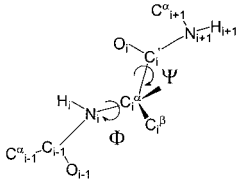


Figure 3. Molecular structure of compounds **3** showing the intra- and intermolecular H-bonding interactions present in the solid state: d(N(11)···O(22) = 2.862(4)Å, d(N(21)···O(12)) = 2.873(4) Å, d(N(31)···O(42) = 2.959(4)Å, d(N(41)···O(32)) = 2.815(4) Å; d(N(22)···O(42) = 2.974(5)Å.

Table 1: Dihedral angles of the podand peptide chain for compounds **1**, **2**, and **3**

	Angle	**1**	**2**	**3**
	Φ_i	65.4(4)° -69.9(5)°	79.0(2)°	-86.2(4) -123.3(5) 93.7(4) 115.6(4)
	Ψ_i	-158.4(3)° 162.3(3)°	-178.60(18)°	176.2(3) -148.8(4) -171.4(3) 135.9(4)

Conclusion

Deprotection of the glycine ethylester **1** to give the free acid **2** results in a dramatic conformational change that is accompanied by a change in the H-bonding pattern. Whereas **1** forms a 1-D H-bonded polymeric chain, compound **2** forms a polymeric H-bonded 2-D network. Upon closure of the ring to give the ferrocenophane the intramolecular H-bonding pattern

remains intact speaking to the robustness of this structural motif. Detailed investigations are currently underway to investigate the use of these ferrocene conjugates as building blocks for the rational assembly of large supramolecular structures.

Acknowledgements

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