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Ferrocenoyl glycylcystamine: organization into a supramolecular helicate structure

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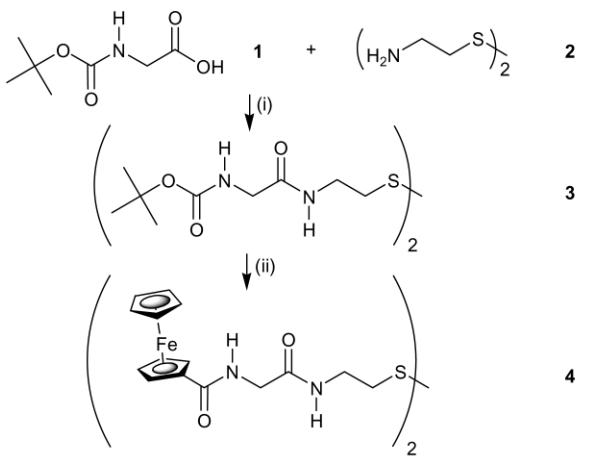
Extensive intermolecular hydrogen bonding in ferrocenoyl glycylcystamine gives rise to a novel ordered double helical arrangement with a helical pitch height of 14 Å.

In solution and in the crystalline state, amino acids and peptides often assemble into extended noncovalent structures guided by hydrogen bonding between individual molecules.[1] Considerable effort has been focussed on the design of naturally occurring secondary structural motifs,[2] and on the design of new peptidic materials, such as nanotubes[3] and hydrogels,[4] with potential applications in drug delivery and biomedical engineering. In many cases, scaffolds are used to assist the design and guide formation of a particular peptide structural mimic. Recently, 1,1′-disubstituted ferrocene derivatives have been explored as templates in an effort to create highly ordered electroactive supramolecular systems.[5] The presence of chiral amino acids directs the formation of the chiral supramolecular arrangement. Our research has focussed on the development of ferrocene (Fc)-peptide conjugates, for the purpose of monitoring the interaction between organic substrates and the podant peptide chain, and for the development of biosensors.[6] More recently, we focussed our attention on Fc-peptide cystamines, which are useful for the formation of Fc-peptide monolayers on gold, allowing the study of electron transfer through the peptide.[7] In this communication, we report the first example of a three-dimensional superstructure, which constitutes a remarkable example of a metal-free chiral helicate self-assembled by hydrogen bonding between adjacent achiral Fc-peptide conjugates. This structure is based on Fc-glycylcystamine ([Fc-Gly-CSA]$_2$, **4**), in which adjacent achiral Fc-Gly-CSA-conjugates form a chiral supramolecular network through intermolecular H-bonding in which each [Fc-Gly-CSA]$_2$ molecule participates in the formation of two types of helicates within the same supramolecular structure.

Compound **4** is readily obtained as a crystalline orange solid by deprotection of the symmetrical tetrapeptide [Boc-Gly-CSA]$_2$ (**3**) (CSA = cystamine), obtained from Boc-Gly-OH (**1**) and cystamine hydrochloride (**2**), followed by coupling with Fc-OBt, as summarized in Scheme 1.† Compound **4** was fully characterized spectroscopically and by elemental analysis. The ^{1}H-NMR spectrum of **4** shows the expected 2:2:5 signal pattern for monosubstituted Fc-peptides. The α-H of Gly is observed as a doublet at δ 4.10. The corresponding amide NH is observed as a triplet at δ 7.32. The cystamine NH are observed as a triplet at δ 7.55 and couple to the adjacent CH_2 group at δ 3.60 (J = 6.3 Hz) and the CH_2-S group at δ 2.83 (J = 6.4 Hz). Correspondingly, the ^{13}C{^{1}H}-NMR spectrum shows two signals due to the two C=O carbons atoms at δ 172.1 and 170.5 and one signal at δ 43.9 due to the α-C of Gly. In $CDCl_3$ solution, **4** engages in intra- and intermolecular H-bonding, as judged from a temperature and concentration dependent amide NH shift of (1mM: −5.9 ppb/K for Gly-NH and −6.0 ppb/K for cystamine NH; at 50 mM: −9.0 ppb/K for Gly-NH and −8.9 ppb/K for cystamine NH).

The compound readily crystallizes from a chloroform solution to produce yellow-orange needles by slow evaporation. A single crystal X-ray diffraction on two of these crystals was carried out showing that the compound crystallizes in the chiral tetragonal space group $P4_3$ as a $CHCl_3$.‡ A graphical representation of compound **3** is shown in Fig. 1. The achiral molecule adopts an extended conformation with a dihedral angle of −93.17(12)° about the S–S bond. The interatomic dimensions of compound **4** are typical for ferrocenoyl-peptides. The Cp rings in both ferrocenoyl groups are co-planar with very small Cp-Fe-Cp bent angles (Cp-Fe1-Cp = 3.1°, Cp-Fe2-Cp = 2.6°). The amide and Cp rings are virtually coplanar (amide/Cp twist angle: 14.0° for Fc1 and 8.7° for Fc2) ensuring effective electronic interactions between the amide and Cp planes. Importantly, the molecules maximize their H-bonding interaction with adjacent molecules. Each Fc-labelled half of the molecule engages in H-bonding through the Fc-amide and cystamine functions with the identical portion of two neighbouring molecules, one on each face, resulting in each molecule interacting with four adjacent molecules. However, the two portions establish different H-bonding patterns, as shown in Scheme 2. The H-bonding O(1)···N(1*) and N(2)···O(2*) is virtually symmetrical and forms a 12-membered ring, as observed in other Fc-peptide structures (Scheme 2a) and commonly found in parallel peptide β-sheets. The pair of H-bond acceptors O(3) and O(4) are *cis* oriented on the same face of the molecule, whereas the H-bond donors N(3) and N(4) are *cis* but located on the other face of the molecule. The result is a H-bonding pattern involving a 12-membered ring novel to Fc-peptides (Scheme 2).

The H-bonding is very asymmetrical (O(3)···N(3*) = 2.965 (12) Å and O(4)···N(4*) = 2.803 (12) Å. This complex intermolecular H-bonding interaction requires the molecules to turn with respect to each other, each Fc-Gly-fragment of **4** being involved in a different supramolecular helical arrangement. The result is a fascinating arrangement of two propeller-shaped helices with H-bonded cores linked to each other through a disulfide bridge. The redox active ferrocenoyl moieties are surrounding a central H-bonded peptide core. Fc(1) is involved in 'Propeller-Helix 1' having a right handed twist, as observed in most ß-sheets, and Fc(2) is involved in 'Propeller-Helix 2',



Scheme 1 Synthesis of ferrocenoylglycylcystamine: (i) EDC, HOBt, CH_2Cl_2; (ii) Fc-OBt, CH_2Cl_2.

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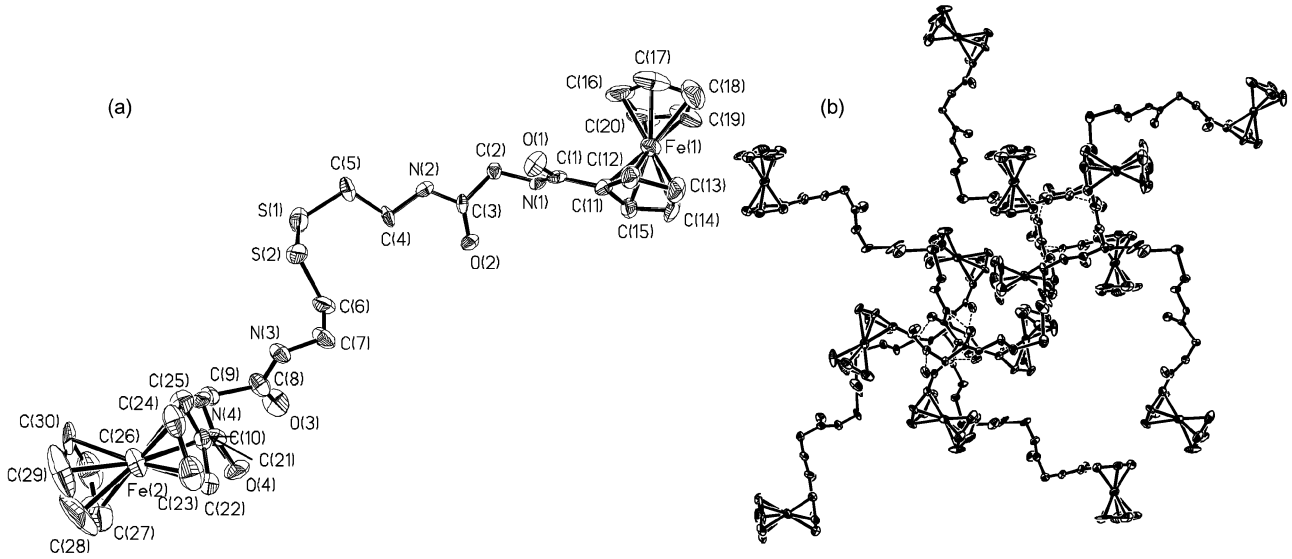
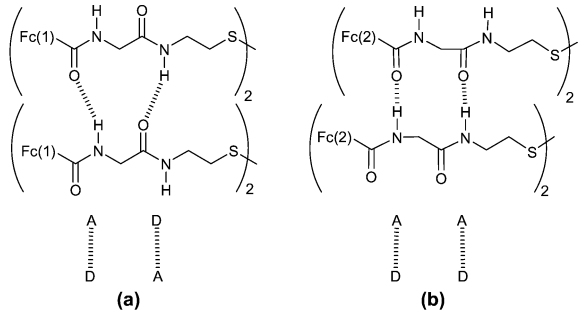


Fig. 1 (a) ORTEP of ferrocenoylglycyl cystamine **4**. The hydrogen atoms and the solvent molecule are omitted for clarity. Ellipsoids are at the 30% probability level. (b) A view down the helical axes. Interaction between molecules resulting in the formation of a supramolecular helicate. The two parts of the molecule participate in two different types of interactions. Fc(1) is involved in the 'square' helix' and Fc(2) in the 'twisted helix'.



Scheme 2 Two types of hydrogen bonding interactions exhibited by the two different Gly-cystamine residues of compound **4**. (a) D···A and A···D interactions and (b) DA and D···A interactions.

both having a pitch height of *ca*. 14 Å. More surprising than the helicity of the supramolecular arrangement and its chirality is the presence of two different helical types, one of which is best described as a 'square helix' with an inner diameter of the H-bonded core of 3.8 Å involving Fc(2) and a 'twisted helix' with an inner diameter of 4.1 Å involving Fc(1). Peptide disulfides often exhibit unusual structural features.[8] However, a supramolecular assembly as exhibited by compound **4** was never before observed in peptide conjugates.

In summary, we have synthesized the novel ferrocene–peptide conjugate **4**, which engages in intermolecular H-bonding in solution. In the crystalline state, H-bonding between the Gly-cystamine substituents results in the formation of a supramolecular double helicate structure. Both helices have the redox active Fc groups decorating an interior H-bonded peptide core. This arrangement may provide a conduit for electron transfer along the helical axis. Studies investigating electron transfer and conduction in this crystalline material are now in progress.

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Notes and references

† *Typical Preparation of* **4**. TFA (4 mL) was added to a solution of **3** in CH_2Cl_2 (5 mL). After 10 min, the solvent was removed and Et_3N (3 mL) was added. The residue was dissolved in CH_2Cl_2 (5 mL) and added to a solution of Fc-OBt (1.15 mmol, 0.27 g) in CH_2Cl_2 (10 mL). After 12 h, the reaction mixture was washed with water and purified by flash chromatography (R_f = 0.15, acetone:hexanes 2:1, silica 200–400 mesh). Recrystallization from $CHCl_3$ yielded yellow-orange crystallography quality crystals (0.26 g, 70%). Elem. Anal. calc. for $C_{30}H_{34}Fe_2O_4N_4S_2$: C, 52.19; H, 4.96; N, 8.11; found: C, 52.32; H, 5.22; N, 7.93%. MW calc for $C_{30}H_{34}Fe_2O_4N_4S_2$ LR-MS [FAB]: 690 $[M + 1]^+$ 129 (10%), 185 (25%), 213 (100%), 364 (24 %), 625 (15%), 691 (80%). ^{1}H-NMR (δ in ppm $CDCl_3$): 7.70 (1H, t, J_{NH} = 5.0 Hz, NH-Ala), 7.45 (1H, t, J_{NH} = 5.6 Hz, NH-cystamine), 4.83 (2H, s, 2H *meta* to carboxy group on Cp ring), 4.35 (2H, s, *ortho* to carboxy group on Cp ring), 4.22 (5H, s, unsubstituted Cp on the ring) 4.05, (1H, d, J_{CH} = 5.3 Hz, H-Gly), 3.58 (2H, m, CH_2-cystamine), 2.80, (2H, t, J_{CH} = 6.4 Hz, CH_2-cystamine).

‡ *Crystal data* for **4**·0.58$CHCl_3$: $C_{30.58}H_{34}Cl_{15}Fe_2N_4O_4S_2$, M = 759.47, tetragonal, space group $P4_3$, a = 14.4663(10), b = 14.4663(10), c = 16.2622(16) Å, V = 3403.3(5) Å^3, Z = 4, T = 193(2) K, D_{calc} = 1.482 g cm^{-1}, μ(Mo-Kα) = 1.153 mm^{-1}, R = 0.0635, wR = 0.0929 for 6971 independent reflections (θ = 26.47°), Flack parameter 0.7(3). The occupancy of the solvent was refined to 0.58. S(2) shows some disorder. A second position was refined with 13.1% occupancy for S(2)A. CCDC no 190034. See http://www.rsc.org/suppdata/cc/b2/b206647e/ for crystallographic data in CIF or other electronic format.

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