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Ordered Conformations in Bis(Amino Acid) Derivatives of 1,1'-Ferrocenedicarboxylic Acid

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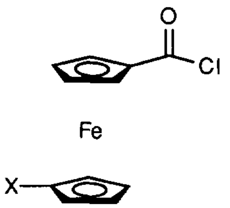
Abstract. Two bis(amino acid) derivatives of 1,1'-ferrocenedicarboxylic acid were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Each was found to adopt an ordered, intramolecularly hydrogen bonded conformation in $CHCl_3$.

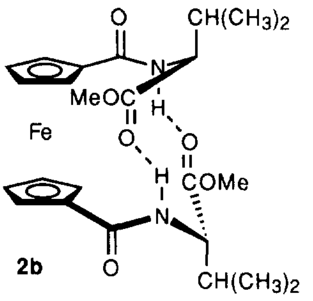
Currently there is interest in developing conformationally constrained molecules that enforce α-helix,[1] β-turn[2] and β-sheet[1] secondary structures when incorporated in a peptide chain. Of these three, the β-sheet has proven to be the most difficult target, primarily because of aggregation problems.[3] Recent work on epindolidiones by Kemp,[4] dibenzofuran-based amino acids[5] and square planar copper complexes[6] by Kelly, and oligoureas by Nowick,[7] has demonstrated that viable β-sheet models can be obtained.

We were intrigued by the possibility of developing a system similar to the dibenzofuran-based amino acids using a disubstituted ferrocene backbone. The advantages of this structure are that ferrocene has an inter-ring separation of 3.32 Å - close to the N-O separation for the hydrogen bond in a β-sheet[8], the co-planarity of the cyclopentadienyl (Cp) rings reduces conformational possibilities, and the rotational capabilities of the ring provide a spectroscopic handle for the transition from random to ordered conformation. The ease of synthesis, the stability of ring substituted ferrocene derivatives, and the strength of the covalent attachment of the peptide chain to the organometallic backbone were also attractive.

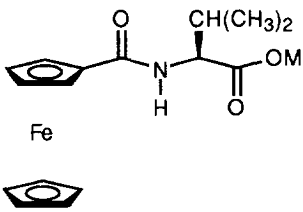
To investigate this possibility we prepared and examined bis(valine) complex, **2b**. This novel compound was prepared by treatment of 1,1'-ferrocenedicarbonyl chloride, **1b**,[9] with valine methyl ester hydrochloride.[10]



1b: X=COCl
1m: X=H



2b



2m

For comparison purposes the corresponding mono(valine) complex, **2m**, was similarly prepared from **1m**.

An ordered conformation for **2b** would be obtained if intramolecular hydrogen bonding exists between the two valine residues. The presence of these intramolecular hydrogen bonds would be proven by spectroscopic properties including: infrared bands associated with N-H and C=O stretches, the carbonyl carbon chemical shifts and the number of Cp carbon signals. Pertinent spectroscopic data for **2b**, **2m** and related compounds are included in Table 1.

Inspection of the infrared spectra of **2b** and **2m** in chloroform shows significant differences for the N-H, ester C=O and amide C=O bands[11]. The IR of **2b** shows only one N-H stretch at 3380 cm^{-1}, 59 cm^{-1} lower than for **2m**. Amide N-H stretches below 3400 cm^{-1} are diagnostic of hydrogen bonded NH protons.[12] In support of this idea, the ester and amide C=O stretches for **2b** appear 8 and 12 cm^{-1} lower in energy, respectively, compared to **2m**.[13] The presence of only one N-H stretch, one amide C=O and one ester C=O stretch suggests that the two valine residues are equivalent by symmetry. The IR data does not support intermolecular hydrogen bonding for **2m**, suggesting the presence of two identical intramolecular hydrogen bonds in **2b**. Supporting this, the ^{1}H NMR spectrum shows only one resonance for both NH protons in **2b**.[14]

The likely identity of the hydrogen bonding partners for the NH protons in **2b** are the ester or amide carbonyl oxygens from the other valine residue. In the ^{13}C NMR spectrum of **2b** there is only one ester carbonyl carbon resonance and it is deshielded 2.1 ppm compared with **2m**, while the only signal for the amide carbonyl carbons is essentially unaffected. This is consistent with the IR data that shows a difference in the frequency of the ester C=O stretch in **2b** and **2m**. All the data indicates that the intramolecular interactions in **2b** are between the ester carbonyl of each valine and the NH of the opposing valine as suggested by the structural drawing of **2b**. The proposed structure is notable for the presence of a C_2 rotational axis and a ten membered ring formed by two hydrogen bonds. This hydrogen bonding pattern resembles that found in an antiparallel ß-sheet.

Further evidence for the ordered conformation in **2b** is obtained from the ^{13}C NMR data for the Cp carbons and from $J_{NH\text{-}CH}$ in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of **2m**, only three resonances are observed for the substituted Cp ring (and one resonance for the unsubstituted ring), implying the Cp rings undergo rapid rotation. In contrast, **2b** shows five separate resonances for the Cp carbon atoms, implying a C_2 symmetrically ordered conformation. In the ^{1}H NMR spectrum, $J_{NH\text{-}CH}$ is 8.8 Hz for **2b**. Coupling constants of this magnitude are commonly observed in β-sheet conformations.[15] A dihedral angle of 160° or 0° are the two possible solutions to the Karplus equation.[16] Of the two, only the 160° angle would permit the intramolecular hydrogen bonding between the NH and the ester carbonyl.

To investigate the generality of this conformational behavior, other amino acid ester complexes were prepared. Given in Table 1 are the spectroscopic data for the bis and mono(phenylalanine) complexes **3b** and **3m**. The spectroscopic properties of **3b** are nearly identical to **2b**, indicating that **3b** assumes an ordered, hydrogen bonded conformation similar to **2b**. Likewise, spectroscopic data for **3m** and **2m** are nearly identical, indicating that **3m** does not adopt a single ordered conformation.

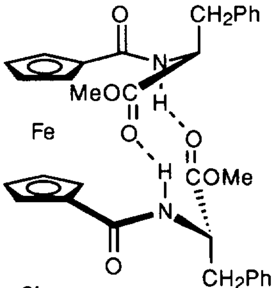
The spectroscopic data for the bis and mono(proline) compounds **4b** and **4m** were acquired because these species do not contain an NH and thus **4b** is precluded from forming the intramolecular hydrogen bonding interactions seen in **2b** and **3b**. As expected the IR carbonyl stretches and the chemical shifts for the carbonyls

Table 1. Selected Spectroscopic Data[a]

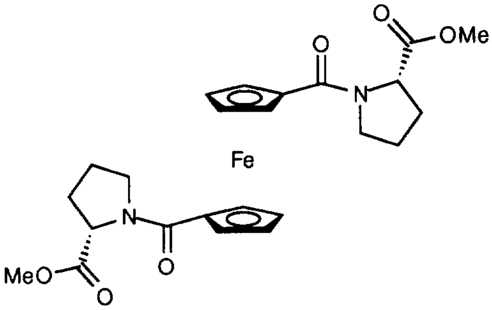
	IR/cm^{-1}			$^1H/\delta$	$^{13}C/\delta$		
No.	ν(N-H)	ν(COOR)	ν(CONR)	N-H	CONR	COOR	Cp C's
2b	3380	1727	1641	7.53 (d, 8.8)	170.7	175.2	77.5,[b] 72.0, 71.7, 70.5, 70.3
2m	3439	1735	1653	6.15 (d, 7.9)	170.5	173.1	75.9, 70.7, 70.0 (C_5H_5), 68.4
3b	3376	1725	1655	7.84 (d, 8.8)	170.5	175.2	76.0, 72.0, 71.4, 70.5, 70.2
3m	3434	1739	1665	6.09 (d, 5.8)	170.6	172.5	76.1, 71.1, 70.3 (C_5H_5), 68.6
4b	-	1744	1608	-	168.7	172.9	76.6, 72.3, 71.2
4m	-	1742	1604	-	169.7	173.1	76.2, 71.4, 70.6 (C_5H_5), 69.8

[a] NMR spectra of amino acid derivatives recorded in $CDCl_3$ at 5 x 10^{-3} M. IR spectra of compounds recorded in $CHCl_3$ or $CDCl_3$ at $1x10^{-3}$ M.

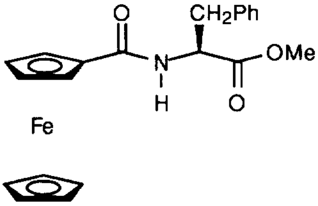
[b] ipso carbon resonance recorded in CD_2Cl_2.



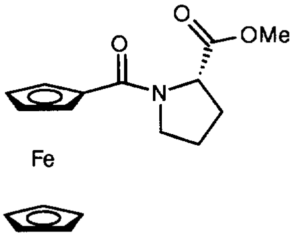
3b



4b



3m



4m

in **4b** and **4m** are nearly identical. In addition, **4b** only shows three Cp carbon resonances while **2b** and **3b** each show five Cp carbon resonances.

Our preliminary study shows that ferrocene can be used to position two amino acid esters in an ordered conformation featuring intramolecular hydrogen bonds between the NH of one amino acid and the ester C=O of the other. The ordered conformation is readily discerned by spectroscopic properties of both the peptide and ferrocene groups. Our findings suggest that other defined peptide secondary structures could be obtained by using different linkages between the ferrocene backbone and amino acids or peptides.

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10. Amino acid derivatives were prepared by mixing **1b** or **1m** with a stoichiometric amount of the appropriate amino acid ester hydrochloride and excess NEt_3 in CH_2Cl_2. Following an extractive workup, the compounds were purified by flash chromatography (silica gel, ethyl acetate/hexanes). Yields (not optimized) ranged from 16 - 69 %. All compounds were fully characterized.
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