

1,*n'*-Disubstituted ferrocenoyl amino acids and dipeptides: Conformational analysis by CD spectroscopy, X-ray crystallography, and DFT calculations

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Abstract

An experimental and computational study on the conformational preference of 1,*n'*-disubstituted ferrocenoyl amino acids and dipeptides is presented. Only L-amino acids were used for the synthesis of $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Met-Met-OMe}]_2$ (**4**), but according to the X-ray structure a 4:1 mixture of L,D,*M*,D,L and L,D,*M*,L,L isomers is obtained (L describes amino acid chirality and *M* the helical chirality of the ferrocene core). This result is in agreement with IR and CD solution phase data and can be explained with a racemization by 1 M NaOH during the synthesis. In order to determine the relative stabilities of the different conformations, DFT calculations on model compounds $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Gly-NH}_2]_2$ (**5**) and $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Ala-OMe}]_2$ (**6**) were performed using the B3LYP/LanL2DZ method with ECPs on the heavy atoms. Conformers **5A–5C** with different hydrogen bond patterns have significantly different stabilities with a stabilization by about 30 kJ mol⁻¹ per hydrogen bond. The “Herrick conformation” **5A** with two hydrogen bonds is the most stable in the gas phase, in accordance with the solution and solid phase data. In contrast, only small energetic differences (less than 10 kJ mol⁻¹) were calculated for conformers L,*P*,L-**6A**, L,*P*,D-**6A** and D,*P*,D-**6A**, which differ only in amino acid chirality.

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1. Introduction

1,*n'*-Disubstituted ferrocenoyl peptides have received growing attention in recent years [1–3]. Herrick, Jarret, Curran and coworkers were the first to report on intramo-

lecular hydrogen bonding between the two peptide strands [4]. The importance of helical chirality in these systems was first recognized by Hirao et al. [5–8]. On the basis of these and other data [9–12], three major conformations of 1,*n'*-disubstituted ferrocenoyl peptides derived from ferrocene dicarboxylic acid can be distinguished (Fig. 1) [13]. The term “Herrick conformation” was coined for the most common structure **A**, which is stabilized by two symmetrical intramolecular interstrand hydrogen bonds. The “van Staveren conformation” **B**, with a single intramolecular hydrogen bond, is a special case found in only one crystal structure so far [11]. The open “Xu conformation” **C**, first

Abbreviations: EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBT, hydroxy-benzotriazole; IBCF, isobutyl chloroformate; NMM, *N*-methyl morpholine.

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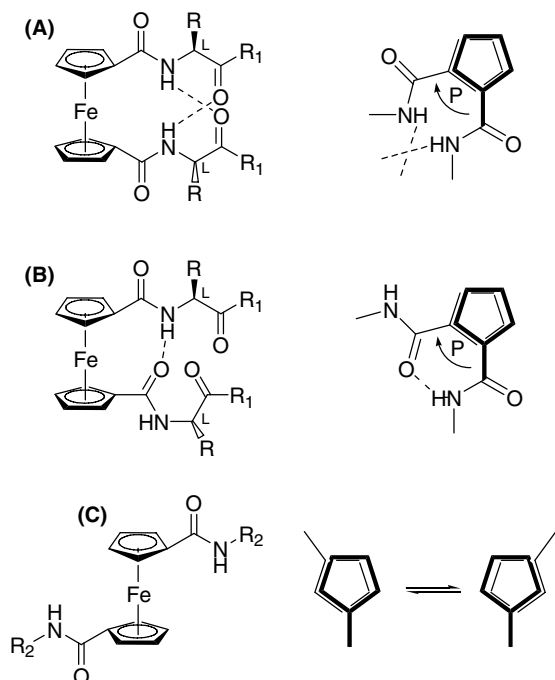


Fig. 1. The three conformations of 1,*n'*-disubstituted ferrocene peptides derived from ferrocene dicarboxylic acid: the “Herrick conformation” **A**, the “van Staveren conformation” **B** and the open “Xu conformation” **C**.

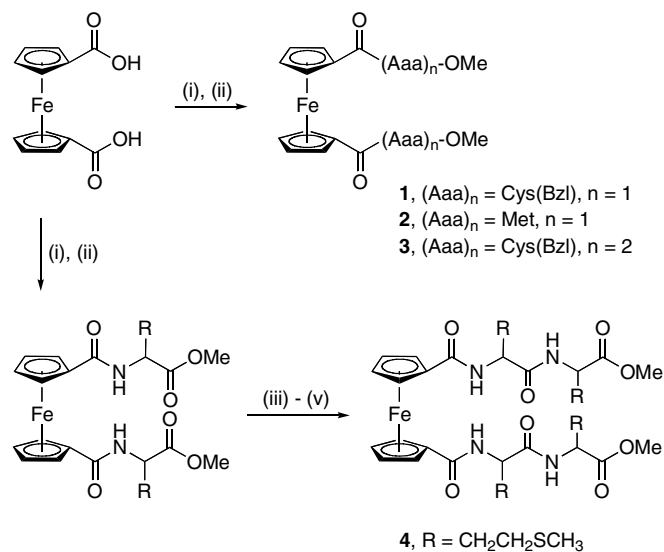
reported by Kraatz et al., has no intramolecular hydrogen bonds [10]. In view of very recent reports on peptide derivatives of ferrocene diamine [14] and ferrocene amino acids [15–17], “Herrick-like conformations” play an important role for these two classes of compounds as well.

It is interesting to point out that for the “Herrick” and “van Staveren conformations”, *L*-amino acids were in all previous studies [3,5–13] found to induce *P*-helical chirality of the ferrocene moiety, while *D*-amino acids induce *M*-helical chirality [4,13]. In unsymmetrical *D,L*-derivatives however, a mixture of *P* and *M* helical conformers is formed [13]. In the present paper, only *L*-amino acids were used as building blocks, but an X-ray crystal structure of a “Herrick conformation” with *M*-helical chirality was obtained. In addition, we present DFT calculations of the relative stability of the three major conformation families **A–C** of ferrocene peptides (see Fig. 1) as well as on “Herrick conformations” **A** with *L,P,L*-, *L,P,D*- and *D,P,D*-configuration, where *L/D* indicates the chirality of the amino acid and *P* the helical chirality of the ferrocene core. These calculations will aid in the understanding of the principles determining the preferential formation of one or the other conformation.

2. Results and discussion

2.1. Synthesis and spectroscopy

Recently, we reported the synthesis and characterization of ferrocenyl peptides with sulfur-containing side chains [12]. The derivatives **1–3** were prepared directly from



Scheme 1. Reaction conditions: (i) HOBt, EDC, *i*Pr₂NEt, CH₂Cl₂; (ii) H-(Aaa)_{*n*}-OMe, CH₂Cl₂; (iii) NaOH, dioxane/water (1:1); (iv) IBCF, NMM, NEt₃, CH₂Cl₂; (v) H-Met-OMe, CH₂Cl₂.

1,1'-ferrocene dicarboxylic acid and the corresponding dipeptide in good yields (Scheme 1). This approach, however, was not successful for Fe[C₅H₄-CO-Met-Met-OMe]₂ (**4**) and this compound had to be synthesized by a stepwise approach. First, coupling of one amino acid was performed, followed by deprotection of the carboxy function and then coupling of the second amino acid (Scheme 1) [12].

The ¹H NMR spectra of **1–4** in dilute CDCl₃ solution (*c* = 10^{−2} M) revealed only one set of signals for both Cp rings and peptide chains, indicating C₂-symmetrical structures. The resonances of the amide NH protons adjacent to the Cp rings are found at δ = 7.5, 7.8, 8.2 and 8.5 ppm for **1–4**, respectively. IR spectra of **1–4** in dilute CHCl₃ solution (*c* = 10^{−3} M) show NH stretching frequencies below 3400 cm^{−1}. It is interesting to note that two amide bands are observed in the IR spectrum of **4**. In this work the CD spectra of **1–4** in dilute CH₂Cl₂ solution (*c* = 10^{−3} M) have been investigated (Fig. 2 and Table 1).

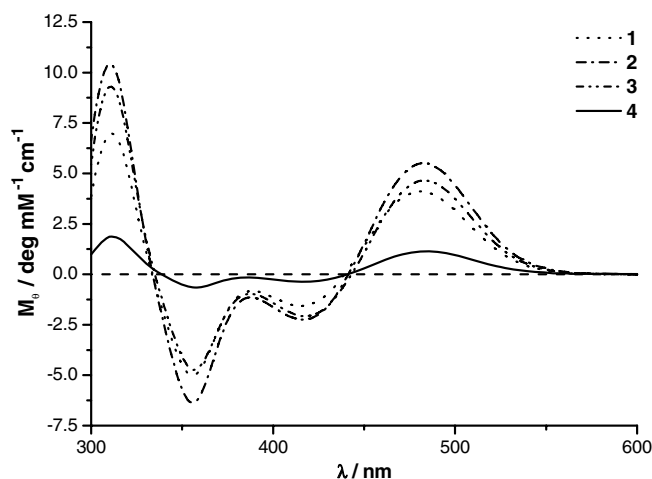


Fig. 2. CD (CH₂Cl₂) spectra of **1–4**.

Table 1
Comparison of CD data (CH₂Cl₂) of ferrocene peptides **1–4** with Fc[C₅H₄-CO-Ala-OMe]₂ (**6**) [13]

Compound	λ_{\max} (nm) (M_0 deg mM ⁻¹ cm ⁻¹)			
1	311 (+7.0)	356 (−5.0)	416 (−1.6)	481 (+4.1)
2	311 (+10.4)	356 (−6.4)	416 (−2.3)	483 (+5.5)
3	311 (+9.3)	356 (−4.7)	417 (−2.1)	482 (+4.6)
4	311 (+1.9)	359 (−0.7)	416 (−0.4)	485 (+1.1)
6	310 (+10.0)	356 (−4.8)	416 (−1.7)	484 (+5.5)

All compounds show the characteristic Herrick pattern with a positive signal at about 480 nm. The intensity of the CD signals of **1–3** is comparable to Fc[C₅H₄-CO-Ala-OMe] (**6**), the most simple compound with “Herrick conformation” [13]. The CD signals of **4** are, however, much weaker.

Spectroscopic results indicate that ferrocene peptides **1–3** adopt a “Herrick conformation” in solution, with two symmetrical intramolecular H-bonds. From comparison with the literature [6,12,13], the configuration is assumed to be *L,P,L* for **1** or **2** and *L,L,P,L,L* for **3**. Compound **4** also shows clear evidence of intramolecular H-bonding, but its configuration remains unclear, because it shows two IR bands and has significantly weaker CD signals.

2.2. X-ray crystallography

In order to determine the hydrogen bonding pattern in the solid state and compare it with the solution data, the X-ray single crystal structure of **4** was studied at 100 K. Suitable crystals could be grown by slow evaporation of

a chloroform/heptane solution of **4** at room temperature. An ORTEP plot of the asymmetric unit is shown in Fig. 3. Metrical parameters of the ferrocene moiety (Table 2) are comparable to those of other ferrocenyl dipeptides reported previously and will therefore be discussed only briefly [11,12].

The Cp(centroid)–Cp(centroid) distance is 3.302 Å and the dihedral angle θ between the two Cp rings is 0.7°. With a torsion angle C(5)–Cp(centroid)–Cp(centroid)–C(35) of $\omega = 67.5^\circ$, the two Cp rings are in a nearly eclipsed conformation. The carbonyl groups are only slightly tilted from the mean plane of the Cp rings with dihedral angles β of 1.7° and 9.0° (see Fig. 4 for a definition of these parameters).

In the solid state, the two Cp rings are eclipsed with in an almost perfect 1,2' conformation. The molecule adopts the “Herrick conformation” A (see Fig. 1) with two symmetrically equivalent hydrogen bonds between the amide NH on one and the proximal (relative to the Fc moiety) methionine carbonyl group on the other peptide chain [4]. In addition, the carbonyl group O(6) adjacent to one Cp ring is bridged to the methyl ester carbonyl atom O(20) on the same peptide chain by a water molecule O(60) forming a 12-membered ring. The distal amide NH on this peptide chain is involved in an additional intermolecular hydrogen bond with a bridging water molecule of an adjacent molecule with a distance of N(40)···O(60)[#] of 2.782 Å, thus forming a zig-zag chain along the crystallographic *b* axis.

Even more remarkable is the stereochemistry of the helical chiral ferrocene moiety. As mentioned above, all ferrocenyl dipeptides studied so far with the “Herrick

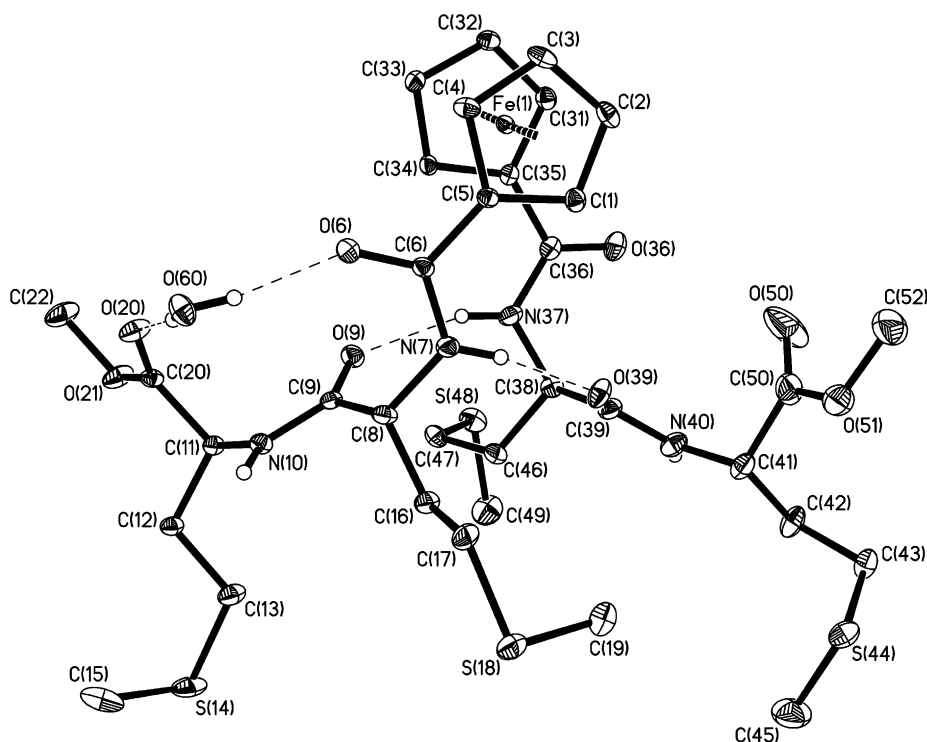


Fig. 3. ORTEP plot of the asymmetric unit of **4**. Thermal ellipsoids are depicted at 50% probability. Only the major isomer (>80%) is shown.

Table 2
Comparison of metrical parameters from X-ray structure of **4** (major isomer) and geometry optimizations for **5** and **6**

	4 ^a	5A	5B	5C	L, <i>P</i> ,L- 6A	L, <i>P</i> ,D- 6A	D, <i>P</i> ,D- 6A
Fe–C (Å)	2.037(2)–2.066(2)	2.102–2.131	2.099–2.134	2.105–2.143	2.099–2.131	2.098–2.132	2.097–2.132
Cp(C–C) (Å)	1.418(3)–1.443(3)	1.407–1.432	1.437–1.453	1.436–1.453	1.436–1.451	1.436–1.451	1.436–1.452
Cp(C–C–C) (°)	107.5(2)–108.9(2)	107.7–108.2	107.4–108.6	107.7–108.4	107.8–108.2	107.7–108.3	107.7–108.3
Cp(centr.)–Cp(centr.) (Å)	3.302	3.452	3.448	3.457	3.449	3.448	3.449
θ (°)	0.7	2.1	4.2	0.2	2.2	2.4	2.7
β (°)	1.7	2.8	32.8	20.3	2.6	5.5	4.0
	9.0	2.8	29.1	18.2	2.6	2.3	4.0
ω (°)	71.2	71.4	69.6	143.8	76.8	70.7	66.7
ΔE (kJ mol ⁻¹)	–	0.00	33.9 ^b	63.6 ^b	0.00	8.8 ^c	17.3 ^c

^a Only major isomer.

^b Relative to **5A**.

^c Relative to L,*P*,L-**6A**.

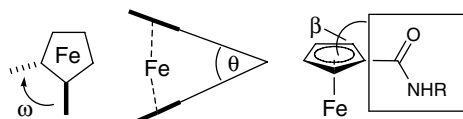


Fig. 4. Some important structural parameters in 1,1'-disubstituted peptides.

conformation" in the solid state were found to have *P* helicity at the ferrocene moiety for *L* amino acid side chains and *M* helicity when using *D* amino acids instead, thus leading preferentially to L,*P*,L or D,*M*,D isomers, respectively [1–3]. In contrast to all other ferrocenyl dipeptides characterized so far, **4** is a mixture of two isomers in the solid state: L,*D*,*M*,D,L (major isomer, >80%) and L,*D*,*M*,L,L (minor isomer). This finding can be explained if a partial racemization of the two Met residues directly bound to the ferrocene during the deprotection of the ester groups in basic media is assumed. The two bands in the IR spectrum and the weak CD signals could result from a mixture of diastereomers. In order to aid in the understanding of the factors that determine the relative stability of the different conformations, energy differences between ferrocenyl dipeptide model compounds **5** and **6** were calculated.

2.3. DFT calculations

Density functional theory (DFT) is the method of choice to study the electronic and geometrical structure of transition metal-based systems [18–20]. It has successfully been applied to investigate the conformational preference of substituted ferrocenes before [16,21,22]. In this work, we used the B3LYP/LanL2DZ method with effective core potentials (ECPs) on all heavy atoms due to the size of the molecules under study. Three different conformations were considered for ferrocene diacid with achiral glycine in the peptide chains Fe[C₅H₄-CO-Gly-NH₂]₂ (**5**) (Fig. 1, R = H, R₁ = NH₂): the "Herrick conformation" **5A** with two symmetrically equivalent hydrogen bonds, the "van Staveren conformation" **5B** with only one hydrogen bond [11], which also differs from **A** by involvement of the carbonyl group directly attached to the Cp ring, and an open "Xu conformation" **5C** without intramolecular hydrogen

bonds. Models of all three structures with truncated side chains to reduce the amount of computer time needed were built from available crystal structure coordinates whenever possible [11,23,24] and fully optimized without symmetry constraints. The results are compared to the data from the X-ray crystal structure of **4** in Table 2. Distances and angles are generally reproduced very well taking into account the known overestimation of metal–ligand bond lengths by DFT methods.

Thus feeling confident that the model chemistry used is able to correctly reproduce the geometrical parameters of the class of compounds under study, we compared the relative energies of conformations **5A–5C**. The "Herrick conformation" **5A** containing two intramolecular hydrogen bonds is the most stable with the "van Staveren conformation" **5B**, which contains only one hydrogen bond, higher in energy by 33.9 kJ mol⁻¹. The "Xu conformation" **5C** lacking intramolecular hydrogen bonds is the least stable and higher in energy by 29.7 kJ mol⁻¹ compared to **5B** (Fig. 5). These results agree well with the hydrogen bonding enthalpy of water estimated to be ~23 kJ mol⁻¹ [25]. They are also in line with the fact that the "Herrick conformer" **A** is the only detectable species in solution. In the solid state, however, the most stable conformation seems to be determined by a delicate balance of the relative strength of the various intra- and intermolecular hydrogen bonds possible [23].

Using chiral amino acids (R ≠ H), an additional three diastereomeric conformations are possible for the "Herrick conformer" **A** depending on the helical chirality of the ferrocene moiety and the chirality of the amino acids. Their conformational preference was investigated using Fe[C₅H₄-CO-Ala-OCH₃]₂ (**6**) as model compound (Fig. 1, R = CH₃, R₁ = OCH₃). Energy differences between the three conformations fell within a range of 8.5–8.8 kJ mol⁻¹ (Fig. 6) and were, however, much smaller than for **A**, **B**, and **C** containing a different number of hydrogen bonds. Obviously, it is not possible to predict any general trend from such small energy differences. A computational study on amino acid derivatives of 1'-aminoferrocene-1-carboxylic acid (Ac-Fca-Aaa-OMe) has been published recently [16]. Energy differences between different minimum conformations with

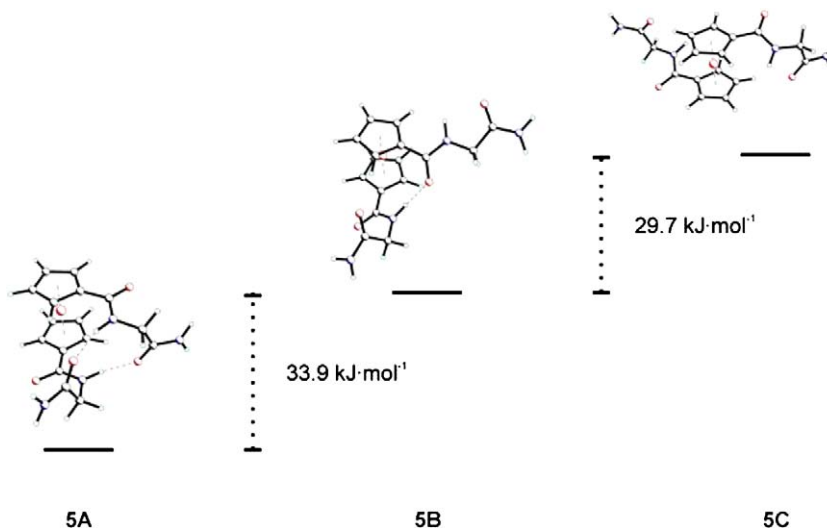


Fig. 5. Relative stability of conformers **5A**, **5B** and **5C** calculated at the B3LYP/LanL2DZ level; **5** = $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Gly-NH}_2]_2$.

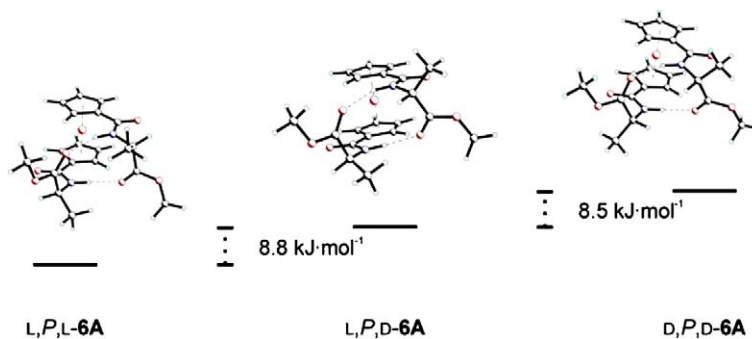


Fig. 6. Relative stability of conformers **L,P,L-6A**, **L,P,D-6A** and **D,P,D-6A** calculated at the B3LYP/LanL2DZ level; **6** = $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Ala-OMe}]_2$.

one hydrogen bond were calculated from 7.0 to 26.7 kJ mol^{-1} . A direct comparison with our data is difficult since torsion and dihedral angles ω and β span a much wider range and different CO and NH groups are involved in the hydrogen bonds in different conformations. Energy differences between the major conformations are however small and comparable in range to our data.

3. Conclusion

The spectroscopic and crystallographic properties of $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Met-Met-OMe}]_2$ (**4**) clearly suggest that a racemization has occurred during the synthesis, presumably in the deprotection step with 1 M NaOH . The two H-bonded amide groups observed in the IR spectrum and the weak CD signal at about 480 nm support the presence of a diastereomeric mixture. While racemization is a well known problem in peptide chemistry, this is the first report in the field of ferrocene peptides.

DFT calculations (B3LYP/LanL2DZ) on model ferrocenoyl peptides $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Gly-NH}_2]_2$ (**5**) and $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Ala-OMe}]_2$ (**6**) were performed. The calculations reveal that conformers with different hydrogen bond-

ing patterns **5A–5C** have significantly different stabilities, with a stabilization of the system by about 30 kJ mol^{-1} per hydrogen bond. The ‘‘Herrick conformation’’ with two hydrogen bonds is the most stable one, which is in agreement with solid state (X-ray) and solution (CD, NMR, IR) studies. On the other hand, conformers **6A**, which differ only in the amino acid chirality, have similar stabilities with $\Delta E < 10 \text{ kJ mol}^{-1}$. Due to the small energy differences and the large number of different conformations possible, it is very difficult to predict the most stable one by DFT calculations.

4. Experimental

4.1. CD spectroscopy

Compounds **1–4** were prepared and characterized as described [12]. CD spectra were recorded on a JASCO J-810 spectropolarimeter in 1 cm quartz Suprasil cells under argon thermostated at $20 \text{ }^\circ\text{C}$. Ellipticity maxima, λ_{max} , are given in nm. Molar ellipticity coefficients, M_θ , were calculated as $M_\theta = 100\theta/c \times l$, where the ellipticity θ is in deg, concentration c in mol l^{-1} and pathlength l in

cm, thus giving $\text{deg mM}^{-1} \text{cm}^{-1}$ for M_θ [13,26]. Stock solutions were obtained by accurately weighting ca. 5 mg of substance on an analytical balance and dissolving this amount in 5 ml of CH_2Cl_2 in a graded analytical flask. $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Cys(Bzl)-OMe}]_2$ (**1**). CD (CH_2Cl_2): λ_{max} (M_θ) 311 (+7.0), 356 (−5.0), 416 (−1.6), 481 (+4.1). $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Met-OMe}]_2$ (**2**). CD (CH_2Cl_2): λ_{max} (M_θ) 311 (+10.4), 356 (−6.4), 416 (−2.3), 483 (+5.5). $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Cys(Bzl)-Cys(Bzl)-OMe}]_2$ (**3**). CD (CH_2Cl_2): λ_{max} (M_θ) 311 (+9.3), 356 (−4.7), 417 (−2.1), 482 (+4.6). $\text{Fe}[\text{C}_5\text{H}_4\text{-CO-Met-Met-OMe}]_2$ (**4**). CD (CH_2Cl_2): λ_{max} (M_θ) 311 (+1.9), 359 (−0.7), 416 (−0.4), 485 (+1.1).

4.2. X-ray crystallographic data collection and refinement of the structures

An orange single crystal of $4 \cdot \text{H}_2\text{O}$ ($0.26 \times 0.26 \times 0.23 \text{ mm}^3$) was coated with perfluoropolyether, picked up with a glass fiber and mounted at a temperature of 100 K in the nitrogen cold stream of a Nonius Kappa-CCD diffractometer. A Mo-target rotating-anode X-ray source and a graphite monochromator (Mo $\text{K}\alpha$, $\alpha = 0.71073 \text{ \AA}$) was used. Final cell constants were obtained from a least squares fit of all integrated reflections. Crystal faces were determined and intensity data were corrected for absorption giving min./max. transmission factors of 0.825 and 0.873. The Siemens SHELXTL [27] software package was used for solution and artwork of the structure, SHELXL97 [28] was used for the refinement. The structure was readily solved by direct methods and subsequent difference Fourier techniques. Crystallographic data of the compound are listed in Table 3. The absolute structure parameter was reliably refined to be 0.029(10). All non-hydrogen atoms in

$4 \cdot \text{H}_2\text{O}$ were refined anisotropically. Hydrogen atoms were placed at calculated positions and refined as riding atoms with isotropic displacement parameters, except for the hydrogen atoms of a solvate water molecule which were located from the difference map. O–H distances in the water molecule were restrained to be equal within errors and a displacement factor of 1.5 times U_{eq} of the oxygen atom was given for both hydrogen atoms. Analysis of displacement parameters and residual electron density in the structure revealed that the compound is not 100% enantiomerically pure. The molecule contains two pairs of stereo centers, namely C(11)/C(8)–C(38)/C(41) which adopt an (L)/(R)–(R)/(L) configuration in the main component (>80%). It was possible to refine a minor split component which has an inverse configuration at C(8) but retains its configuration at C(11). The same seems to be true for the second, chemically related part of the molecule but it was not possible to isolate two split positions in this case. Bonded and non-bonded C–C and C–S distances of split parts were restraint to be equal within errors (SADI instruction) and equal thermal displacement parameters were refined for equivalent split atoms (EADP instruction).

4.3. Computational methods

All calculations were done with the GAUSSIAN98 package [29] on a Compaq ES40 parallel computer at the Max-Planck-Institut für Bioorganische Chemie. The B3LYP exchange-correlation functional [30–32] and double-zeta quality LanL2DZ basis set [33–36] with ECPs on the heavy atoms were used for the geometry optimizations due to the size of the molecules. All converged geometries were characterized as stationary points by analytical calculation of vibrational frequencies due to the absences of imaginary frequencies.

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Appendix A. Supplementary information

Crystallographic data (excluding structure factors) for the structure of **4** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC-279851. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, fax: (internat.) +1 44 212233362033, e-mail: deposit@ccdc.cam.ac.uk. Molden figures and geometrical parameters for the calculated structures. Supplementary data associated

Table 3
Crystallographic data for $4 \cdot \text{H}_2\text{O}$

	$4 \cdot \text{H}_2\text{O}$
Chemical formula	$\text{C}_{34}\text{H}_{52}\text{FeN}_4\text{O}_9\text{S}_4$
F_w	844.89
Space group	$P2_12_12_1$, No. 19
a (Å)	19.8819(3)
b (Å)	11.3307(2)
c (Å)	17.6048(3)
V (Å ³)	3965.94(11)
Z	4
T (K)	100(2)
ρ_{calc} (g cm^{-3})	1.415
Reflections collected/ $2\theta_{\text{max}}$	99 604/62.00
Unique reflections/ $I > 2\sigma(I)$	12 634/12 242
Number of parameters/restraints	508/35
λ (Å)/ $\mu(\text{K}\alpha)$ (cm^{-1})	0.71073/6.47
R_1^a /Goodness-of-fit ^b	0.0409/1.140
wR_2^c ($I > 2\sigma(I)$)	0.1005
Residual density (e \AA^{-3})	+1.19/−0.57

^a Observation criterion: $I > 2\sigma(I)$. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$.

^b $\text{Goof} = [\sum [w(F_o^2 - F_c^2)^2] / (n - p)]^{1/2}$.

^c $wR_2 = [\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]]^{1/2}$ where $w = 1/\sigma^2(F_o^2) + (aP)^2 + bP$, $P = (F_o^2 + 2F_c^2)/3$.

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