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Journal of Organometallic Chemistry 692 (2007) 4209–4214
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis and structural characterization of metallated bioconjugates: C-terminal labeling of amino acids with aminoferrocene

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Received 16 May 2007; received in revised form 8 June 2007; accepted 8 June 2007
Available online 29 June 2007

Abstract

Aminoferrocene, H_2N–Fc, has been substituted to the C-terminus of six amino acids using the HBTU/HOBt coupling protocol. The synthesized bioconjugates Boc-Aaa-NH-Fc, Aaa = Gly (**1**), Leu (**2**), Phe (**3**), Val (**4**), Cys(Acm) (**5**), Tyr(^{t}Bu) (**6**) (Acm = acetamidomethyl, ^{t}Bu = *tert*-butyl), have been characterized by ^{1}H NMR, ^{13}C NMR, EI-MS, EI-HRMS, UV and CD spectroscopies. In addition, a VT NMR study on **4** and the X-ray structure of **1** are presented.

Keywords: Amino acids; Bioorganometallic chemistry; Ferrocene; Peptides; X-ray

1. Introduction

Organometallic compounds are often considered as instable and sensitive to air and water, and therefore not suitable for the use in biology and medicine. However, in addition to vitamin B_{12} and the active sites of the metal-containing hydrogenases found in nature, the rapidly growing field of bioorganometallic chemistry [1–3] has created a number of medicinal applications, for example efficient organometallic derivatives of the anticancer drug tamoxifen [4], the antimalaria drug chloroquine [5], the kinase inhibitor staurosphorine [6] and the dopamine receptor antagonists [7].

An important aspect of bioorganometallic chemistry is the synthesis and characterization of bioconjugates of organometallics with biological molecules like carbohydrates, nucleic acids and peptides [8]. In particular, recent research has focused on ferrocenyl-labeled amino acids and peptides [8,9]. Depending on the substitution pattern of the ferrocene group, different orientations of the peptide strands are realized (see Fig. 1). While extensive studies have been reported for the other four members of the ferrocene-derived peptide family shown in Fig. 1 [8–12], only initial studies have been performed on amino acids labeled with aminoferrocene [12b]. In this paper, we describe the synthesis and characterization of amino acids substituted with aminoferrocene at the C-terminus.

2. Results and discussion

2.1. Synthesis

The unstable aminoferrocene constitutes the simplest amine of ferrocene and was the compound of choice for

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doi:10.1016/j.jorganchem.2007.06.044

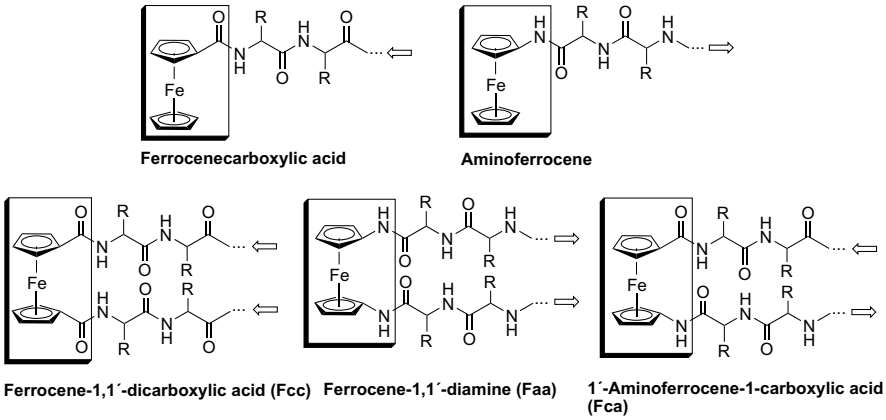
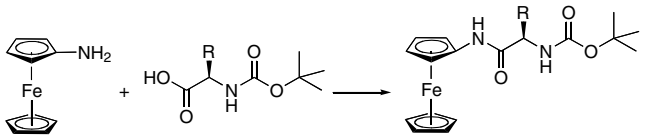


Fig. 1. The ferrocene-derived peptide family. Arrows point from the C to the N termini of the peptides.

the coupling at the C-terminus of the amino acid. From the scarce methods found in the literature for their preparation, we followed the procedure of Leusen and Hessen as the most convenient synthesis route [13]. The procedure involves lithiation of ferrocene with *t*-BuLi followed by reaction with α-azidostyrene at −70 °C and subsequent acidification. The required α-azidostyrene was prepared following a reported procedure from 1,2-dibromo-1-phenylethane [14]. Aminoferrocene was coupled to the C-terminal end of six different amino acids using the HBTU/HOBt protocol, Scheme 1. The bioconjugates **1**–**6** could be obtained in good yields (58–70%) as orange solids.

2.2. Spectroscopy

The molecular structure of **1**–**6** was confirmed by EI mass spectrometry. As known from previous studies [11i,12b], the M^+ peaks of ferrocene peptides are very stable and are found to be the base peak in all compounds presented in this study. The UV/Vis spectra in CH_2Cl_2 show the characteristic ferrocene peak at about 440 nm with $\varepsilon \sim 180\ M^{-1}\,cm^{-1}$. Various methods have been employed in earlier work to elucidate hydrogen bonding interactions in ferrocene peptide bioconjugates. In particular, CD spectra and temperature-dependent NMR studies were helpful to discern inter- and intra-molecular hydrogen bonding. The CD spectra (in CH_2Cl_2) of the compounds in this study display only weak signals with $M_\theta = 5\ mM^{-1}\,cm^{-1}$ or below, as expected for monosubstituted ferrocene peptides [9,11b,11i]. As suggested from the structural drawings in Fig. 1, these data confirm that there is no strong intramolecular hydrogen bonding which might lead to a fixed conformation. These finding are confirmed by NMR spectroscopy. NMR data for all new compounds are listed in Tables 1 and 2. An interesting feature is provided by the ^1H NMR spectra ($CDCl_3$) were the NH protons are found above 7 ppm, indicating the presence of intramolecular hydrogen bonding [9b,11h]. Variable temperature ^1H NMR spectroscopy shows a weakening of both N–H hydrogen bonds when the temperature is increased (see Fig. 2). For the amide proton of the amino acid the temperature dependence is higher than for the amide hydrogen attached to the Cp ring of ferrocene (see Fig. 2b). The fact that these interactions are very likely inter-molecular in nature is further supported by measuring temperature-dependent ^1H NMR spectra at two different concentrations (2 mM and 200 mM). The NMR spectra are concentration-dependent and both acidic protons are shifted to lower field when the concentration is increased, as would be expected for stronger hydrogen-bond interactions. In addition, the temperature dependence $\Delta\delta$ of the amide protons is about four times more pronounced in concentrated solutions, which is a clear indication for inter-molecular hydrogen bonding. The ratio of the two $\Delta\delta$ values for both concentrations under investigation is similar (about 4, see legend for Fig. 2 for numbers), which again indicates the similarity in chemical interactions.



Scheme 1. Synthesis of ferrocene peptides **1**–**6**. Reaction conditions: HBTU/HOBt/DIPEA/DCM.

2.3. X-ray crystallography

The solid state structure of Boc-Gly-Fc **1** was studied by X-ray crystallography. The molecular geometry and atom labeling of **1** are shown in Fig. 3, while the hydrogen bonding pattern is displayed in Fig. 4. The crystal structure confirms the proposed composition of the com-

Table 1
^{1}H chemical shifts of compounds **1**–**6**, ^{1}H,^{1}H coupling constants (in Hz) in parentheses[a,b]

	H_5C_5	H_α	$H_{\alpha'}$	$H_{\beta,\beta'}$	NH	α-CH	NH_{Boc}	$(CH_3)_{3Boc}$	R		
									CH	β-CH_2	CH_3
1	4.16 s	4.60 t (2.0)	4.60 t (2.0)	3.99 t (1.8)	7.64 s	3.82 d (5.8)	5.38 s	1.49 s			
2	4.13 s	4.62 s	4.60 s	3.97 s	7.73 s	3.97 s	5.08 s	1.47 s	1.26 s	1.71 m	0.95 s
3	4.07 s	4.51 m	4.51 m	3.96 t (1.8)	7.36–7.19[c]	4.35 ddd (7.2, 7.2, 7.2)	5.14 d (7.2)	1.44 s		3.10 d (7.0)	
4	4.13 s	4.67 s	4.56 s	3.92 m	7.77 s	3.92 m	5.35 d (8.4)	1.46 s	2.14 d (5.6)	–	1.01 t (6.7)
5	4.16 s	4.57–4.67 m	4.57–4.67 m	3.98 br s	8.53 s	4.57–4.67 m	5.75 d (8.1)	1.48 s		2.78 dd (14.2, 7.6)	2.05 s
6	4.11 s	4.49–4.54 m	4.49–4.54 m	3.96 t (1.9)	7.31 br s	4.33 ddd (7.2, 7.2, 7.2)	5.21 d (6.8)	1.18 s		3.04 dd (7.0, 2.5)	1.23 s

[a] δ(^{1}H) in ppm relative to TMS; $CDCl_3$ as solvent, 2 mM; letters denote signal multiplicities: s, singlet; d, doublet; m, multiplet; t, triplet; br, broad.
[b] ^{1}H chemical shifts of the substituents not included in the table: **3**: $\delta = 7.36$–7.19 m (C_6H_5); **5**: $\delta = 7.34$ br s, (NH), 2.96 dd, $J = 15.0$, 14.0 Hz (S–CH_2–); **6**: $\delta = 7.18$–7.12 m (*meta*-CH of –C_6H_4–O*t*Bu), 6.96–6.90 m, (*ortho*-CH of –C_6H_4–O*t*Bu).
[c] Superimposed with the aromatic protons.

Table 2
^{13}C chemical shifts of compounds **1**–**6**[a,b]

	C_5H_5	C_{ipso}	C_α	$C_{\alpha'}$	$C_{\beta,\beta'}$	CO	α-CH	CO_{Boc}	CH_{3Boc}	C_{Boc}	R		
											β-CH_2	CH	CH_3
1	69.2	80.6	61.6	61.6	64.7	156.4	45.3	167.8	28.3	93.8		–	–
2	69.1	94.1	61.3	61.3	64.4	156.0	53.5	170.0	28.3	80.4	22.8	40.5	22.6
3	69.1	93.5	61.8	61.6	64.6	155.7	56.4	169.8	28.3	80.5	38.1	–	–
4	69.0	94.1	61.5	61.2	64.4	156.0	61.2	170.0	28.3	82.8	–	30.4	19.3
5	69.2	93.6	61.8	61.6	64.7	156.1	53.9	171.2	28.3	80.4	34.8	–	21.0
6	69.1	93.5	61.5	61.5	64.5	156.6	56.3	169.5	28.2	80.3	37.3	–	28.7

[a] δ(^{13}C) in ppm relative to TMS; $CDCl_3$ as solvent, 2 mM.
[b] ^{13}C chemical shifts of the substituents not included in the table; **3**: $\delta = 136.6$ (*ipso*-C_6H_5), 129.3 (*ortho*-C_6H_5), 128.7 (*meta*-C_6H_5), 127.1 (*para*-C_6H_5); **5**: $\delta = 169.0$ (CO), 41.3 (S–CH_2); **6**: $\delta = 154.3$ (*ipso*-CH of –C_6H_4–O*t*Bu), 131.3 (*para*-CH of –C_6H_4–O*t*Bu), 129.6 (*meta*-CH of –C_6H_4–O*t*Bu), 124.0 (*ortho*-CH of –C_6H_4–O*t*Bu), 78.4 (quaternary C of O*t*Bu).

pound. Bond lengths and angles are within the expected range. The ferrocene moiety is found in the eclipsed conformation, $\omega = 5°$ [9b]. The two Cp rings as well as the amide group are coplanar, the angles between the corresponding planes are 1.5°. Two hydrogen bonds, O1···N1A and N2···O3A, dominate the crystal packing and induce the formation of chains along the crystallographic *c*-axis, Fig. 4. Evidently, both NH protons have the capability to engage in intermolecular hydrogen bonding. This finding from the solid state single crystal study is qualitatively in agreement with the NMR data discussed above.

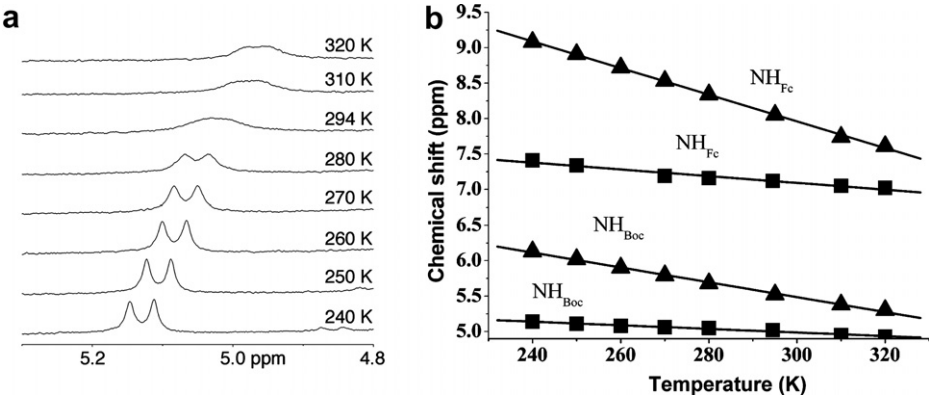


Fig. 2. (a) ^{1}H NMR spectra of compound **4** showing the NH_{Boc} proton at different temperatures in 2 mM solution in $CDCl_3$. The signal is resolved in a doublet below 280 K. (b) Plot of chemical shift *vs.* temperature for compound **4** in 2 mM (■) and 200 mM (▲) in $CDCl_3$. NH_{Fc} (slopes = −18.8 and −4.76 ppb/K for concentrated and diluted dissolutions, respectively) refers to the amide hydrogen attached to the Cp ring of ferrocene and NH_{Boc} (slopes = −10.49 and −2.54 ppb/K for concentrated and diluted dissolutions, respectively) is the amide proton of valine.

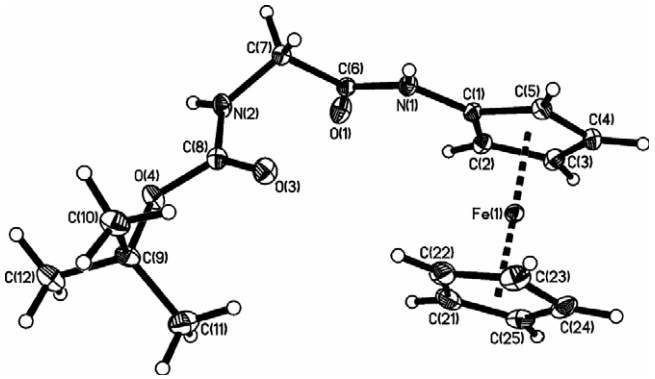


Fig. 3. ORTEP plot of the asymmetric unit of **1**. Thermal ellipsoids are depicted at 50% probability.

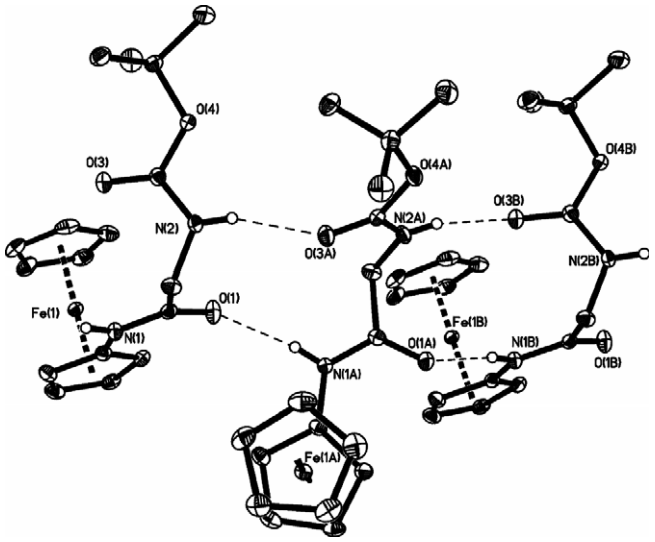


Fig. 4. ORTEP plot of the hydrogen bond pattern in the solid state structure of **1**.

3. Conclusions

This study presents amino acid conjugates to aminoferrocene. While bioconjugates of most other ferrocene derivatives in Fig. 1 have been described in numerous reports [8–12], information on aminoferrocene is rather scarce [12b]. This may be due to the instability of aminoferrocene itself. However, we find that amino acid conjugates can be prepared in good yield without problems. Their characterization is straight forward. The crystal structure of the Boc-glycine derivative is the first one reported for an amino acid conjugate with aminoferrocene. The compounds reported herein thus complete the cycle of ferrocene amino acid derivatives.

4. Experimental

4.1. General remarks

Reactions were carried out in ordinary glassware and chemicals used without further purification. All chemicals were obtained from Aldrich, Iris, Fluka or Novabiochem. Only pure *N*-Boc-protected L-amino acids were used. Variable temperature (320–240 K), ^{1}H (250.13 MHz) and ^{13}C (62.98 MHz) NMR measurements were performed on a Bruker AC 250 spectrometer. The chemical shift standard was internal tetramethylsilane for ^{1}H and ^{13}C (δ 0 ppm). Digital resolutions in the 1D NMR spectra were 0.17 Hz/point for 1H, 0.94 Hz/point for ^{13}C, pulse angles were ca. 30°, and sample concentrations were 2 mM. Signal assignments were assisted by gs-COSY, gs-HMQC, and gs-HMBC experiments performed on a Bruker Avance DPX-400 spectrometer using standard Bruker software. NMR data are collected in Tables 1 and 2. Mass spectra were measured on a Mat 8200 instrument, only characteristic fragments with intensities and possible composition are given in brackets. UV/Vis spectra were measured on a Varian CARY 100 instrument in 1 cm quartz Suprasil cells thermostated at 20 °C. Absorption maxima, λ_{max}, and molar absorption coefficients, ε_{max}, are given in nm and $M^{-1}\,cm^{-1}$, respectively. CD spectra were recorded on a JASCO J-810 spectropolarimeter in 1 cm quartz Suprasil cells under nitrogen thermostated at 20 °C, at 2 ± 0.2 mM concentrations. Ellipticity maxima, λ_{max}, and molar ellipticity coefficients, M_θ, are given in nm and $mM^{-1}\,cm^{-1}$, respectively.

4.2. General procedure of preparation of compounds *1–6*

The corresponding Boc-protected α-amino acid (1 mmol) was dissolved in 35 ml of CH_2Cl_2. Solid HOBt (1 mmol, 0.153 g) was added under cooling (0 °C) and stirred for 10 min. HBTU (1 mmol, 0.380 g) and DIPEA (2 mmol, 0.646 g) were added sequentially and the reaction mixture was allowed to warm up and kept at room temperature for 30 min under stirring. To the reaction solution aminoferrocene (1.1 mmol, 0.220 g) [13] was added. After completion (TLC analysis), the reaction was diluted to 100 ml with CH_2Cl_2 and washed successively with saturated $NaHCO_3$, 10% citric acid, and water. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography using hexane–ethyl acetate as eluent to get the pure product after crystallization.

4.3. Boc-Gly-NH-Fc (*1*)

Orange solid, yield 61%. M_r ($C_{17}H_{22}FeN_2O_3$) = 358.21; MS (EI): 358 (84) $[M]^+$, 302 (100) $[M-tBu]^+$, 284 (20) $[M-tBuOH]^+$, 258 (91) $[M-Boc]^+$, 227 (24) [Fc-NHCO]$^+$, 201 (45) $[M-Gly\text{-}OMe]^+$. HRMS (EI): m/z exp. 358.0980 and calc. 358.0980. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 441 (168).

4.4. Boc-Leu-NH-Fc (*2*)

Orange solid, yield 59%. M_r ($C_{21}H_{30}FeN_2O_3$) = 414.32; MS (EI): 414 (85) $[M]^+$, 358 (100) $[M-tBu]^+$, 340 (54)

$[M-t\text{BuOH}]^+$, 314 (79) $[M-\text{Boc}]^+$, 227 (67) [Fc-NHCO]$^+$, 201 (99) [M−Leu-OMe]$^+$. HRMS (EI): *m/z* exp. 414.1606 and calc. 414.1606. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 441 (174). CD (CH_2Cl_2): λ_{max} (M_θ) 466 (+5.3), 350 (−0.3), 327 (+0.4).

4.5. Boc-Phe-NH-Fc (3)

Orange solid, yield 65%. M_r ($C_{24}H_{28}FeN_2O_3$) = 448.34; MS (EI): 448 (100) $[M]^+$, 392 (88) $[M-t\text{Bu}]^+$, 374 (60) $[M-t\text{BuOH}]^+$, 348 (76) $[M-\text{Boc}]^+$, 227 (64) [Fc-NHCO]$^+$, 201 (85) [M−Phe-OMe]$^+$. HRMS (EI): *m/z* exp. 448.1450 and calc. 448.1449. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 442 (183). CD (CH_2Cl_2): λ_{max} (M_θ) 470 (+1.6), 324 (+0.4).

4.6. Boc-Val-NH-Fc (4)

Orange solid, yield 65%. M_r ($C_{20}H_{28}FeN_2O_3$) = 400.29; MS (EI): 400 (100) $[M]^+$, 344 (96) $[M-t\text{Bu}]^+$, 326 (19) $[M-t\text{BuOH}]^+$, 300 (78) $[M-\text{Boc}]^+$, 227 (39) [Fc-NHCO]$^+$, 201 (83) [M−Val-OMe]$^+$. HRMS (EI): *m/z* exp. 400.1448 and calc. 400.1449. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 441 (196). CD (CH_2Cl_2): λ_{max} (M_θ) 478 (−1.1), 333 (+0.8).

4.7. Boc-Cys(Acm)-NH-Fc (5)

Orange solid, yield 58%. M_r ($C_{21}H_{29}FeN_3O_4S$) = 475.38; MS (EI): 475 (100) $[M]^+$, 419 (15) $[M-t\text{Bu}]^+$, 404 (18) $[M-\text{Acm}]^+$, 375 (43) $[M-\text{Boc}]^+$, 348 (29) $[M-\text{Acm}-t\text{Bu}]^+$; 304 (46) $[M-\text{Acm}-\text{Boc}]^+$; 227 (41) [Fc-NHCO]$^+$, 201 (37) [M−Cys(Acm)-OMe]$^+$. HRMS (EI): *m/z* exp. 475.1230 and calc. 475.1228. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 441 (184). CD (CH_2Cl_2): λ_{max} (M_θ) 471 (−4.4), 304 (+4.4).

4.8. Boc-Tyr(^{t}Bu)-NH-Fc (6)

Orange solid, yield 70%. M_r ($C_{28}H_{36}FeN_2O_4$) = 520.44; MS (EI): 520 (100) $[M]^+$, 464 (100) $[M-t\text{Bu}]^+$, 446 (39) $[M-t\text{BuOH}]^+$, 420 (42) $[M-\text{Boc}]^+$, 390 (23) $[M-t\text{Bu}-t\text{BuOH}]^+$, 227 (50) [Fc-NHCO]$^+$, 201 (61) [M−Tyr(*t*Bu)-OMe]$^+$. HRMS (EI): *m/z* exp. 520.2023 and calc. 520.2024. ^{1}H NMR (250.13 MHz, $CDCl_3$, 294 K), see Table 1. ^{13}C NMR (62.98 MHz, $CDCl_3$, 294 K), see Table 2. UV/Vis (CH_2Cl_2): λ_{max} (ε) 441 (175). CD (CH_2Cl_2): θ_{max} (M_θ) 466 (+3.2), 346 (−0.5), 320 (+0.3).

4.9. X-ray crystallography

Yellowish parallelepiped-shaped crystals of **1** were obtained by slow evaporation from a hexane-ethyl acetate solution mixture (9:1). Crystal data for **1**: $C_{17}H_{22}N_2O_3Fe$, $M = 358.22$ g mol^{-1}, $0.09 \times 0.02 \times 0.01$ mm^3, $a = 11.6361(5)$ Å, $b = 16.1791(7)$ Å, $c = 9.4167(4)$ Å, $\beta = 107.303(5)°$, $V = 1692.57(13)$ Å^3, Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.907 mm^{-1}, monoclinic, space group $P2_1/c$, $Z = 4$, Bruker-Nonius Kappa-CCD diffractometer, $T = 100(2)$ K, 19764 reflections measured, 5168 unique reflections ($R_{int} = 0.046$), 4362 observed reflections ($F_o > 4\sigma(F_o)$), $\Theta_{max} = 30.54°$, $R = 0.0326$ ($F_o > 4\sigma(F_o)$), $R = 0.0427$ (all data), $wR = 0.0784$ ($F_o > 4\sigma(F_o)$), 217 parameters, refinement against F^2, SHELXTL 6.14 Bruker AXS program suite.

5. Supplementary material

CCDC 647542 contains the supplementary crystallographic data for **1**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgements

The Argentinean authors acknowledge Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Comisión de Investigaciones de la Provincia de Buenos Aires (CIC) and Facultad de Ciencias Exactas (UNLP). J.L.J. acknowledges the DAAD (Deutscher Akademischer Austauschdienst, Germany), for a scholarship. Part of the synthesis and characterization was carried out at the IPMB, University of Heidelberg.

References

[1] G. Jaouen (Ed.), Bioorganometallics, Wiley-VCH, Weinheim, 2005.
[2] (a) N. Metzler-Nolte, K. Severin, in: H.-B. Kraatz, N. Metzler-Nolte (Eds.), Concepts and Models in Bioinorganic Chemistry, Wiley-VCH, Weinheim, 2006, pp. 113–136;
(b) N. Metzler-Nolte, in: Gerald Parkin (Ed.), Comprehensive Organometallic Chemistry III, vol. 1, Elsevier, Amsterdam, 2007, pp. 883–920.
[3] U. Schatzschneider, N. Metzler-Nolte, Angew. Chem. Int. Ed. 45 (2006) 1504–1507.
[4] G. Jaouen, S. Top, A. Vessires, G. Leclercq, M.J. McGlinchey, Curr. Med. Chem. 11 (2004) 2505–2517.
[5] C. Biot, Curr. Med. Chem. Anti-Infect. Agents 3 (2004) 135–147.
[6] (a) H. Bregman, D.S. Williams, G.E. Atilla, P.J. Carroll, E. Meggers, J. Am. Chem. Soc. 126 (2004) 13594–13595;
(b) D.S. Williams, G.E. Atilla, H. Bregman, A. Arzoumanian, P.S. Klein, E. Meggers, Angew. Chem. Int. Ed. 44 (2005) 1984–1987;
(c) J.E. Debreczeni, A.N. Bullock, G.E. Atilla, D.S. Williams, H. Bregman, S. Knapp, E. Meggers, Angew. Chem. Int. Ed. 45 (2006) 1580–1585.
[7] K. Schlotter, F. Boeckler, H. Hübner, P. Gmeiner, J. Med. Chem. 48 (2005) 3696–3699.
[8] D.R. van Staveren, N. Metzler-Nolte, Chem. Rev. 104 (2004) 5931–5985.
[9] (a) T. Moriuchi, T. Hirao, Chem. Soc. Rev. 33 (2004) 294–301;
(b) S.I. Kirin, H.-B. Kraatz, N. Metzler-Nolte, Chem. Soc. Rev. 35 (2006) 348–354.

[10] (a) H.-B. Kraatz, J. Lusztyk, G.D. Enright, Inorg. Chem. 36 (1997) 2400–2405;
(b) D. Savage, G. Malone, J.F. Gallagher, Y. Ida, P.T.M. Kenny, J. Organomet. Chem. 690 (2005) 383–393.
[11] (a) See for example: R.S. Herrick, R.M. Jarret, T.P. Curran, D.R. Dragoli, M.B. Flaherty, S.E. Lindyberg, R.A. Slate, L.C. Thornton, Tetrahedron Lett. 37 (1996) 5289–5292;
(b) T. Moriuchi, A. Nomoto, K. Yoshida, A. Ogawa, T. Hirao, J. Am. Chem. Soc. 123 (2001) 68–75;
(c) T. Moriuchi, T. Nagai, T. Hirao, Org. Lett. 7 (2005) 5265–5268;
(d) T. Moriuchi, T. Nagai, T. Hirao, Org. Lett. 8 (2006) 31–34;
(e) F.E. Appoh, T.C. Sutherland, H.-B. Kraatz, J. Organomet. Chem. 689 (2004) 4669–4677;
(f) F.E. Appoh, E.F. Thomas, H.-B. Kraatz, Macromolecules 39 (2006) 5629–5638;
(g) K. Heinze, M. Beckmann, Eur. J. Inorg. Chem. (2005) 3450–3457;
(h) D.R. van Staveren, T. Weyhermüller, N. Metzler-Nolte, Dalton Trans. (2003) 210–220;
(i) S.I. Kirin, D. Wissenbach, N. Metzler-Nolte, New J. Chem. 29 (2005) 1168–1173;
(j) S.I. Kirin, U. Schatzschneider, X. De Hatten, T. Weyhermüller, N. Metzler-Nolte, J. Organomet. Chem. 691 (2006) 3451–3457.
[12] (a) L. Barisic, M. Dropucic, V. Rapic, H. Pritzkow, S.I. Kirin, N. Metzler-Nolte, Chem. Commun. (2004) 2004–2005;
(b) L. Barisic, M. Cakic, K.A. Mahmoud, Y.-n. Liu, H.-B. Kraatz, H. Pritzkow, S.I. Kirin, N. Metzler-Nolte, V. Rapic, Chem. Eur. J. 12 (2006) 4965–4980;
(c) S. Chowdhury, K.A. Mahmoud, G. Schatte, H.-B. Kraatz, Org. Biomol. Chem. 3 (2005) 3018–3023.
[13] D. van Leusen, B. Hessen, Organometallics 20 (2001) 224–226.
[14] G.J. Smolinsky, J. Org. Chem. 27 (1962) 3557.