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Preparation and structural characterisation of a novel ferrocene–amino acid conjugate

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ABSTRACT

A new type of ferrocene–amino acid conjugate, 2-[(methoxycarbonyl)methyl]-2-aza[3]ferrocenophane (1), was obtained in a rather low yield via condensation reaction of 1,1′-bis(hydroxymethyl)ferrocene and glycine methyl ester in the presence of $[RuCl_2(PPh_3)_3]$ as a catalyst. The compound was characterised by combustion analysis and by spectroscopic method, and its solid-state structure was established by single-crystal X-ray diffraction analysis. Compound 1 is reluctant towards alkylation with MeI but readily forms a stable picrate salt. Cyclic voltammetry experiments on 1 (in CH_3CN at Pt electrode) revealed the compound to undergo a one-electron reversible oxidation attributable to ferrocene/ferrocenium couple ($E^{o\prime} = -5$ mV vs. ferrocene itself), which shifts towards more positive potentials upon protonation with HCl.

Ferrocenylated amino acids and peptides have been intensely studied in the recent past mainly due to their attractiveness as redox-active biomolecular probes and structural models for peptides [1]. Most typically such compounds have been obtained by condensation between an appropriate organometallic reagent (usually ferrocenecarboxylic acid or its derivative) and free (terminal) amino group of an amino acid or a peptide chain to give the respective *N*-ferrocenecarbonyl derivative (type **I** in Scheme 1). By contrast, other methods including ferrocenylmethylation at the N-terminus or preparation of amino acids bearing the ferrocenyl moiety in the side chain (structures **II** and **III** in Scheme 1, respectively) remain considerably less explored [1].

While seeking for an alternative "ferrocenylation" method applicable to amino acids, we became inspired with ferrocenophane amines of the type **IV** (Scheme 2). Such compounds have been originally synthesised by condensation of 1,1′-bis(hydroxymethyl)ferrocene with isocyantes (**IV**: R = C_6H_4X-4, where X = H, OMe, NO_2 [2]), by twofold alkylation of an amine (RNH_2) with 1,1′-bis(bromomethyl)ferrocene (**IV**: R = $C_6H_4NO_2$-4 [3]) or 1,1′-bis(*N*-pyridiummethyl)ferrocene dichloride (**IV**: R = Me [4]) and, finally, by reductive ammination of ferrocene-1,1′-dicarbaldehyde (**IV**: R = ω-[(7-chloro-4-quinolyl)amino]alkyl [5]). More recently, Osakada and co-workers devised a practical synthetic route to ferrocenophanes **IV** based on Ru-catalysed condensation of 1,1′-bis(hydroxymethyl)ferrocene with amines [6]. We decided to make use of this approach in the preparation of a novel ferrocene–glycine conjugate **1** (Scheme 2) [7].

Compound **1** was prepared [8] by following the literature method consisting in thermally induced condensation of 1,1′-bis(hydroxymethyl)ferrocene [10] with glycine methyl ester [11] at 170 °C in the presence of $[RuCl_2(PPh_3)_3]$ (3.5 mol.%) using *N*-methylpyrrolidone as the solvent (Scheme 3). Isolation by column chromatography afforded analytically pure **1** as an air-stable orange crystalline solid in 10% yield. Apart from for **1**, only small amount of 2-oxa[3]ferrocenophane, which is evidently the product of dehydration of the starting diol, was isolated from the crude reaction mixtures. Attempts at improving the yield of **1** failed probably because of competitive decomposition pathways operating under the relatively harsh reaction conditions.

Compound **1** was characterised by the conventional spectroscopic methods and by combustion analysis [12]. In ^{1}H NMR spectra, it showed a pair of apparent triplets due to symmetrically 1,1′-disubstituted ferrocene moiety (i.e., due to two identical AA′BB′ spin systems) and resonances attributable to the modifying substituent, namely a singlet for the equivalent, ferrocene-bound CH_2 groups (δ_H 3.10) and two additional singlets for the glycine residue (δ_H 3.66 and 3.75 for CH_2 and CH_3 group, respectively). ^{13}C NMR spectra were also in accordance with the formulation, displaying two ferrocene CH resonances and one down-field shifted C_{ipso} signal (δ_C 83.15) as it is typical for alkyl-substituted ferrocenes. Signals of the amino acid moiety were observed in the expected region (δ_C 58.77 and 51.42 for CH_2 and CH_3 groups, respectively); the glycine C=O was found at δ_C 171.65. Finally, IR spectra of **1** confirmed the presence of the terminal ester group, showing a strong $\nu_{C=O}$ band at 1739 cm^{-1}.

Solid-state structure of **1** was determined by single-crystal X-ray diffraction [13]. A view of the molecular structure is presented

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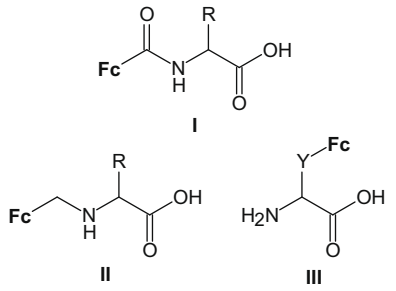
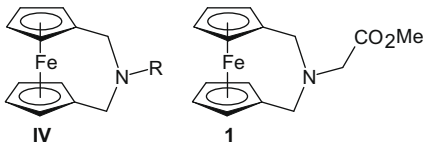


Scheme 1. Selected examples of ferrocenylated amino acids (Fc = ferrocenyl, Y = an organic spacer).



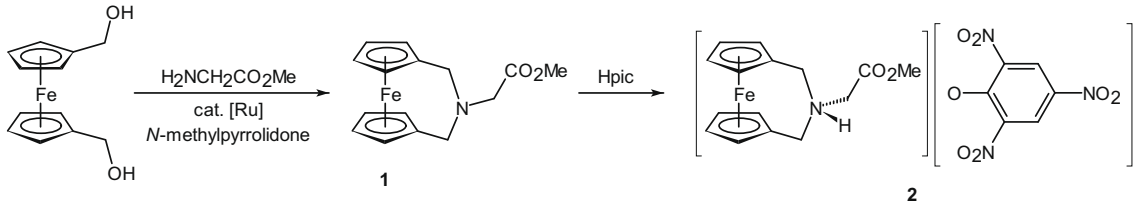
Scheme 2. [3]Ferrocenophane amines (**IV**) and the amino acid derivative under study (**1**).

in Fig. 1 together with selected distances and angles. The bridged cyclopentadienyl rings in the molecule of **1** are mutually eclipsed and symmetrically tilted by ca. 12° (the variation in the Fe-ring centroid distances being statistically insignificant), and the geometry of the ferrocenophane part does not differ much from the structural data reported for the N-methyl analogue (**IV**, R = Me [4]). The CNC bridge in **1** is bent at the nitrogen atom with the C11–N–C12 angle being 113.8(1)°, and symmetrically incorporates the glycine unit (the C11/C12–N–C13 angles differ by only 1°). However, the pendant moiety it is slightly twisted at the C13–C14 bond (N–C13–C14–O1 = 9.1(3)°), which lowers the overall molecular symmetry. As a consequence, the {C13, C14, O1, O2, C15} plane [16] is practically perpendicular to the {C11, N, C12} plane (dihedral angle = 83.6(2)°) but, simultaneously, inclined towards the Cp2 ring as evidenced by the dihedral angles of the {C13, C14, O1, O2, C15} plane and the Cp1/Cp2 rings being 4.5(1)/15.8(1)° (Fig. 2).

Alkylation of **1** with an excess of methyl iodide [17] met with no success, leading only to a complete recovery of unchanged **1**. On the other hand, treatment of **1** with 2,4,6-trinitrophenol in ethyl acetate and subsequent crystallisation [18] yielded picrate **2** as a red crystalline solid (Scheme 3), which was characterised by melting point and by spectroscopic methods [19]. Ions constituting salt **2** were clearly seen in electrospray mass spectra. Likewise, the ^{1}H NMR spectrum of **2** showed signals attributable to cation [**1**H]$^+$ and characteristic resonance due to the picrate protons at δ_H 8.94. The presence of the picrate anion was further manifested in IR spectra via the diagnostic bands at 1556/1567 ($\nu_{as}NO_2$), 1321/1364 (ν_sNO_2), 1615/1629 (ν_{C-C}), and at 1270 cm^{-1} (phenoxide ν_{C-O}) [20]. A band due to glycine C=O group ($\nu_{C=O}$) was observed at 1751 cm^{-1}, shifted by 12 cm^{-1} to higher energies compared to **1**.

Cyclic voltammogram of compound **1** recorded in acetonitrile at a platinum electrode [21] displayed a diffusion-controlled, one-electron reversible oxidation [22] at $E^{o\prime}$ = –0.005 V vs. ferrocene/ferrocenium reference (Fig. 3). Addition of MeI (10 equiv., 30 min) to the analysed solution left the redox response unchanged which is, indeed, in line with the observed reluctance of **1** towards alkylation. On the other hand, addition of HCl (as a methanol solution) led to immediate protonation at the nitrogen atom, which in turn resulted in a pronounced shift of the ferrocene/ferrocenium wave towards more positive potentials (ca. 275 mV with 5 equiv., and ca. 300 mV with 10 equiv. of added HCl), while not affecting its overall reversibility (Fig. 3) [23].

In summary, we have succeeded in preparing of a new type of ferrocene–amino acid conjugate starting from simple precursors



Scheme 3. Preparation of ferrocenophane **1** and its picrate salt **2** (Hpic = 2,4,6-trinitrophenol).

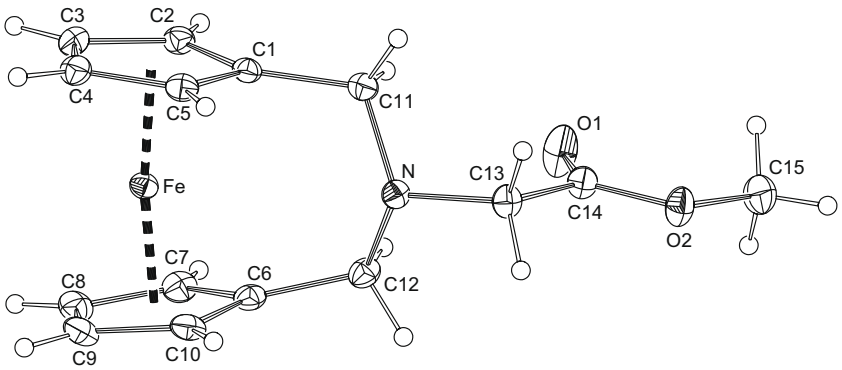


Fig. 1. View of the molecule of **1** showing displacement ellipsoids at the 30% probability level. Selected distances and angles: Fe–Cg1 1.6370(7), Fe–Cg2 1.6353(8), C1–C11 1.499(2), C6–C12 1.496(2), N–C11 1.471(2), N–C12 1.475(2), N–C13 1.454(2), C13–C14 1.518(2), C14–O1 1.201(2), C14–O2 1.332(2), O2–C15 1.445(2); ∠Cp1, Cp2 11.9(1), C11–N–C12 113.8(1), N–C13–C14 116.7(1), O1–C14–O2 123.5(2), C14–O2–C15 116.0(1). Definition of ring planes: Cp1 = C(1–5), Cp2 = C(6–10); Cg1 and Cg2 are the respective centroids.

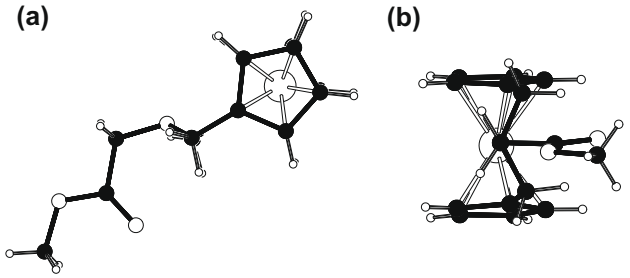


Fig. 2. Projections of the molecule of **1** along (a) the C1–C6 vector, and (b) the C13–N bond (for atom labelling, see Fig. 1).

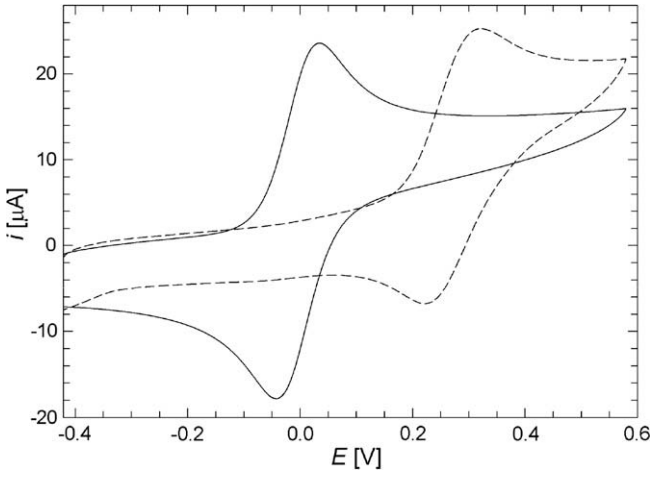


Fig. 3. Cyclic voltammograms of **1** before (solid line) and after (dashed line) addition of 5 equiv. of HCl (recorded in acetonitrile on Pt electrode, 100 mV s^{-1} scan rate).

and using the known synthetic protocol. Although validated only for glycine, this method most likely represents a general approach to structurally unique amino acid derivatives that contain the redox-active ferrocene moiety.

Ferrocenophane **1**, was characterised by a combination of combustion analysis and common spectroscopic methods, and its formulation was corroborated by X-ray crystallography. Cyclic voltammetry measurements have shown the compound to undergo one-electron reversible electron oxidation, presumably at the ferrocene moiety. Upon protonation, this oxidation expectedly becomes more difficult, which is reflected by a shift of the associated redox wave towards more positive potentials. In the case of the related N-methyl derivative (**IV**, R = Me), a shift +380 mV was noted for the ferrocene/ferrocenium wave upon protonation with $H[BF_4]$ in the same solvent [4].

Supplementary material

CCDC 746701 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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[8] A solution of $[RuCl_2(PPh_3)_3]$ (27 mg, 0.03 mmol, 3.5 mol.%) in dry 1-methyl-2-pyrrolidone (1.5 mL) was added to solid 1,1-bis(hydroxymethyl)ferrocene (200 mg, 0.81 mmol) and $[H_3NCH_2CO_2Me]Cl$ (110 mg, 0.88 mmol). After stirring at room temperature under Ar atmosphere for 5 min, triethylamine (0.2 mL, 1.76 mmol) was introduced and the mixture was heated at 170 °C in the dark for 24 h. Then, the volatiles were removed under vacuum and the dark residue was extracted with ethyl acetate. Some insoluble by-products were separated by filtration and the extract was purified by column chromatography (silica gel, hexane:ethyl acetate, 5:1 v/v). The second band was collected and evaporated to afford analytically pure **1** as a yellow solid (24 mg, 10%). The first minor band contains mostly 2-oxa[3]ferrocenophane according to NMR spectra [9].
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[11] Glycine methyl ester is formed *in situ* from glycine methyl ester hydrochloride and triethylamine.
[12] *Analytical data for* **1**: ^{1}H NMR ($CDCl_3$, 400 MHz, $SiMe_4$): δ 3.10 (s, 4H, $C_5H_4CH_2$), 3.66 (s, 2H, CH_2CO_2Me), 3.75 (s, 3H, OMe), 4.09 and 4.12 (2 × apparent t, $J' \approx 1.8$ Hz, 4H, C_5H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz, $SiMe_4$): δ 51.20 ($C_5H_4CH_2$), 51.42 (OMe), 58.77 (CH_2CO_2Me), 69.27 and 69.95 (CH of C_5H_4); 83.15 (C_{ipso} of C_5H_4), 171.65 (CO_2Me). IR (Nujol): ν_{CH} 3101 w, 3094 w, 3080 m; $\nu_{C=O}$ 1739 vs; 1299 m, 1287 w, 1229 w, 1197 vs, 1174 vs, 1144 vs, 1113 m, 1039 s, 1026 s, 996 s, 931 m, 854 s, 849 s, 819 w, 812 w, 801 s, 773 s, 688 m, 569 m, 540 m, 510 vs cm^{-1}. ESI + MS: *m/z* 300 ($[M + H]^+$), 322 ($[M + Na]^+$). Anal. Calc. for $C_{15}H_{17}FeNO_2$: C, 60.22; H, 5.73; N, 4.68%. Found: C, 60.00; H, 5.61; N, 4.57%.
[13] Orange prism from hot heptane (0.05 × 0.25 × 0.25 mm^3). The diffraction data were collected with a Nonius KappaCCD diffractometer (Mo Kα radiation, λ = 0.71073 Å; θ_{max} = 27.5°) at 150(2) K. Crystallographic data: $C_{15}H_{17}FeNO_2$, M = 299.15 g mol^{-1}, orthorhombic, space group *Pccn* (no. 56), a = 12.1391(2) Å, b = 20.8244(3) Å, c = 10.4905(3) Å; V = 2651.9(1) $Å^3$, Z = 8, Total 36709 diffractions of which 3041 were unique (R_{int} = 4.6%) and 2598 observed according to $I_o > 2\sigma(I_o)$ criterion. The structure was solved by direct methods (SIR97 [14]) and refined on F^2 (SHELXL-97 [15]). All non-hydrogen atoms were refined with anisotropic displacement parameters; the hydrogens were included in their calculated positions. Refinement parameters: R (observed diffractions) = 2.93%, R (all data) = 3.72%, wR (all data) = 7.35%, residual electron density: 0.38, −0.37 e $Å^{-3}$.
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[16] Atoms defining the {C13, C14, O1, O2, C15} plane are coplanar within 0.01 Å.
[17] Unchanged **1** was recovered after reacting with an excess of MeI in acetonitrile overnight (5 mg (17 μmol) of **1** and 14 mg (0.1 mmol) of MeI in 1 mL of dry solvent).
[18] Compound **1** (5 mg, 17 μmol) and 2,4,6-trinitrophenol (Hpic; 4.5 mg, 20 μmol) were dissolved in ethyl acetate (1 mL). The mixture was layered with hexane (2 mL) and allowed to crystallise at room temperature. The separated deep red crystalline picrate **2** was filtered off, washed with pentane and dried under vacuum. The yield was not determined.
[19] M.p. 170–172 °C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$, 400 MHz, $SiMe_4$): δ 3.85 (s, 3H, OMe), 4.01 (br s, 4H, $C_5H_4CH_2$ or C_5H_4), 4.21 (s, 2H, CH_2CO_2Me), 4.28 (br apparent t, $J' \approx 1.8$ Hz, 4H, C_5H_4), 4.45 (br s, 4H, $C_5H_4CH_2$ or C_5H_4), 8.94 (s, 2H, $OC_6H_2(NO_2)_3$). ESI MS (methanol): *m/z* 300 ($[\mathbf{1} + H]^+$), 322 ($[\mathbf{1} + Na]^+$); 228 (pic^-), 479 ($[(pic)_2Na]^-$), 730 ($[(pic)_3Na_2]^-$). IR (neat; diffuse reflectance): ν 3115 w, 3096 w, 3085 m, 3078 w, 3007 m, 2995 w, 2970 w, 2947 m, ca.

2850–2599 composite m, 1866 w, 1751 s, 1629 s, 1615 s, 1567 s, 1556 s, 1521 m, 1493 s, 1457 m, 1447 w, 1432 s, 1364 m, 1321 vs, 1270 s, 1242/1235 m, 1212 m, 1161 s, 1075 s, 1044 m, 993 m, 964 m, 940 w, 931 s, 909 m, 865 w, 851 m, 811 m, 790 m, 747 m, 711 s cm^{-1}.

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[21] Electrochemical measurements were performed with a multipurpose potentiostat μAUTOLAB III (Eco Chemie) at room temperature using a standard three-electrode cell (platinum disc working electrode, platinum sheet auxiliary electrode, and saturated calomel reference electrode) and acetonitrile solutions (Aldrich, absolute) containing 1 mM of the analyte and 0.1 M $Bu_4N[PF_6]$ (Fluka, puriss. for electrochemistry). The solutions were deaerated with argon prior to the measurement and then kept under an argon blanket. The redox potentials are given relative to ferrocene/ferrocenium reference. Reactions with HCl and MeI were performed directly in the cell. The reagents were added to the analysed solution (0.7 M HCl in MeOH, neat MeI) and the mixture was stirred for 5 (HCl) or 30 min (MeI) to ensure complete reaction.

[22] The ratio of the anodic and cathodic peak currents (i_{pa}/i_{pc}) remained close to unity at scan rates (v) in the range 0.05–1 V s^{-1}, and the anodic peak current increased with the square root of the scan rate ($i_{pa} \propto v^{1/2}$). The observed separation of the anodic and cathodic peaks (ΔE_p = 75 mV at 100 mV s^{-1}) was close to that of ferrocene itself under the same conditions (ca. 70 mV).

[23] Some ill-defined peaks were observed in the cathodic region of the voltammogram.