Synthesis and electrochemistry of ferrocenemethylamine and its conjugated acid. Crystal structure of ferrocenemethylammonium chloride

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Abstract

Ferrocenemethylamine (2) is conveniently synthesized by reductive ammination of ferrocene carboxaldehyde (1) in methanolic solution. The crystal structure of ferrocenemethylamine hydrochloride (3) is reported. In the solid state, 3 possesses a layered N–H···Cl–H-bonded network, resulting in the formation of 4- and 8-membered rings of alternating nitrogen and chlorine atoms, with an interlayer separation of 9.17 Å. The one-electron oxidation potentials of 2 and 3 in nine solvents are reported (CHCl$_3$, MeCN, MeOH, acetone, DMF, THF, nitrobenzene, EtOH, ^{i}PrOH). The present results have been used to evaluate the effects of different solvent parameters, such as the solvent polarizability and the solvent dielectric constant, on the redox properties of 2 and 3. The redox properties of 3 depend on the dielectric constant ε of the solvent. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Ferrocenemethylamine; Redox behavior; Crystal structure

1. Introduction

We are interested in the electronic and electron transfer properties of ferrocene-modified amino acids and peptides. Using ferrocene carboxylic acid, we were able to modify the N-terminus of the peptide and obtain crystalline materials, which allowed us to probe structural influences on the electrochemistry of the ferrocenoyl group [1]. In order to probe directional effects that may control the electron transfer properties in peptides, we turned to ferrocenemethylamine (2). We are planning to use 2 as a C-terminal electrochemically active probe and will attach it to the C-terminus of a peptide using the DCC/HOBt protocol as outlined before [2]. We were surprised to find that its synthesis, reported recently, requires a multi-step synthesis giving the product in relatively low overall yield [3]. The synthesis of the higher homologue ferroceneethylamine

and other N-dimethylethylamines have been reported as early as the early 1960's [4]. They provided synthetic pathways to ferrocene derivatives with planar chirality and paved the way for the synthesis of substituted phosphinoferrocenes possessing planar chiralilty, which have recently gained widespread popularity as chiral ligands and auxillaries [5]. Other mono-N-substituted aminomethylferrocenes can be obtained from trimethyl-ammoniummethyl ferrocene by reaction with primary amines [6]. N-methylated ferrocene amine derivatives have been incorporated into larger systems and have been widely used as a sensitive electrochemical probes to detect structural changes taking place upon binding of charged and neutral molecules [3,7]. Furthermore they have found application as protecting groups in peptide synthesis. In a multicomponent condensation, N-methylated ferrocene amine derivatives have been incorporated into peptidic sidechains as the acid labile Fem group [8]. In this context the synthesis of ferrocenylalanine should be mentioned [9].

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The local environment (i.e. solvent) can significantly influence the kinetics of reactions and the thermodynamic properties of reactants [10]. Thus, to be able to fully understand the electronic properties of our electrochemical probe and perhaps being able to predict the thermodynamics of chemical reactions, we decided to study the influence of the local environment on the electrochemical properties of the ferrocene group in ferrocenemethylamine **2** and ferrocenemethylammonium chloride **3**.

Here, we report the convenient one-pot synthesis of **2** from commercially available ferrocene carboxaldehyde and full electrochemical characterization of the free base **2** and its conjugated acid ferrocenemethylammonium chloride (**3**), including a study of the solvation effects on the redox potential.

2. Results and discussion

The chemistry described in this paper is summarized in Scheme 1. Ferrocenemethylamine hydrochloride (**3**) was prepared in a simple one-pot reaction by reductive ammination of ferrocene carboxaldehyde (**1**) with $BH_3(CN)^-$ in the presence of NH_4^+ in methanolic solution. This procedure is similar to that described for the preparation of substituted piperidine amines from piperidones [11]. **3** serves as a convenient and stable form of ferrocene methylamine (**2**), which can be easily produced by treatment of **3** with excess triethylamine.

3 is an air-stable yellow solid, which can be obtained in a crystalline form by slow evaporation of solvent from a saturated methanolic solution. Van Leeuwen [3] recently described two methods for the formation of **2**, both involving the use of trimethylammoniomethyl ferrocene iodide. Its reaction with NH_3 at elevated temperatures is similar to that reported by Fabbrizzi and Lanfredi [6] involving the displacement of trimethylamine. In the second synthetic procedure of trimethylammoniomethyl ferrocene iodide is reacted with the potassium phthalimide to form 1-(phthalimidomethyl)ferrocene. This is then reacted with hydrazine to give the desired ferrocenemethylamine.

The ORTEP of **3** is shown in Fig. 1. Both Cp rings are close to coplanar with a small Cp–Fe–Cp bent angle of 1.7°. The intramolecular distances in the Cp rings are as expected for a substituted ferrocene [12]. The chloride Cl(1) is surrounded by three ferrocenylmethylammo-
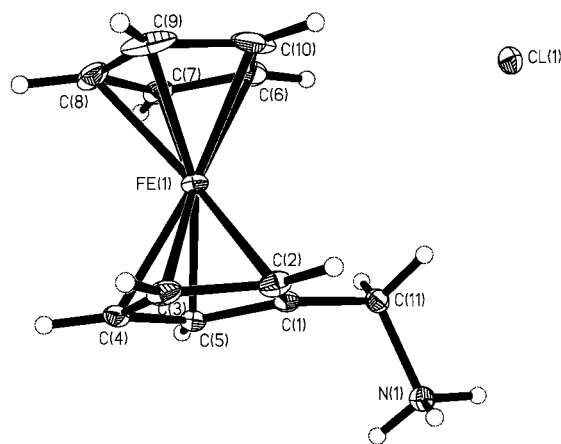

Fig. 1. ORTEP of **3**.

nium groups from three adjacent asymmetric units in a trigonal pyramidal fashion with N–Cl ranging from 3.162 to 3.218 Å. The positions of the H atoms were fully refined. The N–H distances in the ammonium group reflect the presence of hydrogen bonding interaction with the chloride anion [13] as one N–H distance (d(N–H) = 0.99(4) Å) is clearly elongated compared to the other two (d(N–H) = 0.81(6) and 0.86(5) Å). **3** crystallizes in a layered structure, having the cationic methylammonium group from two different layers pointing towards each other (Fig. 2). The chloride anions are in the ionic layer and are strongly hydrogen bonded to the ammonium groups. The organic ferrocene layers are separated by 9.17 Å. H-bonding in the ionic layer between the chloride anion and the ammonium group generates a two dimensional net of 4- and 8-membered rings of alternating Cl and N atoms. Within the 4-membered ring the Cl–N distances being 3.162 and 3.218 Å, with a Cl(1I)–N(1A)–Cl(1E) angle of 94.4° and a N(1A)–Cl(1E)–N(1E) angle of 122.7°. Within the 8-membered ring, the C–N bonds alternate between 3.188 and 3.218 Å. The angles range from 112.5 to 124.8°. The chlorides within a layer are separated by 4.680 Å.

Next we proceeded to investigate the redox chemistry of **2** and **3** and found that they are influenced by the solvent. Solvent influences on the electronic properties of substituted ferrocenes, other organometallic systems and coordination compounds has been studied in detail [14]. Using cyclic voltammetry (CV) we investigated the redox properties of **3** in various solvents and generated the free amine **2** in situ by adding Et_3N to the solution. The results of our CV study are summarized in Table 1. Both **2** and **3** exhibited fully reversible one-electron oxidation waves in most solvents with peak separations ranging from 70 to 90 mV, being within the acceptable limits for reversible one-electron processes [15]. However, there were notable exceptions: **3** only gave an irreversible oxidation wave in DMF at a scan speed of
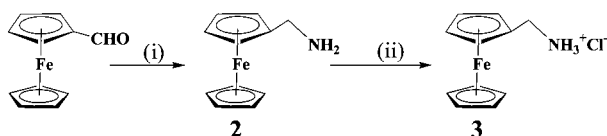
Scheme 1. Synthesis of ferrocene methylamine **2** and ferrocene methylammonioum chloride **3**. (i) a. NH₄OAc, NaBH₃(CN), MeOH; b. KOH; (ii) HCl.
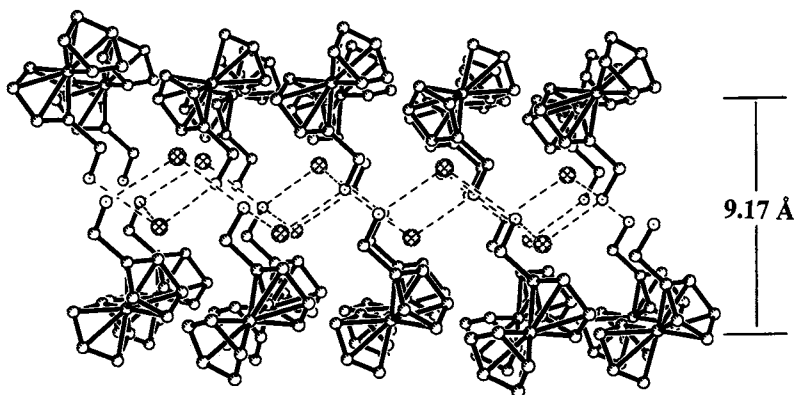
Fig. 2. Hydrogen bonding in **3**: the layered structure of **3**. Shown is a view of the two organometallic layers sandwiching the ionic layer of chloride anions and methylammonium groups.

100 mV s^{-1} and hence it is omitted from Table 1. The redox chemistry of ferrocene in DMF, other strong donor solvents or in the presence of halide anions is irreversible. Under these conditions, the ferrocenium cation will react with the solvent (or the nucleophile) giving rise to free Fe$_3^+$ and organic coupling products [16]. In CHCl$_3$, MeCN and nitrobenzene (NBz) **2** and **3** exhibited a quasireversible one-electron oxidation at a scan rate of 100 mV s^{-1}, with peak separations between the anodic and cathodic peak current in the range of 150–200 mV. At higher scan rates (above 500 mV s^{-1}) the peak becomes fully reversible, as expected for a quasi-reversible process [15]. As would be expected, the electron-rich ferrocene moiety in **2** is easier to oxidize than the one bearing the electron-withdrawing methylammonium group (**3**). It should be noted at this point that Shalev and Evans [17] reported the potential of the ferrocene/ferrocenium couple to be virtually independent of the solvent (THF, DMF,

MeCN, DMSO, and MeOH). More recently, Hupp [14a] pointed out the shortcoming of this assumption and showed that the redox potential of ferrocene will depend on the degree of association of the ferrocenium cation with the counterion and its activity in a particular solvent. For **2** and **3** a significant solvent influence of the redox potential is observed. For **3** there is a shift in the half-wave potential of about 100 mV on going from CHCl$_3$ (608 mV vs. Ag | AgCl) to acetonitrile (510 mV). Similarly, the half-wave potential for **2** exhibits a strong solvent influence and shifts from 572 mV (versus Ag | AgCl) in THF to 423 mV in MeOH. The explanation for this behavior is a change in the solvation energy between oxidized and reduced state, as was described in detail by others. Unfortunately, in the absence of gas phase electron affinities for **2** and **3**, we are unable to calculate the exact values for ΔG°_{sol}, and hence can only give a qualitative discussion of the solvation effects. As shown in Fig. 3, the reversible one-electron redox potential of **3** shows a clear dependence on the solvent dielectric constant ε. Despite the rather poor correlation, there is a clear trend showing

Table 1
Redox potentials ($E_{1/2}$ in mV) of ferrocenemethylamine **2** and ferrocene methylammonium chloride **3** and list of selected solvent parameters (the solvent dipole moment μ, the solvent dielectric constant ε)[a]

Solvent	$E_{1/2}$*		Solvent parameters	
	2	**3**	ε	μ
CHCl$_3$	510	608	4.7	1.01
THF	572	603	7.3	1.63
^{i}PrOH	451	578	18.3	1.66
Acetone	512	560	20.7	2.88
EtOH	456	582	24.3	1.69
MeOH	423	538	32.6	1.70
NBz	490	529	35	4.22
MeCN	433	510	36.2	3.92
DMF	529	–	36.7	3.82

[a] Listed according to increasing ε of the solvent.

* Potentials are measured versus an Ag | AgCl reference electrode in 0.1 M TBAP in dry solvents using a scan rate of 100 mV s^{-1}.
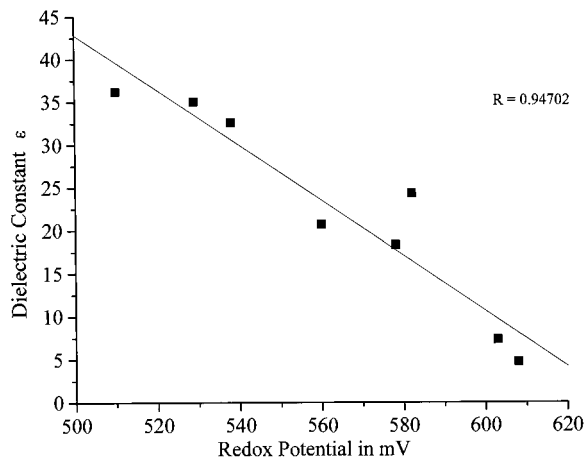

Fig. 3. Dependence of the redox potential of **3** of the dielectric constant ε of the solvent.

that **3** becomes easier to oxidize as ε of the solvent decrease. This result is perhaps not too surprising since oxidation of **3** will result in the formation of a dication, which may have strong electrostatic interactions with a solvent having a high ε and a high μ. The interaction between the ferroceniummethylammonium dication **3**$^+$ and the anion of the supporting electrolyte may be a significant contributor to the observed solvent effect as is the case for ferrocene, where solvent depend shifts of up to 229 mV have been observed [14a]. In addition, various degrees of self-association of **3** and the differences in solvation of **3** may contribute to the observed solvent influence [18].

Surprisingly, the redox behavior of **2** seems not to dependent on μ and ε of the solvent (Table 1). Other empirical solvent parameters [19] such as Gutmann's AN, Reichhardt's ET(30) and Kosover's Z give only poor correlations. The redox behavior of **2** does not exhibit a convincing dependence with any of the Kamlet–Taft parameters [20], such as the hydrogen donor ability of the solvent α, the hydrogen (electron pair) acceptor abililty of the solvent β or the polarity/polarizability parameter π^*. This is surprising, since the Kamlet–Taft linear solvation energy relationship (LSER) [20] has been successfully applied by others to describe a variety of properties, such as the rate of a reaction, the free energy and enthalpy of an equilibrum and the solubility [20,21]. At present, we cannot rationalize the observed redox behavior of **2** but suggest that specific interactions with the solvent are responsible for the observed behavior.

Future experiments are aimed at exploring the redox behavior of ferrocenemethylamine- and ferrocenoyl-modified peptides and possible solvent influences on their redox behavior.

3. Experimental

3.1. General

Ferrocenecarboxaldehyde, NH_4OAc, KOH and $NaBH_3(CN)$ were used as received (Aldrich). All solvents were used as received without further treatment, except where noted. ^{1}H-NMR spectra were recorded at 200.132 MHz on a Bruker AC200 NMR spectrometer. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. The ^{1}H chemical shifts are relative to tetramethylsilane ($\delta = 0.00$ ppm), which was added as an internal standard. All measurements were carried out at 293 K.

3.2. Preparation of ferrocenemethylamine hydrochloride (3)

Solid ammonium acetate (7.7 g, 0.1 mol) was added to a cooled solution (0°C) of ferrocenecarboxaldehyde (2.14 g, 10 mmol) in methanol (100 ml) and stirred for 30 min. $NaBH_3(CN)$ (0.44 g, 7 mmol) was added to the cold solution. After stirring overnight, the volume of the solution was reduced in vacuo to about 20 ml and water (10 ml) was added. The pH of the solution was adjusted with 1 N HCl to pH 2. Then solid KOH was added until pH 8 was reached (about 2 g). The resulting dark-brown solution was extracted with CH_2Cl_2 (4×50 ml). The organic phase was collected, washed with water (3×50 ml), dried over anhydrous $MgSO_4$ and then pumped to dryness to yield a brown oily solid (2.1 g). The material was redissolved in MeOH (10 ml) and 1N HCl (5 ml) was added and then pumped to dryness. The crude product was dissolved in a minimal amount of MeOH and transferred onto an alumina plug (5 cm; Brockmann Activity V). Impurities were removed using CH_2Cl_2 as an eluant. The product was eluted using MeOH. After evaporation of the solvent in vacuo, **3** was obtained as a yellow microcrystalline solid (yield: 1.95 g; 78%). Crystallographic quality crystals were obtained by slow evaporation of MeOH from a saturated solution at room temperature. ^{1}H-NMR (δ in ppm, $CDCl_3$): 4.19 (2H, s, ortho H of Cp), 4.10 (5H, s, unsubstituted Cp ring), 4.05 (2H, s, meta H of Cp), 3.54 (2H, s, CpCH_2N), 1.81 (3H, br s, $-NH_3$). Electrospray MS analysis after adding excess Et_3N to a methanolic solution of **3**: Calc. for $C_{11}H_{13}NFe$ (**2**): 215.1. Found 216.0.

3.3. Electrochemical studies

All electrochemical experiments were carried out using a CV-50W Voltammetric Analyzer (BAS) at room temperature. No special precautions were take to exclude oxygen. All solvents were dried using the appropriate drying agents ($CHCl_3/CaH_2$; MeOH/Mg; $MeCN/CaH_2$; acetone/Na_2SO_4/molecular sieves; EtOH/Na; ^iPrOH/Na; DMF/$MgSO_4$/molecular sieves, THF/Na/benzophenone, nitrobenzene/Na_2SO_4/ molecular sieves) and freshly distilled prior to use. Tetrabutylammonium perchlorate (TBAP) was used as supporting electrolyte (0.1 M). For the cyclic voltammetry studies a glassy carbon working electrode (BAS, diameter 2 mm) and a platinum wire counter electrode were used. The reference electrode was a Ag|AgCl electrode (BAS). IR compensation was applied. Backgrounds of the solvent containing 0.1 M TBAP were collected before each set of experiments and then subtracted from the spectra.

3.4. Structural studies

All pertinent crystallographic information is summarized in Table 2. A yellow crystal of **2** was mounted on a glass fiber using epoxy resin. Data collection pro-

Table 2
Crystal data for $[FcCH_2NH_3]^+Cl^-$ (**3**)

Compound	$[FcCH_2NH_3]^+Cl^-$ **(3)**
Empirical formula	$C_{11}H_{14}ClFeN$
F_w	251.53
Space group	*Pbca* (# 61)
a (Å)	9.1710 (3)
b (Å)	9.2025 (3)
c (Å)	25.1420 (8)
V (Å^3)	2121.89 (12)
Z	8
ρ_{calc} (g cm^3)	1.575
Crystal size (mm)	$0.70 \times 0.55 \times 0.50$
μ, Mo–K$_\alpha$ (cm^{-1})	16.3
Radiation (monochromated in incident beam)	Mo–K$_\alpha$ (0.71073 Å)
Reflections collected	2763
Reflections observed ($I > 2\sigma(I)$)	2197
GOF	1.102
Final R, R_w[a] ($I > 2s(I)$)	0.0423, 0.0744
Final R, R_w[a] (all data)	0.0610, 0.0813

[a] $R = \Sigma(|F_o| - |F_c|)/\Sigma(|F_o|)$; $R_w = [\Sigma(w(|F_o| - |F_c|)2/\Sigma(w|F_o|2)]^{1/2}$

ceeded at room temperature on a CAD4 diffractometer (Mo–K$_\alpha$). The data were collected up to a 2θ limit of 57.5°, using the omega scan mode. Of 2763 reflections measured, 2197 were observed ($I > 2\sigma(I)$). An empirical absorption correction was applied. The merging R value on significant intensities was 0.019. The cell parameters were determined from 20 well-centered reflections. The refinement was carried out with the SHELXTL program suite [22]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located in the density map and were refined with isotropic temperature factors. Weights based on statistics were used. The refinement (based on F^2_{obs}) converged to $R = 0.0423$, $R_W = 0.0744$. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 112049 for compound **3**. Copies of this information may be obtained from of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ UK, Fax: + 44-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk.

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