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ORIGINAL RESEARCH PAPER

N^6,9-BIS(FERROCENYLMETHYL)ADENINE: SYNTHESIS, CYCLIC VOLTAMMETRIC, SPECTROSCOPIC CHARACTERIZATION, AND DFT CALCULATIONS

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Abstract: In this paper we investigate the synthesis of N^6,9-bis(ferrocenylmethyl)adenine starting from the well known quaternary salt (ferrocenylmethy)trimethylammonium iodide and adenine. The obtained compound was characterized by different analytical techniques like: cyclic voltammetry, electronic absorption FT-IR, and ^{1}H NMR spectroscopy. The cyclic voltammogram shows well distinct, stable and reversible redox peaks for the couple ferrocenium-ferrocene in the studied potential range. The lower standard rate constant values of the N^6,9-bis(ferrocenyl-methyl)adenine as compared to ferrocene further indicated slower electron transfer kinetics. UV-Vis measurements show three absorption bands attributed to the transitions n→π* and π→π* of aromatic ring and the imine group for N^6,9-bis(ferrocenylmethyl)adenine derivative. Finally the energy of border molecular orbitals (E_{HOMO} and E_{LUMO}) of the optimized structure was calculated using DFT/B3LYP method combined with 6-31G basis set in acetonitrile.

Keywords: *adenine, electrochemistry, Nicholson equation, nucleobase, rate constant, UV-Vis spectroscopy*

INTRODUCTION

The discovery of the first recognized sandwich compound, ferrocene, and determination of its remarkable stable structure in the 1950s has opened an entire new area of research in the field of organometallic chemistry, and since that time ferrocene chemistry has developed very quickly and become an independent area of chemistry which links conventional organic chemistry to organometallic chemistry [1, 2]. The non-toxicity of ferrocene, the stability of the ferrocenyl group of ferrocene derivatives in aqueous solutions, the ease of the synthesis of a large diversity of ferrocene derivatives, and its exceptional electrochemical properties have revolutionized ferrocene chemistry and have made ferrocene derivatives very interesting molecules for biological applications and medicinal chemistry [3, 4]. Ferrocene derivatives are also known to display antitumor activity; such activity would be likely to be depending on the functionalities attached to the ferrocenyl group [5 – 7]. Among these functionalities are nucleobases which, when attached to ferrocenyl group, could provide considerable scope for the preparation of ferrocene derivatives capable of binding to DNA or RNA and other key cellular targets via non-covalent bonds. However, the chemistry of ferrocenylmethylnucleobases [8 – 10] is still an undeveloped area compared with well-established classical medicinal chemistry of purely organic nucleobase derivatives [11 – 15]. The first ferrocenylmethyl-nucleobase was synthesized by Chen in 1980 [16] who prepared the compound 9N-(ferrocenylmethyl)adenine from the reaction of 6-chloropurine and ferrocenylmethyl-amine in methosyethanol. After that numerous ferrocenylmethylnucleobases and ferrocene-modified nucleosides were described [17 – 20]. In addition, the anticancer activity of many ferrocenylmethylnucleobases was evaluated in vitro and in vivo using electrochemical and spectroscopic assays [21, 22], ferrocenylmethylnucleobases also have been used as a useful set of building blocks for supramolecular chemistry due to their capacity for base-pair hydrogen bonding allied with redox properties [23].
Herein we describe the synthesis, characterisation, DFT calculation and electrochemical behavior of the complex N^6,9-bis(ferrocenylmethyl)adenine. The compound was prepared from the reaction of adenine with an excess of (ferrocenylmethy)trimethyl-ammonium iodide which can be either obtained commercially or easily prepared according to a known scientific literature procedure [24].

MATERIALS AND METHODS

Reagents

Adenine (99 %) and tetrabutylammonium tetrafluoroborate (99 %) were purchased from Sigma-Aldrich (Finland)), ferrocene (99 %) and orthophosphoric acid (85 %) were purchased from Alfa Aesar (Germany), magnesium sulphate anhydrous (97 %) and iodomethane were purchased from Acros Organics (Belgium), ethanol (95 %) and acetic acid (99-100 %) were purchased from Biochem Chemopharma Co (Canada). All other reagents used were of analytical grade.

Synthesis

(Ferrocenylmethyl)trimethylammonium iodide was prepared according to literature procedures [24].

N^6,9-bis(ferrocenylmethyl)adenine

Adenine (270 mg, 2 mmol) was added in small portions to well-stirred solution of trimethylferrocenylmethylammonium iodide (1.75 g, 4.5 mmol) in water (100 cm^3). The resulting mixture was then heated to reflux temperature under an atmosphere of nitrogen for 6 hours. It was then allowed to cool to room temperature. The resulting yellow precipitate was separated by filtration, washed with water to remove any trace of unchanged quaternary ammonium salt. The crude product was chromatographed on neutral alumina using chloroform as eluent to produce a yellow precipitate which was recrystallized from a mixture of acetonitrile/methanol to yield N^6,9-bis(ferrocenylmethyl)adenine (1.52 g, 63 %), m.p. 244 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.1 (10H, s, η^5-C_5H_5), 4.2 (4H, t, *β* protons of η^5-C_5H_4), 4.3 (4H, t, *α*-protons of η^5-C_5H_4), 4.37 (2H, d, J= 3 Hz, HN-CH_2), 5.6 (1H, br s, NH), 5.8 (2H, s, N-CH_2), 7.7 (1H, s, =N-CH=), 8.5 (1H, s, =N-CH=).

IR (KBr, *ν*, cm^{-1}): 3585-3265, 3120-3080, 1610, 1410, 1110, 1020, 850, 775, 490.

RESULTS AND DISCUSSION

Synthesis

N^6,9-bis(ferrocenylmethyl)adenine was synthesized in a two-step starting from ferrocene. In the first step the well known quaternary salt (ferrocenylmethy)trimethylammonium iodide was prepared via the aminomethylation reaction of ferrocene [24], then in the second step an excess of the quaternary salt was reacted with adenine to produce a mixture of three products, the major product was identified as the target compound N^6,9-bis(ferrocenylmethyl)adenine. The molecular structure of the obtained compound is presented in Figure 1.

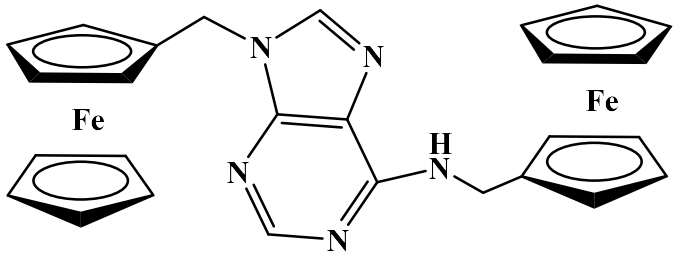

Figure 1. *Molecular structures of N^6,9-bis(ferrocenylmethyl)adenine*

Cyclic voltammetry characterization

Cyclic voltammetry was employed to access electrochemical characteristics of N^6,9-bis(ferrocenylmethyl)adenine. Measurements were performed on a PGZ301 potentiostat/galvanostat (Radiometer Analytical SAS, France)) using a three-electrode

electrochemical cell of 25 mL containing a glassy carbon (GC) working electrode with a geometric area of 0.013 cm^2, a platinum wire counter electrode of surface area 0.05 cm^2, and an Hg/Hg_2Cl_2 reference electrode (saturated with KCl). The potential was swept starting from -0.2 to 1.2 V with a scanning rate of 100 $mV \cdot s^{-1}$. All electrochemical experiments were performed in acetonitrile under nitrogen atmosphere at 298 K. Tetrabutylammonium tetrafluoroborate (TBATFB) was used as supporting electrolyte and its concentration was kept 0.1 M. The obtained voltammogram is presented in Figure 2.

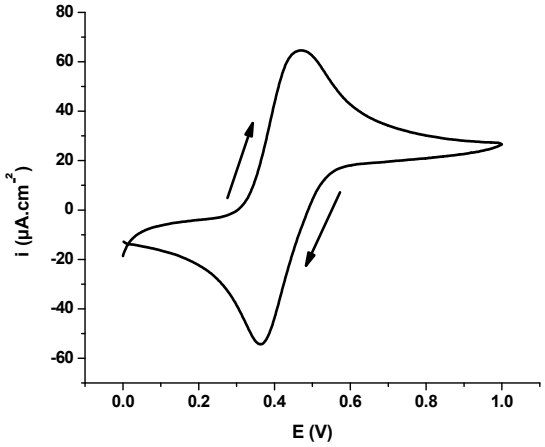

Figure 2. *Cyclic voltammogram of 10 mM of N^6,9-bis(ferrocenylmethyl)adenine on GC electrode in 0.1 M TBATFB/acetonitrile at scan rate 0.1 $V.s^{-1}$ at 298K*

The voltammogram in Figure 2 shows a couple of well distinct, stable and reversible redox peaks in the studied potential range, the anodic and cathodic peak potentials were appeared at 0.469 and 0.357 V. The formal potential, 0.413 V, is greater compared to ferrocene, 0.287 V, under similar conditions. This shift may be explained to the electron withdrawal effect of the adenine nucleobase introduced to the cyclopentadienyl ring of ferrocene. The peak to peak separation ΔEp = Epa-Epc was, however, notably higher than the acceptable value of 60 mV for a totally reversible one-electron processes. This could be due to the uncompensated solution resistance. The anodic and cathodic peak current ratio of 0.90 is indicative of reversible electrochemical process, Table 1.

Table 1. *Electrochemical parameters for the oxidation of ferrocene and N^6,9-bis(ferrocenylmethyl)adenine*

Entry	Epa [V]	Epc [V]	Ipa[mA]	Ipc[mA]	ΔEp[mV]	E0[V]	ipa/ipc
Fc*	0.324	0.251	0.259	-0.240	73	0.287	0.85
$(FcMe)_2Ad$*	0.469	0.357	0.065	0.072	112	0.413	0.90

**Fc and $(FcMe)_2Ad$ refer to ferrocene and N^6,9-bis(ferrocenylmethyl)adenine*

The diffusion coefficient of N^6,9-bis(ferrocenylmethyl)adenine in acetonitrile was calculated based on the trace of the intensity of the peak current as function of the square root of the scan rates of Figure 3 using the following Randles-Sevcik equation (1) [25];

$$ip_a = 2.69\times10^5 \left(\sqrt{n}\right)^3 SC\sqrt{D}\sqrt{v} \quad (1)$$

where i is the peak current (A), n is the number of electrons transferred during the oxidation, S is the surface area of the electrode (cm^2), C is the bulk concentration ($mol\cdot cm^{-3}$) of the electro-active spice, D is the diffusion coefficient ($cm^2\cdot s^{-1}$), and v is the scan rate ($V\cdot s^{-1}$).

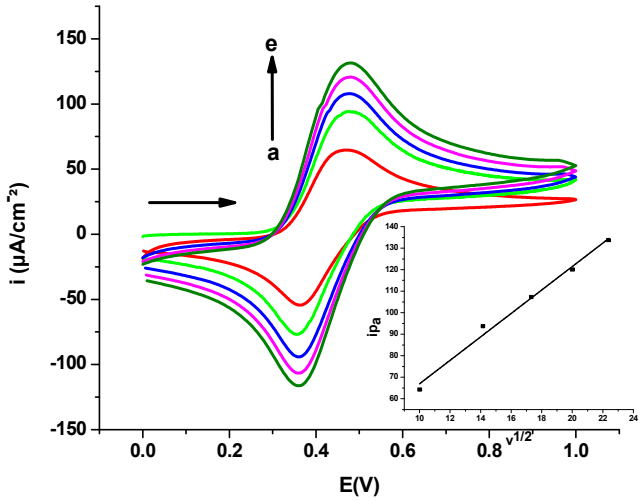

Figure 3. *Cyclic voltammetric behavior of 10 mM of N^6,9-bis(ferrocenylmethyl)adenine on GC electrode in 0.1 M TBATFB/acetonitrile at scan rates 0.5(e), 0.4(d), 0.3(c), 0.2 (b) and 0.1(a)$V\cdot s^{-1}$ at 298K. The vertical arrowhead indicates increasing scan rate. Inset: Plots of $\sqrt{v}$ versus ip_a used to calculate the coefficient diffusion of N^6,9-bis(ferrocenylmethyl)adenine*

The plot of the square root of the scan rates versus the anodic peak current density, (Figure 3), suggests that the redox process is diffusion controlled. The value of the diffusion coefficient, D = 2.43×10^{-7} $cm^2\cdot s^{-1}$, was deducted from the slope of the linear regression of equation (1). This value is higher than that of ferrocene under the same conditions (1.56×10^{-7} $cm^2\cdot s^{-1}$) which can be attributed to the higher molecular weight of the complex N^6,9-bis(ferrocenylmethyl)adenine compared to ferrocene.

The value of standard rate constant of the electron transfer reaction of N^6,9-bis(ferrocenylmethyl)adenine at the electrode surface was calculated from the following Nicholson's equation [26],

$$\Psi = \frac{K_s}{\sqrt{\pi D \frac{nFv}{RT}}} \quad (2)$$

ψ is a dimensionless parameter, it can be obtained from scientific literature [27], v is the scan rate, 0.1 $V\cdot s^{-1}$, D is the diffusion coefficient of the electro-active spice, F is the faraday constant, 96500 $C\cdot mol^{-1}$, n is the number of electrons transferred during the oxidation, R is the gas constant, 8.32 $J\cdot mol^{-1}\cdot K^{-1}$ and T is the absolute temperature, 298K. The obtained values of Ks was found to be equal to 0.84×10^{-3} $cm\cdot s^{-1}$ for N^6,9-

bis(ferrocenylmethyl)adenine and 2.88×10^{-3} $cm\cdot s^{-1}$ for ferrocene . The magnitude of the standard rate constant is due to the reversible character of the redox processes with slow electron transfer kinetics. The sequence ferrocene > N^6,9-bis(ferrocenylmethyl)adenine of the Ks values, indicates that the fast diffusing ferrocene with no methyladenine is more favorable for electron transfer than compound N^6,9-bis(ferrocenylmethyl)adenine. The slow electron transfer of N^6,9-bis(ferrocenylmethyl)adenine may be due to the bulky methyladenine group attached to the ferrocenyl group.

Electronic Spectroscopy Characterization

Electronic spectra measurements were carried out on a UV-Vis spectrometer, (Shimadzu 1800, Japan). The spectroscopic response of 10 mM of N^6,9-bis(ferrocenylmethyl)-adenine in acetonitrile was recorded at 298K. Three absorption bands were observed at 322, 380 and 449 nm, Figure 4, the first two bands at 322 and 380 nm are attributed to the transitions n→π* of aromatic ring. The third band at 449 nm corresponds to π →π* electronic transitions of the imine group, Figure 4.

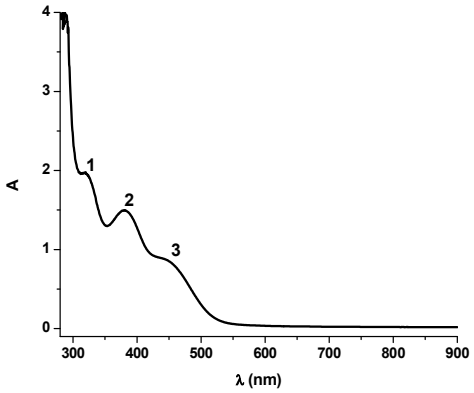

Figure 4. *UV-visible absorption spectra of 10 mM of N^6,9-bis(ferrocenylmethyl)adenine in acetonitrile at 298K*

DFT Calculations

All computational studies were conducted with the Gaussian-09 Revision C.01 program package and the GaussView 5 molecular visualization program [28, 29].
The molecular structure of N^6,9-bis(ferrocenylmethyl)adenine in acetonitrile was optimized without any symmetry restrictions by density functional theory / The Becke's three parameter hybrid functional and Lee-Yang-Parr correlation functionals (DFT/B3LYP) with the basis set 6-31G [30 – 32].
The geometry optimized structure of N^6,9-bis(ferrocenylmethyl)adenine obtained from DFT calculations is shown in Figure 5 and the corresponding bond lengths are tabulated in Table 2.

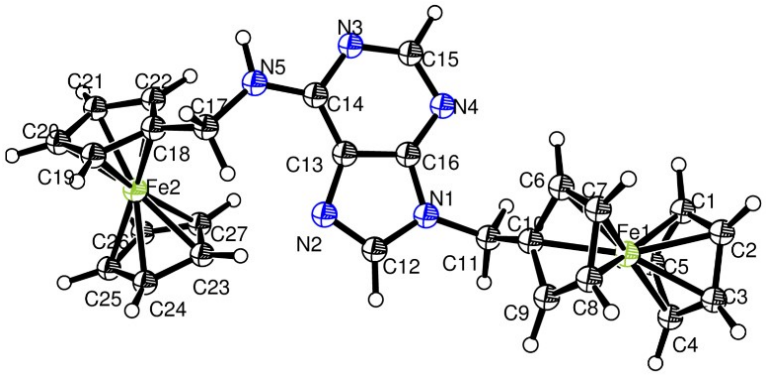

Figure 5. *ORTEP representation of N^6,9-bis(ferrocenylmethyl)adenine. Displacement ellipsoids are drawn at the 30 % probability level and H atoms are shown as small spheres of arbitrary radii*

Table 2. *List of calculated bond lengths of N^6,9-bis(ferrocenylmethyl)adenine*

Atoms A-B	length [Å]	Atoms A-B	length [Å]	Atoms A-B	length [Å]
Fe1-C1	2.080	C9-C10	1.440	C20-C21	1.434
Fe1-C2	2.080	C10-C11	1.500	C21-C22	1.434
Fe1-C3	2.081	C11-N1	1.475	C22-C18	1.438
Fe1-C4	2.083	N1-C12	1.388	C23-C27	1.436
Fe1-C5	2.081	C12-N2	1.328	C23-C24	1.436
Fe1-C6	2.075	N2-C13	1.404	C24-C25	1.436
Fe1-C7	2.083	C13-C14	1.417	C25-C26	1.436
Fe1-C8	2.081	C14-N3	1.368	C26-C27	1.436
Fe1-C9	2.075	N3-C15	1.349	Fe2-C18	2.089
Fe1-C10	2.065	C15-N4	1.351	Fe2-C19	2.075
C1-C2	1.435	N4-C16	1.350	Fe2-C20	2.074
C1-C5	1.435	C16-C13	1.408	Fe2-C21	2.074
C2-C3	1.436	C16-N1	1.384	Fe2-C22	2.078
C3-C4	1.435	C14-N5	1.357	Fe2-C23	2.080
C4-C5	1.436	N5-C17	1.463	Fe2-C24	2.080
C6-C7	1.432	C17-C18	1.511	Fe2-C25	2.082
C6-C10	1.440	C18-C19	1.440	Fe2-C26	2.083
C7-C8	1.437	C19-C20	1.436	Fe2-C27	2.080
C8-C9	1.434				

Figure 6 shows a schematic representation of the energies of molecular orbitals and contours of lowest unoccupied molecular orbitals (LUMOs) and highest occupied molecular orbital (HOMOs) of N^6,9-bis(ferrocenylmethyl)adenine. The HOMO to LUMO energy gap in N^6,9-bis(ferrocenylmethyl)adenine is -4.560 eV. Here it is observed that both the LUMOs and HOMOs are composed of both the ferrocene moiety and the adenine orbitals.

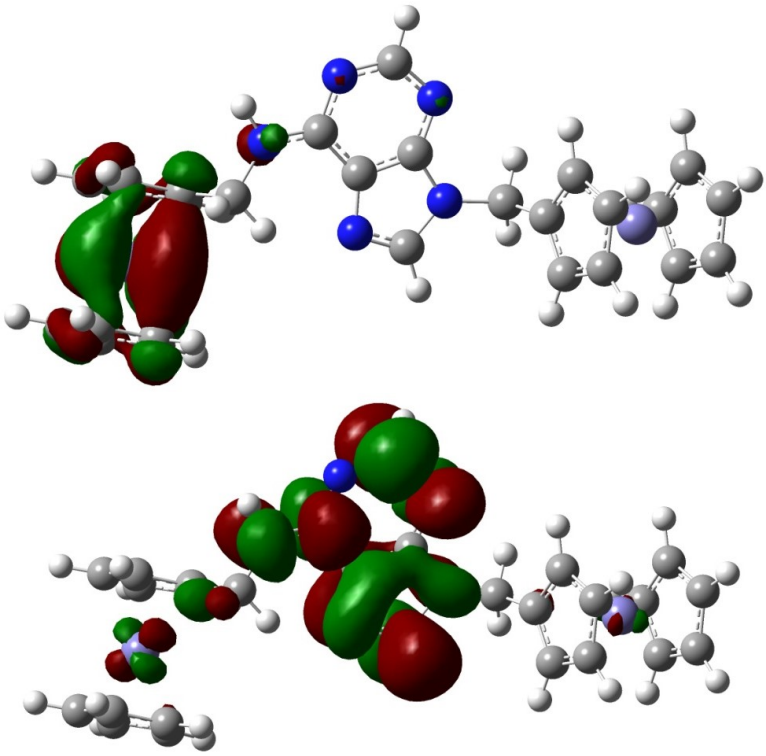

Figure 6. *The molecular orbital energy and frontier of the molecular orbitals of N^6,9-bis(ferrocenylmethyl)adenine*

Other parameters including separation energies ΔE, absolute hardness η, absolute electronegativities, χ, chemical potentials, Pi, absolute softness, σ, global softness S, global electrophilicity, Ω, and additional electronic charge, ΔN_{max}, have been calculated according to the following equations (3-10) [33]:

$$\Delta E = E_{LUMO} - E_{HUMO} \tag{3}$$

$$\eta = \frac{\Delta E}{2} \tag{4}$$

$$\chi = \frac{-E_{HUMO} - E_{LUMO}}{2} \tag{5}$$

$$Pi = -\chi \tag{6}$$

$$\sigma = \frac{1}{\eta} \tag{7}$$

$$S = \frac{1}{2\eta} \tag{8}$$

$$\Omega = \frac{Pi^2}{2\eta} \tag{9}$$

$$\Delta N_{max} = \frac{-Pi}{\eta} \tag{10}$$

Table 4. *The calculated quantum chemical parameters for the investigated N^6,9-bis(ferrocenylmethyl)adenine and ferrocene*

Entry	E_{LUMO}	E_{HUMO}	ΔE [eV]	η [eV]	χ [eV]	Pi [eV]	σ [eV^{-1}]	S [eV^{-1}]	Ω [eV]	ΔN_{max}
Fc*	-0.697	-5.632	4.935	2.47	3.16	-3.16	0.41	0.20	2.03	1.28
$(FcMe)_2Ad$*	-1.129	-5.689	4.560	2.28	3.41	-3.41	0.44	0.22	2.55	1.50

**Fc and $(FcMe)_2Ad$ refer to ferrocene and N^6,9-bis(ferrocenylmethyl)adenine*

CONCLUSIONS

N^6,9-bis(ferrocenylmethyl)adenine was synthesized and structurally characterized by cyclic voltammetry and spectroscopic techniques and have been optimized through DFT calculations in acetonitrile. Redox studies of the compound in acetonitrile reveal one reversible Fe(II)/Fe(III) oxidative couple. The standard rate constant was determined by the application of Nicholson equation, the lower *Ks* value of the N^6,9-bis(ferrocenylmethyl)adenine as compared to ferrocene indicated slower electron transfer kinetics. Moreover, the energy of contours molecular orbitals E_{HOMO} and E_{LUMO} of the studied compound was determined using DFT/B3LYP method combined with 6-311++G(d,p) basis set in acetonitrile.

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