# Ethyl 5-ferrocenyl-1*H*-pyrazolecarboxylates: the synthesis and redox properties\*

V. N. Kulikov,<sup>a,b\*</sup> O. M. Nikitin,<sup>a</sup> Yu. A. Borisov,<sup>a</sup> A. S. Makarov,<sup>a</sup> A. N. Rodionov,<sup>a</sup> R. S. Nikulin,<sup>a,b</sup> L. V. Kovalenko,<sup>b</sup> and Yu. A. Belousov<sup>a</sup>

 <sup>a</sup>A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085. E-mail: belyur@ineos.ac.ru
 <sup>b</sup>D. Mendeleyev University of Chemical Technology of Russia, 9 Miusskaya pl., 125047 Moscow, Russian Federation. Fax: +7 (495) 609 2964. E-mail: kulikov\_v\_n@mail.ru

Redox potentials of isomeric ethyl 5-ferrocenyl-1*H*-pyrazole-3-carboxylates **2** and ethyl 5-ferrocenyl-1*H*-pyrazole-4-carboxylates **4** were measured and their dependences on the acidity of the medium were determined. The structures of various conformers of neutral molecules and corresponding radical cations were calculated by the B3LYP/6-31G\* method. The results of calculations for neutral molecules were confirmed by X-ray data.

**Key words:** ferrocene, ferrocenylazoles, voltammetry, quantum chemical calculations, density functional theory, B3LYP method, ferricinium radical cation.

Ferrocenylazoles exhibit antitumor,<sup>1-3</sup> antibacterial,<sup>4-8</sup> and fungicidal<sup>4,9</sup> activity. Ferrocene derivatives are of low toxicity and can be used as pharmaceuticals. For instance, Ferroceron, a ferrocene-containing stimulator of erythropoiesis,<sup>10</sup> is included in the State Pharmacopoeia of the Russian Federation. A number of ferrocene derivatives are under clinical trials for antitumor and antimalarial activity.<sup>11</sup>

Medicinal applications of ferrocene derivatives are based on unique properties of the ferrocene nucleus, viz., stability in biological media,<sup>12</sup> lipophilicity that favors easy penetration through cell membranes, as well as aromatic character and a small size typical of aromatic hydrocarbons. Besides, ferrocene exhibits ideal electrochemical properties, namely, a low redox potential and high chemical stability of the oxidized and reduced forms (ferricinium and ferrocene, respectively) and a high rate of electron transfer between them, which favors not only enhanced membranotropicity, but also facilitates transport in cell cytoplasm. Yet another important factor is the interaction of the ferrocene-ferricinium system with the plasma membrane. This system spans from the interface into membrane interior and thus provides with coupled transmembrane electron and ion transport which leads to changes in the membrane polarization.13

Thus, it is clearly seen that ferrocene derivatives are promising for solving problems in medicinal chemistry. Also, knowledge of the electrochemical properties of these compounds and their dependence on the environmental conditions is required for rational design of ferrocenecontaining drugs and for modelling their distribution and metabolism in living organisms.

### Experimental

Ethyl 5-ferrocenyl-1*H*-pyrazole-3-carboxylates (2) and ethyl 5-ferrocenyl-1*H*-pyrazole-4-carboxylates (4) were synthesized as reported earlier.<sup>14,15</sup> The physicochemical parameters of compounds 2 and 4 agree with the published data. Acetonitrile was purified immediately prior to use following a known procedure,<sup>16</sup> HBF<sub>4</sub> and [Bu<sub>4</sub>N]OH (Acros Organics) were utilized in the form of aqueous solutions.

The oxidation potentials of substrates were measured with an IPC Win digital potentiostat/galvanostat. Cyclic voltammograms (CVs) were recorded in a 10-mL electrochemical cell at a concentration of 1 mM under argon in deoxygenated acetonitrile solution containing 0.05 M [Bu<sub>4</sub>N]BF<sub>4</sub> as supporting elelctrolyte at 20 °C. The potential scan rate was  $0.1 \text{ V s}^{-1}$ . A platinum stationary disk electrode ( $S = 0.1 \text{ cm}^2$ ) and a platinum auxiliary electrode were used. Electrolysis at a controlled potential was performed using a P-5827 M potentiostat in an electrochemical cell with separated anodic and cathodic compartments. The working electrode ( $S = 0.6 \text{ cm}^2$ ) and the auxiliary electrode were Pt plates. In all measurements, the reference electrode was a saturated chlorine-silver electrode (Ag/AgCl/ KCl (sat.), the potential is 0.48 V vs.  $Fc/Fc^+$  in MeCN). The measured potential values were recalculated taking into account ohmic losses.

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Kulikov et al.

Quantum chemical calculations were carried out within the framework of the density functional theory (DFT) by the Becke— Lee—Yang—Parr (B3LYP) method<sup>17,18</sup> with the 6-31G\* basis set<sup>19</sup> using the GAUSSIAN-98 program.<sup>20</sup> Closed-shell systems were calculated by the RB3LYP method and open-shell systems (radical cations) were calculated by the UB3LYP method.

## **Results and Discussion**

Synthesis. Condensation of hydrazine hydrate and monosubstituted hydrazines with ethyl ester of ferrocenoylpyruvic acid (1) results<sup>14</sup> in ethyl 5-ferrocenyl-1*H*pyrazole-3-carboxylates (2) in 65-90% yields (Scheme 1). If the reaction is conducted in ethanol in the presence of catalytic amounts of AcOH, only one possible regioisomer is formed.

## Scheme 1



*i*. RNHNH<sub>2</sub>, EtOH, AcOH<sub>cat</sub>, Ar,  $\Delta$ .

Ethyl 5-ferrocenyl-1*H*-pyrazole-4-carboxylates (4) were obtained by condensation of ethyl (*Z*,*E*)-3-(dimethyl-amino)-2-ferrocenoyl acrylate (3) with monosubstituted hydrazines and hydrazine hydrate (Scheme 2).<sup>14,15</sup> The reactions also occur regioselectively and their yields vary in the range from 65 to 95%.

Scheme 2



*i*. RNHNH<sub>2</sub>, EtOH, AcOH<sub>cat</sub>, Ar,  $\Delta$ .

**Electrochemical studies.** A series of ferrocenylpyrazoles with different substituents in the pyrazole ring was studied by cyclic voltammetry. The influence of the ester group position and the nature of substituent at the heteroatom in the pyrazole ring on the electrochemical properties of ferrocenylpyrazoles was elucidated. Measurements were carried out in a three-electrode cell. The concentration of solutes under study was 1 mmol  $L^{-1}$ . The cyclic voltammograms of all compounds studied exhibit one-electron reversible oxidation peaks (Fig. 1) whose potentials are listed in Table 1.

The introduction of aromatic substituents into position 1 of the pyrazole ring causes the oxidation potential of the ferrocene moiety to increase by 60-110 mV compared to the oxidation potentials of unsubstituted pyrazoles **2a** and **4a**. Variation of substituents at the nitrogen atom has almost no effect on the oxidation potential of the substrate. This is most probably due to the absence of conjugation between the aromatic substituent and the pyrazole



**Fig. 1.** Cyclic voltammograms of 1 m*M* solutions of compounds **2e** (*1*) and **4e** (*2*) obtained in acetonitrile solution containing 0.05 *M* [Bu<sub>4</sub>N]BF<sub>4</sub> as supporting electrolyte (Pt working electrode (*vs.* Ag/AgCl/KCl (sat.)); potential scan rate was 100 mV s<sup>-1</sup>).

**Table 1.** Oxidation potentials  $(E, \Delta E/mV)$  of ferrocenylpyrazoles under study

| Com-<br>pound | Ε   | $\Delta E$ | Com-<br>pound | Ε   | $\Delta E$ |
|---------------|-----|------------|---------------|-----|------------|
| 2a            | 560 | 60         | <b>4</b> a    | 530 | 60         |
| 2b            | 645 | 60         | 4b,c          | 595 | 70         |
| 2c            | 630 | 60         | <b>4</b> d    | 625 | 60         |
| 2d            | 670 | 60         | <b>4</b> e    | 590 | 60         |
| 2e            | 625 | 60         | <b>4</b> f    | 595 | 70         |

*Note:* determined at a concentration of compounds of 1 mmol  $L^{-1}$  using a Pt working electrode (*vs.* Ag/AgCl/KCl (sat.)) in acetonitrile solution containing 0.05 *M* [Bu<sub>4</sub>N]BF<sub>4</sub> as supporting electrolyte at a potential scan rate of 100 mV s<sup>-1</sup>.

ring, as was confirmed by the results of quantum chemical calculations and by X-ray data. Therefore, only the electron-withdrawing -I-effect of the sp<sup>2</sup>-hybridized carbon atom appears to be valuable.

Variation of position of the ester group in the pyrazole ring led to an unexpected result, namely, the oxidation potential of the ferrocene unit is shifted by 35-50 mVtoward the cathodic potential region on going from compounds **2** to compounds **4**. That is, the oxidation occurs easier when the electron-withdrawing substituent in the pyrazole ring is close to the ferrocene moiety. This can be explained by electronic interaction between the carboxylic oxygen and the iron atom. A Fe<sup>3+</sup> ion formed upon oxidation is stabilized through coordination to oxygen atom of the COOH group. An X-ray study revealed a short contact between the iron atom and the carboxylic group in esters **4b** (3.59 Å) and **4d** (3.74 Å).\*

The addition of HBF<sub>4</sub> (2 eq.) to solutions of substituted ferrocenylpyrazoles causes no changes in their oxidation potentials, whereas those of the unsubstituted pyrazoles **2a** and **4a** increase by 60 to 75 mV (Table 2) as a result of the protonation of pyrazole and enhancement of its electron-withdrawing properties compared to ferrocene. The basicities of the substituted pyrazoles seem to be too low for protonation to occur under these conditions.

In a basic medium, the oxidation potential of ferrocene remains almost unchanged; however, a new peak in the region of 315-340 mV appears in the CV curve. Carrying out a potentiostatic electrolysis of **2e** and **4e** at the corresponding oxidation potentials in the presence of [Bu<sub>4</sub>N]OH led to a gradual decrease in the concentrations of the starting compounds. The reaction mixtures turned dark-brown. No ferrocene derivatives were found in the mixtures after electrolysis. By analogy with the results of a recent study<sup>21</sup> one can suggest that electrolysis in basic media causes the ferrocene nucleus to decompose to form inorganic iron and cyclopentadiene polymers.

**Table 2.** Oxidation potentials  $(E, \Delta E/mV)$  of ferrocene derivatives

| Com-<br>pound | Neutral medium |            | HBF <sub>4</sub><br>(2 eq.) |            | [Bu <sub>4</sub> N]OH<br>(2 eq.) |  |
|---------------|----------------|------------|-----------------------------|------------|----------------------------------|--|
|               | E              | $\Delta E$ | E                           | $\Delta E$ | E                                |  |
| 2a            | 560            | 60         | 640                         | 60         | 315                              |  |
| 4a            | 530            | 60         | 595                         | 60         | 340                              |  |
| 2e            | 625            | 60         | 625                         | 60         | 330                              |  |
| <b>4e</b>     | 590            | 60         | 605                         | 60         | 340                              |  |

*Note*: determined at a concentration of compounds of 1 mmol  $L^{-1}$  using a Pt working electrode (*vs.* Ag/AgCl/KCl (sat.)) in acetonitrile solution containing 0.05 *M* [Bu<sub>4</sub>N]BF<sub>4</sub> as supporting electrolyte at a potential scan rate of 100 mV s<sup>-1</sup>.

Quantum chemical calculations. To determine the reason for the decrease in the oxidation potential on going from isomers 2 to isomers 4, we carried out quantum chemical calculations of the molecular structures of neutral ferrocenylpyrazoles and corresponding radical cations within the framework of the density functional theory. It was shown that for one of the possible conformers of compounds 4 the distance between the iron atom and the carbonyl oxygen atom in the ester group lies in the range from 3.64 to 3.77 Å (Fig. 2)

The short contact between the carbonyl oxygen atom and iron atom was also found in the structures of corresponding radical cations of compounds **4**. Moreover, the radical cations are characterized by about 0.2 Å shorter distances between the iron and oxygen atoms (Table 3). This makes transfer of positive charge from the iron atom in the ferricinium moiety to the oxygen carboxylic atom possible and leads to a decrease in the oxidation potential. In compounds **2**, such a coordination is impossible owing to the long distance between the ferrocene iron atoms and oxygen atoms in the ester group (Fig. 3). The results of



Fig. 2. Pyrazole 4b: molecular structure from DFT calculations for neutral molecule (a) and radical cation (b) and from X-ray data (c).

\* Cambridge Structural Database System, Version 5.35, 2014, CCDC 1013395 (2b), 1013396 (4b), 1013397 (4d).



Fig. 3. Pyrazole 2b: molecular structure from DFT calculations for neutral molecule (a) and radical cation (b) and from X-ray data (c).

calculations for neutral molecules were confirmed by X-ray data.

Table 3 lists the results of calculations. It follows that the adiabatic ionization potentials of pyrazoles 2 are 0.27-0.32 eV higher than those of isomeric pyrazoles 4. This agrees with the results of electrochemical measurements. No correlation was found between the oxidation potentials, *E*, and the calculated gas-phase adiabatic ionization potentials, *I*, of compounds 2a and 4a. This seems to be due to the absence of aromatic substituents at the nitrogen atom. Ignoring compounds 2a and 4a, one gets a linear correlation between the experimental and calculated gas-phase adiabatic oxidation potentials of the compounds studied (Fig. 4).

Summing up, we have shown that ethyl 5-ferrocenylpyrazolecarboxylates are readily oxidized in neutral media (E = 530-645 mV). Electrolysis in the presence of a base leads to the decompositon of the ferrocene nucleus; HBF<sub>4</sub> has no effect on the oxidation of *N*-substituted pyrazoles, whereas the oxidation of unsubstituted pyrazoles **2a** and **4a** in the presence of HBF<sub>4</sub> is much more difficult (oxidation potential increases by 60-75 mV). The short contact between the carbonyl oxygen atom and the iron atom of the ferrocene nucleus in compounds **4** causes their oxidation potentials to decrease by 30-50 mV compared to those of isomeric compounds **2**.

**Table 3.** Vertical  $(I_v)$  and adiabatic  $(I_{ad})$  ionization potentials of neutral molecules and radical cations derived from them

| Com-       | <i>E<sup>a</sup></i> (au) | $I_{\rm v}/{\rm eV}$ | I <sub>ad</sub> /eV | d (FesO=C)/Å   |                    |
|------------|---------------------------|----------------------|---------------------|----------------|--------------------|
| pound      |                           |                      |                     | N <sup>a</sup> | R-Cat <sup>b</sup> |
| 2a         | -2142.909                 | 7.143                | 6.339               | 6.588          | 6.599              |
| 2b         | -2389.983                 | 6.523                | 6.263               | 6.263          | 6.169              |
| 2e         | -2473.190                 | 6.410                | 6.213               | 6.331          | 6.319              |
| <b>4</b> a | -2142.916                 | 6.279                | 6.073               | 3.773          | 3.537              |
| 4b         | -2389.995                 | 6.227                | 5.981               | 3.639          | 3.462              |
| <b>4</b> e | -2473.194                 | 6.149                | 5.932               | 3.692          | 3.498              |

<sup>a</sup> For neutral molecule.

<sup>b</sup> Radical cation.



Fig. 4. Correlation between calculated gas-phase adiabatic ionization potentials  $(I_{ad})$  and experimental oxidation potentials  $(E_{ox})$  in solution for compounds **2b**, **e** and **4b**, **e**.

The correlation found between the calculated adiabatic ionization potentials of the molecules studied and the experimentally determined oxidation potentials of the substituted ferrocene derivatives makes it possible to estimate the redox potentials of other ferrocene derivatives using on the results of calculations.

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