



Novel Ferrocene Derivatives with Polycyclic Spatial Groups: Synthesis and Application†

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New bioactive compounds for special purpose containing ferrocene, spatial polycyclic groups and transition metals have been synthesized and studied. By using of spectral (IR, UV), thermal (TG/DTA) analyses the structure and composition of the obtained compounds have been established. The ligand acts as a bidentate organometallic ligand (O-N). Theoretical bioscreening of obtained compounds have been carried out. Their antiviral, antimicrobial and antibacterial activities have been established. Application area of the obtained bioactive compounds has been recommended.

Keywords: Ferrocene, Coordination compound, Transition metal, Hydrazone, Bioactivity.

INTRODUCTION

Ferrocene derivatives because of their high stability and the ability to transformation into more complicated complex structures, represents an universal material for synthesis of new compounds and ligand-systems with interesting chemical and physical properties for special purpose and for synthesis of coordination compounds based on them. Ferrocene containing complexes are of great interest due of their unique structure and wide field of applications in different areas of science and technology. The organometallic complexes have a completely new potential of action for suppression of action of various aggressive microorganisms^{1,2}. Among ligand systems, hydrazide-hydrazones belong to a special place because of their vast variety of biological activities ranging from pharmacological, antitumor, fungicide, bactericide, antiviral, antioxidative and cytotoxic activities³. By complex formation of hydrazide-hydrazones with transition metals resulted in increase of biological activities. Intensified interest in high biological active transition metal complexes with hydrazide-hydrazones developed because of their increasing application in medicine, analytical chemistry and synthesis of novel heterogeneous catalysts of oxido-reduction processes, as well as in numerous fields of science and technology⁴.

For the time being in the various spheres of science and technique are giving scientist's special attention to polycyclic

spatial groups containing compounds and its derivatives⁵. Introduce of immunotropic and membranotropic polycyclic spatial groups in the molecule of bioactive compounds frequently provoke the shortening of preparation toxicity and reinforcement of biological action. The polycyclic spatial groups and nitrogen-containing derivatives are known to have unique pharmacological activity, among them suppressive effect on rabies virus and human immune deficiency virus⁶.

EXPERIMENTAL

Physical measurements: IR spectra are obtained with a FT-IR "THERMO NICOLET" spectrophotometer in KBr plates and in liquid paraffin (4000-400 cm⁻¹). UV spectra are obtained with a UV/VIS "Varian" CARRY-100 spectrophotometer in the 200-800 nm region using a solution in chloroform (CHCl₃). TG/DTA is determined using a Paulik, Paulik & Erdey systems of Q1500 thermal analyzer, heating rate 10 °/min, sensibility DTA 1/10. Melting points are determined by apparatus MPM-HV2, Germany. The reaction course and the purity of the obtained compounds have monitored by thin-layer chromatography on silufol UV-254. Quantum-chemical calculations carried out on PC with AMD processor with the built coprocessor by using Mopac 2000 and CS Chem3D Ultra, v8. We gave the following key words to guide each computation: EF GNORM = 0.100 MMOK GEO-OK AM1 MULLIK LET DDMIN = 0.0 GNORM = 0.1 GEO-OK.

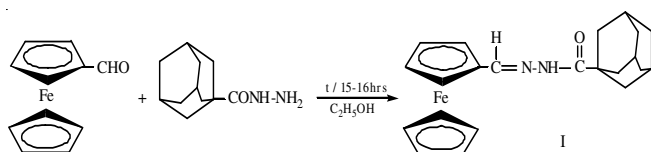
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Synthesis of formylferrocenyl-N-(1-adamantoyl)-hydrazone: To the mixture of formylferrocene in ethanol was added in equimolar ratio of adamantane-1-carboxylic acid hydrazide in ethanol with stirring. Then the mixture was heated for 15-16 h under reflux. The reaction mixture was cooled at room temperature and precipitate was filtered, the obtained red-brown crystals was washed by ethyl ether and dried *in vacuum* over CaCl_2 .

Synthesis of the complexes: A solution of corresponding transition metal salt [$\text{Co}(\text{CH}_3\text{COO})_2$, $\text{Ni}(\text{CH}_3\text{COO})_2$, CuSO_4] in dry ethanol was added dropwise to solution of formylferrocenyl-N-(1-adamantoyl)hydrazone in dry ethanol [molar ratio $\text{MX}_n:\text{L}:1:2$]. The reaction mixture was stirred under boiling condition during 5-6 h. The reaction mixture was cooled at 0-5 °C, separated crystals filtered washed by ethanol and dried *in vacuum* over CaCl_2 .

RESULTS AND DISCUSSION

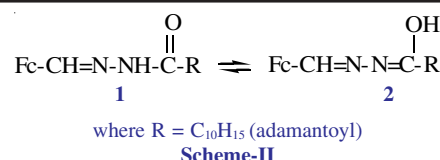
For developing of synthesis and study of new derivatives containing of ferrocene, spatial alicyclic polyfunctional components with asymmetric structure⁷ and some biogenic metals simultaneously and on purpose to establish the relationship between the chemical structure and specific activity the synthesis of formylferrocenyl-N-(1-adamantoyl)hydrazone (**I**) have been carried out:



Scheme-I: Synthesis of formylferrocenyl-N-(1-adamantoyl) hydrazone

For preliminary estimation of complex forming ability of obtained ligand and study of its electron structure quantum-chemical investigation by semi empirical method AM1 CS MOPAC (Chem3D Ultra-version 8.03) have been carried out⁸. It was established that formylferrocenyl-N-(1-adamantoyl)hydrazone because of contains two potentially electron donor atoms -O and N acts as a bidentate ligand and forms 5-membered chelate with transition metals ions.

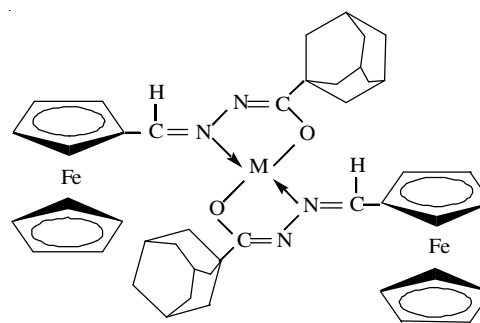
Formylferrocenyl-N-(1-adamantoyl)hydrazone can undergo enolization (**Scheme-II**), -hydrazone (**1**) convert into enol form (**2**), when reacts with transition metals salts and form chelate complexes (**Scheme-III**) with transition metals ions:



Scheme-II

The composition and structure of synthesized compounds were established by IR, UV spectral and thermal analyses methods (Table-1).

The analysis of IR spectra of the synthesized compounds has shown that the molecule of ligand behaved as cyclic-bidentate and is coordinated to the central metal atoms through the carbonyl oxygen and the azomethyne nitrogen atom which corresponds to the results obtaining by quantum-chemical calculation. Particularly in the IR spectra of the coordination compounds the decrease of absorption band corresponding to valence oscillation of carbonyl group [$\Delta\nu(\text{C}=\text{O}) \approx 30\text{-}40\text{ cm}^{-1}$] comparison with free ligand point at coordination of ligand to the central metal atom by means of carbonyl oxygen $\text{M} \leftarrow \text{O}=\text{C}$. On the other hand, absorption band corresponding to $\nu(\text{N}-\text{N})$ comparison with non-coordinated ligand moved in high-frequency wave number, which indicates on coordination of azomethyne nitrogen atom with transition metals.



where M = Co(II), Ni(II), Cu(II)

Scheme-III: Proposed structure of synthesized coordination compounds (**II-IV**)

In IR spectra of the synthesized compounds the characteristic frequencies of adamantoyl group appear at 2923-2908 cm^{-1} , the characteristic frequencies of ferrocenyl group appear at 3085, 1458, 1180 and 815 cm^{-1} ; The IR spectra of free ligand (**I**) gives bands at 3178, 1643, 1566 and 995 cm^{-1} which are assignable to $\nu(\text{N}-\text{H})$, $\nu(\text{C}=\text{O})$, $\delta(\text{N}-\text{H})$ and $\nu(\text{N}-\text{N})$, respectively. In IR spectra of the complexes (**II-IV**) the $\nu(\text{N}-\text{H})$, $\nu(\text{C}=\text{O})$, $\delta(\text{N}-\text{H})$ bands disappear and new bands observed at 1612, 1511, 1242, 410 cm^{-1} which are observed which can be assigned to $\nu(\text{C}=\text{N}-\text{N}=\text{C})$, $\nu(\text{NCO})$, $\nu(\text{C}-\text{O})$, $\nu(\text{M}-\text{O})$. In IR

TABLE-1
PHYSICAL-CHEMICAL CHARACTERISTICS OF OBTAINED COMPOUNDS

No.	m.p. (°C)	UV/VIS, λ_{max} (nm), (abs)	IR, ν (cm^{-1})
I	230*	252 (0.5); 294 (0.57); 438 (0.18)	3178.2, 1565.9 (NH); 2923.7, 2854.2 (CH, Ad); 1643.1 (C=O); 995.1 (N-N); 3085.7, 1457.9, 1180.3, 817.7, 493.7 (CH, Fc).
II	>280*	244 (0.57); 328 (0.51); 440 (0.15)	2923.7, 2854.3 (CH, Ad); 1612.3 (C=N-N=C); 1234.3 (C-O); 410 (M-O, M-N); 3085.7, 1457.9, 1187.9, 810.0, 478.3 (CH, Fc).
III	>300*	–	2923.7, 2854.3 (CH, Ad); 1612.7 (C=N-N=C); 1234.3 (C-O); 3085.7, 1457.9, 1187.93, 810.0, 478.3 (CH, Fc).
IV	>280*	–	3386.5 (O-H); 2923.7, 2854.3 (CH, Ad); 1619.5 (C=N-N=C); 1272.8 (C-O); 3085.7, 1457.9, 1180.3, 810.0, 486.0 (CH, Fc).

*Decomp.

spectra of complex **IV** has characteristic frequency for O-H group at 3386 cm^{-1} .

In UV spectra of the synthesized compounds (**I-IV**) the maximum absorption characteristic band are observed at λ_{max} : 246-256, 262-294, 320-328 and 438-450 nm. It can be seen that the UV spectra of complexes are similar, but they are different from that of the ligand. The peak at 252 nm in the ligand changes into peak at 244 nm in complexes. The broad band in the range 438-450 nm was attributed to charge-transfer in the ferrocene group (transition of the $3d$ electrons on iron to either the nonbonding or antibonding orbitals of the cyclopentadienyl ring)⁹. The position of this band in complexes as compared with that of the ligand hardly changes. In addition, new bands near 320-328 nm appeared and suggested that the whole molecule changed into a large conjugated system due to chelation in the enolic form.

By using of the thermal analysis method-thermogravimetry (TG) and differential thermal analysis (DTA) temperature intervals of thermolysis and thermal stability of obtained coordination compounds were established.

Formylferrocenyl-N-(1-adamantyl)hydrazone melted endothermally at 220 and 360 °C, then decomposed exothermally at 400 and 500 °C. The decomposition was complete at 520 °C (Fig. 1a). The coordination compound CoL decomposed exothermally at 360 and 520 °C, then continued endothermally at 560 °C. The decomposition was complete at 990 °C, perhaps it is oxide or salt of transition metal (Fig. 1b).

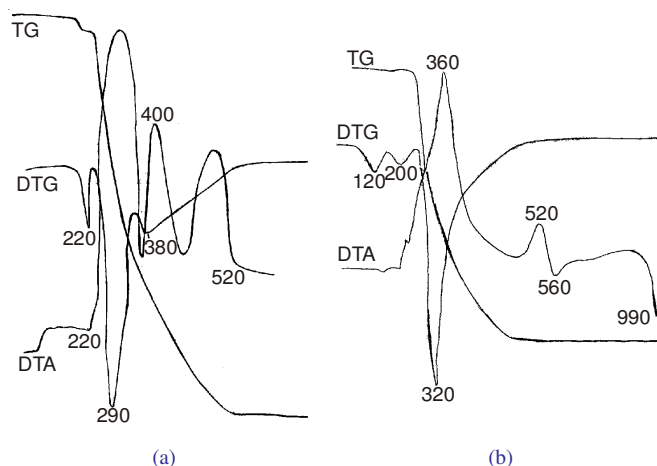


Fig. 1. TG/DTA diagrams of formylferrocenyl-N-(1-adamantyl)hydrazone (a) and of the coordination compound CoL (b)

Thermogravimetric analysis shown that thermolysis of obtained compounds is a complicated process. It was established that the thermostability of coordination compounds increased much more than that of the ligand after chelation with transition metal ions.

The theoretical bioscreening of obtained compounds by using of computer-system program PASS C & T have been carried out¹⁰. The estimation of probable bioactivity of chosen

compounds was carried out *via* parameters Pa (active) and Pi (inactive); when $P_a > 0.5$, the compound could also be shown bioactivity experimentally. Based on virtual bioscreening the synthesized compounds, with experimentally high probability ($P_a \sim 0.55-0.80$) showed virtually antibacterial, antiviral and antimicrobial activities. It was shown, that the initial ligand is expressing the bactericidal properties more passively than corresponding coordination compounds.

The preliminary investigation has shown, that the obtained compounds may be recommended for suppression of action of various aggressive microorganisms and for human protection during its contact with microorganisms.

Conclusion

New bioactive compounds for special purpose containing ferrocene, spatial alicyclic fragments and transition metals have been synthesized. By using of the data of IR, UV spectral and thermal (TG/DTA) analyses the structure and composition of the obtained compounds have been established. It was established that the thermostability of coordination compounds increased much more than that of the ligand after chelation with transition metal ions. By using model system and semi empirical quantum-chemical AM1 method have been shown that obtained ligand behaved as a bidentate and forms with transition metals by 5-membered chelate. Theoretical bioscreening of obtained compounds have been carried out. Their antiviral, antimicrobial and antibacterial activities have been established. The initial ligand is expressing the bactericidal properties more passively than corresponding coordination compounds. Area of their application has been established.

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