

## SYNTHESIS OF IRON(II)-COMPLEXES WITH GLYOXIMES AND BORIC ACID DERIVATIVES, AND THEIR PHYSICAL-CHEMICAL AND BIOLOGICAL STUDIES

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### Abstract

Iron(II) complexes obtained with glyoximes are macrobicyclic ligand systems, which are formed under mild conditions with high yields [1]. The biological activity of these compounds is of particular importance. Some boric acid derivatives have been proposed as new radiopharmaceuticals for boron neutron capture therapy of cancer [2].

In our research work new iron(II) complexes were synthesized with  $\alpha$ -dioximes, amines, boric acid derivatives, such as  $[\text{Fe}(\text{Ph-Me-DioxH})_2\text{L}_2]$ ,  $[\text{Fe}(\text{Me-i-Pr-DioxH})_2\text{L}_2]$ ,  $[\text{Fe}(\text{Ph-Me-Diox})_3(\text{BO-R})_2]$ ,  $[\text{Fe}(\text{Bu-Me-Diox})_3(\text{BO-R})_2]$ ,  $[\text{Fe}(\text{i-Pr-Me-Diox})_3(\text{BO-R})_2]$ , where DioxH, Diox = mono- or bi-deprotonated dioxime, L = 1-naphthylamine, 2-methylimidazole, 2-amino-4-methyl-pyridine, lepidine, m-toluidine, dicyclohexylamine, 2-amino-5-picoline, R = H, methyl, ethyl, isopropyl, n-propyl, isobutyl, n-butyl. For preparation iron<sup>II</sup>-sulfate was dissolved in water and mixed with alcoholic solution of the glyoxime, then the corresponding amines or the other complexing agents were added. The mixture so obtained was refluxed under an inert atmosphere.

The molecular structures of our products were studied using a range of techniques, including IR, Raman, Mössbauer and UV-VIS spectroscopies, mass spectrometry (MS) and thermoanalytical measurements (TG-DTG-DTA). In addition, their biological activity, including the antimicrobial effect against certain bacterial strains, was also investigated.

### Introduction

Iron compounds are widely used, especially in pharmaceuticals and nanotechnology. The use of nanoparticles in medicine in the fight against bacteria can be beneficial because their size is much smaller than that of bacteria (they are micrometres in size), or more precisely, the right size nanoparticles are able to penetrate the pores of their cell membrane [3]. The use of iron complexes as antibacterial agents which contain N- and O-donor ligands are also advantageous because they show more pronounced antibacterial effect against both Gram-positive and Gram-negative bacteria than the free ligands themselves [4].

$[\text{M}(\text{Dioximate})_3(\text{BOR})_2]$  type complexes were discovered by Schrauzer, who noted that the classic  $[\text{Ni}(\text{Me}_2\text{DioxH})_2]$  complex easily reacts with  $\text{BF}_3$  and alkylboranes in ethereal

media. Voloshin et al. prepared a series of  $[\text{Fe}(\text{Dioximate})_3(\text{BOR})_2]$ -type complexes and characterized them using different physicochemical methods. Clathrochelates containing transition metals are used in HIV infections treatment [5].

In this paper we report the synthesis, characterization and biological evaluation of novel iron complexes with glyoximes and boric acid derivatives.

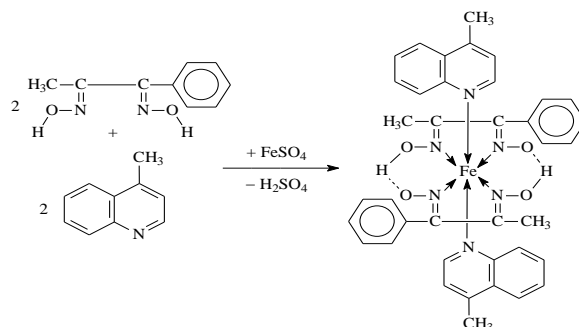
## Experimental

**Used materials:**  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ , Ph-Me-DioxH<sub>2</sub>, Me-i-Pr-DioxH<sub>2</sub>, Bu-Me-DioxH<sub>2</sub>, 1-naphthylamine, 2-methyl-imidazole, 2-amino-4-methyl-pyridine, lepidine, m-toluidine, dicyclohexylamine, 2-amino-5-picoline, boric acid, borax, ascorbic acid, MeOH, EtOH, *i*-PrOH, *n*-PrOH, *i*-BuOH, *n*-BuOH.

### Methods:

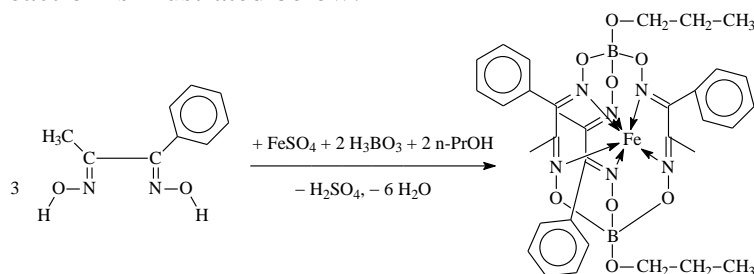
#### - Synthesis of $[\text{Fe}(\text{DioxH})_2\text{L}_2]$ type complexes

0.002 mol phenyl-methyl-DioxH<sub>2</sub>, methyl-isopropyl-DioxH<sub>2</sub> or butyl-methyl-DioxH<sub>2</sub> was dissolved in 20 ml EtOH and this solution was added to the aqueous solution of 0.001 mol (0.3 g)  $\text{FeSO}_4$  and 0.4 g ascorbic acid dissolved in 10 ml water. Then 0.002 mol amine (1-naphthylamine, 2-methyl-imidazole, 2-amino-4-methyl-pyridine, lepidine, m-toluidine, dicyclohexylamine, 2-amino-5-picoline) dissolved in 5 ml EtOH was added. The obtained solution was heated for 2–3 hours on a water bath under inert atmosphere. The filtered crystalline complexes were washed with EtOH–water mixture (1:1) and diethyl ether. A typical reaction as an example:



#### - Synthesis of $[\text{Fe}(\text{Diox})_3(\text{BO-R})_2]$ type complexes

0.0075 mol phenyl-methyl-DioxH<sub>2</sub>, methyl-isopropyl-DioxH<sub>2</sub> or butyl-methyl-DioxH<sub>2</sub> was dissolved in 20 ml MeOH, EtOH, *i*-PrOH, *n*-PrOH, *i*-BuOH or *n*-BuOH, then this solution was added to an aqueous solution of 0.0025 mol (0.7 g)  $\text{FeSO}_4$  and 0.4 g ascorbic acid dissolved in 25 ml water. The role of ascorbic acid is to prevent the oxidation of  $\text{Fe}^{\text{II}}$  to  $\text{Fe}^{\text{III}}$ . Afterwards 0.0075 mol (0.46 g) boric acid dissolved in 15 ml  $\text{H}_2\text{O}$  was added. The mixture was refluxed for 15 min under inert atmosphere, and then 0.00375 mol (1.4 g) borax dissolved in 15 ml distilled water and 55 ml of the corresponding alcohol were added. The obtained solution was heated for 2–3 hours on a water bath, under inert atmosphere. After cooling the crystalline complexes were filtered off, washed with the used alcohol and diethyl ether, then dried in air. A representative reaction is illustrated below:



Microscopic characterization and yields of the prepared complexes are presented in Table 1.

Table 1. Microscopic characterization, calculated molecular weights and yields of the prepared complexes.

Nr.	Compound	Calc. mol. weight	Yield (%)	Microscopic characterization
1.	[Fe(Ph-Me-DioxH) <sub>2</sub> (1-naphthylamine) <sub>2</sub> ]	696.58	51	Reddish-brown triangle-based prisms
2.	[Fe(Ph-Me-DioxH) <sub>2</sub> (2-methyl-imidazole) <sub>2</sub> ]	574.42	74	Reddish-brown triangle-based prisms
3.	[Fe(Ph-Me-DioxH) <sub>2</sub> (2-amino-4-methyl-pyridine) <sub>2</sub> ]	626.49	56	Reddish-brown triangle-based prisms
4.	[Fe(Ph-Me-DioxH) <sub>2</sub> (lepidine) <sub>2</sub> ]	696.58	99	Dark reddish-brown triangle-based prisms (microcrystals)
5.	[Fe(Ph-Me-DioxH) <sub>2</sub> (m-toluidine) <sub>2</sub> ]	624.52	98	Reddish-brown triangle-based prisms (microcrystals)
6.	[Fe(Ph-Me-DioxH) <sub>2</sub> (dicyclohexylamine) <sub>2</sub> ]	772.85	59	Reddish-brown triangle-based prisms (microcrystals)
7.	[Fe(Bu-Me-DioxH) <sub>2</sub> (m-toluidine) <sub>2</sub> ]	584.54	20	Brown triangle-based prisms
8.	[Fe(Bu-Me-DioxH) <sub>2</sub> (dicyclohexylamine) <sub>2</sub> ]	732.87	23	Brown triangle-based prisms (microcrystals)
9.	[Fe(Me-i-Pr-DioxH) <sub>2</sub> (1-naphthylamine) <sub>2</sub> ]	628.55	52	Dark reddish-brown triangle-based prisms (microcrystals)
10.	[Fe(Me-i-Pr-DioxH) <sub>2</sub> (2-amino-5-picoline) <sub>2</sub> ]	558.46	33	Purple-brown small triangle-based prisms (microcrystals)
11.	[Fe(Ph-Me-Diox) <sub>3</sub> (BO-i-Bu) <sub>2</sub> ]	752.22	96	Greenish-brown triangle-based prisms (microcrystals)
12.	[Fe(Ph-Me-Diox) <sub>3</sub> (BO-2-propil) <sub>2</sub> ]	724.16	79	Red triangle-based prisms
13.	[Fe(Ph-Me-Diox) <sub>3</sub> (BO-n-Bu) <sub>2</sub> ]	752.22	53	Brown triangle-based prisms
14.	[Fe(Ph-Me-Diox) <sub>3</sub> (BO-n-Pr) <sub>2</sub> ]	724.16	90	Reddish-brown triangle-based prisms
15.	[Fe(Bu-Me-Diox) <sub>3</sub> (BO-2-Pr) <sub>2</sub> ]	664.19	99	Reddish-brown triangle-based prisms (microcrystals)
16.	[Fe(Bu-Me-Diox) <sub>3</sub> (BO-Et) <sub>2</sub> ]	636.14	83	Reddish-brown irregular microcrystals
17.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BOH) <sub>2</sub> ]	537.95	57	Reddish-brown triangle-based prisms
18.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BO-Et) <sub>2</sub> ]	594.06	64	Brown irregular microcrystals
19.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BO-Me) <sub>2</sub> ]	566,00	16	Dark brown triangle-based prisms
20.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BO-i-Pr) <sub>2</sub> ]	622.11	75	Reddish-brown irregular microcrystals
21.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BO-i-Bu) <sub>2</sub> ]	650.16	94	Brown triangle-based prisms (microcrystals)
22.	[Fe(Me-i-Pr-Diox) <sub>3</sub> (BO-n-Pr) <sub>2</sub> ]	622.11	90	Brown triangle-based prisms

*Infrared spectroscopic study*

The mid-IR spectra were recorded with a Bruker Alpha FTIR spectrometer (Platinum single reflection diamond ATR), at room temperature, in the wavenumber range of 4000–400 cm<sup>-1</sup>, and the far-IR range of 500–50 cm<sup>-1</sup>, respectively, on a Bio Rad – FTS 60A, PIKE Gladi ATR spectrometer, with a resolution of 4 cm<sup>-1</sup>. The samples were measured in solid state (in powder

form). The data of the most characteristic IR bands for some selected complexes are presented in Table 2.

Table 2. IR data of the selected complexes.

Comp. cm <sup>-1</sup>	1	4	5	6	7	8	11	14	15	17
VO-H	3648 w	-	-	3592 w	-	-	-	-	-	3648 w
VN-H	3217 w	3237 m	3237 m	3219 m	3220 w	3246 m	3206 m	3231 m	3201 s	3254 m
VC-H	3058 w 2930 w	3085 w 3066 w	3065 w 2927 w	3054 m 2931 m	2955 m 2928 m	2956 m 2929 m	2952 m 2869 m	3067 w 2887 w	2959 m 2872 m	2964 s 2873 s
VC=C	1653 vs	1637 s	1651 m	1645 vs	1649 vs	1646 vs	1651 w	1735 w	1634 w	1682 s
VC=N	1577 s	1604 vs	1611 s 1593 m	1578 m	1558 s	1557 s	1507 m	1578 m 1495 s	1574 m	1558 m
δCH <sub>2</sub>	1445 s	1413 m	1418 s	1424 s	1456 s	1455 m	1449 s	1405 m	1393 vs	1456 vs
δCH <sub>3</sub>	1315 s	1356 s	1369 m	1354 s	1379 s	1379 s	1361 vs	1370 m	1378 vs	1363 s
VN-O	1239 vs	1230 m	1198 m	1200 s	1182 vs	1181 s	1192 vs	1200 m	1175 vs	1189 vs
VN-OH	1110 vs	1100 vs	1109 m	1107 s	1106 vs	1104 vs	-	-	-	-
VB-O	-	-	-	-	-	-	1114 vs	1016 s	1109 vs	1092 vs
τO-H	955 vs	1020 vs	976 vs	975 vs	1023 vs	1023 vs	971 vs	975 vs	978 s	968 vs
γC-H	695 vs	696 vs	695 vs	697 vs	746 s	743 s	695 vs	709 vs	703 vs	676 m
VFe-N	556 s 422 vs	560 s 507 s	505 m 498 m	484 s 418 s	533 vs 424 s	528 s 419 s	511 m 492 s	492 vs	544 vs	566 vs
δN-Fe-N	376 s	363 m	361 m	357 s	380 vs	376 s	359 s	359 s	378 w	372 w

(Abbreviations: vs = very strong, s = strong, m = medium, w = weak)

The most important bands for the characterization of complexes are ν<sub>C=N</sub> (1495 – 1611 cm<sup>-1</sup>) and ν<sub>Fe-N</sub> (418 – 566 cm<sup>-1</sup>) [6]. In the far IR region appears the δ<sub>N-Fe-N</sub> deformation bands, which demonstrate the stability of complexes. In case of [Fe(Diox)<sub>3</sub>(BO-R)<sub>2</sub>] type complexes ν<sub>B-O</sub> valence band appear with high intensity.

#### Mass spectrometry

Mass spectra of the samples were recorded on an Agilent 1200/6410B Triple Quad LC-MS/MS system using electrospray ionization (ESI). In the spectra we could detect the molecular ions and some decomposition fragments.

#### Mössbauer spectroscopy

The Mössbauer spectra were recorded at room temperature (295 K) and liquid nitrogen temperature (78 K) with Wissel type Mössbauer spectrometer in constant acceleration mode and in transmission geometry.

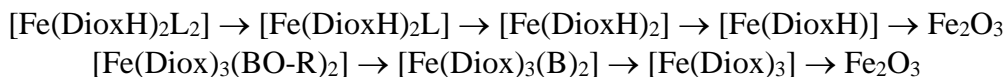
The Mössbauer spectroscopic measurements indicate the oxidation and spin state of Fe, and also the purity of the complexes. In case of aromatic ligands the high spin Fe<sup>III</sup> oxidation state is observed due to the electron attraction of the ligand, however, in case of aliphatic ligands we obtain low spin Fe<sup>II</sup>.

#### Thermoanalytical measurements (TG-DTG-DTA)

Thermal measurements were performed with a 951 TG and 910 DSC calorimeter (TA Instruments), in Ar or N<sub>2</sub> at a heating rate of 10 K·min<sup>-1</sup> (sample mass of 4–10 mg).

The thermal stability of complexes in the case of [Fe(DioxH)<sub>2</sub>L<sub>2</sub>] type is limited within the temperature range of 74–141 °C. The first step of the decomposition is the loss of the amino

group until 300 °C, then the dioxime units leave. The end of the process is between 379–650 °C. The decomposition of the dioxime unit is accompanied by big exothermic peaks. In the case of  $[Fe(Diox)_3(BO-R)_2]$  type complexes the thermal stability is limited between 96–98 °C. The first decomposition step belongs to leaving RO group, until 140 °C, then the  $BO_x$  part is lost until 250 °C. Subsequently, the decomposition of the glyoxime unit takes place, which is accompanied by big exothermic peaks. This behavior can be explained with the presence of oxygen in the molecule. The process ends at 700 °C. The general mechanism for decomposition is as follows:



#### UV–VIS spectroscopy

The electronic spectra were recorded with a Jasco V-670 Spectrophotometer in 10% EtOH/water solutions containing the substance in  $10^{-4}$  mol/dm<sup>3</sup> concentration. Using Sørensen buffer solutions the electronic spectra were also recorded as a function of pH, and then the acidity constants were calculated, too. The obtained values were between  $9.1 \cdot 10^{-13}$  –  $1.1 \cdot 10^{-10}$ .

#### Biological study

The antimicrobial effects of three complexes:  $[Fe(Ph-Me-Diox)_3(BO-i-Bu)_2]$ ,  $[Fe(Ph-Me-Diox)_3(BO-n-Pr)_2]$  and  $[Fe(Ph-Me-Diox)_3(BO-i-Pr)_2]$  were studied against *Staphylococcus aureus*, *Bacillus cereus* Gram-positive and *Escherichia coli*, *Serratia marcescens* Gram-negative bacteria, respectively. The investigations were carried out by Kirby-Bauer disk diffusion method. The complexes were dissolved in DMSO at 10 mmol/l concentration, and 30 µl was applied on sterile paper discs. Antibacterial effect was observed only in case of  $[Fe(Ph-Me-Diox)_3(BO-i-Bu)_2]$  against *Staphylococcus aureus*. The inhibition zone was 15.33 mm, which is a good value in comparison with the literature data.

#### **Conclusion**

New iron(II) complexes were synthesized and characterized using a range of physicochemical methods. The thermal decomposition mechanism was monitored by thermoanalytical measurements. The antibacterial activity of the compounds was also investigated.

#### **Acknowledgement**

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#### **References**

- [1] Y.Z. Voloshin, N.A. Kostromina, A.Y. Nazarenko, *Inorganica Chimica Acta* 170 (1990) 181
- [2] S.Y. Erdyakov, Y.Z. Voloshin, I.G. Makarenko, E.G. Lebed, T.V. Potapova, A.V. Ignatenko, A.V. Vologzhanina, M.E. Gurskii, Y.N. Bubnov, *Inorganic Chemistry Communications* 12 (2009) 135
- [3] A. Azam, A.S. Ahmed, M. Oves, M.S. Khan, S.S. Habib, A. Memic, *International Journal of Nanomedicine*, 7 (2012) 6003–6009
- [4] A.N. Srivastva, S.C. Pahwa, P.C. Jain, N.P. Singh, *Research on Chemical Intermediates*, 42 (2016) 8023–8037
- [5] Y.Z. Voloshin, N.A. Kostromina, A.Y. Nazarenko, *Inorganica Chimica Acta* 110 (1990) 181–190
- [6] K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds*. Part B: Applications in Coordination, Organometallic and Bioinorganic Chemistry, Wiley J., 38, NY 1997