NOVEL IRON COMPLEXES WITH GLYOXIMES, SCHIFF BASES AND BORIC ACID DERIVATIVES: SYNTHESIS, PHYSICO-CHEMICAL ANALYSIS AND BIOLOGICAL STUDY

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Abstract

Iron(II) clathrochelate complexes obtained with glyoximes are macrobicyclic ligand systems, which completely encapsulate the metal ion, and are formed under mild conditions with high yields [1]. In particular, the riblike-functionalized clatrochelates both with the inherent and with the terminal closo-borate substituents synthesized recently 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 α-glyoximes, boric acid derivatives, amines, Schiff bases, such as $[Fe(Me\text{-}Pr\text{-}Glyox)_3(BO\text{–}Et)_2]$, $[Fe(Et\text{-}Bu\text{-}Glyox)_3(BO\text{–}R)_2]$ (R = methyl, propyl, butyl), $[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2(amine)_2]$, $[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(amine)_2]$, $[Fe(2\text{-}heptanone)_2(en)(amine)_2]$, where GlyoxH, Glyox = mono- or bi-deprotonated glyoxime, en = ethylenediamine and the used amines: dibutylamine, 3-picoline, 4-aminopyridine, 6-amino-3-picoline, 3-amino-1-propanol, imidazole, 2-aminopyrimidine, 3-methylpiperidine, 3-amino-1*H*-1,2,4-triazole. For preparation $iron^{II}$-sulfate was dissolved in water and mixed with alcoholic solution of the glyoxime, then the corresponding amines and the other complexing agents were added. The mixture so obtained was refluxed under inert atmosphere.

The molecular structures of our products were studied by IR, Mössbauer and UV–VIS spectroscopies, mass spectrometry (MS) and thermoanalytical measurements (TG-DTG-DTA). The biological activity, like antimicrobial effect, was studied for a few bacteria.

Introduction

The unique properties of a metal ion encapsulated in the cage of a macropolycyclic ligand and isolated from the influence of external factors have allowed the use of clathrochelates as models of important biological systems, electron carriers, and catalysts of photochemical and redox processes [3].

Several iron chelates have been reported for application in the treatment of thalassaemia, other transfusion-dependent diseases, and also used as MRI contrast agents. Other iron complexes are also known for their antibacterial, antifungal and biomimetic activities [4].

Schiff bases play an important role in inorganic chemistry as they easily form stable complexes with most transition metal ions. These days, bioinorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve

as models for biologically important species. The remarkable biological activity of the acid hydrazide (R–CO–NH–NH_2) class of Schiff base, their corresponding aroyl hydrazones (R–CO–NH–N=CH–R) and the dependence of their mode of chelation with transition metal ions present in the living systems have been of significant interest. The coordination compounds of aroyl hydrazones have been reported to act as enzyme inhibitors and are useful due to their pharmacological applications [5].

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

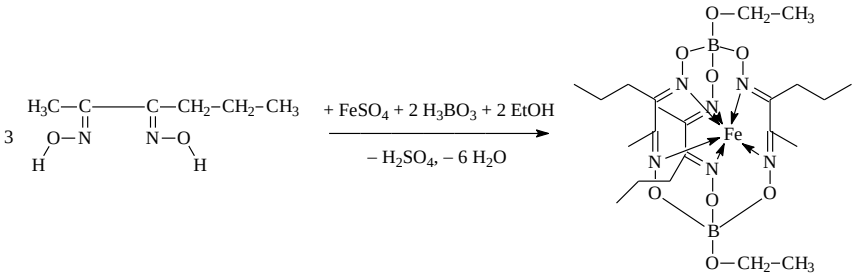
Experimental

Used materials: $FeSO_4 \cdot 7H_2O$, Me-Pr-GlyoxH_2, Ph-Me-GlyoxH_2, Et-Bu-GlyoxH_2, boric acid, borax, ascorbic acid, 2-heptanone, ethylenediamine, dibutylamine, 3-picoline, 4-aminopyridine, 6-amino-3-picoline, 3-amino-1-propanol, imidazole, 2-aminopyrimidine, 3-methylpiperidine, 3-amino-1*H*-1,2,4-triazole, MeOH, EtOH, *n*-PrOH, *n*-BuOH.

Methods:

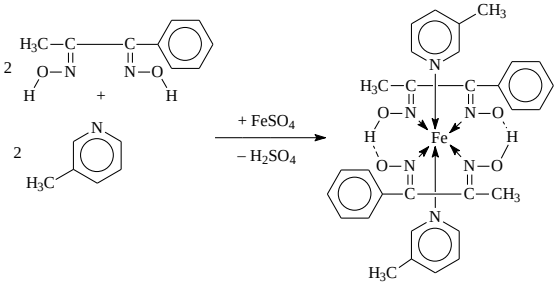
- *Synthesis of [Fe(Glyox)$_3$(BO-R)$_2$] type complexes*

0.0075 mol Me-Pr-GlyoxH_2 or Et-Bu-GlyoxH_2 was dissolved in 20 ml MeOH or EtOH or PrOH or *n*-BuOH, then this solution was added to an aqueous solution of 0.0025 mol (0.7 g) $FeSO_4$ and 0.4 g ascorbic acid dissolved in 25 ml water. The role of ascorbic acid is to prevent the oxidation of Fe^{II} to Fe^{III}. Afterwards 0.0075 mol (0.46 g) boric acid dissolved in 15 ml H_2O 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 typical reaction is shown below:



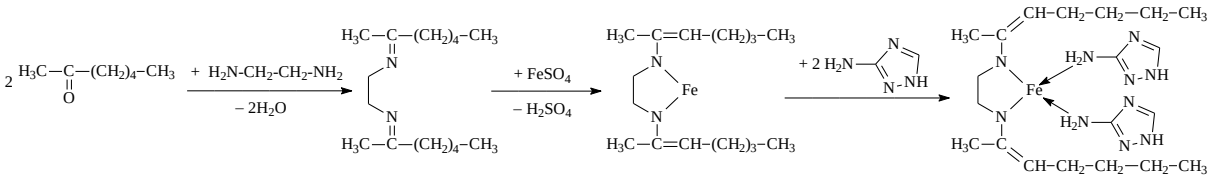
- *Synthesis of [Fe(GlyoxH)$_2$(amine)$_2$] type complexes*

0.005 mol phenyl-Me-GlyoxH_2 or Et-Bu-GlyoxH_2 was dissolved in 20 ml EtOH and this solution was added to the aqueous solution of 0.001 mol (0.3 g) $FeSO_4$ and 0.4 g ascorbic acid dissolved in 10 ml water. After that 0.002 mol amine (dibutylamine, 3-picoline, 4-aminopyridine, 6-amino-3-picoline, 3-amino-1-propanol, imidazole, 2-aminopyrimidine, 3-methylpiperidine) 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 [Fe(2-heptanone)$_2$(en)(amine)$_2$] type complexes*

0.005 mol 2-heptanone (0.7 ml) and 0.0025 mol (0.19 ml) ethylenediamine were dissolved in 5 ml EtOH, then refluxed for 1–2 hours. The resulting colored solution was added to the aqueous solution of 0.0025 mol (0.7 g) $FeSO_4$ and 0.4 g ascorbic acid dissolved in 15 ml water. At last 0.005 mol amine (imidazole, 3-amino-1*H*-1,2,4-triazole) dissolved in 10 ml EtOH was added. The obtained mixture was refluxed in a water bath for 2–3 hours. After cooling the crystalline complexes were filtered off, washed with EtOH–water mixture (1:1) and diethyl ether. Finally the crystalline complexes were dried in air. A typical reaction:



Results and discussion

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.	$[Fe(Me\text{-}Pr\text{-}Glyox)_3(BO\text{-}Et)_2]$	594.06	76	Brown, small triangle-based prisms (microcrystals)
2.	$[Fe(Et\text{-}Bu\text{-}Glyox)_3(BOMe)_2]$	650.16	10	Greenish-brown triangle-based prisms (microcrystals)
3.	$[Fe(Et\text{-}Bu\text{-}Glyox)_3(BO\text{–}n\text{-}propyl)_2]$	706.27	84	Black triangle-based prisms
4.	$[Fe(Et\text{-}Bu\text{-}Glyox)_3(BO\text{–}n\text{-}butyl)_2]$	734.33	95	Dark brown triangle-based prisms
5.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2]$	410.21	45	Reddish-brown irregular microcrystals
6.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2((n\text{-}Bu)_2NH)_2]$	668.70	42	Reddish-brown triangle-based prisms
7.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2(3\text{-}picoline)_2]$	596.46	45	Reddish-brown triangle-based prisms (microcrystals)
8.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2(4\text{-}amino\text{-}pyridine)_2]$	598.44	32	Reddish-brown triangle-based prisms
9.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2(6\text{-}amino\text{-}3\text{-}picoline)_2]$	626.49	70	Reddish-brown triangle-based prisms
10.	$[Fe(phenyl\text{-}Me\text{-}GlyoxH)_2(3\text{-}amino\text{-}1\text{-}propanol)_2]$	560,43	90	Purple-brown, small triangle-based prisms (microcrystals)
11.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2((n\text{-}Bu)_2NH)_2]$	656.77	40	Reddish-brown irregular microcrystals
12.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(6\text{-}amino\text{-}3\text{-}picoline)_2]$	614.57	96	Brown triangle-based prisms (microcrystals)
13.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(3\text{-}amino\text{-}1\text{-}propanol)_2]$	548.50	48	Brown triangle-based prisms
14.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(imidazole)_2]$	534.44	65	Reddish-brown triangle-based prisms (microcrystals)
15.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(2\text{-}amino\text{-}pyrimidine)_2]$	588.49	89	Reddish-brown triangle-based prisms (microcrystals)
16.	$[Fe(Et\text{-}Bu\text{-}GlyoxH)_2(3\text{-}Me\text{-}piperidine)_2]$	596.63	34	Reddish-brown triangle-based prisms
17.	$[Fe(2\text{-}heptanone)_2(en)(imidazole)_2]$	442.43	48	Brown triangle-based prisms (microcrystals)
18.	$[Fe(2\text{-}heptanone)_2(en)(3\text{-}amino\text{-}1H\text{-}1,2,4\text{-}triazole)_2]$	474.43	23	Dark brown triangle-based prisms

Infrared spectroscopic study

The mid-IR spectra were recorded with a Bruker Alpha FTIR spectrometer (Platinum single reflection diamond ATR) and Bruker Vector 22 at room temperature, in the wavenumber range of 4000–400 cm^{-1}. The samples were measured in solid state (in powder form) or in KBr pellets, respectively. The data of the most characteristic IR bands for the selected complexes are presented in Table 2.

Table 2. IR data of the selected complexes.

Comp. / cm^{-1}	1	2	3	4	5	6	11	14	17	18
ν_{O-H}	-	-	-	-	3402 w	3281 w	3721 w	3721 w	-	-
ν_{N-H}	3184 s	3447 s	3385 s	3447 s	3227 m	3175 w	3185 w	3553 w	3393 vs	3354 vs
ν_{C-H}	2956 w	2928 w	-	2928 m	3057 w	2956 w	2918 m	2917 m	2995 m	2781 w
$\nu_{C=C}$	-	1684 w	1734 m	1747 vs	1678 m	1643 s	1646 vs	1646 vs	-	1647 vs
$\nu_{C=N}$	1400 vs	1636 m	1636 s	1647 s	1645 m	1541 m	1552 s	1553 s	1636 vs	1553 s
δ_{CH2}	-	1420 m	1420 m	1456 m	1414 s	1440 s	1451 s	1451 m	-	1454 w
δ_{CH3}	-	1385 s	1385 s	1383 m	1365 m	1372 s	1392 m	1391 m	1396 m	1398 w
ν_{N-N}	-	-	-	-	-	-	-	-	-	1124 vs
ν_{N-O}	-	-	-	1115 vs	1195 m	1230 s	1173 s	1175 s	-	-
ν_{N-OH}	-	-	-	-	1015 s	1106 vs	1103 vs	1102 s	-	-
ν_{B-O}	1185 vs	1140 vs	1111 vs	1016 vs	-	-	-	-	-	-
τ_{O-H}	1044 m	995 m	945 s	934 s	972 vs	947 vs	963 vs	967 s	1069 s	984 s
γ_{C-H}	711 vs	621 s	617 s	619 s	708 vs	694 vs	734 s	734 s	627 s	615 s
ν_{Fe-N}	543 vs	-	-	-	483 s	557 s 426 vs	516 s 418 vs	530 s 418 vs	-	-

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

The most important bands for the characterization of complexes are $\nu_{C=N}$ (1400 – 1647 cm^{-1}) and ν_{Fe-N} (418 – 557 cm^{-1}). If we compare the influence on the nature of the glyoxime ligand (aliphatic or aromatic), we can observe the displacement of $\nu_{C=N}$ band to higher values and the displacement of ν_{Fe-N} band to lower values in case of aliphatic ligand, which are in accordance with the electronic effects.

Mass spectrometry

Mass spectra of the samples were recorded 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^{III} oxidation state

is observed due to the electron attraction of the ligand, however, in case of aliphatic ligands we obtain low spin Fe^{II}.

Thermoanalytical measurements (TG-DTG-DTA)

Thermal measurements were performed with a 951 TG and 910 DSC calorimeter (DuPont Instruments), in Ar or N_2 at a heating rate of 10 $Kmin^{-1}$ (sample mass of 4–10 mg).

The thermal stability of complexes is limited within the temperature range of 50–100 °C. In the case of $[Fe(Glyox)_3(BO\text{-}R)_2]$ type complexes the first decomposition step belongs to leaving RO group, until 170 °C, then the BO_x part is lost until 300 °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. In the case of $[Fe(GlyoxH)_2(amine)_2]$ type complexes the first step of the decomposition mechanism is the loss of the amino group between 50–200 °C, then the glyoxime units leave. The end of the process is at 500 °C. The decomposition of $[Fe(2\text{-heptanone})_2(en)(amine)_2]$ type complexes begins with leaving of the amino groups until 300 °C, then the heptanone unit leaves. Finally the $N\text{-}CH_2\text{-}CH_2\text{-}N$ unit is lost between 500 – 700 °C. The general mechanism for decomposition is as follows:

$$[Fe(Glyox)_3(BO\text{-}R)_2] \rightarrow [Fe(Glyox)_3(B)_2] \rightarrow [Fe(Glyox)_3] \rightarrow Fe_2O_3$$

$$[Fe(GlyoxH)_2(amine)_2] \rightarrow [Fe(GlyoxH)_2(amine)] \rightarrow [Fe(GlyoxH)_2] \rightarrow [Fe(GlyoxH)] \rightarrow \rightarrow Fe_2O_3$$

$$[Fe(2\text{-heptanone})_2(en)(amine)_2] \rightarrow [Fe(2\text{-heptanone})_2(en)(amine)] \rightarrow [Fe(2\text{-hept.})_2(en)] \rightarrow \rightarrow [Fe(2\text{-heptanone})(en)] \rightarrow [Fe(en)] \rightarrow Fe_2O_3$$

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^3 concentration. Using Sörensen 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 $1.2 \cdot 10^{-11} – 1.1 \cdot 10^{-10}$.

Biological study

The antimicrobial effects for two complexes: $[Fe(Et\text{-}Bu\text{-}Glyox)_3(BOMe)_2]$ and $[Fe(Et\text{-}Bu\text{-}Glyox)_3(BOPr)_2]$ were studied with Bacillus Subtilis Gram-positive and Escherichia Coli Gram-negative bacteria. The observation was made with the disk method. The complexes were dissolved in DMSO with 10 mmol/l concentration. In both cases antibacterial effect was not observed.

Conclusion

In this work new iron(II) complexes were synthesized and characterized with physico-chemical methods. Thermal decomposition mechanism was monitored with thermoanalytical measurements. Antibacterial activity was also investigated.

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