NOVEL COBALT COMPLEXES WITH GLYOXIMES: SYNTHESIS, PHYSICO-CHEMICAL ANALYSIS AND BIOLOGICAL STUDY

Csaba Várhelyi jr.[1], Roland Szalay[2], György Pokol[3,4], Firuţa Goga[1], Péter Huszthy[3], János Madarász[3], Melinda Simon-Várhelyi[1], Róbert Tötös[1], Alexandra Avram[1]

[1] Faculty of Chemistry and Chemical Engineering, "Babeş-Bolyai" University, RO-400 028 Cluj-N., Arany János str. 11, Romania
[2] Institute of Chemistry, "Eötvös Loránd" University, H-1117 Budapest, Pázmány Péter str. 1/a, Hungary
[3] Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, H-1111 Budapest, Műegyetem rkp. 3, Hungary
[4] Research Centre for Natural Sciences, H-1117 Budapest, Magyar tudósok körútja 2, Hungary
e-mail: ifj.varhelyi.cs@gmail.com

Abstract

Azomethine derivatives have several applications, especially as reagents for the determination of transition metal ions. Furthermore these ligands and their cobalt complexes were also reported to possess biological activities, such as antimicrobial, anti-tubercular, anticonvulsant, anti-inflammatory, anti-proliferative activities as well as antifungal inhibition potential [1]. Another reason for using metal-containing compounds as structural scaffolds is related to the kinetic stability of their coordination spheres in the biological environment. Metallic ions have been shown to play important role in the biological activity of different compounds in such away that, in some cases, activity is enhanced or only takes place in the presence of these ions [2].

In our research new cobalt(III) complexes were synthesized with α-glyoximes, azides, amines, thiocyanate and halogens, such as $[Co(Me\text{-}propyl\text{-}GlyoxH)_2(N_3)(amine)]$, $[Co(Me\text{-}pentyl\text{-}GlyoxH)_2(N_3)(amine)]$, $[Co(Et\text{-}propyl\text{-}GlyoxH)_2(N_3)(amine)]$, $[Co(Et\text{-}propyl\text{-}GlyoxH)_2(Br)(amine)]$, $[Co(Et\text{-}propyl\text{-}GlyoxH)_2(SCN)(amine)]$, $H[Co(Et\text{-}propyl\text{-}GlyoxH)_2(SCN)_2]$, $[Co(phenyl\text{-}Me\text{-}GlyoxH)_2(amine)_2]I$, $[Co(Et\text{-}propyl\text{-}GlyoxH)_2(amine)_2]I$, $[Co(Et\text{-}Bu\text{-}GlyoxH)_2(amine)_2]I$, where GlyoxH = mono deprotonated glyoxime, and the used amines: imidazole, 3-hydroxy-aniline, lepidine, 3,5-dimethyl-pyridine, di(*n*-butyl)-amine, diisopropyl-amine, 2-amino-pyrimidine, diphenyl-amine, 2-picoline, 3-picoline. The Co(II)-acetate salt dissolved in water and mixed with the glyoxime alcoholic solution was oxidized by air bubbling, then the corresponding diamines and the other complexing agents were added.

The molecular structure of our products was investigated by IR, UV–VIS spectroscopy, mass spectrometry (MS), thermoanalytical measurements (TG-DTG-DTA), and powder XRD. The biological activity, like antimicrobial effect, was studied for a few bacteria.

Introduction

The importance of metal compounds in medicine dates back to the 16th century, with reports on the therapeutic use of metals or metal-containing compounds in the treatment of cancer. Metal ions are often electron deficient species whereas most biological molecules (proteins and DNA) are electron rich molecules, consequently, there is a general tendency for metal ions to bind to and interact with many important biological molecules. Several metal ions also have high affinity towards small molecules, e.g. O_2, that are crucial to life. These considerations alone have fueled much of the past and current interest in developing novel means to use metals or metal-containing agents to modulate biological systems [3].

Some Co-glyoximato complexes show antibacterial activity. The B_{12}-vitamine molecule, which is used in the treatment of pernicious anemia, is also regarded as a Co(III)-glyoxime coordiantion compound. Some other cobalt complexes are also used in analytical chemistry and moreover, they act as catalysts in water-splitting reaction for hydrogen generation [4].

In this paper we report the synthesis, characterization and biological evaluation of some Co(III) complexes with glyoximes, amines and other ligands.

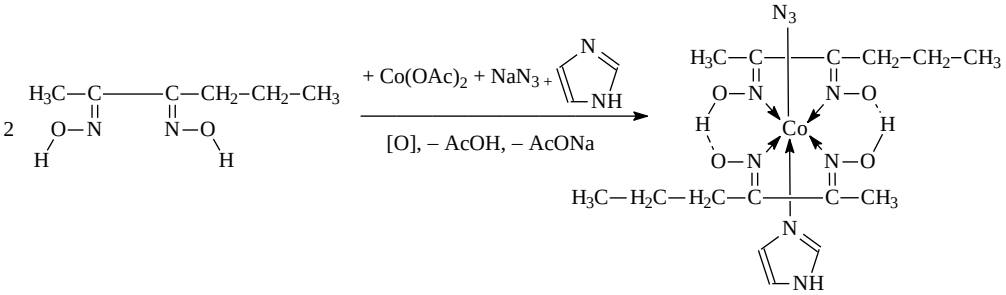
Experimental

Used materials: $Co(OAc)_2$, Me-propyl-GlyoxH_2, Me-pentyl-GlyoxH_2, Et-propyl-GlyoxH_2, phenyl-Me-GlyoxH_2, Et-Bu-GlyoxH_2, imidazole, 3-hydroxy-aniline, lepidine, 3,5-dimethyl-pyridine, $(n\text{-Bu})_2NH$, diisopropyl-amine, 2-amino-pyrimidine, diphenyl-amine, 2-picoline, 3-picoline, sodium azide, potassium thiocyanate, potassium bromide, potassium iodide, EtOH.

Methods:

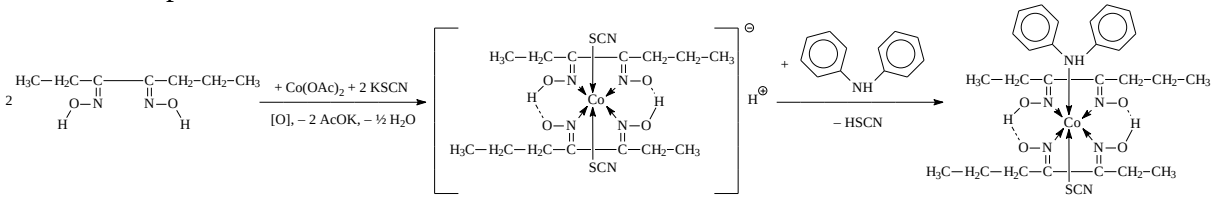
- *Synthesis of [Co(GlyoxH)$_2$(N$_3$)(amine)] type complexes*

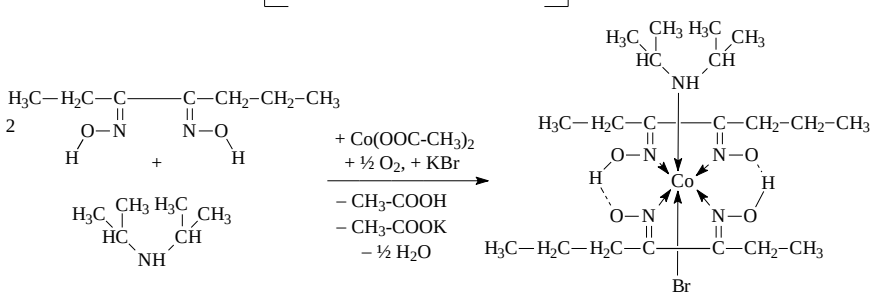
0.005 mol Me-propyl-GlyoxH_2 or Me-pentyl-GlyoxH_2 or Et-propyl-GlyoxH_2 was dissolved in 20 ml EtOH then added to an aqueous solution of 0.0025 mol $Co(OAc)_2$ with 5 ml water. To oxidize Co(II) to Co(III) air was bubbled into the mixture for 2–3 hours, then 0.0025 mol NaN_3 dissolved in 5 ml water and 0.0025 mol amine (imidazole, 3-hydroxy-aniline, lepidine, 3,5-dimethyl-pyridine, di(*n*-butyl)-amine or diisopropylamine) dissolved in 5 ml EtOH were added. The obtained solutions were heated for 2–3 hours on water bath. After cooling the crystalline complexes were filtered out, washed with EtOH–water mixture (1:1), and then dried on air. One example is shown below:



- *Synthesis of [Co(GlyoxH)$_2$(SCN)(amine)] and [Co(GlyoxH)$_2$Br(amine) type complexes*

The syntheses are similar to the procedure above, however, KSCN or KBr was used instead of NaN_3. Examples for the reactions are shown below:

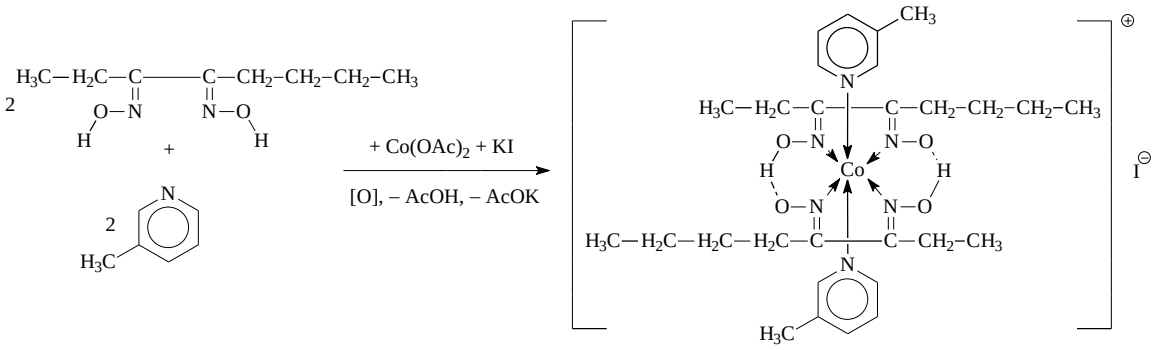




- *Synthesis of [Co(GlyoxH)$_2$(amine)$_2$]$^+I^-$ type complexes*

0.005 mol phenyl-Me-GlyoxH_2 or Et-propyl-GlyoxH_2 was dissolved in 20 ml EtOH was added to the aqueous solution of 0.0025 mol $Co(OAc)_2$ with 5 ml water. Air was bubbled into the

mixture for 2–3 hours, then 0.005 mol amine (3-hydroxy-aniline, di(*n*-butyl)-amine, 2-amino-pyrimidine, diphenyl-amine, 2-picoline or 3-picoline) dissolved in 5 ml EtOH was added. The obtained solutions were heated for 2–3 hours on water bath. In the final step 0.0025 mol KI solved in 10 ml water was added. After cooling the crystalline complexes were filtered out, washed with EtOH–water mixture (1:1), and then dried on air. One example is shown below:



Results and discussion

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

Table 1. Microscopic characterization, calculated molecular weight and the yield of prepared complexes.

Nr.	Compound	Calc. mol. weight	Yield (%)	Microscopic characterization
1.	[Co(Me-Pr-GlyoxH)$_2$(N$_3$)(imidazole)]	455.36	53	Dark brown triangle-based prisms
2.	[Co(Me-Pr-GlyoxH)$_2$(N$_3$)(3-hydroxy-aniline)]	496.41	95	Dark brown triangle-based prisms (microcrystals)
3.	[Co(Me-Pr-GlyoxH)$_2$(N$_3$)(lepidine)]	530.47	60	Dark brown triangle-based prisms
4.	[Co(Me-Pr-GlyoxH)$_2$(N$_3$)(3,5-dimethyl-pyridine)]	494.43	34	Brown triangle-based prisms
5.	[Co(Me-pentyl-GlyoxH)$_2$(N$_3$)((n-Bu)$_2$NH)]	572.63	16	Dark brown triangle-based prisms
6.	[Co(Me-pentyl-GlyoxH)$_2$(N$_3$)(diisopropyl-amine)]	544.58	29	Brown triangle-based prisms (microcrystals)
7.	[Co(Et-Pr-GlyoxH)$_2$Br(diisopropyl-amine)]	554.41	86	Brown triangle-based prisms (microcrystals)
8.	[Co(Et-Pr-GlyoxH)$_2$Br((n-Bu)$_2$NH)]	582.46	14	Dark brown triangle-based prisms (microcrystals)
9.	[Co(Et-Pr-GlyoxH)$_2$(SCN)(diphenyl-amine)]	600.62	20	Black needle-like triangle-based prisms
10.	H[Co(Et-Pr-GlyoxH)$_2$(SCN)$_2$]	491.49	3	Brown triangle-based prisms
11.	[Co(phenyl-Me-GlyoxH)$_2$((n-Bu)$_2$NH)$_2$]I	798.68	7	Dark brown triangle-based prisms (microcrystals)
12.	[Co(phenyl-Me-GlyoxH)$_2$(3-hydroxy-aniline)$_2$]I	758.45	3	Dark brown triangle-based prisms (microcrystals)
13.	[Co(phenyl-Me-GlyoxH)$_2$(3-picoline)$_2$]I	726.45	50	Dark brown triangle-based prisms

14.	[Co(phenyl-Me-GlyoxH)$_2$ (2-amino-pyrimidine)$_2$]I	730.40	12	Dark brown triangle-based prisms (microcrystals)
15.	[Co(Et-Pr-GlyoxH)$_2$ (2-amino-pyrimidine)$_2$]I	690.42	26	Dark brown triangle-based prisms
16.	[Co(Et-Pr-GlyoxH)$_2$ (2-picoline)$_2$]I	686.47	15	Dark brown triangle-based prisms (microcrystals)
17.	[Co(Et-Bu-GlyoxH)$_2$ (t-Bu-amine)$_2$]I	674,54	15	Dark brown triangle-based prisms (microcrystals)
18.	[Co(Et-Bu-GlyoxH)$_2$ (3-amino-1-propanol)$_2$]I	678.49	1	Black triangle-based prisms (microcrystals)
19.	[Co(Et-Bu-GlyoxH)$_2$ (3-amino-pyrimidine)$_2$]I	716.50	28	Brown laminar crystals
20.	[Co(Et-Bu-GlyoxH)$_2$ (3-picoline)$_2$]I	714.52	1	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), at room temperature, in the wavenumber range of 4000–400 cm^{-1}, and the far-IR range of 650–150 cm^{-1}, respectively, on a Perkin–Elmer System 2000 FTIR spectrometer, with a resolution of 4 cm^{-1}. The samples were measured in solid state (in powder form) and in polyethylene 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**	**7**	**8**	**9**	**10**	**14**	**15**	**16**
ν_{O-H}	3735 m	3567 w	3649 w	3649 w	3649 w	3406 m	-	3405 m	3487 w	3526 w
ν_{N-H}	3649 m	3446 w	3566 w	3447 w	3566 w	3382 s	3446 w	3204 w	3293 w	3385 w
ν_{C-H}	2970 m	2969 s	2927 s	2929 s	2955 s	2964 w	2960 s	2920 w	2928 s	2927 s
ν_{N3}	2359 m 2018 s	2360 m 2032 vs	2359 m 2013 vs	-	-	-	-	-	-	-
$\nu_{S-C\equiv N}$	-	-	-	-	-	2066 m	2108 s	-	-	-
$\nu_{C=C}$	1739 vs	1740 vs	1739 vs	1740 vs	1739 vs	-	-	1629 m	1638 m	1637 m
$\nu_{C=N}$	1559 s	1559 vs	1558 vs	1558 vs	1558 vs	1582 s	1556 vs	1577 vs	1552 vs	1549 vs
δ_{CH2}	1457 s	1457 s	1457 s	1456 s	1457 s	1457 s	1456 s	1444 s	1455 s	1455 s
δ_{CH3}	1373 vs	1373 vs	1374 s	1373 vs	1374 vs	1307 s	1376 s	1360 s	1365 m	1376 m
ν_{N-O}	1217 vs	1217 vs	1216 vs	1217 vs	1217 vs	1220 m	1227 vs	1241 vs	1188 vs	1186 vs
ν_{N-OH}	1105 s	1112 s	1106 vs	1107 vs	1107 s	1149 m	1113 vs	1119 vs	1108 vs	1107 vs
τ_{O-H}	978 s	1041 s	1034 s	1034 s	1034 s	1084 m	1036 s	966 vs	1004 s	1004 s
γ_{C-H}	752 m	764 m	748 m	747 m	747 m	741 vs	747 m	744 vs	747 s	748 s
ν_{Co-N}	516 s	516 m	529 m	528 m	528 s	504 s	505 s	556 s	538 s	530 m
ν_{Co-S}	-	-	-	-	-	470 s	472 s	-	-	-
ν_{Co-Br}	-	-	-	409 m	398 m	-	-	-	-	-

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

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.

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 at 90–120 °C. In the case of $[Co(GlyoxH)_2(N_3)(amine)]$ type complexes the first decomposition step is belonging to the leaving amine group, then the azide group is lost. Subsequently, the decomposition of glyoxime groups takes place which is accompanied by big exothermic peaks. This behavior can be explained with the presence of oxygen in the molecule. In the case of $[Co(GlyoxH)_2Br(amine)]$ type complexes the decomposition mechanism is similar, unlike azide, here bromine leaves. In the case of $[Co(GlyoxH)_2(amine)_2]^+I^-$ type complexes the iodide ion leaves at 30–190 °C, then the amine and glyoxime groups are lost. The general decomposition mechanisms are the followings:

$$[Co(GlyoxH)_2N_3(amine)] \rightarrow [Co(GlyoxH)_2N_3] \rightarrow [Co(GlyoxH)_2] \rightarrow [Co(GlyoxH)] \rightarrow Co_2O_3$$

$$[Co(GlyoxH)_2Br(amine)] \rightarrow [Co(GlyoxH)_2Br] \rightarrow [Co(GlyoxH)_2] \rightarrow [Co(GlyoxH)] \rightarrow Co_2O_3$$

$$[Co(GlyoxH)_2(amine)_2]^+ I^- \rightarrow [Co(GlyoxH)_2(amine)_2] \rightarrow [Co(GlyoxH)_2(amine)] \rightarrow$$
$$\rightarrow [Co(GlyoxH)_2] \rightarrow [Co(GlyoxH)] \rightarrow Co_2O_3$$

Powder X-ray diffraction measurements

The crystal structure of the complexes was studied with powder XRD measurements, carried out on a PANalytical X'pert Pro MPD X-ray diffractometer. As being novel compounds their diffractograms can not found in the Cambridge database.

UV–VIS spectroscopy

The electronic spectra were recorded with Jasco V-670 Spectrophotometer in 10% EtOH/water solutions containing substrate 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 of complexes were studied for Serratia Marcescens Gram-negative bacteria. The observation was made with the disk method. The complexes were dissolved in DMSO in 100 mmol/l concentration. In the case of $[Co(Me\text{-}Pr\text{-}GlyoxH)_2(N_3)(lepidine)]$ antibacterial effect was observed with 30 µl solution. The inhibition zone was 46.66 mm.

Conclusion

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

Acknowledgement

The authors wish to express their thankfulness to the "Domus Hungarica Foundation" of Hungary for the several fellowships provided to Csaba Várhelyi jr.

References

[1] A. Barakata, S.M. Solimanb, M. Alia, A. Elmarghanya, A.M. Al-Majida, S. Yousufd, Z. Ul-Haqe, M.I. Choudharyd, A. El-Faham, *Inorganica Chimica Acta* 503 (2020) 119405

[2] N.A. Mathews, A. Jose, M.R.P. Kurup, *Journal of Molecular Structure* 1178 (2019) 544

[3] R. Huang, A. Wallqvist, D.G. Covell, *Biochemical Pharmacology* 69 (2005) 1009

[4] A.K. Renfrew, E.S. O'Neill, T.W. Hambley, E.J. New, *Coordination Chemistry Reviews* 375 (2018) 221