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Synthesis of new Co(II) complexes with 3-methoxy-salicylaldehyde based hydrazones as a possible approach in the treatment of cobalt poisoning

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***Abstract*—Hydrazones play an important role in bioinorganic chemistry as they easy form stable complexes with most of the transition metals. Many hydrazones are used as chelating agents in medical treatment for reducing the toxic effects of metals. By coordinating with metal ions these compounds can promote the excretion of the metals out the body. Cobalt ions are essential to human body as a part of Vitamin B_{12}. Although cobalt is important for human health, the excess of cobalt can be harmful. Two new Co (II) complexes with 3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone and 3-methoxysalicylaldehyde isonicotinoylhydrazone have been synthesized as a possible approach in the treatment of harmful health effects of cobalt poisoning. The hydrazones reacted with cobalt ions as monobasic tridentate ligands to yield mononuclear complexes with 1:2 metal:ligand molar ratio. The cobalt complexes were characterized by elemental analyses and IR spectroscopy. The spectral data of the complexes were interpreted on the basis of comparison with the spectra of the free ligands. This analysis revealed coordination to the metal ion through phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms. The complexes are quite stable and therefore these aroylhydrazones can be used as chelators in the cases of poisonings with cobalt.**

Keywords— hydrazones, Co(II) complexes, Co poisoning

I. INTRODUCTION

Cobalt is beneficial for humans because it is a constituent of cobalamin, also known as vitamin B_{12}, which is essential to maintain human health [1,2]. Vitamin B_{12} plays a key role in the normal functioning of the brain and the nervous system, and for the formation of blood. It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid metabolism and amino acid metabolism [1]. Naturally, the body stores a certain level of cobalt for healthy cellular function. Although cobalt is an essential requirement for good health, excess of cobalt in the human body can be harmful and chronic cobalt ingestion has caused serious health problems at doses far less than the lethal dose [3]. In the rare cases of cobalt poisoning with large levels of cobalt in the blood, people may need hemodialysis to reverse the effects of the poison. A possible approach in the treatment of cobalt poisoning can be the use of ligands that avidly bind cobalt. By coordinating with the intracellular and extracellular cobalt these ligands can promote the excretion of the metal out the body. Many hydrazones are used as chelating agents in medical treatment for reducing the toxic effects of metals as they easy form stable complexes with most of the transition metals. Salicylaldehyde benzoylhydrazone (SBH) belongs to a series of tridentate iron chelators effective in chemotherapy of Fe overload diseases such as β-thalassemia [4-7]. Various derivatives of salicylaldehyde benzoylhydrazone and their metal complexes have been synthesized in order to discover new pharmacologically active compounds [8-13]. Besides the ability to mobilize iron *in vivo*, it is interesting to investigate the affinity of these hydrazones to other metal ions. In view of the importance of the affinity towards cobalt ions, herein we report the synthesis and physicochemical characterization of new Co(II) complexes with two iron chelators 3-methoxy-salicylaldehyde-4-hydroxybenzoylhydrazone and 3-methoxy-salicylaldehyde isonicotinoylhydrazone.

II. MATERIALS AND METHODS

A. Reagents

All chemicals used for the synthesis of the compounds: 3-methoxysalicylaldehyde, 4-hydroxybenzhydrazide, iso-nicotinoyl hydrazide, $Co(CH_3COO)_2.4H_2O$ and 96 % ethanol were purchased from commercial sources and used as received. All of the other chemicals were of analytical grade.

The carbon, nitrogen and hydrogen content of the compounds were determined by elemental analyses on Euro EA 3000 – Single, EuroVector SpA. The melting points were determined using a Buchi 535 apparatus.

The IR-spectra were recorded using KBr pallets on Bruker Tensor 27 spectrophotometer in the range of 4000-400 cm^{-1}.

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 250 spectrophotometer at 250 MHz in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Chemical shifts (*d*) were reported in parts per million (ppm), *J* values were given in Hz. Splitting patterns were indicated by the symbols: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad).

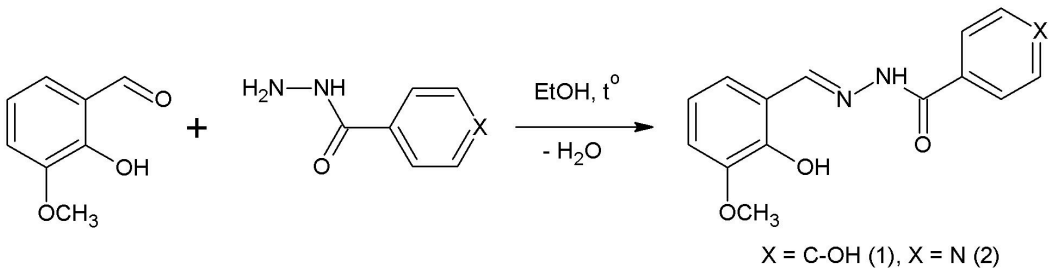

Fig. 1. Scheme of the synthesis of hydrazones.

B. *Synthesis of the ligands*

A solution of 3-methoxysalicylaldehyde (0,01 mol) in 96% ethanol (10 ml) was added to the solutions of 4-hydroxybenzhydrazide (0,01 mol) and isonicotinoyl hydrazide (0,01 mol) in 50 % aqueous ethanol (40 ml) and immediately precipitates were formed. An extra 96 % ethanol was added and the mixtures were stirred and heated until the solid phases were dissolved. The solutions were allowed to cool and stand at room temperature for 24 hours. During this time crystals of the products **1** and **2** were obtained, then filtered off. The solid hydrazones were dried for 2 days in a vacuum desiccator.

3-methoxysalicylaldehyde 4-hydroxybenzoylhydrazone (3mShBH) (**1**). Yield 85 %; Whitish solid; m.p. 196-197 °C; Anal. Calcd for $C_{15}H_{14}O_4N_2.H_2O$: C 59.21, H 5.30, N 9.21. Found: C 59.38, H 5.22, N 9.28; IR (KBr) ν (cm^{-1}): 3449, 3360 (Ar-OH), 3218 (N-H), 1646 (C=O), 1608 (C=N); ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 3.81 (s, 3H, -OCH_3), 6.86 (m, 3H, CH, aromatic protons of aldehyde), 7.01 (d, 1H, CH, aromatic proton of hydrazide, J=7.75 Hz), 7.11 (d, 1H, CH, aromatic proton of hydrazide, J=7.75 Hz), 7.84 (d, 2H, CH, aromatic protons of hydrazide, J=8.75 Hz), 8.61 (s, 1H, N=CH), 10.23 (br s, 1H, O-H, hydrazide), 11.11 (br s, 1H, N-H), 11.87 (br s, 1H, O-H, aldehyde); ^{13}C NMR (DMSO-d_6, 250 MHz) δ (ppm): 160.90 (C=O), 147.93 (CH=N), 55.82 (OCH_3).

3-methoxysalicylaldehyde isonicotinoylhydrazone (3mSIH) (**2**). Yield 89 %; Brightly yellow solid; m.p. 236-237 °C; Anal. Calcd for $C_{14}H_{13}O_3N_3$: C 61.99, H 4.83, N 15.49. Found: C 62.10, H 4.94, N 15.67; IR (KBr) ν (cm^{-1}): 3350 (Ar-OH), 3203 (N-H), 1691 (C=O), 1604 (C=N); ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 3.82 (s, 3H, -OCH_3), 6.87 (t, 1H, CH, aromatic proton of aldehyde, J=8 Hz), 7.05 (d, 1H, CH, aromatic proton of aldehyde, J=8 Hz), 7.20 (d, 1H, CH, aromatic proton of aldehyde, J=7.75 Hz), 7.85 (d, 2H, CH, aromatic protons of hydrazide, J=6 Hz), 8.72 (s, 1H, N=CH), 8.80 (d, 2H, CH, aromatic protons of hydrazide, J=6 Hz), 10.72 (br s, 1H, N-H), 12.23 (br s, 1H, O-H); ^{13}C NMR (DMSO-d_6, 250 MHz) δ (ppm): 161.29 (C=O), 150.34 (CH=N), 55.82 (OCH_3).

C. *Synthesis of the Co(II) complexes*

The metal complexes were obtained using the following general procedure: Aqueous ethanolic solution of Co-acetate was added to a solution of the ligands in 96 % ethanol in 1:2 metal-to-ligand molar ratios which resulted in immediate precipitation of metal complexes. The mixtures were stirred for 30 min to complete the reaction and then were allowed to stand undisturbed overnight at room temperature. Fine crystals were collected after filtration, washed with ethanol and dried over P_2O_5 in a vacuum desiccator.

Bis(3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone) cobalt (II) $[Co(C_{15}H_{13}O_4N_2)_2]$ **(3)** ; Yield 89 %; Brown greenish solid; Anal. Calcd for $[Co(C_{15}H_{13}O_4N_2)_2]$: C 57.24, H 4.6 N 8.90. Found: C 56.97, H 4.38, N 9.12; IR (KBr) ν (cm^{-1}): 3211 (N-H), 1620 (C=O), 1585 (C=N), 530 (Co-O), 435 (Co-N).

Bis-(3-methoxysalicylaldehyde isonicotinoylhydrazone) cobalt (II) $[Co(C_{14}H_{12}O_3N_3)_2]$ **(4)** ; Yield 86 %; Dark brown solid; Anal. Calcd for $[Co(C_{14}H_{12}O_3N_3)_2]$: C 56.10, H 4.04, N 14.02. Found: C 55.81, H 4.39, N 13.79; IR (KBr) ν (cm^{-1}): 3197 (N-H), 1640 (C=O), 1593 (C=N), 540 (Co-O), 445 (Co-N).

III. Results and Discussion

The ligands 3-methoxysalicylaldehyde 4-hydroxy-benzoylhydrazone and 3-methoxysalicylaldehyde isonicotinoylhydrazone were synthesized as previous described [10] according to the scheme on Fig.1.

The new cobalt compounds were characterized by elemental analyses. Experimental and calculated C, H, N values reveal 1:2 metal:ligand molar ratio in the complexes and suggest molecular formula $[ML_2]$. The complexes are quite stable and could be stored on air without any visible change. They are insoluble in water and ethanol and slightly soluble in DMSO.

The comparative IR spectral study of the ligands and their complexes revealed the coordination mode of the hydrazones during the complex formation. The medium intensity band at 3350-3360 cm^{-1} in the IR spectra of the ligands due to phenolic OH group had disappeared in the spectra of the complexes. This supports the suggestion for deprotonation of the ligands during the coordination and the displacement of a proton by the Co^{2+} ion. The band observed at 1604-1607 cm^{-1} in the spectra of the ligands which is attributed to azomethine C=N group is shifted in spectra of the complexes to lower wave number indicating the involvement of N-atom of the azomethine group in the complex formation. An intense band which appears at 1646-1691 cm^{-1} in the spectra of the ligands is assigned to the

frequency vibration of the carbonyl group C=O. In the spectra of the complexes a considerable negative shift is observed showing coordination through the carbonyl–oxygen atom of the free ligands. The NH stretching vibration in the free ligands occurs at 3203-3218 cm^{-1} and remains unaffected after complexation. This precludes the possibility of coordination through imine nitrogen atom. In addition, the appearance of medium bands at 530–540 cm^{-1} and 435–445 cm^{-1} in the spectra of the complexes can be assigned to ν(Co–O) and ν(Co–N), respectively.

The comparison of the IR data of the Co-complexes with those of the free ligands suggest that 3-methoxysalicylaldehyde 4-hydroxybenzoylhydrazone and 3-methoxysalicylaldehyde isonicotinoylhydrazone act as monobasic tridentate ligands and coordinate through phenolic-oxygen, azomethine–nitrogen and amide–oxygen atoms forming a six-membered chelate ring. Based on the above results, the structure in Fig.2 for the Co(II) complexes is suggested.

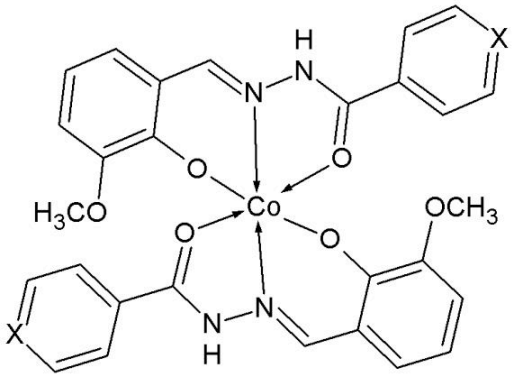

Fig. 2. The suggested structure of the cobalt complexes.

IV. Conclusion

New cobalt complexes were synthesized and characterized with elemental analyses and spectral investigations. The analytical data suggest stoichiometry [CoL_2]. The 3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone and 3-methoxysalicylaldehyde isonicotinoylhydrazone act as monobasic tridentate ligands coordinating to the cobalt ion through ONO donor sites and thus forming stable six-membered chelates. The complexes are quite stable and insoluble in water. It can be concluded that these aroylhydrazones possess high affinity towards cobalt ions and can be used as chelators in the cases of poisonings with cobalt ions.

Acknowledgment

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