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# Synthesis of New Bisamidoxime Ligands and their Monocharged Metal Complexes

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This paper describes the synthesis of two new bisamidoxime ligands with dithioether connecting groups. The ligands were obtained from ethane dithiol in two steps; i) cyanoalkylation ii) oximation with hydroxylamine. Cyanoalkylation of ethanedithiol was carried out by condensing with chloro acetonitrile and base-catalysed addition of acrylonitrile, yielding bis(cyanomethylthio) ethane and bis(cyanoethyl thio) ethane, respectively. Upon subsequent oximation with hydroxylamine, these bisnitrile compounds gave corresponding bis(amidoxime) ligands in reasonable yields. The ligands behave as tetradentate ligands and on interaction with Cu(II), Ni(II), Co(II) chlorides produces monocharged metal complexes in a  $[ML]^+ Cl^-$  composition.

**Keywords:** bis-amidoximes, dithioethers, monocharged metal complexes, mixed donor complexes.

## Introduction

Transition metal complexes of vic-dioximes are structurally well-known compounds, in which metal ions coordinate through nitrogen atoms. Generally coordination occurs through deprotonation of two ligands, to give neutral complexes which are soluble in organic solvents. However, dioximes in syn-configurations are coordinated through oxygen atoms of oxime groups by transition metal ions<sup>1</sup>. The most common example of dioxime complexes is the dimethylglyoxime-Ni(II) complex, which is also used for the analytical determination of Ni(II) ions<sup>2</sup>. Complexation with vic-diamidoxime ligands occurs in a similar fashion, yielding neutral complexes of transition metal ions<sup>3</sup>. There are only a few reports of metal complexes of bis amidoximes other than 1,2 diamidoximes<sup>4</sup>. One of these is polymeric amidoxime, obtained by the oximation of polyacrylonitrile. It has been shown that polymers with amidoxime pendant ligands are useful in the recovery of  $UO_2$  (II) ions from sea water<sup>5</sup>.

In this study, the complex-forming behaviour of two new bis(amidoxime) ligands with two thioether connecting groups, was examined because these ligands were expected to form three different types of transition metal complex:

- i) Neutral complexes in which metal ions coordinate through only amidoxime groups to give macrocyclic chelates with L/M (2:1).
- ii) Monocharged complexes in which metal ions, coordinating through both thioether and amidoxime groups, with L/M (1:1).

iii) Coordination polymers forming by chelation through thioether and amidoxime groups at both ends.

This study shows that the second possibility is preferred and only mononuclear complexes form by coordination through two thioether and two amidoxime groups. Complexation results in the formation of monocharged cationic complexes with chloride as the counter ion.

## Experimental

Acrylonitrile, chloroacetonitrile and ethane dithiol were analytical grade commercial products (Fluka) and used without any further purification. Magnetic susceptibility measurements were carried out using the Guy Balance technique in the inorganic chemistry laboratory of Strathclyde University, Glasgow. Elementary microanalysis (Perkin Elmer 120) and NMR (Bruker AW-80) were used in the structural analysis.

### **1,2 Bis(cyanomethyl thio) ethane (CME):**

4.6 g (0.2 mol) sodium was added portionwise to 50 ml of absolute ethanol in a two-necked flask equipped with a reflux condenser and dropping funnel. When the reaction subsided the flask was transferred into an ice-bath. With constant stirring, 8.4 ml. (9.4 g., 0.1 mol) of 1,2 ethane dithiol in 50 ml of dioxane was added dropwise to the flask. The mixture was stirred for 30 min. at room temperature and refluxed for 30 min. Then 12.60 ml (0.2 mol) chloroacetonitrile was added. The mixture was refluxed for 30 h. After cooling, the reaction content was poured into 500 ml. of cold water and filtered. The precipitate was recrystallized from 60 ml ethanol and dried at 40°C for 12 h. Yield 17 g (99%), mp: 69.5°C. The product was soluble in ethanol, acetone. THF, dioxane and DMF.

Elementary analysis (Calculated from  $C_6H_8N_2S_2$ ) revealed: C:(41.86%), 41.66 H:(4.55%), 4.39, N:-(16.27%), 16.10 S:(37.20%), 37.00.

IR spectra (from KBr disk): CN stretching vibration was exhibited at  $2250\text{ cm}^{-1}$ , and asymmetrical and symmetrical stretching vibrations of aliphatic C-H groups appeared at  $2950$  and  $2910\text{ cm}^{-1}$ , respectively.

$^1\text{H-NMR}$  spectra: ( $\delta$  ppm, in acetone- $d_6$  with TMS internal standard): 3.72 ppm. (s, 4H, S-CH<sub>2</sub>-CN), 3.11 ppm. (s, 4H, -S-CH<sub>2</sub>-CH<sub>2</sub>-S).

### **1,2 Bis(2-cyanoethyl thio) ethane (CEE):**

This compound was prepared by cyanoethylation of 1,2 ethane dithiol<sup>6</sup>.

### **1,2 Bis(2-amino, 2-oximino ethyl thio) ethane (BHE):**

6.95 g (0.1 mol) hydroxylamine hydrochloride was dissolved in 5 ml water in a 500-ml-volume two-necked flask. The solution of 8.6 g (50.0 mmol) 1,2 bis (2-cyanomethyl thio) ethane in 100 ml. ethanol was added slowly. To this solution, 50 ml ethanolic NaOH (2.3 g sodium in 50 ml ethanol) was added portionwise. The mixture was refluxed with constant stirring for 96 h. Then the precipitated NaCl was filtered while hot and the filtrate left overnight. The crystalline precipitate was filtered, washed with 15 ml acetone and recrystallized from ethanol.

Yield 2.8 g (23.5 %), mp:106°C, soluble in ethanol, DMF and insoluble in water.

Elementary Analysis (Calculated  $C_6H_{14}N_4S_2O_2$ ) revealed: C:(30.2%), 30.16, H:(5.88%), 5.89 N:(23.5%), -22.8.

$^1\text{H-NMR}$  spectra ( $\delta$  ppm, in DMSO- $d_6$ , TMS as internal Standard): 9.34 ppm (broad s, 2H, oxime protons), 5.50 ppm (s, 4H, NH<sub>2</sub>), 3.18 ppm (s, 4H, CH<sub>2</sub>), 2.73 ppm (s, 4H, S-CH<sub>2</sub>-CH<sub>2</sub>-S).

IR spectra (with KBr disk): The stretching vibration of the nitrile group of the starting bis nitrile at  $2250\text{ cm}^{-1}$  disappeared completely. New bands arising from NH asymmetrical and symmetrical stretching vibrations appeared at  $3485$  and  $3360\text{ cm}^{-1}$ , respectively. Plane bending vibration of the N-H bond was

observed at  $1660\text{ cm}^{-1}$ . OH stretching and N-O stretching vibration bands associated with oxime groups were observed at  $3100$  and  $960\text{ cm}^{-1}$ , respectively.

**1,2 Bis(3-amino, 3-oximino propyl thio) ethane(BHP):**

The same procedure as for CEE was followed in the preparation of this compound. Yield 30.8%, mp:  $136^\circ\text{C}$ , soluble in hot ethanol, DMF, insoluble in acetone.

Elementary Analysis (Calculated from  $\text{C}_8\text{H}_{18}\text{N}_4\text{S}_2\text{O}_2$ ) revealed: C:(36.09%) 36.8 H:(6.76%) 6.50 N:(21.05%) 19.57.

$^1\text{H-NMR}$  spectra ( $\delta$  ppm, in  $\text{DMSO}_{d-6}$ , TMS as internal Standard): 8.58 ppm (s, 2H, oxime protons); 5.42 ppm (s, 4H,  $\text{NH}_2$ ); 2.6-3.1 ppm (m, 8H,  $\text{CH}_2\text{-CH}_2\text{-S}$ ,  $\text{S-CH}_2\text{-CH}_2\text{-C}$  with  $\text{A}_2\text{B}_2$  splitting pattern).

IR spectra (with KBr disk): The nitrile group vibration band of the starting compound disappeared completely. New bands of the amidoxime groups were as follows;  $3450\text{ cm}^{-1}$  (asymmetric N-H str.),  $3360\text{ cm}^{-1}$  (N-H sym. str.),  $1592\text{ cm}^{-1}$  (N-H plane bending),  $3150\text{ cm}^{-1}$  (O-H str.),  $1195\text{ cm}^{-1}$  (C-N str.),  $950\text{ cm}^{-1}$  (N-O str.).

**General Procedure for Preparation of Metal Complexes:**

$\text{NiCl}_2.6\text{H}_2\text{O}$ ,  $\text{CoCl}_2.6\text{H}_2\text{O}$  and  $\text{CuCl}_2.2\text{H}_2\text{O}$  salts were used to prepare the metal complexes. In each procedure 10 mmol of the metal salt in 20 ml ethanol and 10 mmol of the ligand were mixed by stirring. A voluminous colored complex was precipitated. Then the mixture was heated to reflux for 30 min. and 0.6 ml of concentrated ammonia solution was added dropwise. The resulting mixture was filtered and washed with cold water, alcohol and ether. This was dried at  $60^\circ\text{C}$  for 24 h. None of the complexes melted below  $300^\circ\text{C}$ , but were soluble in DMSO and pyridine-methanol (1:1), and slightly soluble in water.

The elementary analysis and UV-visible spectral data of the resulting metal complexes are listed in Table 1. However, the sulphur contents of the copper complexes were not determined by elementary micro analysis due to interference from copper ions.

## Results and Discussion

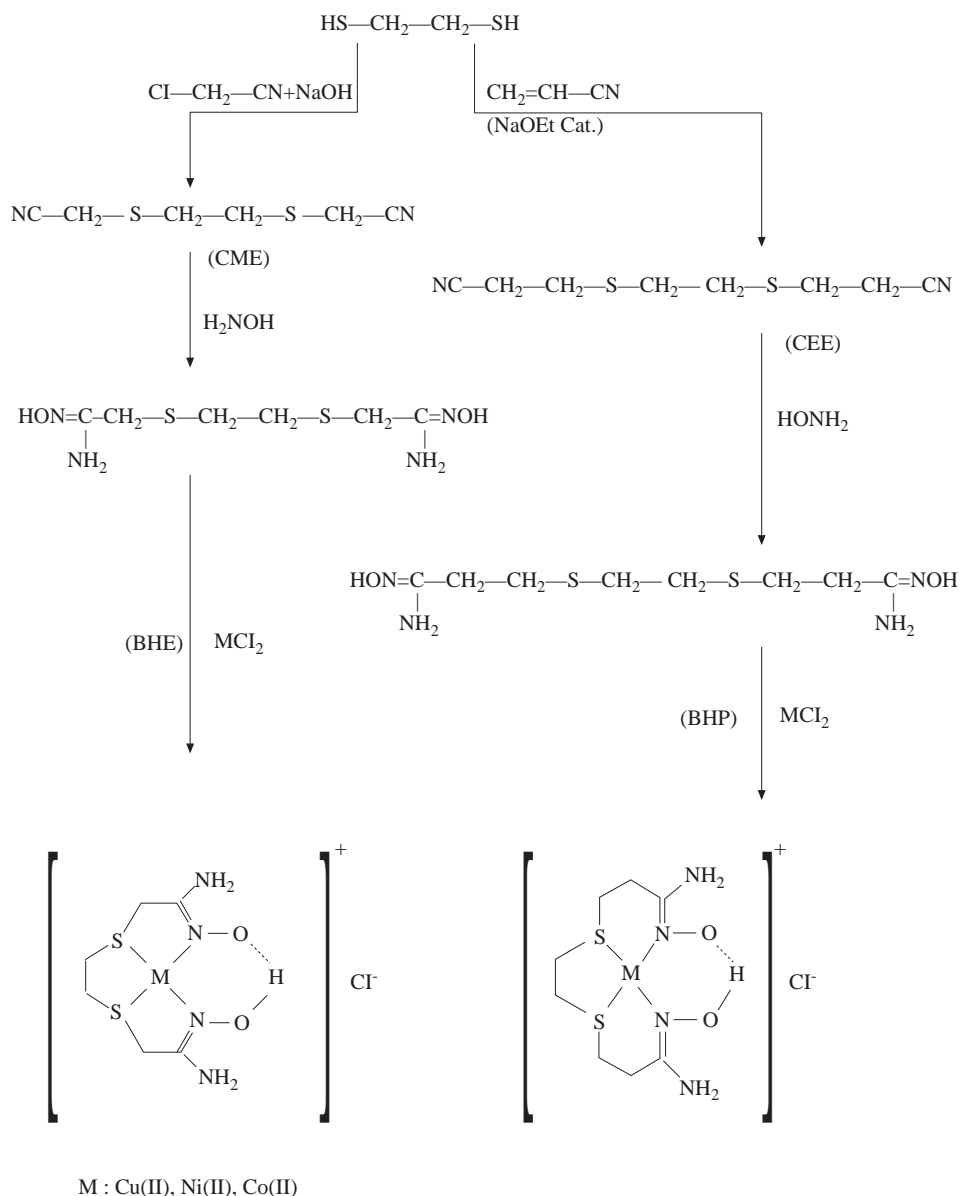
There are two common methods of preparing amidoximes:

- i) by reacting chloro oximes with amines<sup>4</sup>.
- ii) by oximation of nitrile compounds with hydroxylamine<sup>7</sup>.

In this study, the second method was used to obtain the amidoxime ligands. In this way two new ligands having both amidoximes and thioether groups were prepared from ethanedithiol. For this purpose, first, ethane dithiol was cyanomethylated by condensation with chloroacetonitrile to give 1,2 bis (cyanomethylthio) ethane (CME). The cyanoethyl derivative was prepared with a classical cyanoethylation reaction of acrylonitrile with ethanedithiol (CEE). The conversion yields of the cyano derivatives were almost quantitative.

Oximation of the resulting bis-nitrile compounds with hydroxylamine in alcohol gave corresponding bis amidoximes, as outlined in Scheme 1. The structures of the resulting 1,2 bis (2-hydroximino, 2-aminoethylthio) ethane (BHE) and 1,2 bis (3-hydroximino, 2-aminopropylthio) ethane (BHP) were elucidated by elementary microanalysis,  $^1\text{H-NMR}$  and FT-IR.

Although the oximation reactions gave low yields, the NMR spectra indicate that the bis-oxime compounds obtained were fairly pure. The conversion of the nitriles was easily followed by the disappearance of nitrile stretching vibrations exhibited at  $2250\text{ cm}^{-1}$  in FT-IR spectra.



**Scheme 1.**

After comparing the NMR spectra of BHE with those of CME, it is clear that replacement of the strong deshielding nitrile group by amidoxime causes a shift in the signals of methylene protons from 3.72 ppm to 3.18 ppm. The singlet of ethylene protons also shifts from 3.11 ppm to 2.73 ppm. Two additional signals associated with  $\text{NH}_2$  and oxime groups of BHE are  $\text{D}_2\text{O}$  exchangeable and appear at 5.50 and 9.34 ppm, respectively. In the case of BHP, oxime and  $\text{NH}_2$  proton signals are clearly observed at 8.58 and 5.42 ppm, respectively. The signals arising from bridged ethylene protons and ethyl group carrying amidoxime are observed between 2.6-3.1 ppm as a multiplet.

Having both amidoxime and thioether functions, these compounds have received attention in relation to medical applications and are expected to antitumor activities. A careful examination of these activities against nine different kinds of cancer tumor (leukemia, lung cancer, CNS cancer, melanoma, ovarian cancer,

renal cancer, prostate cancer and breast cancer) in vitro by the National Institute of Health, USA (Maryland) indicates that only the second ligand, BHP, exhibits inhibiting effects on prostate cancer, but not on other tumors.

**Table 1.** The properties of the metal complexes obtained.

Ligand	Complex (colour)	Elementary Analysis % Calculated (found)	UV-Visible Data		Magnetic Moment (BM)	Unpaired electron	Assigned Coordination
			Absorption Bands $\lambda_{\max}(\epsilon_{\max})$	Transitions			
	NiC <sub>6</sub> H <sub>13</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (green)	C: 21.74 (21.21) H: 3.95 (4.21) N: 16.90 (15.95) Cl:10.70 (11.02)	265 nm (951) 290 nm (broad) 600 nm (62)	L → Ni(II), n → π* L → Ni(II) d → d	0	0	Planar
C <sub>6</sub> H <sub>14</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> (BHE)	CoC <sub>6</sub> H <sub>13</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (black)	C:21.72 (20.09) H: 3.92 ( 4.31) N:16.89 (15.72) Cl:10.69 (11.04) S : 19.33 (19.37) Co:17.76 (17.70)	270 nm (1627) 615 nm (20)	L → Co(II), n → π* d → d	2.117	1.3	Planar
	CuC <sub>6</sub> H <sub>13</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (dark green)	C: 21.42 (20.76) H : 3.86 ( 3.77) N :16.66 (16.23) Cl:10.55 (10.21) Cu:18.89 (18.15)	264 nm (4057) 290 nm (broad) 680 nm (6.5)	L → Cu(II), n → π* L → Cu(II) d → d	1.8	1.1	Planar
	NiC <sub>8</sub> H <sub>17</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (green)	C :26.73 (26.15) H : 4.76 ( 4.79) N :15.58 (14.79) Cl: 9.86 (10.18) S :17.83 (16.83) Ni:16.33 (15.94)	263 nm (723) 295 nm (broad) 340 nm (broad) 647 nm (24)	L → Ni(II), n → π* L → Ni(II) d → d	0	0	Planar
C <sub>8</sub> H <sub>18</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> (BHP)	CoC <sub>8</sub> H <sub>17</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (black)	C :26.71 (26.21) H : 4.76 ( 4.39) N :15.57 (14.98) Cl: 9.85 (10.25) S :17.82 (17.18) Co:16.38 (16.50)	273 nm (2136) 310 nm (broad) 620 nm (198)	L → Co(II), n → π* L → Co(II) d → d	4.509	3.6	Tetrahedral
	CuC <sub>8</sub> H <sub>17</sub> N <sub>4</sub> S <sub>2</sub> O <sub>2</sub> Cl (dark green)	C :2.37 (24.92) H : 4.67 ( 3.99) N :15.38 (14.40) Cl: 9.74 (10.61) Cu:17.44 (17.05)	262 nm (4017) 290 nm (broad) 640 nm (43)	L → cu(II), n → π* L → Cu(II)	1.49	0.8	Planar

### Metal Complexes:

Elementary microanalysis of C, H, N, S and chlorine analysis of the metal complexes indicated that all the metal complexes have a L/M (1:1) composition. According to elementary analysis there one chlorine atom for each metal ion. They were slightly soluble in water. In order to decide whether the chlorine was bounded ionically or covalently, a small amount of a complex sample was dispersed in distilled hot water and filtered. AgNO<sub>3</sub> testing of the filtrates gave a precipitate of AgCl. This qualitative chlorine test implies that in all metal complexes chlorine is bounded to the complex ionically. Hence, complexation gives cationic complexes with accompanying chloride ions in the form of counter anions.

The coordination geometries of the metal complexes were assigned by magnetic susceptibility measurements. Based on the simple spin-only formula the coordination geometries of all the complexes, except for Co(II) complexes of BHP, were found to be planar (Table 1).

According to these observations, the complexes obtained must be monocharged cationic complexes in which metal ions coordinate through two sulphide and two oxime groups so that one bridged hydrogen locates between two oxime groups. The counter anion is the anion of the metal salt, chlorine.

In the case of copper complexes, both the tetrahedral and planar forms have one unpaired electron and, on the basis of magnetic susceptibility measurements, it was not possible to predict the coordination geometry. Their structures were assigned by visible spectra. Only one broadened absorption maxima was observed in the visible spectra of both the Cu-BHE and Cu-BHP complexes, at 680 nm ( $\epsilon_{\max} = 6.5$ ) and

640 nm ( $\epsilon_{\max} = 43$ ), respectively. The corresponding ligand field splitting energies were in the range 14700-15600  $\text{cm}^{-1}$ , which was a much wider range than that of tetrahedral complexes of Cu(II). Hence, these complexes must have planar coordination with the  $C_{2v}$  point group and these observed visible transitions were  $^1A_1 \rightarrow ^1A_2$ .

Complex formations through metal ions were also followed through IR spectra. C=N stretching vibration peaks of the ligands at about 1660  $\text{cm}^{-1}$  shifted to 1640  $\text{cm}^{-1}$  after complexation with the metal ions. Another indication of the complex formation was N-O stretching vibrations which were observed at 1000  $\text{cm}^{-1}$ . In the case of the ligands these vibrations appeared in the 960-990  $\text{cm}^{-1}$  range. This shift was because of the coordination effect of the metal ion, which caused an increase in the covalency of the N-O bond. Moreover, the strengths of O-H stretching vibrations in the 3100-3150  $\text{cm}^{-1}$  range decreased somewhat upon complexation.

In conclusion, the new amidoxime ligands with thioether connecting units behave as tetradentate ligands and give monocharged cationic L/M (1:1) complexes. Complexation with metal ions proceeds via cyclization of the flexible ligands and thermodynamically stable five or six membered chelates form around the metal ion.

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