

Synthesis and experimental/theoretical evaluations on redox potentials and electronic absorption spectra for copper symmetric bis (thiosemicarbazone) complexes

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ABSTRACT

Two new bis(thiosemicarbazone) ligands 2-[1-(2-{3-[2-({(methyl)carbothioyl}hydrazono)-methyl]phenoxy}propoxy)phenyl)methylidene]-N¹-(methyl)-1-hydrazinocarbothiamide (**H₂L5**), 2-[1-(2-{3-[2-({(methyl)carbothioyl}hydrazono)methyl]phenoxy}-2-hydroxypropoxy)-phenyl)methylidene]-N¹-(methyl)-1-hydrazinocarbothiamide (**H₂L6**), and their Cu(II) complexes were synthesized and characterized by physico-chemical and spectroscopic methods. Among eight DFT calculation methods PBE0/6-311+G(d,p)//B3LYP/6-31+G(d) method was the best method to predict one-electron reduction potentials (E_{calc}) of these two new and four previously prepared copper complexes in DMF. The effects of solvation in DMF is incorporated as a self-consistent reaction field (SCRF) using the PCM solvent model. This model was capable to predict the experimental results with an error in the range of -0.200 to -0.002 V in comparison with experimental values (E_{exp}) derived from CV. The changes in solvation energy, $\Delta\Delta_{\text{solv}}G^\circ$, play important role and without considering the effects of solvation in the calculations, the results are more different from the experimental ones. The calculated one-electron reduction potentials correlated with the energies of both the LUMO of the Cu^{II} and the HOMO of the Cu^I complexes.

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1. Introduction

An estimation of 12 million deaths from cancer is expected in the world in 2030 [1]. Since the discovery of the importance of metal containing compounds used in cancer treatment, reports around the use of metal complexes are increasing [2–6]. Among these cancer treatment compounds, thiosemicarbazones (TSC) due to their wide pharmacologic applications [7] including anti-cancer [8], antitumor [9–11], antibacterial [12], antifungal [13], antiviral [14] and antimalarial [15,16] activities are of increasing interest. For example, copper complexes of bis(thiosemicarbazone) (BTSC) ligands act as radiopharmaceuticals for the specific targeting of hypoxic tissue [12,17–19]. It is accepted that bioreduction of Cu^{II} to Cu^I by intracellular reducing agents and forming an unstable Cu^I complex is at the heart of this mechanism [20]. It was suggested [21,22] that lowering the reduction potential (i.e., making it harder to be reduced) would prevent trapping in less reducing (i.e., well-oxygenated) cells, leading to hypoxia-selective

uptake. We have reported Cu^{II} complexes of four BTSC ligands, **H₂L1**, **H₃L2**, **H₂L3**, and **H₃L4** (Fig. 1) recently, which showed a prominent ability to stabilize low oxidation state of Cu^I [23,24]. The effects of halogen groups on phenyl rings at R₂ positions and a hydroxyl group at R₁ position on the redox couple Cu^{II}/Cu^I, have been investigated experimentally. However in some cases it was found that, changes in the redox potentials are not consistent with changes expected on the basis of substituent inductive effects. The results showed that, the link between redox potential and inductive effect was complicated and other factors were in play. For this purpose, accurate calculation and prediction of their one-electron reduction potentials in solution phase would be beneficial, not only to help to explain observed trends, but also in the rational designing of more highly selective complexes for hypoxia.

Density functional theory (DFT) has proven to be an efficient and comparatively reliable tool for electronic structure computation of transition metal complexes [25,26]. Theoretical calculations of redox potentials, typically refer to a free energy cycle. An example of this cycle, named Born–Haber cycle, is represented in Scheme 1 where the standard Gibbs free energy change of redox half reaction, $\Delta_{\text{EA}}G^\circ(\text{sol})$, consists of the free energy change in the

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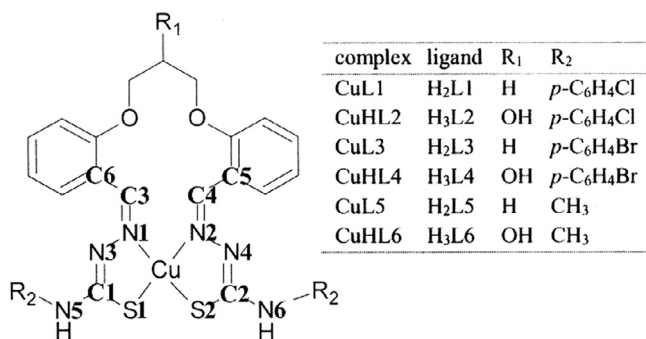
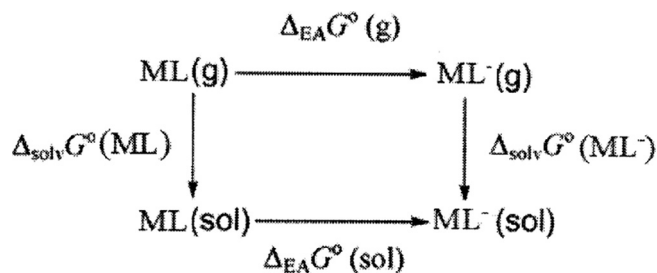


Fig. 1. Structures of the copper bis(thiosemicarbazone) complexes studied in this investigation.



Scheme 1. Thermodynamic cycle used to determine one-electron reduction potential in solution.

gas phase, $\Delta_{EA}G^\circ(g)$, the solvation free energy changes of the oxidized, $\Delta_{sol}G^\circ(ML)$, and reduced, $\Delta_{sol}G^\circ(ML^-)$, species. Herein, this method was used to calculate the reduction potential of half reaction.

Therefore, we calculated the redox potentials of the Cu^{II} complexes of previous reported works and two Cu^{II} complexes of new BTSC ligands, **H₂L5** and **H₃L6** with more negative potentials based on prediction.

2. Experimental

2.1. Materials and physical measurements

2-[3-(2-Formylphenoxy)propoxy]benzaldehyde (**1**) and 2-[3-(2-formylphenoxy)-2-hydroxypropoxy]benzaldehyde (**2**) were prepared according to the literature methods [27,28]. Other reagents and solvents were obtained from Alfa Aesar and Merck and were used without any purification. ¹H NMR and ¹³C NMR spectra were collected using a Bruker Avance 400 spectrometer in DMSO solvent. Infrared spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer in the region of 400–4000 cm⁻¹ using KBr pellets. Electronic absorption spectra were recorded in the region of 230–1100 nm with a Shimadzu UV–Vis 1700 spectrometer in CH₂Cl₂ solvent. Melting points were obtained with an Electrothermal 9100. Electrochemical studies were carried out with an Autolab PGSTAT 302 ECO CHEMIE apparatus, using a glassy carbon as a working electrode, a platinum wire as an auxiliary electrode, and an Ag/AgCl reference electrode. The ferrocene/ferrocenium couple (Fc/Fc⁺; E_{1/2} = 0.505 V) was used as an internal standard but all potentials in the paper are referenced to the Ag/AgCl reference electrode. Solutions containing 10⁻³ M of complexes and 0.10 M LiClO₄ as supporting electrolyte were deoxygenated by a stream of high purity nitrogen for at least 10 min.

2.2. Synthetic procedures

2.2.1. Synthesis of the ligands

H₂L1, **H₃L2**, **H₂L3**, and **H₃L4** were synthesized according to the literature methods [23,24].

2.2.1.1. Synthesis of H₂L5. **1** (2 mmol, 0.57 g) was dissolved in 20 ml methanol. Then a methanolic solution of 4-methyl-3-thiosemicarbazide (4 mmol, 0.42 g) was added and refluxed for 4 h. The milk-white precipitate was formed before finishing the whole time of reflux. The mixture was filtered and the milk-white precipitate was washed with hot methanol. Yield (0.83 g, 90%). m.p. 233 °C. Calcd for C₂₁H₂₆N₆O₂S₂ (F.W = 458.602), %: C, 55.00; H, 5.71; N, 18.33; Found, %: C, 55.21; H, 5.49; N, 18.11. FT-IR (ν/cm⁻¹): 3154 w (NH), 2996 w, 2937 w (CH_{aliphatic}), 1602 s (C=C_{aromatic}), 1546 s (C=N), 1451 s (C=C_{aromatic}), 1330 m (C=S), 1292 w, 1251 s (C—O—C)_{asym}, 1160 w, 1080 s (C—O—C)_{sym}, 753 s (δ CH_{aromatic})_{o.o.p.}. ¹H NMR (DMSO-*d*₆): δ 2.24 (2H, quintet, CH₂), 2.99 (6H, s, NCH₃), 4.26 (4H, t, ArOCH₂), 6.97 (2H, t, ArH), 7.09 (2H, d, ArH), 7.37 (2H, t, ArH), 8.09 (2H, d, ArH), 8.49 ((2+1)H, s, ArCHN+NH—Me), 11.47 (1H, s, C(S)—NH—N) ppm. ¹³C{¹H} NMR (DMSO-*d*₆): δ 177.43(CS), 157.06 (C=N), 137.73, 131.35, 125.96, 122.49, 120.72, 112.60 (Aromatics), 64.53 (ArOCH₂), 30.90 (NCH₃), 30.77 (NCH₃), 28.88 (CH₂) ppm.

2.2.1.2. Synthesis of H₃L6. **H₃L6** ligand was synthesized in a similar procedure to that of **H₂L5**, except that **2** (2 mmol, 0.60 g) was used instead of **1** as dialdehyde. Yield (0.87 g, 92%). m.p. 242 °C. Calcd for C₂₁H₂₆N₆O₃S₂ (F.W = 474.602), %: C, 53.14; H, 5.52; N, 17.71; Found, %: C, 53.32; H, 5.38; N, 17.87. FT-IR (ν/cm⁻¹): 3308 m (OH), 3224 m (NH), 3000 w (CH_{aromatic}), 2839 w (CH_{aliphatic}), 1600 s (C=C_{aromatic}), 1551 s (C=N), 1455 s (C=C_{aromatic}), 1336 s (C=S), 1293 w, 1250 s (C—O—C)_{asym}, 1162 m, 1081 s (C—O—C)_{sym}, 756 s (δ CH_{aromatic})_{o.o.p.}. ¹H NMR (DMSO-*d*₆): δ 3.00 (3H, s, NCH₃), 3.09 (3H, s, NCH₃), 3.41 (4H, s, ArOCH₂), 4.22 (5H, m, CH₂CH(OH)CH₂) 5.39 (1H, d, CHO), 6.98 (2H, t, ArH), 7.11 (2H, d, ArH), 7.37 (2H, dt, ArH), 8.08 (2H, dd, ArH), 8.48 ((2+2)H, s, ArCHN+NH—CH₃), 11.46 (2H, s, C(S)—NH—N) ppm. ¹³C{¹H} NMR (DMSO-*d*₆): δ 177.46 (CS), 157.06 (C=N), 137.88, 131.26, 126.03, 122.55, 120.71, 112.65 (Aromatics), 69.32 (HCOH), 67.55 (ArOCH₂), 30.87 (NCH₃) ppm.

2.2.2. Synthesis of copper complexes

CuL1, **CuHL2**, **CuL3**, and **CuHL4** complexes were synthesized according to the literature methods [23,24]. Synthetic procedures of other two new copper complexes were the same; so it is just stated that general procedure and details of each complex are reported as below.

A methanol solution of Cu(CH₃COO)₂·H₂O (1 mmol, 0.20 g) was added to a hot solution of corresponding ligand (1 mmol) dissolved in dichloromethane–methanol mixture (4:1) under reflux. Reaction mixture was stirred at reflux for 4 h. The solvent was concentrated and products were filtered off.

2.2.2.1. CuL5. A dark green precipitate. Yield (0.45 g, 86%). m.p. 189–191 °C. Calcd for C₂₁H₂₄CuN₆O₂S₂ (F.W = 520.133), %: C, 48.49; H, 4.65; N, 16.16; Found, %: C, 48.55; H, 4.34; N, 16.02. FT-IR (ν/cm⁻¹): 3378 m (NH), 2930 m, 2879 m (CH_{aliphatic}), 1598 s (C=C_{aromatic}), 1499 s (C=N), 1452 s (C=C_{aromatic}), 1331 w (C—S), 1285 m, 1241 s (C—O—C)_{asym}, 1161 s, 1108 m, 1051 s (C—O—C)_{sym}, 751 s (δ CH_{aromatic})_{o.o.p.}

2.2.2.2. CuHL6. A dark green precipitate. Yield (0.38 g, 70%). m.p. 185 °C. Calcd for C₂₁H₂₄CuN₆O₃S₂ (F.W = 536.132), %: C, 47.05; H, 4.51; N, 15.68; Found, %: C, 47.20; H, 4.31; N, 15.47. FT-IR (ν/cm⁻¹): 3419 m (NH, OH), 2930 m (CH_{aliphatic}), 1596 s

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