Syntheses, Structures, and Electrochemical Studies of *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine Cu(II) Complexes as Pendent Alkoxy Derivatives of Cu(ATSM)

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Abstract

A series of N_2S_2 -Cu(II) complexes based on N,N' -bis(alkylthiocarbamate)butane-2,3-diimine ligands have been synthesized and characterized by spectroscopic, electrochemical, and single crystal x-ray diffraction methods. This class of ligands contains a conjugated N_2S_2 chelate framework with a non-coordinating, terminal alkoxy (-OR) group. Ligands and Cu(II) complexes were investigated for $R = \text{Me, Et, } ^n\text{Pr, } ^i\text{Pr, and octyl}$. Additionally, N,N' -bis(ethylthiocarbamate)hexane-3,4-diimine and its Cu(II) complex were analyzed. Single crystal x-ray diffraction studies on all six Cu(II) complexes confirm a square planar Cu(II) environment with no significant changes in the core structure as a function of R . Spectroscopic studies are consistent with a similar electronic environment in all complexes. However, electrochemical investigations reveal significant shifts in the $\text{Cu}^{(\text{II/I})}$ and $\text{Cu}^{(\text{III/II})}$ reduction potentials throughout the series. The complexes are analogues of the well-known bis(thiosemicarbazone) Cu(II) which contain a similar donor core with terminal, non-coordinating amines. Substitution of the terminal amines of bis(thiosemicarbazones) with the alkoxy groups of N,N' -bis(alkylthiocarbamate)butane-2,3-diimines allows tuning of redox potentials with minimal changes in the physical and electronic structure.

Introduction

The biological applications of the copper complex Cu(ATSM) (ATSM = diacetyl-bis(4-methylthiosemicarbazonato) as a diagnostic and therapeutic agent have been extensively studied. The Cu(II) ion sits in a conjugated dianionic N₂S₂ framework with terminal –NHMe functional groups that do not participate in metal-ligand binding, Scheme 1. Cu(ATSM) has been evaluated as a ⁶⁴Cu and ⁶²Cu radiopharmaceutical for selective imaging of hypoxia.¹⁻⁵ The neutral, planar Cu(ATSM) is proposed to diffuse through cell membranes with no net uptake under normoxic conditions. However, under the low oxygen conditions of hypoxia Cu(ATSM) is reduced preventing it from exiting the cell. More recently, Cu(ATSM) has been evaluated for the treatment of cancer⁶ and neurodegenerative diseases.⁷⁻¹⁰ Phase I clinical trials as a therapeutic for amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) are currently underway.¹¹

The biological importance of Cu(ATSM) has led to the synthesis and characterization of a large number of related copper bis(thiosemicarbazonato) complexes with symmetric and asymmetric variation at the R₁ and R₂ positions.¹²⁻²¹ Substitution at the R₁ position has largely focused on other amine derivatives to investigate the impact on selectivity and/or reduction potential. In general, chain extension has a small effect on the Cu^{II/I} potential,¹²⁻¹³ although modification with aromatic rings can lead to stabilization of Cu(I) by as much as +240 mV.¹⁴ Que and co-workers recently reported symmetric and asymmetric R₁ derivatives with the –NHMe groups replaced with –NHCH₂CF₃ with stabilization of Cu(I) by ~70 mV per –NHCH₂CF₃. Interestingly, these complexes allow for hypoxia imaging by ¹⁹F MRI, thus avoiding the need for ⁶⁴Cu.¹⁵ Variation of the R₂ backbone methyl groups with hydrogen or phenyl substituents also stabilize Cu(I), with the later showing a larger effect of ~240 mV.^{12, 14} The effect of R₂ group substitution for a wide variety of functional groups was evaluated using

experimentally benchmarked density functional theory calculations of Cu(II/I) reduction potentials. A Hammett analysis of the theoretical Cu(II/I) potentials is consistent with an inductive effect with Cu(I) stabilized by electron-withdrawing substituents.²²

The numerous derivatives of Cu(ATSM) reported to date have by and large maintained an N₂S₂ donor core with terminal amine based R₁ groups. Our research highlights a modification to the ligand framework by incorporation of alkoxy groups at the terminal R₁ position. As outlined in Scheme 1, a series of six ligands and their Cu(II) derivatives have been synthesized and fully characterized. One compound was previously synthesized and characterized by UV-visible spectroscopy.²³ As detailed below, this results in a substantial shift in the Cu(II/I) reduction potential relative to Cu(ATSM).

Scheme 1. Syntheses of complexes **7 – 12**.

Experimental Section

Materials and Methods. All reagents and solvents were purchased from commercial sources and used as received unless otherwise indicated. Reactions were conducted open to air and under

ambient conditions unless otherwise noted. Xanthates²⁴ and hydrazinecarbothioic acid *O*-alkyl esters²⁵ were synthesized according to literature methods.

***N,N'*-bis(methylthiocarbamate)butane-2,3-diimine, H₂MTCB (1).** The hydrazinecarbothioic acid *O*-methyl ester (3.2 g, 0.030 mol) was dissolved in ethanol (50 mL). To this solution 2,3-butanedione (1.3 mL, 0.015 mol) was added via syringe with stirring. A catalytic amount (5 drops) of concentrated sulfuric acid was added resulting in a white precipitate. The suspension was stirred for 16 hours. The white precipitate was isolated by filtration and washed with ethanol and ether. Yield = 3.6 g (93%). ¹H NMR, (C₂D₆SO, 400 MHz) δ 2.11 (s, 6H) 4.03 (s, 6H) 11.46 (s, 1H) 11.77 (s, 1H). ¹³C{¹H} NMR, (CDCl₃, 100 MHz) δ 12.3, 58.5, 117.8, 188.0. IR cm⁻¹: 3240 (w) and 1503 (m) (NH) 1419 (m) (CH) 1341 (m) and 1222 (s) (CN) 1137 (s) (CO) 1060 (s) (CS).

***N,N'*-bis(ethylthiocarbamate)butane-2,3-diimine, H₂ETCB (2).** Compound **2** was prepared using the same protocol as for **1**. Addition of 2,3-butanedione (2.3 mL, 0.027 mol) to hydrazinecarbothioic acid *O*-ethyl ester (6.4 g, 0.053 mol) in ethanol (50 mL) yielded **2** as a white solid. Yield = 7.74 g (98%). ¹H NMR, (C₂D₆NO, 400 MHz) δ 1.51 (br, 6H) 2.46 (br, 4H) 4.74 (s, 6H) 11.51 (s, 1H) 11.92 (s, 1H). IR cm⁻¹: 3241 (w) and 1498 (s) (NH) 1403 (m) (CH) 1317 (m) and 1211 (s) (CN) 1135 (m) (CO) 1049 (m) (CS).

***N,N'*-bis(*n*-propylthiocarbamate)butane-2,3-diimine, H₂PTCB (3).** Compound **3** was prepared as described for **1** from hydrazinecarbothioic acid *O*-propyl ester (2.1 g, 0.015 mol) and 2,3-butanedione (0.66 mL, 0.0075 mol) in ethanol (50 mL). Yield = 0.95 g (40%). ¹H NMR, (CDCl₃, 400 MHz) δ 0.99 (t, 6H, *J*=7.28) 1.84 (quint, 4H, *J* = 6.24 Hz) 2.13 (s, 6H) 4.55 (t, 4H, *J* = 6.22 Hz) 9.15 (s, 2H). ¹³C{¹H} NMR, (CDCl₃, 100 MHz) δ 9.78, 10.3, 21.9, 29.7, 187.6. IR

cm⁻¹. 3234 (w) and 1497(s) (NH) 1402 (m) (CH) 1334 (m) and 1207 (s) (CN) 1135 (s) (CO) 1052 (s) (CS).

***N,N'*-bis(isopropylthiocarbamate)butane-2,3-diimine, H₂ⁱPTCB (4).** Compound **4** was prepared as described for **1** from hydrazinecarbothioic acid *O*-isopropyl ester (5.1 g, 0.038 mol) and 2,3-butanedione (1.7 mL, 0.019 mol) in ethanol (50 mL). Yield = 1.4 g (23%). ¹H NMR, (CDCl₃, 400 MHz) δ 1.41 (br, 12H) 2.12 (s, 6H) 5.63 (br, 2H) 9.10 (s, 2H). ¹³C{¹H} NMR, (CDCl₃, 100 MHz) δ 10.3, 21.9. IR cm⁻¹. 3234 (w) and 1497(s) (NH) 1402 (m) (CH) 1334 (m) and 1207 (s) (CN) 1135 (s) (CO) 1052 (s) (CS).

***N,N'*-bis(octylthiocarbamate)butane-2,3-diimine, H₂OTCB (5).** Compound **5** was prepared as described for **1** from hydrazinecarbothioic acid *O*-octyl ester (2.72 g, 0.013 mol) and 2,3-butanedione (0.58 mL, 0.0067 mol) in ethanol (50 mL). Yield = 1.77 g (58%). ¹H NMR, (CDCl₃, 400 MHz) δ 0.87 (br, 6H) 1.28 (m, 16H) 1.43 (br, 4H) 1.81 (br, 4H) 2.13 (s, 6H) 4.59 (br, 4H) 9.12 (s, 2H). ¹³C{¹H} NMR, (CDCl₃, 100 MHz) δ 14.1, 22.6, 25.8, 28.4, 29.1, 31.7. IR cm⁻¹: 3230 (w) and 1497 (vs) (NH) 2950-2850 (m) and 1404 (s) (CH) 1326 (s) and 1206 (vs) (CN) 1136 (s) (CO) 1056 (s) (CS).

***N,N'*-bis(ethylthiocarbamate)hexane-3,4-diimine, H₂ETCH (6).** Compound **6** was prepared as described for **1** from hydrazinecarbothioic acid *O*-ethyl ester (1.53 g, 0.013 mol) and 3,4-hexanedione (0.77 mL, 0.0065 mol) in ethanol (50 mL). Yield = 1.2 g (60%). ¹H NMR, (400 MHz, CDCl₃) δ 1.08 (br, 6H) 1.41 (br, 6H) 2.63 (br, 4H) 4.63 (br, 4H) 9.23 (br, 2H). ¹³C{¹H} NMR, (100 MHz, CDCl₃) δ 10.49, 14.02, 17.01, 68.87, 152.27, 187.47. IR cm⁻¹: 3235 (w) and 1498 (m) (NH) 1433 (w) (CH) 1314 (m) and 1206 (s) (CN) 1152 (m) (CO) 1059 (s) (CS).

Cu(MTCB) (7). Compound **1** (0.273 g, 0.00129 mol) was suspended in methanol (25 mL). To this suspension copper (II) acetate monohydrate (0.285 g, 0.00149 mol) was added with stirring

giving a red-brown precipitate. The suspension was heated to reflux for 4 hours with stirring. The suspension was allowed to cool to room temperatures and then filtered and the solid was washed with methanol and ether. Yield = 0.216 g (52%). X-ray quality crystals were obtained by slow evaporation of a dichloromethane solution of **7** layered with ethanol. IR cm^{-1} : 1471 (s) and 1398 (m) (CH) 1241 (vs) and 1218 (vs) (CN) 1091 (w) (CO) 948 (w) (CS) 848 (w) (CuS) 771 (w) (CuN). Elemental analysis calc. for $\text{C}_8\text{H}_{12}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 29.67, H, 3.73, N, 17.30. Found C, 28.49, H, 3.58, N, 15.97. Mass spectrum calc. for $\text{C}_8\text{H}_{12}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 322.9698. Found: 322.9775.

Cu(ETCB) (8). Compound **8** was prepared using the methods described for **7** from **2** (0.309 g, 0.00129 mol) and copper (II) acetate monohydrate (0.285 g, 0.00149 mol) in methanol (25 mL). Complex **8** was isolated as a red-brown solid. Yield = 0.237 g (52%). X-ray quality crystals were obtained by using the technique described for **7**. IR cm^{-1} : 1413 (s) (CH) 1216 (s) (CN) 1020 (m) (CO) 867 (w) (CS) 792 (w) (CuS) 673 (w) (CuN). Elemental analysis calc. for $\text{C}_{10}\text{H}_{16}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 34.13, H, 4.58, N, 15.92, O, 9.09, S, 18.22. Found C, 34.08, H, 4.40, N, 15.46, O, 9.18, S, 18.22. Mass spectrum calc. for $\text{C}_{10}\text{H}_{16}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 351.0011. Found: 351.0086

Cu(PTCB) (9). Compound **9** was prepared using the methods described for **7** from **3** (0.408 g, 0.00129 mol) and copper (II) acetate monohydrate (0.285 g, 0.00149 mol) in methanol (25 mL). Complex **9** was isolated as a red-brown solid. Yield = 0.322 g (68%). X-ray quality crystals were obtained by using the technique described for **7**. IR cm^{-1} : 1467 (w) and 1423 (s) (CH) 1236 (s) (CN) 1093 (w) (CO) 956 (m) (CS) 844 (w) (CuS) 632 (w) (CuN). Elemental analysis calc. for $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 37.93, H, 5.31, N, 14.74, O, 8.42, S, 16.88. Found, C, 37.99, H, 5.10, N, 14.67, O, 8.32, S, 16.75 Mass spectrum calc. for $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 379.0324. Found: 379.0417

Cu(ⁱPTCB) (10). Compound **10** was prepared using the methods described for **7** from **4** (0.408, 0.00129 mol) and copper (II) acetate monohydrate (0.285 g, 0.00149 mol) in methanol (25 mL).

Complex **10** was isolated as a red-brown solid. Yield = 0.291 g (60%). X-ray quality crystals were obtained by using the technique described for **7**. IR cm^{-1} : 1427 (s) (CH) 1213 (vs) (CN) 1103 (vs) (CO) 910 (m) (CS) 831 (w) (CuS) 671 (w) (CuN). Elemental analysis $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 37.93, H, 5.31, N, 14.74, O, 8.42, S, 16.88. Found, C, 37.38, H, 5.16, N, 14.39, O, 8.61, S, 17.10. Mass spectrum cal. For $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 379.0324. Found: 379.0401

Cu(OTCB) (11). Compound **11** was prepared using the methods described for **7** from **5** (0.589 g, 0.00129 mol) and copper (II) acetate monohydrate (0.285 g, 0.00149 mol) in methanol (25 mL). Complex **11** was isolated as a red-brown solid. Yield = 0.554 g (83%). X-ray quality crystals were obtained by using the technique described for **7**. IR cm^{-1} : 2960-2852 (m) and 1423 (s) (CH) 1238 (vs) (CN) 1079 (w) (CO) 946 (m) (CS) 846 (m) (CuS) 676 (w) (CuN). Elemental analysis $\text{C}_{22}\text{H}_{40}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 50.79, H, 7.75, N, 10.77, O, 6.15, S, 12.33. Found, C, 50.49, H, 7.57, N, 10.65, O, 6.34, S, 12.59. Mass spectrum calc. for $\text{C}_{22}\text{H}_{40}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 519.1889. Found: 519.1986

Cu(ETCH) (12). Compound **12** was prepared using the methods described for **7** from **6** (0.408, 0.00129 mol) and copper (II) acetate monohydrate (0.285 g, 0.00149 mol) in methanol (25 mL). Complex **12** was isolated as a red-brown solid. Yield = 0.401 g (82%). X-ray quality crystals were obtained by using the technique described for **7**. IR cm^{-1} : 1417 (s) (CH) 1221 (s) (CN) 1016 (s) (CO) 974 (w) (CS) 874 (m) (CuS) 630 (m) (CuN). Elemental analysis for $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: C, 37.93, H, 5.31, N, 14.74, O, 8.42, S, 16.88. Found, C, 37.71, H, 4.96, N, 14.43, O, 8.33, S, 16.95. Mass spectrum calc. for $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}_2\text{N}_4\text{Cu}$: 379.0324. Found: 379.0315

Physical Methods. Elemental analysis was performed by Midwest Micro lab (Indianapolis, IN). The electronic spectra were collected as dichloromethane solution in 1 cm quartz cuvettes using an Agilent 8453 diode array spectrometer. Mass spectrometry (+ESI-MS) was performed by the Regenerative Medicine Research Center at the West China Hospital, Sichuan University,

Chengdu, China. All EPR data were collected on powder samples at room temperature using a Bruker EMX X-band spectrometer. EPR spectra were simulated using EasySpin. The infrared spectra were recorded as powders on a Nicolet 360 FT-IR with a smart iTR attachment. NMR spectra were obtained on Varian 400-M Hz spectrometer at 25 °C.

Electrochemical Measurements. Electrochemical data were collected using a Gamry Interface 1000E Potentiostat/Galvanostat/ZRA. Complexes were dissolved in dichloromethane (~2 mM) under air free conditions in a standard three electrode cell with 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte. Glassy carbon was used as the working electrode with a platinum wire counter electrode and a silver wire pseudo reference electrode. A small quantity of ferrocene was added as internal standard and all potentials are referenced versus ferrocenium/ferrocene (Fc^+/Fc).

Crystallographic Studies.

Single crystal x-ray diffraction studies were conducted on complexes **7** to **12**. Details of the data collection and refinement are displayed in Table S1 with full experimental details provided in the Supplementary Information. Crystals **7** and **8** were mounted on a CryoLoop and **9** – **12** were mounted on a glass fiber for collection of x-ray data on an Agilent Technologies/Oxford Diffraction Gemini CCD diffractometer. The CrysAlisPro²⁶ CCD software package (v 1.171.36.32) was used to acquire ω -scan exposures of data at 100K using monochromated $\text{MoK}\alpha$ radiation (0.71073 Å) from a sealed tube. Frame data were processed using CrysAlisPro²⁶ RED to determine final unit cell parameters to produce raw hkl data that were then corrected for absorption using SCALE3 ABSPACK.²⁷ The structures were solved by Direct Methods using SHELX²⁸ and refined by least squares methods on F^2 using SHELXL-97.²⁸ For each crystal, non-hydrogen atoms were refined anisotropically while hydrogen atoms were refined as described in

the Supplementary Information. For all unique reflections the final anisotropic full matrix least-squares refinement on F^2 for all variables converged with R1, wR2, GOF as listed in Table S1.

Results

Synthesis and Characterization. A series of N_2S_2 N,N' -bis(alkylthiocarbamate)butane-2,3-diimine ligands (**1** – **5**) with varying O-alkyl chain lengths and N,N' -bis(methylthiocarbamate)hexane-3,4-diimine (**6**) have been prepared and complexed with Cu(II) yielding the square planar complexes **7** – **12**, Scheme 1. The ligands were obtained in three steps from inexpensive bulk commodity chemicals, Scheme 2. Using previously reported methods, xanthates were prepared from the appropriate alcohol and carbon disulfide²⁴ and subsequently condensed with hydrazine monohydrate to yield the hydrazinecarbothioc acid O-alkyl esters.²⁵ Condensation of the ester with butanedione (**1** – **5**) or hexanedione (**6**) yielded the desired ligand in a reaction similar to H_2ATSM synthesis.²⁹ Addition of copper acetate monohydrate to suspensions of the ligands in methanol yielded **7** – **12** as dark red powders in 52 – 83 % yield.

Scheme 2. Syntheses of ligands **1** – **6**.

The electronic spectra of **7** – **12** recorded in dichloromethane display a ligand to metal charge transfer band near 485 nm and two more intense ligand to ligand charge transfer bands near 248 and 290 nm. The transition energies are largely insensitive to the identity of the O-alkyl group

R1 or the backbone substituent R₂, Table 1. The infrared spectra of ligands **1** – **6** display an N-H stretch between 3230 and 3241 cm⁻¹ that is lost upon metal complexation. The EPR spectra of **7** – **12** were recorded as powders at room temperature. Complexes **8** – **12** display an axial spectrum with $g_{||} > g_{\perp} > 2$ (Table 1) consistent with square planar Cu(II) and a single unpaired electron located in dx^2-y^2 . Simulated values for $g_{||}$ and $g_{\perp}$ fall in the narrow ranges of 2.031 – 2.042 and 2.089 – 2.131, respectively, consistent with the similarities observed for **8** – **12** in the electronic spectrum. The spectrum of **7** is too broad to resolve the axial signal, but the observed g-value of 2.061 is near the average g-values of the other complexes.

Table 1. UV-visible^a, EPR^b, and electrochemical^c data for *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine Cu(II) complexes **7** – **12** and selected Cu(ATSM) derivatives.

Complex	R ₁	R ₂	λ_{max}^a (nm) (ϵ)	$g_{ }, g_{\perp}$ (g_{avg}) ^b	Cu ^{III/II} $E_{1/2}$ (i_{pc}/i_{pa}) (mV) ^c	Cu ^{II/I} $E_{1/2}$ (i_{pc}/i_{pa}) (mV) ^c	Ref.
7	OMe	Me	246 (16,000) 290 (20,000) 486 (2,680)	(2.061)	585 (0.934)	-857 (0.941)	this work
8	OEt	Me	248 (16,300) 290 (22,700) 485 (2,920)	2.131, 2.036 (2.068)	528 (0.933)	-879 (0.965)	this work
9	O ⁿ Pr	Me	248 (16,600) 291 (23,800) 484 (2,930)	2.127, 2.034 (2.065)	542 (0.964)	-892 (0.997)	this work
10	O ⁱ Pr	Me	248 (16,500) 292 (23,600) 484 (3,210)	2.089, 2.042 (2.058)	505 (0.867)	-904 (0.964)	this work
11	O-octyl	Me	248 (15,900) 291 (23,600) 485 (3,100)	2.130, 2.034 (2.066)	545 (0.929)	-884 (0.867)	this work
12	OEt	Et	249 (18,300) 292 (25,000)	2.124, 2.031	549 (0.934)	-874 (0.975)	this work

			485 (3,340)	(2.062)			
13	NHMe	Me	261 314 477	2.113, 2.029 2.026 (2.056)	200	-1110	12 ^{a,c} 31 ^b
14	NH ₂	Me	263 310 477	N/A	-180	-1110	12
15	NMe ₂	Me	320 450 490 525	2.085 2.033 2.024 (2.047)	N/A	N/A	31
16	N(C ₄ H ₈)	Me	321 368 515 566	N/A	N/A	-1050 (1.03)	14
17	NPhMe	H	323 381 512 567	N/A	N/A	-700 (0.99)	14
18	NHEt	Me	N/A	N/A	N/A	-1120 ^d	32
19	NHMe	H	194 262 324 495	N/A	N/A	-950	12
20	NHMe	Et	194 267 316 483	N/A	190	-1100	12

a) Electronic spectra measured in CH₂Cl₂ (**7 – 12**), DMSO (**13, 14, 19, 20**), or DMF (**15 – 17**) solution b) Powder EPR spectra collected on solids at room temperature (**7 – 12, 13, 15**); $g_{avg} = 1/3[g_{||} + 2g_{\perp}]$. c) Electrochemical potentials versus Fc⁺/Fc measured versus an internal standard in CH₂Cl₂ with 0.1 M ⁿBu₄NBF₄ (**7 – 12**) or calculated from reported potentials versus Ag/AgCl in DMSO with 0.1 M ⁿBu₄NBF₄ (**13, 14, 19, 20**) or versus SCE in DMF with 0.1 M ⁿBu₄ClO₄ (**16, 17**) using the following conversions: E_{1/2} = -0.52 for Fc⁺/Fc vs.

Ag/AgCl in DMSO; $E_{1/2} = -0.51$ for Fc^+/Fc vs. SCE in CH_2Cl_2 (**7** – **13**), DMSO (**13**, **14**, **19**, **20**), or DMF (**16**, **17**). d) Reported as 10 mV more negative than **13**.

Crystallographic Studies. X-ray quality diffraction crystals of **7** – **12** were obtained as orange needles or plates upon slow evaporation of a dichloromethane solution of the complex layered with ethanol. Crystal data and structure refinement details are listed in Table S1. All complexes crystallize as discrete, square planar Cu(II) complexes with no solvent molecules in the crystal lattice. An ORTEP representation of **7** is shown in Figure 1 with selected bond distances and angles provided in Table 2. The structures of **8** – **12** are highly similar to **7** with core structure bond distances and angles statistically indistinguishable from those in **7**, see Supplementary Information. The following discussion of **7** is representative of the entire group of complexes.

Figure 1. ORTEP³⁰ view (50% probability) of **7** showing atom labeling for all non-hydrogen atoms in the asymmetric unit and symmetry generated (1-x, -y, 1/2-z) donor atoms.

Table 2. Selected bond distances (Å) and bond angles (°) for **7** and **13**³³ as representative examples of Cu(alkoxythiocarbamides) and Cu(thiosemicarbazones), respectively.^a

Bond Distance	7	13
Cu-N1	1.958(4)	1.9584(16)
Cu-S1	2.2498(12)	2.2453(5)
N1-N2	1.384(5)	1.369(2)
N1-C1	1.295(5)	1.300(2)
N2-C3	1.301(6)	1.325(3)
S1-C3	1.714(5)	1.760(2)
C1-C1'	1.484(8)	1.474(3)
C3-O1	1.331(5)	
C3-N3 ^b		1.338(3)
Bond Angle		
N1-Cu-S1	85.00(11)	85.11(5)
N1-Cu-N1'	79.9(2)	80.61(7)
S1-Cu-S1'	110.12(7)	109.21(2)
a) Atom labels for both complexes correspond to the numbering scheme of 7 in Figure 1. B) N3 the nitrogen of R ₁ group NHCH ₃ .		

The Cu of **7** occupies an N₂S₂ square plane provided by the *N,N'*-bis(methylthiocarbamate)butane-2,3-diimine ligand with Cu-N1 and Cu-S1 bond distances of 1.958(4) and 2.2498(12) Å, respectively. The S1' and N1' donors are symmetry generated as Cu1 sits on the special position (0.5, *y*, 0.25) in the orthorhombic space group *Pbcn*. A similar phenomenon occurs in **9**, **11**, **12**, whereas in **8** and **10** the asymmetric unit contains independent atoms in the entire complex. Within the chelate ligand, bond distances are consistent with a

conjugated π -system of alternating single and double bonds, Figure 2. The C3-S1, N1-N2, and C1-C1' bond distances of 1.741(5), 1.384(5), and 1.484(8) Å, respectively, are typical of single C-S, N-N, and C-C bonds. The shorter N1-C1 and N2-C3 bond distances of 1.295(5) and 1.301(6), respectively, reveal C=N character. The sum of the four bond angles about the Cu is 360.0(3)°. Complex **7** is rigorously planar with the largest deviation from the best fit plane of all 17 non-hydrogen of ± 0.118 Å for C3/C3' and a standard deviation of only 0.061 Å.

Figure 2. Representation of the conjugated π -network of the *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine ligand of **7** highlighting localization of the C=N bonds.

Electrochemical Studies. The cyclic voltammograms of **7** – **12** in dichloromethane each show two reversible events assigned to $\text{Cu}^{\text{III/II}}$ and $\text{Cu}^{\text{II/I}}$ couples, Table 1. The $E_{1/2}$ values for the $\text{Cu}^{\text{III/II}}$ and $\text{Cu}^{\text{II/I}}$ events of **7** are observed at +585 and -857 mV versus ferrocenium/ferrocene, respectively, Figure 3. Increasing the length of the R1 from -OMe to -OEt and -O-octyl decreases the $\text{Cu}^{\text{II/I}}$ potential of **8** and **11** to -879 and -884 mV, respectively. A similar $\text{Cu}^{\text{II/I}}$ potential of -892 mV is found for the O^{*n*}Pr derivative **9**. However, the branched -O^{*i*}Pr complex **10** further destabilizes Cu(I) as indicated by the $\text{Cu}^{\text{II/I}}$ potential of **10** at -904 mV. Changes at

the R₂ position results in no statistically significant change in the Cu^(II/I) potential based on a comparison of **8** and **12**, which are within 5 mV of each other.

Figure 3. Cyclic voltammogram of **7** in CH₂Cl₂ with 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte. Scan rate = 100 mV/s; potentials referenced versus Fc⁺/Fc.

Discussion

A series of *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine Cu(II) complexes as pendent alkoxy derivatives of Cu(ATSM) has been synthesized and characterized. The synthetic methodology involves condensation reaction of a dione with a hydrazinecarbothioc acid O-alkyl ester, analogous to the synthesis of H₂ATSM and related derivatives from diones and thiosemicarbazides. As shown in Scheme 1, the hydrazinecarbothioc acid O-alkyl esters are readily prepared from a variety of alcohol precursors in two steps with carbon disulfide and hydrazine monohydrate. Notably, all ligand syntheses are conducted open to the atmosphere in ethanol solution with facile purification by filtration and washing. The simplicity of these methods and the variety of available alcohols and diones make *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine and similar ligands a potentially useful new class of ligands related to the bis-thiosemicarbazone family.

A comparison of the room temperature EPR and UV-visible data shows only small changes in the spectroscopic features of complexes **7** – **12** as compared to similar bis-thiosemicarbazone analogues, **13** – **17**. Since the EPR spectra of **13**, **15**, and related complexes did not change significantly between room temperature powder data and 77 K frozen DMF solution data,³¹ only room temperature powder data was evaluated for **7** – **12**. The axial EPR spectra of **13**, Cu(ATSM), is indistinguishable from those of **8** – **12**. The reported $g_{||}$ and $g_{\perp}$ values of 2.115 and 2.038 for **13** fall within the narrow ranges of 2.031 – 2.042 and 2.089 – 2.131 for **8** to **12**, Table 1, indicating no significant changes in the relative energies of the d-orbital manifold. There is a small shift in the charge transfer band energies upon substitution of –NHR with –OR. As shown in Table 1, the high energy bands for **7** at 246 and 290 nm are red shifted by 2340 and 2640 cm^{-1} with respect to the bands at 261 and 314 nm in Cu(ATSM), **13**. The lower energy band of **7** at 486 nm is blue shifted by 388 cm^{-1} relative to the band at 477 nm in Cu(ATSM).¹² The shifts are attributed to electronic differences within the ligand framework and no solvent effects. The spectra of **7** in DCM and DMSO are not substantially different.

A comparison of the structural parameters of **7** and **13** provide a representative example of the similarities and differences of the *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine and bis-thiosemicarbazone complexes. The selected bond distances and angles in Table 2 reveal a highly similar structural core. The Cu-N1 and Cu-S1 bond lengths in **7** of 1.958(4) and 2.2498(12) Å, respectively, are statistically equivalent with the values of 1.9592(16) and 2.2474(5) Å in **13**. Within the ligand framework, the bond distances are also statistically similar. Both complexes exhibit bond distances consistent with alternating single and double bonds in an extended conjugated network as depicted in Figure 2 for **7**. A comparison of bond angles associated with

the metal-ligand core of **7** and **13** reveals values that are statistically equivalent or that vary less than one degree.

The structural and electronic features of our new *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine ligand system show little deviation from related bis-thiosemicarbazone complexes. However, the substitution of the terminal –NHR groups of the bis-thiosemicarbazone with –OR groups in the new ligand class results in significant changes in the Cu^{II/I} and Cu^{III/II} reduction potentials. A comparison of the –OMe derivative **7** with the –NHMe derivative **13** show a +253 mV shift in the Cu^{II/I} reduction potential. A similar shift of +241 mV is observed upon substitution of –NHEt (**18**) with –OEt (**8**). These large shifts can be attributed to an inductive effect consistent with the electron withdrawing properties of the alkoxides and prior Hammett analysis of the –NHR functional group effect on reduction potentials.²² Variations of the R group within the new ligand class reveals that alkyl extension in the R₁ position results in a small decrease in reduction potential from -857, to -879 and -892 mV for compounds **7**, **8**, and **9** respectively. Extension of the carbon chain in the R₂ position from Me to Et (**8** to **12**) increases the potential by only 5 mV, which is within experimental error of these measurements. In the related bis-thiosemicarbazone analogues **13** and **20**, the same substitution increases the Cu^(II/I) potential by 10 mV. In total, six new complexes with Cu^{II/I} reduction potentials in the range of -904 mV to -857 mV have been prepared demonstrating that substitution of –NHR with –OR yields a large anodic shift in the Cu^(II/I).

Conclusions

In summary, a new class of *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine ligands and their Cu complexes have been reported as derivatives of bis-thiosemicarbazones. Substitution of the terminal –NHR functional group with –OR allows tuning of the Cu^(II/I) and Cu^(III/II) reduction

potentials with minimal impact on the physical and electronic structures of the complexes. The ease of synthesis of these new ligands and the wide variety of commercially available alcohols and diones provides for a large variety of new bis-thiosemicarbazone like complexes for future development.

ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR of **1** - **6**, UV-visible and EPR spectra of **9**, experimental crystallographic details including a table of crystal data and structural refinement for **7** – **12**, and ORTEP representations and tables of bond distances and angles of **7** – **12** in PDF and crystallographic data in CIF (CCDC 1517907 – 1517912). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

This research was supported in part by the National Science Foundation (CHE-1361728). MSM thanks the Department of Energy (DEFG02—08CH11538) and the Kentucky Research Challenge Trust Fund for upgrade of our X-ray facilities.

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Table of Contents (TOC) Image and Synopsis

A series of N_2S_2 -Cu(II) complexes based on *N,N'*-bis(alkylthiocarbamate)butane-2,3-diimine ligands have been synthesized and characterized. The ligands contain a conjugated N_2S_2 chelate with non-coordinating, terminal by alkoxy (-OR) groups. The ligands are analogues of the well-known bis(thiosemicarbazones), which contain a similar donor core with terminal, non-coordinating amines. Substitution of the terminal amines with the alkoxy groups allows tuning of redox potentials with minimal changes in the physical and electronic structure.