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Investigations of Bis(alkylthiocarbamato)copper Linkage Isomers

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ABSTRACT: Linkage isomers are coordination compounds with the same composition but different donor atoms, resulting in distinct physical and electronic structures. A pair of linkage isomers, **CuL^{555}** and **CuL^{465}**, derived from phenylglyoxal bis(ethylthiocarbamate) were synthesized, isolated, and characterized by structural, electrochemical, and spectroscopic methods. The isomers are stable in solution under ambient conditions, but **CuL^{465}** converts to **CuL^{555}** in acid, consistent with quantum-chemical calculations. The complexes were screened against a lung adenocarcinoma cell line (A549) and a nonmalignant lung fibroblast cell line (IMR-90) to evaluate the antiproliferation activity. **CuL^{555}** and **CuL^{465}** possessed EC_{50} values of 0.113 ± 0.030 and 0.115 ± 0.038 μM for A549 and 1.87 ± 0.29 and 0.77 ± 0.22 μM for IMR-90, respectively.

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The presence of multiple donor types within a ligand can result in the formation of different linkage isomers that have the same composition but distinct physical and electronic structures. The structure of linkage isomers was first described by Werner over a century ago regarding the different coordination modes of nitrite in the yellow (Co-NO_2) and red (Co-ONO) isomers of $[Co(NH_3)_5(ONO)]^{2+}$.[1] Classic simple ligands known to display linkage isomerism include NO_2^-, CN^-, SCN^-, and NCO^-.[2] The variability provided by linkage isomers has been employed in the design of metallosupramolecules[3] and the self-assembly of ruthenium(II) metallarectangles with antiproliferation activity.[4] Examples of linkage isomerism with chelate ligands include variable coordination modes for amino acids,[5] Schiff bases,[6] oximes,[7,8] and bis(thiosemicarbazones) (BTSCs).[9−13]

CuBTSC complexes, including CuATSM and CuGTSM (Figure 1A), have received significant attention as diagnostic[14−18] and therapeutic[15,19−22] agents. To date, all structurally characterized CuBTSC complexes display square-planar N_2S_2 coordination environments containing two imine nitrogen and two sulfur atoms, resulting in three five-membered chelate rings, herein referred to as the 555 linkage isomer. An alternative square-planar 465 linkage isomer has been observed for nickel and palladium derivatives of phenylglyoxal BTSC in which one imine nitrogen, one hydrazino nitrogen, and two sulfur atoms coordinate to the metal, resulting in the formation of four-, six-, and five-membered chelate rings (Figure 1B).[9,10] Notably, the 465 and 555 isomers of a five coordinate Ga(III) BTSC complex with an acenaphthoquinone backbone have been structurally characterized.[11]

Recently, we reported a series of copper(II) complexes based on bis(alkylthiocarbamate) ligands as pendent alkoxy derivatives of CuBTSCs[23] and the antiproliferation activity of metal complexes with hybrid alkylthiocarbamate−thiosemicarbazones.[20] In this paper, we report the synthesis, characterization, and conversion of the 555 and 465 linkage isomers of copper(II) with phenylglyoxal bis(ethylthiocarbamate) (H_2L;

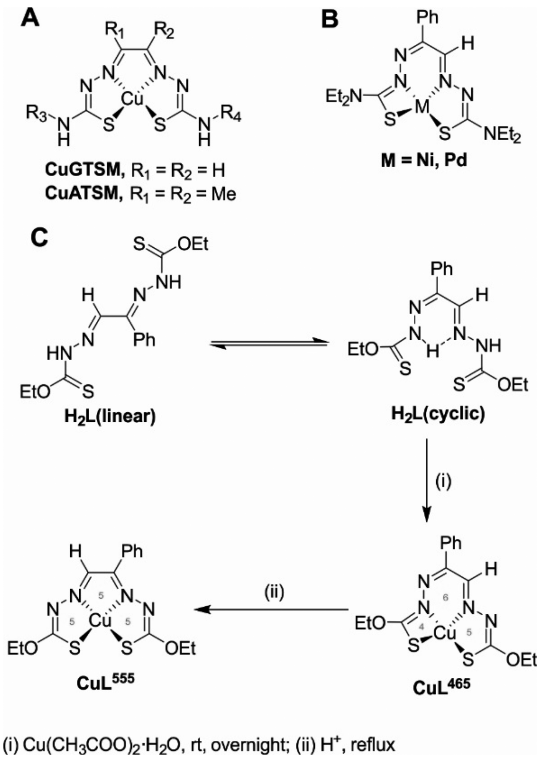

Figure 1. (A) CuGTSM and CuATSM. (B) 465 isomers of BTSCs. (C) Interconversion of H_2L (linear) and H_2L (cyclic) and the synthesis of **CuL^{555}** and **CuL^{465}** linkage isomers, with chelate ring sizes indicated by the numbers in light gray.

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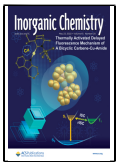

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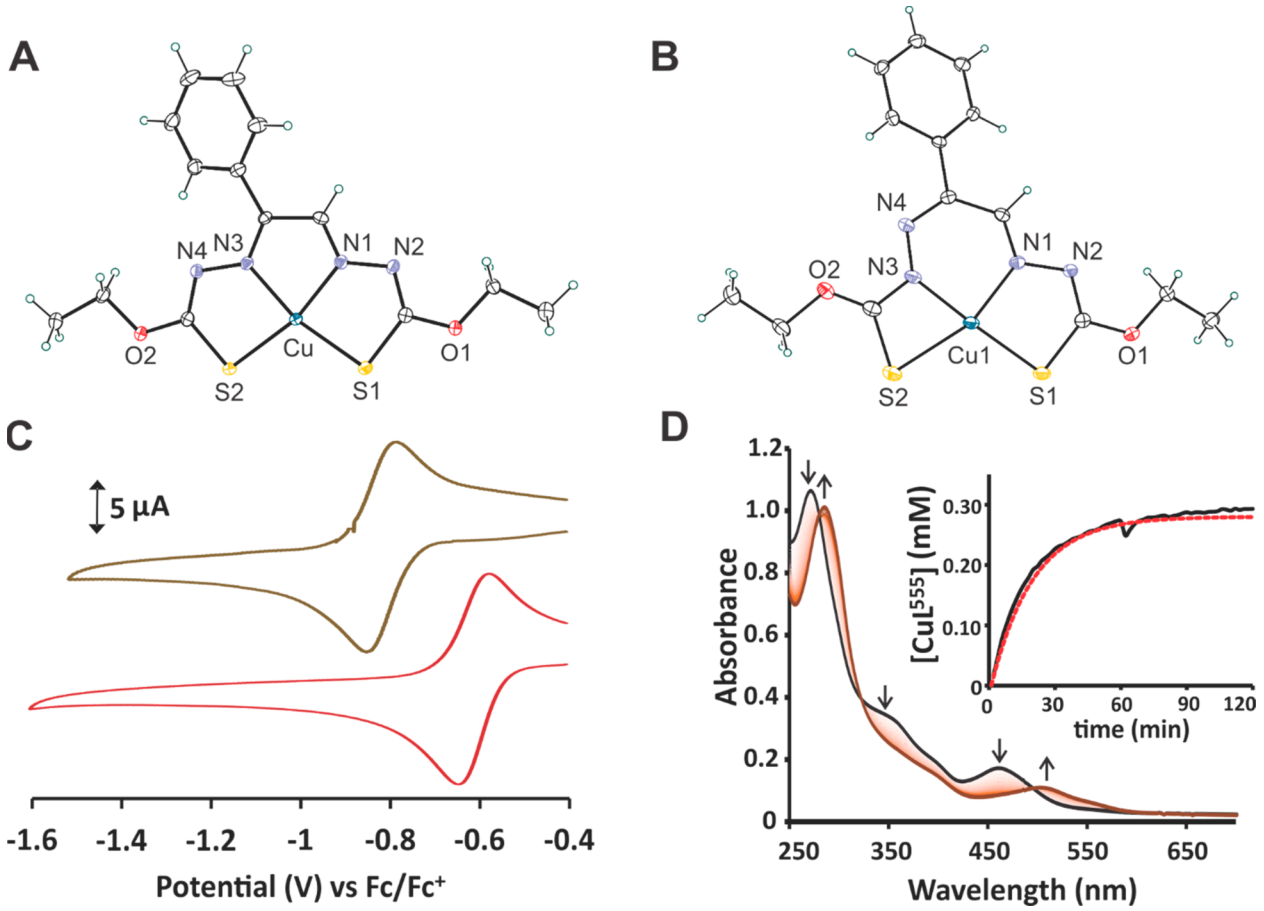

Figure 2. ORTEP[24] representations of **CuL**^{555} (A) and **CuL**^{465} (B) with thermal ellipsoids displayed at the 50% probability level. (C) Cyclic voltammograms for 0.3 mM **CuL**^{555} (top) and 0.3 mM **CuL**^{465} (bottom) in anhydrous acetonitrile with a 0.1 M NBu_4PF_6 supporting electrolyte at a scan rate of 200 mV s^{-1}. (D) Electronic spectra collected during the conversion of 0.30 mM **CuL**^{465} (black) to **CuL**^{555} (deep red) with 0.60 M TFA in methanol at room temperature. Inset: Experimental (black) and simulated (red) [**CuL**^{555}] as a function of time.

Figure 1C) and evaluate their antiproliferation activity against lung adenocarcinoma cells (A549) and nonmalignant lung fibroblast cells (IMR90). This represents a rare investigation of a fully characterized pair of linkage isomers based on a chelate ligand including their conversion and antiproliferation activity.

The ligand H_2L was prepared by the condensation of phenylglyoxal monohydrate with hydrazinecarbothioic acid *O*-ethyl ester, similar to previously reported bis(alkylthiocarbamates).[23] Variable-temperature ^1H NMR studies revealed fluxional behavior (Figures S4 and S5), indicating the presence of two ligand forms that interconvert slowly at room temperature. Structural studies on BTSCs have revealed both cyclic and linear geometries in the solid state.[25,26] The fluxional behavior of H_2L in solution is attributed to interconversion between these forms (Figure 1C). Structurally, the two isomers differ only in the orientation of the phenyl and hydrazinecarbothioic acid O-ethyl ester groups with respect to the phenyl-substituted C═N bond. In H_2L (linear), the two groups are in the *E* configuration with respect to the C═N bond; in contrast, in the H_2L (cyclic) conformer, they lie in the *Z* configuration.

Gas-phase optimization of a single molecule using quantum-chemical (QC) calculations (see the Supporting Information for details on the methods) confirmed that both the cyclic and linear conformers of H_2L are thermodynamically accessible. Three stable conformers, H_2L (linear), H_2L (open), and H_2L (cyclic), were optimized (Figure S1), and the linear and cyclic conformers with similar energies were found to be preferred (Table S4). The energetic trend of the isomers did not change when placed in an implicit solvent medium (simulated by the continuum solvation model COSMO)[27] with a dielectric constant of methanol (32.613).

The addition of copper acetate monohydrate to H_2L in methanol yielded **CuL**^{465} as a yellow-brown solid at room temperature or **CuL**^{555} as a red solid under reflux conditions. X-ray crystallography identified the two solids as linkage isomers (Figure 2A,B and Tables S2−S4). The **CuL**^{555} isomer crystallized as dark-orange plates, and **CuL**^{465} crystallized as dark-purple prisms. Each isomer displayed a square-planar N_2S_2 environment but with different coordinating atoms.

The copper atom in **CuL**^{555} binds to two imine nitrogen atoms (N1 and N3) and two sulfur atoms (S1 and S2), resulting in three five-membered rings, as is typically observed in BTSC complexes (Figure 2A). The Cu−N bond distances of 1.9537(14) and 1.9875(14) Å for Cu−N1 and Cu−N3, respectively, and the Cu−S bond distances of 2.2657(5) and 2.2522(5) Å for Cu−S1 and Cu−S2, respectively, are consistent with other copper alkylthiocarbamate complexes.[23] The S1−Cu−N1 and S2−Cu−N3 bond angles are 84.79(4) and 85.35(4)°, respectively, resulting in an acute N1−Cu−N3 bond angle of 80.11(6)° due to fusion of the three coplanar five-membered chelate rings. For **CuL**^{465}, the copper is coordinated to one imine nitrogen (N1), one hydrazino nitrogen (N3), and two sulfur (S1 and S2) atoms, resulting in

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a four-atom, a six-atom, and a five-atom chelate ring configuration (Figure 2B). The Cu−N bond distance for the imine nitrogen, N1, of 1.958(2) Å is similar to that of the **CuL**^{555} isomer. However, the Cu−N distance for the hydrazino nitrogen, N3, is significantly shorter at 1.908(2) Å. The Cu−S bond distances are 2.2141(7) Å for S1 in the five-membered ring and 2.3930(8) Å for S2 in the four-membered ring. The six- and five-membered chelate rings have bond angles approaching 90°: S1−Cu−N1, 87.95(7)°, and N1−Cu−N3, 88.77(9)°. The S2−Cu−N3 bond angle associated with the four-membered chelate ring is very acute at 70.69(7)°.

The difference in the physical structure of the two isomers results in significantly different electronic structures. Cyclic voltammetry studies in acetonitrile display a single reversible reduction assigned to the $Cu^{II/I}$ couple for each isomer (Figure 2C). The $E_{1/2}$ values for **CuL**^{555} and **CuL**^{465} are observed at −0.603 and −0.807 V versus ferrocenium/ferrocene (Fc^+/Fc), respectively. The $Cu^{II/I}$ couple of **CuL**^{555} is shifted anodically by 250−300 mV relative to the previously reported bis(alkylthiocarbamate)copper complexes.[23] This is consistent with substitution of the diacetyl backbone in the prior complexes with phenylglyoxal in **CuL**^{555}. Relative to the BTSC complexes, both **CuL**^{555} and **CuL**^{465} are easier to reduce than CuATSM, −1.11 V, and CuGTSM, −0.950 V.[20]

The electron paramagnetic resonance (EPR) spectra of **CuL**^{555} and **CuL**^{465} in dimethylformamide (DMF) at 77 K are consistent with their CuN_2S_2 coordination (see the Supporting Information). The spectra of each complex displays two species assigned to the parent four-coordinate complex and a five-coordinate DMF adduct. When **CuL**^{555} and **CuL**^{465} were dissolved in DMF, their color changed to blue and green, respectively, consistent with DMF coordination. Electrochemical measurements in DMF revealed the presence of two distinct species for **CuL**^{555} and two unique species for **CuL**^{465} with no evidence of interconversion (Figure S17).

Because **CuL**^{555} and **CuL**^{465} were obtained using the same starting materials under different synthetic conditions, we evaluated the conditions required for their conversion. The **CuL**^{465} complex yielded yellow solutions in methanol with a charge transfer band at 457 nm, whereas **CuL**^{555} was red in methanol with a band at 503 nm. Heating the solid or a methanolic solution of either compound yielded no observable color change. However, **CuL**^{465} does convert to **CuL**^{555} in methanol upon the addition of trifluoracetic acid (TFA; Figure 2D). A preliminary kinetic analysis reveals that the reaction is first-order in **CuL**^{465} and second-order in TFA, suggesting an initial rapid equilibrium between **CuL**^{465} and TFA, followed by a rate-determining step that is also TFA-dependent (see the Supporting Information). Further studies on the mechanism are underway.

To gain a fundamental understanding of the factors governing the conversion of **CuL**^{465} to **CuL**^{555}, we used QC calculation of the gas-phase-optimized structure in the presence of an implicit solvent medium (simulated by the continuum solvation model COSMO) with a dielectric constant of methanol at the density functional level of theory (see the Supporting Information for details) to examine the effects of protonation. Upon protonation of H_2L within a methanol solvent, the cyclic and open conformers are more stable than the linear conformer by ∼6.9 and ∼4.3 kcal mol^{-1}, respectively (Table S5). However, the two metal isomers (**CuL**^{465} and **CuL**^{555}) are energetically close to each other (within 1−2 kcal mol^{-1} of each other) in both unprotonated and protonated conditions (Tables S6 and S7). This indicates that **CuL**^{465} and **CuL**^{555} are likely to coexist. This finding along with our experiments suggests that acid helps to overcome the kinetic barrier associated with the conversion of **CuL**^{465} to **CuL**^{555}.

The isomers **CuL**^{555} and **CuL**^{465} were screened against a lung adenocarcinoma cell line (A549) and a nonmalignant lung fibroblast cell line (IMR-90) to evaluate the antiproliferation activity (Figures 3 and S19). The copper complexes

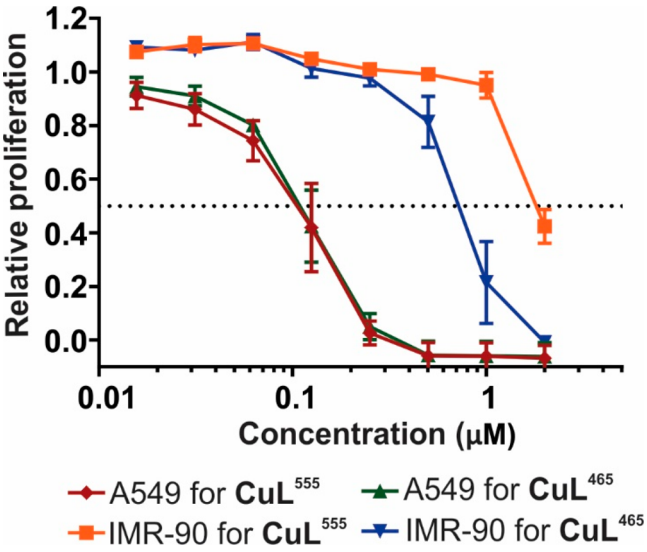

Figure 3. Cell proliferation results for A549 and IMR-90 cell lines treated with **CuL**^{555} (red and orange) and **CuL**^{465} (green and blue).

CuL^{555} and **CuL**^{465} possess similar EC_{50} values of 0.113 ± 0.030 and 0.115 ± 0.038 μM for A549. For IMR-90, the EC_{50} values of 1.87 ± 0.29 and 0.77 ± 0.22 μM for **CuL**^{555} and **CuL**^{465}, respectively, are statistically different (p = 0.0062), suggesting that **CuL**^{555} may have slightly higher selectivity. As a control, each complex was separately incubated at 37 °C in phosphate-buffered saline for 72 h, confirming that **CuL**^{555} and **CuL**^{465} do not isomerize in the medium (Figures S20 and S21). Copper loading by A549 cells was confirmed by inductively coupled plasma mass spectrometry. The copper levels in **CuL**^{555}- and **CuL**^{465}-treated cells were 10.97 and 6.27 μg g^{-1}, respectively, which are significantly higher than that in vehicle-treated cells, 0.11 μg g^{-1} (Table S11). Overall, the antiproliferation activities of **CuL**^{555} and **CuL**^{465} are similar to that of our previously reported bis(alkylthiocarbamate) complex, which is greater than CuATSM but less than those of our hybrid alkylthiocarbamate−thiosemicarbazone complexes.[20] Efforts to evaluate the mechanism of action are ongoing.

This study reports a rare pair of isolated and structurally characterized linkage isomers. The **CuL**^{555} isomer is thermodynamically favored in solution, although the isomerization of **CuL**^{465} to **CuL**^{555} requires the presence of acid. Under ambient conditions, no interconversion of the isomers is observed. These complexes provide a unique opportunity to study the effect of linkage isomers on biological activity because they have the same composition but differ in their electronic and physical structures. The nearly identical A549 EC_{50} values for **CuL**^{555} and **CuL**^{465}, despite a 204 mV difference in the $Cu^{II/I}$ reduction potential, suggests that the antiproliferation activity of these complexes is not just related

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to the $Cu^{II/I}$ potential. While the isomers are stable in the medium used for the cell studies, we cannot exclude the possibility that the isomers converge to the thermodynamically favorable **CuL**^{555} or demetalate upon interactions with/within the cells. Further studies are required to evaluate the extent to which the shape and electronic structure influence the potency and selectivity. This could be more directly tested by the evaluation of complexes where the ligands themselves are isomers such that the physical structure varies but the electronic structure remains constant. Such studies are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.2c00371.

Experimental details, figures of NMR, FT-IR, and electronic spectra, ORTEP representations, EPR spectra and discussion, and kinetic interconversion studies and discussion, and tables of crystal data and refinement, selected bond distances and bond angles, and energies obtained from theoretical calculations (PDF)

Accession Codes

CCDC 2109500 and 2109501 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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