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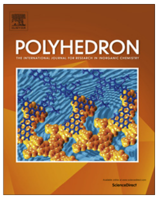

# New Zn(II) complexes with $N_2S_2$ Schiff base ligands. Experimental and theoretical studies of the role of Zn(II) in disulfide thiolate-exchange

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ABSTRACT

Described are the synthesis and characterization of two, potentially tetradentate, $N_2S_2$ Schiff-base ligands, containing a disulfide bond, N,N′-bis(3-phenylprop-2-en-1-ylidene)-2,2′-disulfanediyldianiline (**$L^1$**) and N,N′-bis(3,3-diphenylprop-2-en-1-ylidene)-2,2′-disulfanediyldianiline (**$L^2$**), and their reaction with $Zn^{2+}$. Surprisingly, both **$L^1$** and **$L^2$** undergo reductive disulfide bond scission upon reaction with $Zn^{2+}$ in alcoholic media to give, under alcohol oxidation, the respective $Zn(NS)_2$ complexes $Zn(L^3)_2$ (**1**) and $Zn(L^4)_2$ (**2**), where the **$L^3$** and **$L^4$** are the respective bidentate thiolate-imine anions. The ligands **$L^1$** and **$L^2$** and the complexes **1** and **2** have been characterized spectroscopically, and the crystal and molecular structures of the two complexes have been determined by single crystal X-ray diffraction. The coordination geometry around Zn(II) centers in both complexes is a distorted tetrahedron. In addition, DFT calculations (B3LYP/LANL2DZ/6-311++G(d,p)) support the structure of **1**. Cyclic voltammetric studies demonstrate that Zn(II) shifts the reduction potential of the disulfide ligands **$L^1$** and **$L^2$** to less negative values thus making them more susceptible to reductive cleavage of the disulfide bond. The results of semi-empirical PM6 calculations offer key insight into the nature of the transition state for this reaction.

## 1. Introduction

Zinc, which is always present in the +2 oxidation state in organisms, plays a number of important roles in protein chemistry [1–5]. Examples include the interactions of the thiols of cysteine (Cys) residues with $Zn^{2+}$ in various metallothioneins and zinc fingers [1,2]. Notably, since cysteine is redox active, although $Zn^{2+}$ is not, zinc coordination environments with multiple thiol or thiolate ligands can be oxidized and then reduced again at the sulfur centers with concomitant release and binding of $Zn^{2+}$ (Scheme 1) [6]. For example, in zinc fingers a thiol-disulfide exchange reaction can occur between a protein bearing small thiol-containing residues, such as glutathione, and a protein containing a disulfide bond [7–10]. The proposed mechanism involves mixed glutathione disulfide formation coupled with association and dissociation of the catalytic zinc ion. In a similar example of a non-innocent ligand, S-hydroxymethylglutathione is oxidized by the zinc enzyme alcohol dehydrogenase to S-formylglutathione (Scheme 1) [11].

The dielectric properties of the protein and electrostatic screening of zinc sites also affect the reactivity as does the redox potential of the Zn/S site [12,13]. Because entropic factors have a great influence on the redox potential of thiol/disulfide pairs, the zinc ion is an important determinant of the redox potential. As a result, the redox potential shifts to such a low value that mild cellular oxidants such as glutathione disulfide react with Zn/S sites and release $Zn^{2+}$ [14]. This ligand-centered redox process can also lead to the release of cadmium(II) and copper(I) when these metal ions bind to metallothioneins under specific conditions [15].

In the context of on-going interest in the synthetic analogues of zinc proteins [3,16–25], we report the syntheses, spectral characterizations and structures of two tetradentate Schiff base ligands **$L^1$** and **$L^2$** (Scheme 2) and the products of these ligands reactions with $Zn^{2+}$ in alcoholic media, $Zn^{II}(L^3)_2$ (**1**) and $Zn^{II}(L^4)_2$ (**2**). These products are the $Zn^{II}$ complexes of the (NS) bidentate Schiff base ligands **$L^3$** and **$L^4$** (Scheme 3) formed by the reductive cleavage of the disulfide bond of **$L^1$** and **$L^2$** respectively. The direct synthesis of $Zn^{II}(L^3)_2$ from the thiol ligand, N-trans-cinnamylidene-2-mercaptoaniline, has been previously reported, but without a concomitant X-ray crystal structure [26]. We also discuss the prospective mechanism of the disulfide to thiolate transformation promoted by the $Zn^{2+}$ centers.

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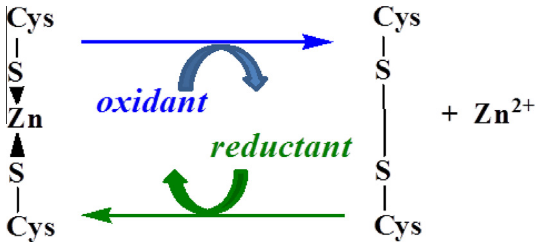
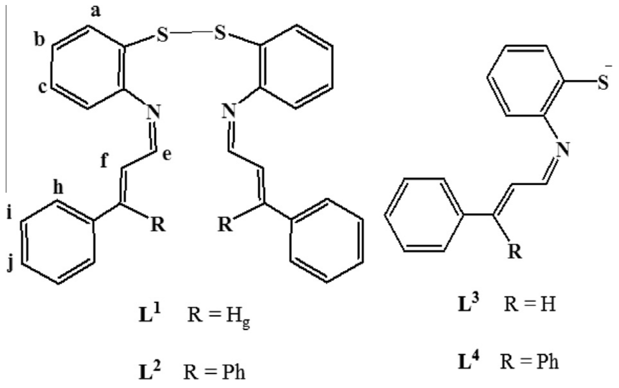
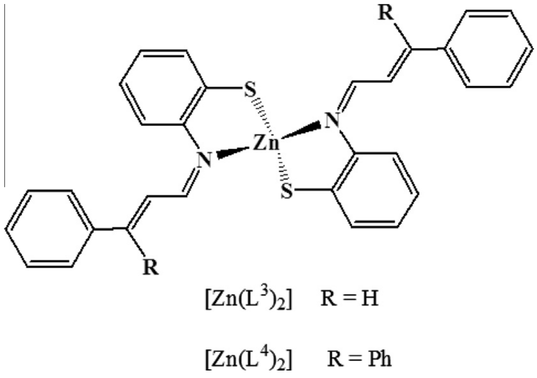


**Scheme 1.** Cartoon illustrating how a $Zn^{II}(Cys^{-})_2$ motif can display redox activity.



**Scheme 2.** The chemical formula of the Schiff base ligands $\mathbf{L^1}$, $\mathbf{L^2}$, $\mathbf{L^3}$ and $\mathbf{L^4}$.



**Scheme 3.** The chemical formula of $[Zn(L^3)_2]$ and $[Zn(L^4)_2]$.

## 2. Experimental

### 2.1. Materials and general methods

All solvents and chemicals were of commercial reagent grade and were used as received from Aldrich and Merck. The Schiff base ligand $\mathbf{L^1}$ was prepared as reported elsewhere [27]. Infrared spectra from KBr pellets were collected on a FT-IR JASCO 680 plus spectrophotometer in the range 4000–400 $cm^{-1}$. UV–Vis absorption spectra were recorded on a JASCO V-570 spectrophotometer. $^1H$ NMR spectra were measured with a Bruker AVANCE III 400 spectrometer (400 MHz). Proton chemical shifts are reported in ppm relative to $Me_4Si$ as internal standard. Elemental analyses were performed by using a Perkin–Elmer 2400II CHNS–O elemental analyzer. GC/MS analysis was performed with GC–MS-Agilent 5975C.

Electrochemical properties of these compounds were studied by cyclic voltammetry. Cyclic voltammograms were recorded by using a SAMA 500 Research Analyzer using a three electrode system, a glassy carbon working electrode (Metrohm 6.1204.110 with 2.0 ± 0.1 mm diameter), a platinum disk auxiliary electrode and Ag wire as reference electrode. CV measurements were performed in $CH_3OH$ with lithium perchlorate as supporting electrolyte. The solutions were deoxygenated by purging with Ar for 5 min. All electrochemical potentials were calibrated versus internal $Fc^{+/0}$ ($E^0 = 0.431$ V versus SCE) couple under the same conditions [28].

### 2.2. Synthesis of ligands $\mathbf{L^1}$ and $\mathbf{L^2}$

The ligand $\mathbf{L^1}$ was prepared according to the literature [27] in 90% yield. *Anal.* Calc. for $C_{30}H_{24}N_2S_2$: C, 75.59; H, 5.08; N, 5.88; S, 13.45. Found: C, 75.20; H, 5.01; N, 5.95; S, 13.60%. FT-IR (KBr, $cm^{-1}$) $\nu_{max}$: 1624 s (C=N). UV–Vis: $\lambda_{max}$ (nm) ($\varepsilon$, L $mol^{-1}$ $cm^{-1}$) ($CHCl_3$). 353 (18160), 294 (57840). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 7.02$ (dd, $J = 6.8$, 1.6 Hz, 2H, $H_a$), 7.17–7.24 (m, 8H, $H_{b,c,d,g}$), 7.39–7.46 (m, 6H, $H_{i,j}$), 7.59 (dd, $J = 8$, 1.6 Hz, 4H, $H_h$), 7.66 (dd, $J = 7.6$, 1.6 Hz, 2H, $H_f$), 8.31 (dd, $J = 6.8$, 1.6 Hz, 2H, $H_e$).

The ligand $\mathbf{L^2}$ was synthesized by adding a solution of β-phenylcinnamaldehyde (0.416 g, 2 mmol) in methanol (2 mL) to a stirring solution of bis(2-aminophenyl)disulfide (0.250 g, 1 mmol) in methanol (5 mL). The mixture was stirred for 10 h to give a yellow precipitate. The product was filtered off and washed with cold methanol. Yield 93%; *Anal.* Calc. for $C_{42}H_{32}N_2S_2$: C, 80.22; H, 5.13; N, 4.45; S, 10.20. Found: C, 80.06; H, 5.02; N, 4.57; S, 10.05%. FT-IR (KBr, $cm^{-1}$) $\nu_{max}$: 1605 s (C=N). UV–Vis: $\lambda_{max}$ (nm) ($\varepsilon$, L $mol^{-1}$ $cm^{-1}$) ($CHCl_3$): 367 (21650), 316 (42980). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 6.79$ (m, 2H, $H_a$), 7.11 (m, 4H, $H_{b,c}$), 7.19 (d, $J = 9.2$ Hz, 2H, $H_d$), 7.34–7.47 (m, 20H, $H_{i,j,h}$), 7.60 (m, 2H, $H_f$), 8.16 (d, $J = 9.2$ Hz, 2H, $H_e$).

### 2.3. Synthesis of $[Zn(L^3)_2]$ (**1**)

To a solution of $Zn(OAc)_2.2H_2O$ (22 mg, 0.1 mmol) in methanol (10 mL) was added a solution of $\mathbf{L^1}$ (47.6 mg, 0.1 mmol) in $CHCl_3$ (10 mL), and the mixture was stirred at room temperature for two days to give a clear orange solution. Orange single crystals of complex **1** suitable for X-ray crystallography were obtained by slow evaporation of solvents. Yield 57%. *Anal.* Calc. for $C_{30}H_{24}N_2S_2$ Zn: C, 66.47; H, 4.46; N, 5.17; S, 11.83. Found: C, 65.87; H, 4.25; N, 5.38; S, 11.68%. FT-IR (KBr, $cm^{-1}$) $\nu_{max}$: 1616 s (C=N). UV–Vis: $\lambda_{max}$ (nm) ($\varepsilon$, L $mol^{-1}$ $cm^{-1}$) ($CHCl_3$): 459 (7790), 341 (32,760). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 7.01$–7.54 (m, 20H, $H_{a,b,c,d,g,h,i,j}$), 7.88 (d, $J = 7.6$ Hz, 2H, $H_f$), 8.61 (d, $J = 10$ Hz, 2H, $H_e$).

### 2.4. Synthesis of $[Zn(L^4)_2]$ (**2**)

The complex **2** was prepared by a procedure similar to that of **1** except that $\mathbf{L^2}$ (62.9 mg, 0.1 mmol) was used instead of $\mathbf{L^1}$. Orange crystals were collected by filtration and washed with small amounts of methanol. Yield 37%. *Anal.* Calc. for $C_{42}H_{32}N_2S_2Zn$: C, 72.66; H, 4.65; N, 4.04; S, 9.24. Found: C, 71.31; H, 4.87; N, 4.18; S, 9.22%. FT-IR (KBr, $cm^{-1}$) $\nu_{max}$: 1604 s (C=N). UV–Vis: $\lambda_{max}$ (nm) ($\varepsilon$, L $mol^{-1}$ $cm^{-1}$) ($CHCl_3$) 475 (1825), 321 (38,522). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 6.84$–7.42 (m, 28H, $H_{aromatic}$), 7.65 (dd, $J = 8$, 1.2 Hz, 2H, $H_f$), 8.38 (d, $J = 10$ Hz, 2H, $H_e$).

### 2.5. Crystal structure determination and refinement for **1** and **2**

Orange single crystals of **1** and **2** were obtained by slow evaporation of a methanol solution of **1**, and a dichloromethane-methanol solution of **2** (2.5:1 v/v) at room temperature. **2** crystallized as a solvate incorporating obviously both solvents in a slightly disordered and non-stoichiometric fashion. Due to the very small size of the available crystals the diffraction data of **1** were collected at the ESRF with a synchrotron source ($\lambda = 0.70135$ Å) at $T = 100$ K and a diffractometer with a Dectris Pilatus 2 M pixel