Bioinorganic Chemistry

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# A Bio-Inspired Switch Based on Cobalt(II) Disulfide/Cobalt(III) Thiolate Interconversion**

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***Abstract:*** *Disulfide/thiolate interconversion supported by transition-metal ions is proposed to be implicated in fundamental biological processes, such as the transport of metal ions or the regulation of the production of reactive oxygen species. We report herein a mononuclear dithiolate* $\text{Co}^{III}$ *complex,* $[\text{Co}^{III}\text{LS(Cl)}]$ *(**1**; LS = sulfur containing ligand), that undergoes a clean, fast, quantitative and reversible* $\text{Co}^{II}$ *disulfide/*$\text{Co}^{III}$ *thiolate interconversion mediated by a chloride anion. The removal of* $\text{Cl}^-$ *from the* $\text{Co}^{III}$ *complex leads to the formation of a bis(μ-thiolato) μ-disulfido dicobalt(II) complex,* $[\text{Co}_2^{II,II}\text{LSSL}]^{2+}$ *(**2**$^{2+}$). The structures of both complexes have been resolved by single-crystal X-ray diffraction; their magnetic, spectroscopic, and redox properties investigated together with DFT calculations. This system is a unique example of metal-based switchable* $\text{M}^{n}_{2}\text{-RSSR}/2\,\text{M}^{(n+1)}\text{-SR}$ *(M = metal ion, n = oxidation state) system that does not contain copper, acts under aerobic conditions, and involves systems with different nuclearities.*

The conversion of thiolates into disulfide bridges is one of the major biological redox processes due to its fundamental role in the folding and stability of most proteins. When this reaction becomes reversible, it can switch "on" or "off" the reactivity of a protein.[1] On the other hand, thiolates act as terminal or bridging ligands for transition-metal ions to generate self-assembled complexes of different nuclearities.[2] The idea that metal ions can play an active role in the disulfide/thiolate interconversion of essential biological processes has only emerged during the last decade.[3] However, this hypothesis has never been undoubtedly demonstrated nor completely understood.[4]

In chemistry, the disulfide/thiolate interconversion has been largely explored as well as the effect of a metal ion on the kinetics. However, only a few investigations, limited to copper complexes, report on the role of the metal ion directly bound to the sulfur atoms involved in the $\text{RSSR}/2\text{RS}^-$ interconversion.[5] In those three examples, the interconversion is mediated by either halides or protons and requires anaerobic conditions. Surprisingly, such processes have never been reported for other transition-metal ions.

We report herein on a mononuclear dithiolate $\text{Co}^{\text{III}}$ complex, $[\text{Co}^{\text{III}}\text{LS(Cl)}]$ (**1**, LS = sulfur containing ligand), that undergoes a very clean, quantitative and fully reversible $\text{Co}^{\text{III}}$ thiolate/$\text{Co}^{\text{II}}$ disulfide interconversion mediated by a chloride anion (Scheme 1). Remarkably, compound **1** is a rare example of a triplet five-coordinated $\text{Co}^{\text{III}}$ complex.[6] The removal of the $\text{Cl}^-$ ion from the $\text{Co}^{\text{III}}$ complex leads to the formation of a bis(μ-thiolato) μ-disulfido dicobalt(II) complex, $[\text{Co}_2^{\text{II,II}}\text{LSSL}]^{2+}$ (**2**$^{2+}$), containing the unusual $\{\text{M}_2\text{S}_2(\text{SS})\}$ core, only found in Mn, Re and Ir complexes until now.[7]

The mononuclear complex **1** was obtained as black crystals by electrochemical oxidation of $[\text{Co}^{\text{II}}\text{LS}]$[8] at $-0.50$ V vs $\text{Fc/Fc}^+$ ($\text{Fc} = [(\eta\text{-C}_5\text{H}_5)_2\text{Fe}]$) in presence of $\text{Et}_4\text{NCl}$ as electrolyte in $\text{CH}_3\text{CN}$. The X-ray structure of **1** (Figure 1) shows that the $\text{Co}^{\text{III}}$ ion is in the center of a distorted square pyramidal $\text{N}_2\text{S}_2\text{Cl}$ coordination sphere, with the two N and two S atoms of the ligand located in the equatorial plane, and the $\text{Cl}^-$ ion occupying the axial position. The $\text{Co}^{\text{III}}$ ion is shifted 0.485 Å from the mean $\text{N}_2\text{S}_2$ plane toward the axial Cl ligand. As expected, the Co–S and the Co–N bonds in **1** are slightly longer than those in $[\text{Co}^{\text{II}}\text{LS}]$.[8]

From the magnetic properties of **1**, it can be concluded that it is an $S = 1$ $\text{Co}^{\text{III}}$ species both in solid state and in solution. The $\chi T$ product at 320 K of 1.3 $\text{cm}^3\,\text{K}\,\text{mol}^{-1}$ (Figure 2) is in agreement with the expected values for such $S = 1$ species. Its decrease observed at low temperature is consistent with very large zero-field splitting, estimated by fitting the experimental data with $D/k_B = +50(1)$ K and $g = 2.27(5)$ (with $\mathbf{H} = D\,S_{\text{T},z}{}^2$). For comparison, the unique previously reported $D$ value for an $S = 1$ five-coordinated $\text{Co}^{\text{III}}$

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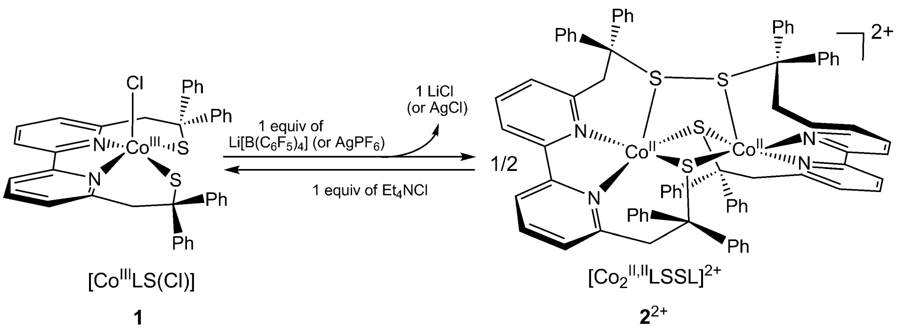

***Scheme 1.***

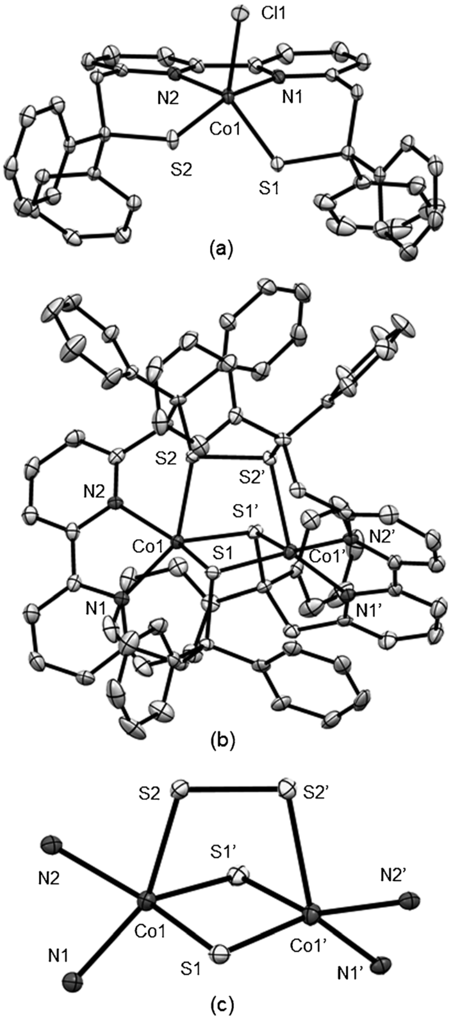

***Figure 1.*** ORTEP-type views (thermal ellipsoids set at 30% probability, hydrogen atoms removed for clarity) of a) **1**, b) **2**$^{2+}$, c) the binuclear $\{N_4Co_2S_2(SS)\}$ core of **2**$^{2+}$.

complex is of +154 K.[6] The effective magnetic moment determined in $CH_2Cl_2$ solution ($\mu_{eff} = 2.44\ \mu_B$ at 20 °C by Evans method, corresponding to $\chi T = 0.74\ cm^3\,K\,mol^{-1}$)[9] evidence that the triplet state is conserved in solution ($2.82\ \mu_B$ is expected for $S = 1$), thus confirming that the mononuclear structure of **1**, with a five-coordinate $Co^{III}$ center, is retained in solution. The absorption spectrum of the brown **1** solution in $CH_2Cl_2$ (Figure 3) displays an intense transition at 477 nm and two weaker features at 675 nm and 795 nm, which have been assigned, based on TD-DFT calculations, to ligand-to-metal charge transfer (LMCT) transitions involving both the chloride anion and thiolate ligands (Figure S8 in the Supporting information). The cyclic voltammogram (CV) of a $CH_2Cl_2$ solution of **1** displays a poorly reversible reduction wave at $Ep_c = -0.78$ V vs. $Fc/Fc^+$ ($Ep_{a1} = -0.63$ V, $Ep_{a2} = -0.27$ V). This can be assigned to the $Co^{III}/Co^{II}$ redox couple followed by a partial decoordination of the $Cl^-$ ion. An irreversible oxidation wave is observed at $Ep_a = +0.50$ V ($Ep_c = -0.08$ V) (Figure 4), most likely due to a ligand-based process.

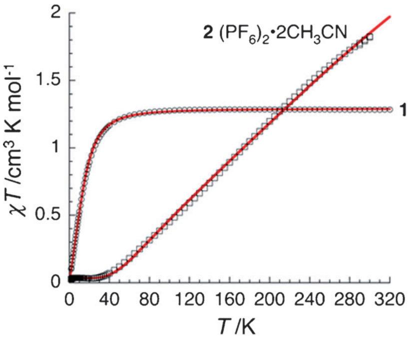

***Figure 2.*** Temperature dependence of the $\chi T$ product (where $\chi$ is the molar magnetic susceptibility equal to $M/H$ per cobalt complex) measured at 0.1 T for **1** and **2**$^{2+}$. The solid lines are the best fits of the experimental data to the models described in the text.

Black crystals of **2**$(PF_6)_2\cdot 2\,CH_3CN$ were obtained by reaction of complex **1** with $AgPF_6$ in $CH_2Cl_2$:$CH_3CN$ 9:1 (Scheme 1). The dinuclear **2**$^{2+}$ complex can be also electrogenerated by an exhaustive electrolysis of $[Co^{II}LS]$ carried out in $CH_2Cl_2$ at 0 V. The X-ray structure of **2**$^{2+}$ (Figure 1) displays a rare $\{M_2S_2(SS)\}$ core, with a disulfide binding the two $Co^{II}$ ions in a *cis*-μ-1,2 mode. The slightly shorter Co–N distances in **2**$^{2+}$ in comparison with those in the $Co^{III}$ complex **1**, are consistent with the +II oxidation state for both Co ions. A $C_2$ axis is at the origin of the structural equivalence of the two $Co^{II}$ centers. Each $Co^{II}$ ion displays a highly distorted square-pyramidal geometry, with two N atoms and two μ-S atoms of the ligand forming the square planar base and one S atom of the disulfide bridge in axial position. As expected, the axial $Co^{II}$–$S_{S\text{-}S}$ bond (2.5341(8) Å) is significantly longer than the basal $Co^{II}$–(μ-$S_{thiolate}$) bonds (2.3796(8) and 2.3272(7) Å), the latter being in the expected range (2.21–2.39 Å).[10] The long distance between the two Co ions (3.1188(5) Å) implies the absence of a direct metal–metal bond. The temperature dependence of the magnetic susceptibility of **2**$(PF_6)_2\cdot 2\,CH_3CN$ was collected over the 300–1.8 K temper-

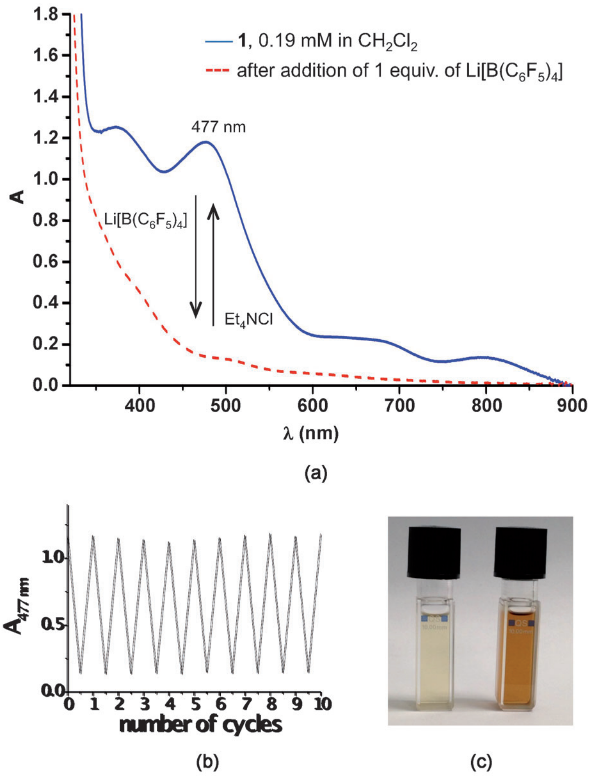

***Figure 3.*** a) UV/Vis spectra of **1** (0.19 mM in $CH_2Cl_2$, 1 cm path length, room temperature, aerobic conditions) recorded before (——) and (-----) after the addition of Li[B($C_6F_5$)$_4$] (1.05 equiv) forming $\mathbf{2}^{2+}$. b) By monitoring the absorbance at 477 nm, the complete reversibility of the process is attested by a subsequent addition of $Et_4NCl$ (1.05 equiv): no loss of conversion is observed after 10 cycles. c) UV cells with **1** (right) and $\mathbf{2}^{2+}$ (left).

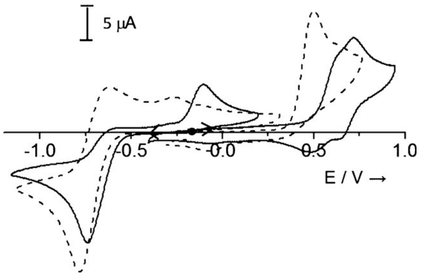

***Figure 4.*** Cyclic voltammograms of an 1.70 mM solution of **1** (-----) and an 0.85 mM solution of $\mathbf{2}^{2+}$ (——) in $CH_2Cl_2$, 0.1 M $Bu_4NPF_6$ (carbon vitreous electrode, scan rate of 100 mV s$^{-1}$, potentials vs $Fc^+$/Fc).

ature range (Figure 2). The magnetic behavior is consistent with the presence of two high spin Co$^{II}$ ions ($S=3/2$) interacting by a strong antiferromagnetic coupling, $J/k_B=-200(5)$ K ($g=2.37(5)$; $\mathbf{H}=-2JS_1S_2$). The effective magnetic moment determined in $CH_2Cl_2$ solution ($\mu_{eff}=3.77\ \mu_B$ at 20 °C, corresponding to $\chi T=1.8\ cm^3\,K\,mol^{-1}$) is consistent with the magnetic properties measured on the powder. The dinuclear structure of $\mathbf{2}^{2+}$ is thus retained in solution, as confirmed by ESI mass spectrometry ($m/z$ 1419.2 for [**2**-(PF$_6$)]$^+$). The UV/Vis spectrum of the pale yellow solution of $\mathbf{2}^{2+}$ (Figure 3) displays several low-intense shoulders at around 400, 505, and 600 nm. The CV of $\mathbf{2}^{2+}$ (Figure 4) shows an irreversible two-electron reduction process[11] located at $Ep_c=-0.74$ V ($Ep_a=-0.10$ V), attributed to the reduction of the disulfide bridge. Two consecutive one-electron oxidation processes, electrochemically reversible, are located at $E_{1/2}=+0.56$ V and $+0.68$ V ($\Delta Ep=140$ mV and 80 mV, respectively). These can be assigned to the oxidation of either the Co$^{II}$ ions or the remaining thiolates. Remarkably, the cathodic peak of $\mathbf{2}^{2+}$ is only 40 mV shifted (to less negative potentials) with respect to the cathodic peak of **1**, assigned to the reduction of Co$^{III}$ into Co$^{II}$.

In presence of two equivalents of $Et_4NCl$, the dinuclear $\mathbf{2}^{2+}$ complex is immediately and quantitatively converted into two equivalents of the mononuclear **1** species in $CH_2Cl_2$ under aerobic conditions (20 °C), as shown by UV/Vis spectroscopy (Figure 3). This internal redox process, induced by the coordination of one chloride anion on each Co center, involves the reduction of the disulfide bridge with the concomitant oxidation of the Co$^{II}$ centers of $\mathbf{2}^{2+}$. This reaction is completely reversible as the stoichiometric addition of Li[B($C_6F_5$)$_4$] is sufficient to quantitatively regenerate $\mathbf{2}^{2+}$ from **1** (Figure 3). The process is clean without formation of any by-products. Indeed, $\mathbf{2}^{2+}$ is the only species detected in solution after the addition of Li[B($C_6F_5$)$_4$] to **1**, as attested by ESI mass spectrometry (signal at $m/z$ 1953.1 for [**2**(B($C_6F_5$)$_4$)]$^+$) and electrochemistry (the CV being identical to that of $\mathbf{2}^{2+}$). The reverse is also true, that is, when adding two equivalents of $Et_4NCl$ to $\mathbf{2}^{2+}$, the resulting CV is identical to that of **1**. More interestingly, this chemical interconversion can be repeated several times (at least 10 cycles) without loss of efficiency (Figure 3).

The geometric and electronic changes induced on **1** by removing the cobalt-bound $Cl^-$ ion have been tentatively rationalized through DFT calculations. The Mulliken spin population analysis performed on the DFT-optimized structure of [CoLS]$^+$ highlights a remarkable increase of the spin distribution on the sulfur atoms in comparison to **1** (0.18 for [CoLS]$^+$ and 0.01 for **1**, Figure S9). The clear "thiyl" character of the thiolates can then explain their enhanced reactivity and the immediate formation a disulfide bridge between two [CoLS]$^+$ units to generate $\mathbf{2}^{2+}$. Such a phenomenon has been described for a mononuclear Ni$^{II}$ thiyl radical complex, which rapidly undergoes an irreversible dimerization process involving the formation of an S–S bond.[12]

Two conditions seem to be required for such metal-based disulfide/thiolate interconversion process to occur reversibly. First, the redox potential of the RSSR/2RS$^-$ and M$^{n+}$/M$^{(n-1)+}$ redox couples should be close enough to allow a small structural modification to address the direction of the internal electron transfer between the ligand and the metal. In this specific case, this is owing to the coordination of a $Cl^-$ ion that the redox potential of the Co$^{III}$/Co$^{II}$ redox couple becomes lower than that of the RSSR/2 RS$^-$ couple, thus stabilizing the Co$^{III}$SR species. In contrast, decoordination of the $Cl^-$ ion leads to the stabilization of the Co$^{II}_2$(R)SSR form with respect to the Co$^{III}$SR one. Secondly, the chemical reversibility of the process seems to be also favored by the disulfido bridge remaining coordinated to the metal centers (in this case, two $Co^{II}$ ions), as it has been observed in copper-based systems.[5a,b] This behavior is relatively rare; when metal thiolate complexes are oxidized with the concomitant formation of a disulfide bridge, the reaction is commonly followed by decoordination of the disulfide bridge. In addition, the coordination of the disulfide prevents the generation of highly reactive thiyls and/or free thiolate species during the interconversion process.

In conclusion, we have described a rare example of a metal-based switchable system involving a disulfide/thiolate interconversion. Most importantly, this work reports the first $M^{n}_{2}$-(R)SSR/2 $M^{(n+1)}$-SR switch ($n$ = oxidation state) that 1) does not contain copper, 2) acts under aerobic conditions, and 3) involves systems with different nuclearities. In addition, these results also confirm that an external stimulus (in this case, the addition of a chloride anion) can lead to the fine-tuning of the electronic properties of the metal ion, thereby permitting the shift of the disulfide/thiolate equilibrium. However, the exact role of the mediator deserves to be further elucidated with the determination of the key properties for the process to occur. More interestingly, this work opens the door to a broader field of applications if other external stimuli such as pH value, light, or pressure can control this molecular switch.

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