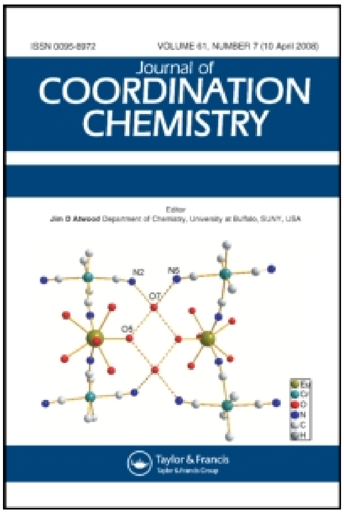

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# Synthesis, characterization, and antioxidant activities of three Cu(II) complexes with Schiff-base ligands

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# Synthesis, characterization, and antioxidant activities of three Cu(II) complexes with Schiff-base ligands

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Cu(II) complexes of three bis(pyrrol-2-yl-methyleneamine) ligands were synthesized and characterized by elemental analyses, mass spectra, and IR spectra. X-ray diffraction analysis shows that $[CuL^3]_2$ is a dinuclear complex with an extremely distorted square-planar geometry. Furthermore, the antioxidant activities of the compounds have been investigated. The electrochemical properties of the Cu(II) complexes have also been studied by cyclic voltammetry. The Cu(II) complexes show similar superoxide dismutase (SOD) activity compared with that of the native Cu, Zn-SOD.

*Keywords*: Schiff base; Cu(II) complex; Antioxidant activity; Cyclic voltammetry

## 1. Introduction

Superoxide ($O_2^{\bullet -}$), a product of cellular respiration, is involved in the pathogeneses of diseases such as hypertension, carcinogenesis, and photoaging due to the exposure to ultraviolet radiation. In addition, $O_2^{\bullet -}$ reacts with hydrogen peroxide ($H_2O_2$) and nitric oxide radicals to generate the extremely reactive hydroxyl radical ($OH^{\bullet}$) and peroxynitrite ($ONOO^-$), respectively [1, 2].

Superoxide dismutase (SOD) catalyzes the dismutation of superoxide into hydrogen peroxide and dioxygen to keep the free radical density in the body at a normal level. However, SOD is easily excreted through kidneys *in vivo* and cannot enter the cells due to its high molecular weight. Furthermore, studies on Cu, Zn-SOD have demonstrated that only the Cu site is active [2–4], taking part in reduced and oxidized reactions with $O_2^{\bullet -}$. Thus, more and more lower molecular weight Cu(II) complexes have been designed and synthesized as mimics for Cu, Zn-SOD, e.g., Cu(II) complexes of Schiff base, imidazole-bridged Cu(II) complexes, and heterodinuclear Cu–Zn complexes [1–7]. These models may help to understand the action of the enzymes.

Mono- and binuclear metal complexes of linear-spaced bis(pyrrol-2-yl-methyleneamine) ligands have been generated through the work of Ma and co-workers [8–12].

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Most of them have excellent fluorescent properties and good solubilities. Our group has also reported the DNA-binding properties of Zn(II) complexes bearing bis(pyrrol-2-yl-methyleneamine) [13].

As a continuation of our research, Cu(II) complexes of these bis(pyrrol-2-yl-methyleneamine) ligands have been synthesized and characterized. In addition, antioxidant activities of all compounds were investigated. Information obtained from this study will be helpful to develop new antioxidants.

## 2. Experimental

### 2.1. *Materials*

Nitroblue tetrazolium (NBT), methionine (MET), and vitamin $B_2$ (Vit $B_2$) were purchased from Sigma Chemical Co. Vitamin C, safranin, ethylenediaminetetraacetic acid disodium salt (EDTA), $FeSO_4 \cdot 7H_2O$, and $Cu(OAc)_2 \cdot H_2O$ were produced by Shang Hai Reagent Co. (P. R. China). All materials and solvents were of analytical grade. EDTA–Fe(II) and $Na_2HPO_4$–$KH_2PO_4$ buffers were prepared with twice-distilled water.

### 2.2. *Methods*

Elemental analyses were carried out on an Elemental Vario EL analyzer and the metal content was determined by titration with EDTA. The IR spectra were obtained in KBr discs on a Nicolet 5-DX spectrophotometer from 4000–400 $cm^{-1}$. Mass spectra of $[CuL^1]_2$ was obtained on a Bruker Apex II mass spectrometer. Crystal of $[CuL^3]_2$ was mounted on a Bruker Smart Apex II diffractometer and determined with graphite monochromated Mo-K$\alpha$ radiation (0.71073 Å) in $\omega/2\theta$ scan mode. Antioxidant activities were tested on a 721E spectrophotometer (Shanghai Analytical Instrument Factory, China) according to the literature methods [2]. Cyclic voltammetric studies were recorded on a CHI660B electrochemical analyzer (Shanghai Chenhua Corporation).

### 2.3. *Synthesis*

The bis(pyrrol-2-ylmethyleneamine) ligands were synthesized and characterized in our previous work [13] and are shown in figure 1. The Cu(II) complexes were prepared by the reaction of each ligand with $Cu(OAc)_2 \cdot H_2O$ in ethanol. $H_2L^n$ (0.1 mmol) was dissolved in EtOH (5 mL), then an EtOH (5 mL) solution containing $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.1 mmol) was added. After a few minutes, a precipitate was formed. After stirring for 4 h at room temperature, the precipitate was separated by suction filtration, washed with EtOH, and then dried in a vacuum. All of the Cu(II) complexes were prepared under the same procedure.

$[CuL^1]_2$: Yield: 51%. $C_{44}H_{56}N_8O_8Cu_2$: Calcd (%): C 55.51, H 5.93, N 11.77; Found (%): C 55.62, H 5.72, N 11.56. IR (KBr): $\nu = 1688$s (C=O), 1597s (C=N).

$[CuL^2]_2$: Yield: 50%. $C_{44}H_{56}N_8O_8Cu_2$: Calcd (%): C 58.68, H 6.82, N 10.53, Cu 11.94; Found (%): C 58.85, H 7.10, N 10.29, Cu 12.23. IR (KBr): $\nu = 1694$s (C=O), 1600s (C=N).

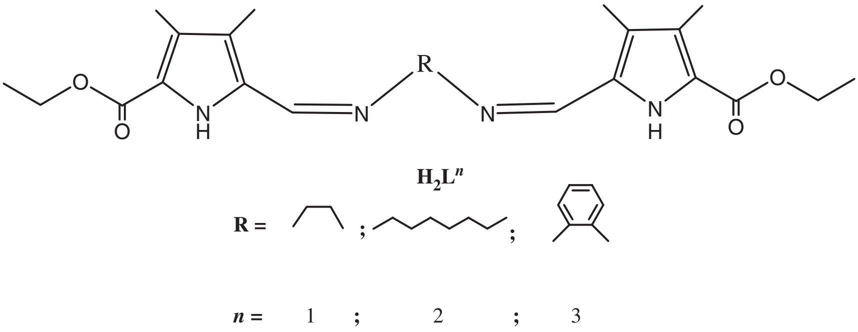

Figure 1. The corresponding ligands.

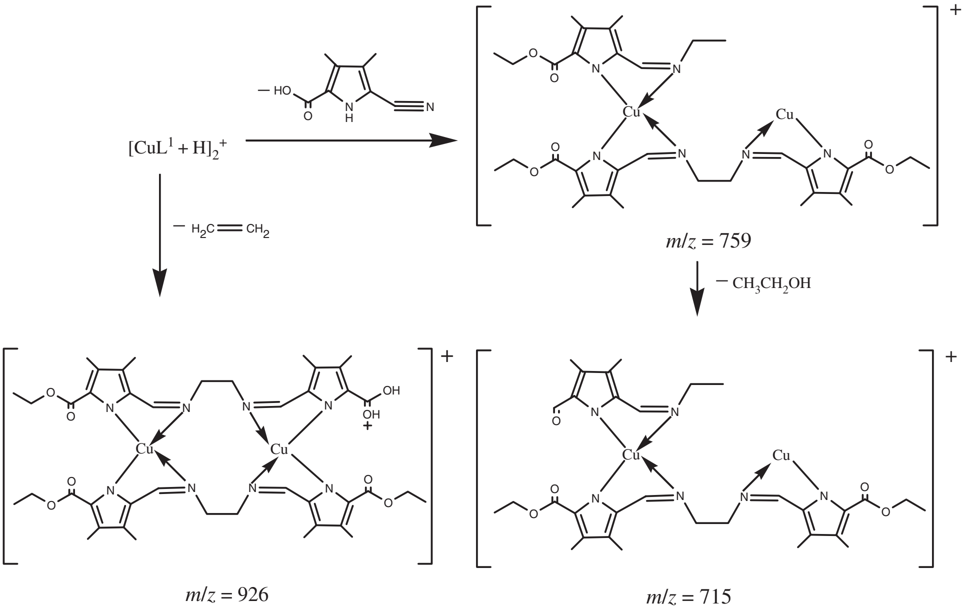

Figure 2. The fragmentation pattern of $[CuL^1]_2$.

$[CuL^3]_2$: Yield: 57%. $C_{52}H_{56}N_8O_8Cu_2$: Calcd (%): C 59.59, H 5.39, N 10.69; Found (%): C 59.75, H 5.52, N 10.54. IR (KBr): $\nu = 1703$s (C=O), 1605s (C=N).

## 3. Results and discussion

### 3.1. *The structures of the Cu(II) complexes*

All the Cu(II) complexes are soluble in DMF, THF, and DMSO, slightly soluble in methanol, ethanol, ethyl acetate, and acetone and insoluble in water and ether. Elemental analyses show that in the complexes the molar ratios of the ligand and Cu(II) are 1 : 1.

Mass spectrometry was especially informative in identifying the structure. The suggested fragments of $[CuL^1]_2$ and their $m/z$ values, shown in figure 2, reveal that the largest $m/z$ value is 926.5 $[(\mathrm{M+H})-(\mathrm{CH_2{=}CH_2})]^+$, which was therefore assigned as a dimeric complex with a ligand : metal ratio of 2 : 2. Usually, similar ligands result in the same coordination behavior. Since the structure of $[\mathrm{CuL^1}]_2$ is similar to that of Cu(II) complex of 1,2-bis(pyrrol-2-ylmethyleneamine)ethane [8], it can be concluded that the possible composition of the other two complexes should be $[\mathrm{CuL^2}]_2$ and $[\mathrm{CuL^3}]_2$.

IR spectra of the Cu(II) complexes are similar to Zn(II) complexes that we have reported [13]. The $\nu_{\mathrm{NH}}$ vibrations are at 3279–3317 $\mathrm{cm^{-1}}$ [13] but disappeared in the corresponding complexes, indicating that nitrogen of the pyrrole takes part in coordination and active hydrogens are substituted by Cu(II). The $\nu_{\mathrm{C=N}}$ of the ligands at 1617–1641 $\mathrm{cm^{-1}}$ [13] shift to 1597–1605 $\mathrm{cm^{-1}}$ in the complexes, indicating azomethine nitrogens coordinate to Cu(II). The $\nu_{\mathrm{C=O}}$ of ester in the complexes (1688–1703 $\mathrm{cm^{-1}}$) are higher than in the ligands (1669–1673 $\mathrm{cm^{-1}}$) [13], probably due to the coordination between nitrogen of the pyrrole and Cu(II).

X-ray diffraction data of $[\mathrm{CuL^3}]_2$ are given in table 1. As shown in figure 3, the crystal structure of $[\mathrm{CuL^3}]_2$ consists of two unsymmetrical Cu(II) ions, each bound to four nitrogens from two ligands in an extremely distorted square-planar geometry [the maximum deviation is 0.5360 Å for Cu(1) coordination plane and 0.5390 Å for the Cu(2) one]. Selected bond lengths and angles are summarized in table 2. The N–Cu–N angles range from 82.57(11)° to 155.37(11)° and the bonds distances of Cu–N span from 1.925(3) to 2.051(2) Å. The distance between two copper centers in $[\mathrm{CuL^3}]_2$ is 3.426 Å. On the basis of the above evidence and analyses, the possible structures of the complexes are shown in figure 4.

Table 1. Crystallographic and experimental data of $[\mathrm{CuL^3}]_2$.

| | |
|---|---|
| Formula | $\mathrm{C_{52}H_{56}N_8O_8Cu_2}$ |
| Formula weight | 1048.13 |
| Crystal color | Dark |
| Crystal size ($\mathrm{mm^3}$) | 0.25 × 0.25 × 0.23 |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| Temperature (K) | 294(2) |
| Unit cell dimensions (Å, °) | |
| $a$ | 14.4951(9) |
| $b$ | 20.7920(12) |
| $c$ | 16.5725(10) |
| $\alpha$ | 90.00 |
| $\beta$ | 91.5710(10) |
| $\gamma$ | 90.00 |
| Volume (Å$^3$), $Z$ | 4992.8(5), 4 |
| Calculated density ($\mathrm{g\,cm^{-3}}$) | 1.394 |
| Radiation (Å) (Mo-K$\alpha$) | 0.71073 |
| Reflections collected | 25,720 |
| Independent reflections ($R_{\mathrm{int}}$) | 9284 (0.0518) |
| $F(000)$ | 2184 |
| Number of parameters refined | 644 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0498$; $wR_2 = 0.0704$ |
| $R$ indices (all data) | $R_1 = 0.0906$; $wR_2 = 0.0762$ |
| Measurement | CCD area detector |
| Monochromator | Graphite |
| Structure determination | SHELXS-97 and SHELXL-97 |
| Refinement | Full-martrix least-squares on $F^2$ |

### 3.2. *Hydroxy radical scavenging activity*

Antioxidant activities of the ligands and their complexes with Zn(II) and Cu(II) ions were investigated. Because of their slight solubility in organic solvents, antioxidant activities of $[ZnL^2]_2$ were not measured. The ligands cannot scavenge $OH^{\bullet}$ in the tested concentration range. The other tested compounds can scavenge $OH^{\bullet}$ in a concentration-dependent manner (figure 5). Usually, mannitol is employed as a standard since it is known to selectively inhibit the $OH^{\bullet}$ radical. The $IC_{50}$ values of the complexes (table 3) are far less than that of mannitol [14]; all complexes show highly active scavenging effect on $OH^{\bullet}$ with $[CuL^2]_2$ better than that of the other tested complexes.

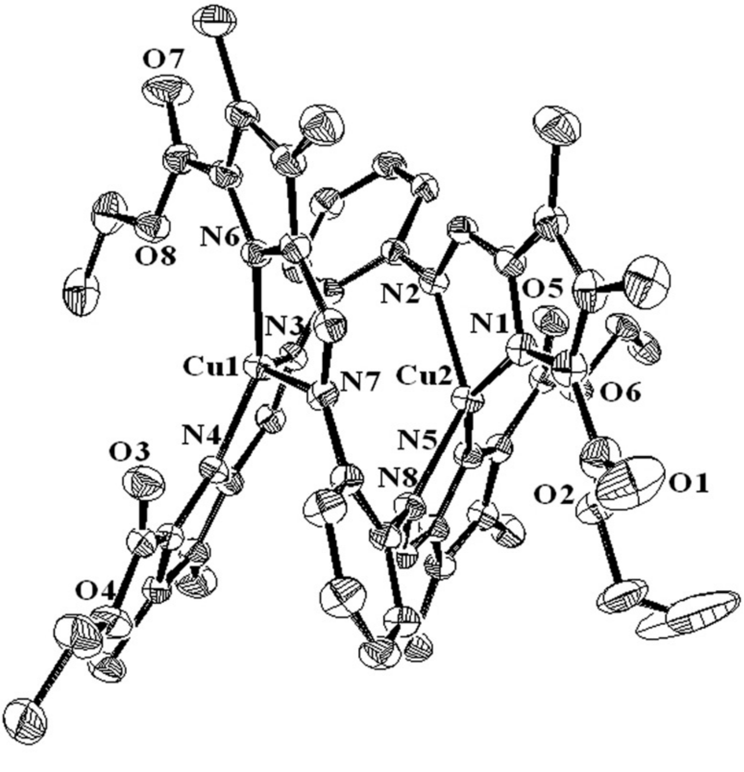

Figure 3. X-ray crystal structure of $[CuL^3]_2$, here H atoms are omitted for clarity.

Table 2. Selected bond lengths (Å) and angles (°).

| | | | |
|---|---|---|---|
| Cu(1)–N(4) | 1.925(3) | Cu(2)–N(1) | 1.929(3) |
| Cu(1)–N(6) | 1.936(3) | Cu(2)–N(5) | 1.932(2) |
| Cu(1)–N(7) | 2.038(3) | Cu(2)–N(2) | 2.038(3) |
| Cu(1)–N(3) | 2.051(2) | Cu(2)–N(8) | 2.048(2) |
| N(4)–Cu(1)–N(6) | 155.37(11) | N(1)–Cu(2)–N(5) | 153.46(11) |
| N(4)–Cu(1)–N(7) | 105.65(11) | N(1)–Cu(2)–N(2) | 83.11(11) |
| N(6)–Cu(1)–N(7) | 83.02(11) | N(5)–Cu(2)–N(2) | 106.77(10) |
| N(4)–Cu(1)–N(3) | 82.57(11) | N(1)–Cu(2)–N(8) | 106.89(11) |
| N(6)–Cu(1)–N(3) | 107.68(11) | N(5)–Cu(2)–N(8) | 83.04(11) |
| N(7)–Cu(1)–N(3) | 135.52(10) | N(2)–Cu(2)–N(8) | 136.82(10) |

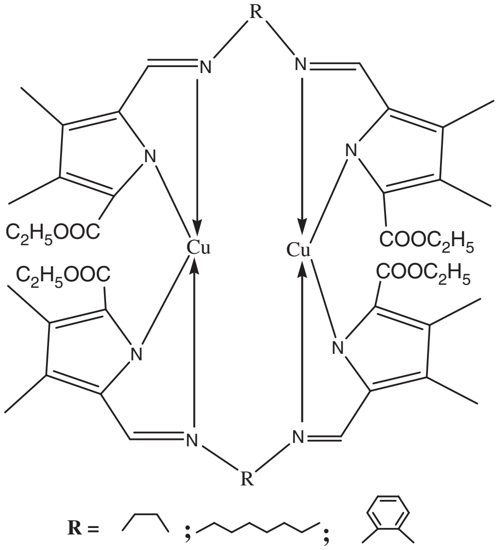

Figure 4. Possible molecular structures of the Cu(II) complexes.

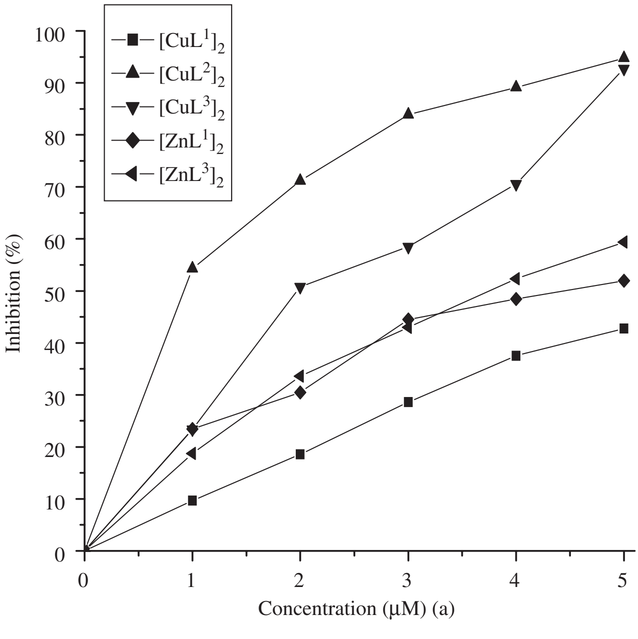

Figure 5. Effect of the tested compounds on OH•.

### 3.3. *Superoxide radical scavenging activity*

Of the ligands, only $H_2L^3$ scavenges $O_2^{\bullet -}$ in the tested concentration range. The inhibitory effects of the active compounds on $O_2^{\bullet -}$ are concentration related and the suppression ratio increases with increasing sample concentration (figure 6). The scavenger effect on $O_2^{\bullet -}$ is enhanced by the formation of metal–ligand coordination

Table 3. $IC_{50}$ values of the investigated compounds for $OH^{\bullet}$ and $O_2^{\bullet -}$.

| Compound | $[CuL^1]_2$ | $[CuL^2]_2$ | $[CuL^3]_2$ | $H_2L^3$ | $[ZnL^1]_2$ | $[ZnL^3]_2$ | Standard |
|---|---|---|---|---|---|---|---|
| $IC_{50}$ (μM)[a] | > 5 | < 1 | 2.42 | – | 4.36 | 3.86 | 10.34 [14] |
| $IC_{50}$ (μM)[b] | ~0.1 | ~0.1 | 0.22 | 3.7 | > 5 | 2.35 | 0.04 [1, 5] |

[a]Values of the investigated compounds for $OH^{\bullet}$.
[b]Values of the investigated compounds for $O_2^{\bullet -}$.

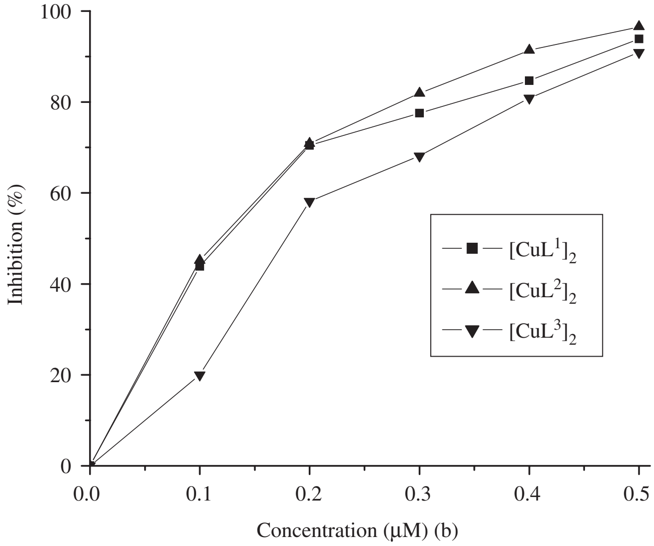

Figure 6. Effect of the Cu(II) complexes on $O_2^{\bullet -}$.

complexes and the $IC_{50}$ values of the Cu(II) complexes (table 3) are much less than other active compounds and some reported mononuclear Cu(II) complexes [$(C_9H_7NO_3)Cu(C_{12}H_8N_2)$, $IC_{50} = 6.15\,\mu M$; $[Cu(dtne)] \cdot (ClO_4)_2 \cdot CH_3CH_2OH$, $IC_{50} = 3.34\,\mu M$] [15, 16], but slightly higher than that of native Cu, Zn-SOD [1, 5]. Thus the Cu(II) complexes show similar SOD activity to native Cu, Zn-SOD.

### 3.4. *Electrochemical activity*

To further investigate redox of the Cu(II) complexes, their electrochemistry activity was investigated by cyclic voltammetry (CV). In the CV measurement, the three-electrode system was composed of a Pt working electrode, a Pt wire auxiliary electrode, and a saturated calomel electrode as the reference electrode. Measurements were performed in DMF (testing complexes concentration: $10^{-4}\,mol\,L^{-1}$) containing tetrabutylammonium perchlorate ($n$-$Bu_4NClO_4$) ($0.1\,mol\,L^{-1}$) as the supporting electrolyte. The potential was scanned from $-2.0$ to $+1.8$ V at a scan rate of $0.2\,V\,s^{-1}$.

The CV curves (figure 7) of the three Cu(II) complexes are similar, displaying one irreversible reductive response at about $-0.907$ V and two quasi-reversible one-electron

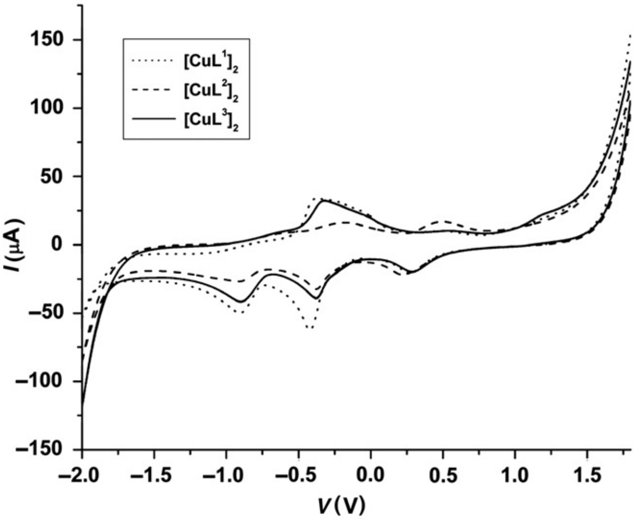

Figure 7. Cyclic voltammograms of the Cu(II) complex.

Table 4. The data of $E_{pa}$, $E_{pc}$, $E_{1/2}$, and $\Delta E_p$ of the Cu(II) complexes.

| Complex | $E_{pa}$ (V) | $E_{pc}$ (V) | $E_{1/2}$ (V) | $\Delta E_p$ (V) |
|---|---|---|---|---|
| $[CuL^1]_2$ | 0.485 | 0.273 | 0.379 | 0.212 |
| | −0.380 | −0.421 | −0.401 | 0.041 |
| | | −0.907 | | |
| $[CuL^2]_2$ | 0.492 | 0.216 | 0.354 | 0.276 |
| | −0.180 | −0.376 | −0.278 | 0.196 |
| | | −0.915 | | |
| $[CuL^3]_2$ | 0.531 | 0.288 | 0.410 | 0.243 |
| | −0.315 | −0.380 | −0.348 | 0.065 |
| | | −0.899 | | |

redox waves ($E_{1/2}$ in the range −0.401 to 0.410 V, shown in table 4) which are in the range –0.40 V to +0.65 V (*vs.* SCE) [17], indicating that they are the good range for superoxide dismutation. Compared with native Cu, Zn-SOD (+0.42 V or +0.35 V *vs.* NHE) [18], the Cu(II) complexes exhibit higher redox potential, which leads to a higher stability of Cu(I) and similar SOD activity [17, 18].

## 4. Conclusion

The three Cu(II) complexes bearing bis(pyrrol-2-yl-methyleneamine) are dimeric and show similar SOD activity compared with native Cu, Zn-SOD. The higher SOD activity is clarified by their electrochemical activity. Cu(II) plays an active role in the scavenge superoxide process; to better define the relationship between structure and activity requires further research.

## Supplementary material

X-ray data of $[CuL^3]_2$ is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, www.ccdc.cam.ac.uk/data_request/cif, on request quoting deposition number 670112.

## Acknowledgment

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