Mononuclear copper (II) salicylate complexes with 1,2-dimethylimidazole and 2-methylimidazole: Synthesis, spectroscopic and crystal structure characterization and their superoxide scavenging activities

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**A B S T R A C T**

The complexes ce:italic>&bis (1,2-dimethylimidazole) bis (salicylato) copper (II) (1) and tris (2-methylimidazole) (salicylate) copper (II) (2) have been prepared by the reaction of appropriate methylimidazole derivative with binuclear copper (II) aspirinate. Spectral and X-ray structural studies for complex 1 showed that the copper ion is coordinated in a ce:italic>& arrangement to two imidazole nitrogen atoms and two carboxylate oxygen atoms from the salicylate mono-anion ligands. The second carboxylate oxygen atoms form weak axial interactions with the copper ion. Spectral, magnetic and analytical data for complex 2 showed that the copper ion is bonded to three 2-methylimidazole nitrogen atoms and one doubly deprotonated salicylate di-anion, which is chelated to Cu (II) ion through one of its carboxylate oxygen atoms and the deprotonated hydroxyl oxygen atom to form distorted square-pyramidal geometry having CuN3O + O chromophore. The superoxide dismutase (SOD) mimetic activities (IC50) of the complexes 1, 2 and the structurally known mixture complexes Cu (imidazole)3(salicylato)3 (where n = 2, 5 and 6) were determined using the xanthine–xanthine oxidase assay and compared with those reported for other copper (II) complexes with anti-inflammatory drugs. The results obtained indicated that complexes 1–3 have high SOD-like activities, which may act as good mimics for native Cu, Zn-SOD enzyme.

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1. Introduction

Many copper (II) complexes of pharmacologically active ligands have been shown to be more effective in treatment diseases than the parent ligands [1,2]. Salicylic acid (a) and its derivatives have been used for many years as anti-inflammatory, antipyretic and analgesic drugs. Binary and ternary Cu (II) complexes of salicylic acid and its derivatives with basic ligands have been found to exhibit several pharmacological effects suggesting treatment of many pathological disease states [3–10]. These disease states include many inflammations, seizures, gastric and intestinal ulcers, diabetes, neoplasias carcinogenesis, convulsion, mutagenesis, ischemia–reperfusion injury, and radiation injury. All of these pharmacological effects of Cu (II) salicylate type complexes have been attributed to their anti-oxidative activities against the reactive oxygen species, especially superoxide radical anion (O2–), which are the cause of these diseases.

Reactive superoxide which is produced through metabolic reactions resulting from aerobic respiration is controlled by one of the enzymes Cu, Zn-superoxide dismutase (SOD) [11]. In this enzyme the copper (II) ion is the active center and coordinated to four imidazole nitrogen atoms from histidine residues in which one imidazole is bridging ligand between Cu (II) and Zn (II) ions. In addition, a water molecule is coordinated to copper ion at the axial position of a distorted square pyramidal configuration. The main function of the Zn (II) ion is to stabilize the enzyme structure and can be replaced by another atom or removed without any significant effect on the activity of the enzyme [11b]. The use of SOD enzyme as a pharmaceutical agent is limited because of its instability and low membrane permeability, resulting from its high molecular weight (about 32 KDa). So, low molecular weight mononuclear and binuclear Cu (II) complexes have been designed and synthesized as mimics for Cu, Zn-SOD [5–7,12–33], including binary and ternary copper complexes of anti-inflammatory drugs [2,5–7,2–22]. Because the native SOD enzyme has four imidazole nitrogen atoms coordinated to Cu (II) [11], it was proposed that the presence of coordination sites belonging to nitrogen hetero-aromatic rings such as imidazole, pyridine and pyrazole is important for high SOD activity [15,29,30]. Therefore, we selected imidazole and its methyl derivatives as auxiliary ligands to prepare ternary copper (II) salicylate complexes. Recently, we reported the characterization of mononuclear copper (II) salicylate imidazole and N-methylimidzole com-

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plexes [20,34]. The imidazole ligand has formed a mixture of three mononuclear geometries in a unit cell: the ce:italic>bis, pentakis- and hexakis-imidazole complexes of copper (II) salicylate [34]. The N-methylimidazole has formed a mononuclear hexakis – adduct of copper (II) salicylate, and was found to be active SOD mimic [20]. To study the influence of substituent of the imidazole ring in the coordination polyhedron of copper (II) ion which might have influence on the superoxide activity of copper (II) salicylate adducts, we have studied the interaction of 1,2-dimethylimidazole (b) and 2-methylimidazole (c) with copper (II) salicylate. Herein, we report the synthesis, spectral characterization of the ternary copper (II) salicylate complexes with 1,2-dimethylimidazole and 2-methylimidazole (Scheme 1), as well the X-ray molecular structure of 1,2-dimethylimidazole adduct. Because the pharmacological effects, mentioned above, of Cu (II) salicylate type complexes are attributed to their superoxide dismutase (SOD) activity and to throw some light on the structure–SOD activity relationship of this simple class and low molecular weight of complexes, we studied the SOD like activity of these new complexes and of the copper (II) salicylate imidazole mixture adducts [34] and compared to that activity previously determined for the hexakis

(N-methylimidazole) copper (II) salicylate adduct [20]. In addition, the activities of the complexes are also compared to the activities of native Cu, Zn–SOD and other mononuclear and binuclear copper (II) complexes with imidazoles and with anti-inflammatory drugs.

Scheme 1. Syntheses of complexes 1 and 2.
2. Experimental

2.1. Reagents and materials

All chemicals were of high purity grade (Aldrich or Sigma chemicals) and were used without further purifications. Tetrakis-
μ-aspirinato dicopper (II) [Cu2(asp)4] was prepared as described previously [35]. The three copper geometries mixture of mononuclear complexes of the type Cu(imidazole)n(salicylate)2 (where n = 2, 5 and 6) was previously prepared in our laboratory [34].

2.2. Preparation of complexes

2.2.1. Preparation of bis(1,2-dimethylimidazole) bis(salicylato) copper (II)

\[
\text{[Cu(1,2-Melm)2(sal)]2} \quad (1)
\]

A solution of excess 1,2-dimethylimidazole (4 mL = 45 mmol) in 15 mL of methanol was added to 0.5 g (0.59 mmol) of copper(II) aspirinate [Cu2(asp)4], and the bluish-green solution was stirred at 50–60 °C for 3 h, filtered and left in the hood to evaporate. Re-crystallization of the bluish-green precipitate from hot CH2Cl2 produced green crystal. Anal. Calc.: for C19H22N6O3Cu: C, 51.18; H, 4.94; N, 18.85%. Found: C, 51.31; H, 4.85; N, 10.43%.

2.2.2. Preparation of tris(2-methylimidazole) (salicylato) copper (II)

\[
\text{[Cu(2-MelIm)3(sal)]} \quad (2)
\]

An excess of 2-methylimidazole (1 g = 12 mmol) in a 10 mL of chloroform was added to 0.5 g (0.59 mmol) of copper(II) aspirinate [Cu2(asp)4]. The mixture was stirred in an ice bath for 10 h. Anhydrous diethyl ether was added to the mixture and stirring was continued at room temperature until a green precipitate was formed. The solution was filtered under reduced pressure and the green precipitate was washed several times with chloroform and anhydrous diethyl ether and air dried. Attempts to grow crystals suitable for X-ray analysis were unsuccessful. Anal. Calc.: for C24H26N4O6Cu: C, 54.39; H, 4.91; N, 10.58%. Found: C, 54.31; H, 4.85; N, 10.43%.

The syntheses of these complexes are summarized and presented in Scheme 1 as shown below.

2.3. Physical measurements

Room temperature (298 K) magnetic susceptibility measurements of powdered samples were determined by the Gouy method, with HgCo(NCS)4 as calibrant, and corrected for diamagnetism with the appropriate Pascal constant. The effective magnetic moment was calculated from the expression: \(\mu_{eff} = 2.84(\chi_M \cdot T)^{1/2}\). Electronic spectra of methanol solutions were obtained on Hewlett Packard 8425A diode array spectrophotometer. Nujol mulls sealed between polyethylene sheets were used to obtain IR spectra of the complexes in the 4000–450 cm\(^{-1}\) region with an FTS-7 Bio-Rad SPC 3200 Fourier transform infrared spectrometer. The ESR spectra of powered and methanol/toluene solutions were taken at different temperatures with a Varian E-4 X-band spectrometer equipped with a variable temperature unit and 100 kHz field modulation. Diphenylpicrylhydrazide (DPPH, \(g = 2.0036\)) was used as the calibrating field marker. Elemental analysis for C, H and N were performed by Galbraith Laboratories, Knoxville, TN, USA.

2.4. X-ray structure determination

The method for obtaining and acquisition of crystallographic data was as described previously [34]. A summary of these data is given in Table 1. Green crystals of complex 1 were grown from hot CH2Cl2. Data were collected over the 2θ range of 3.5–45° (0 ≤ h ≤ 12, 0 ≤ k ≤ 26, −11 ≤ l ≤ 11). The unit cell parameters were obtained from the least squares fit of 20 reflections. Of the 1600 unique reflections measured, 1292 with \(F_2 > 4.0\sigma(F_2)\) were used during full-matrix least squares refinement. The weighting scheme used was \(w^{-1} = \sigma^2(F) + 0.0005P^2\). The largest peak in the final difference map was 0.32 e Å\(^{-3}\).

2.5. Superoxide dismutase assay

Superoxide dismutase activity was assayed, as described previously [16,20], using the xanthine–xanthine oxidase system for the production of superoxide and idophenyl-nitrophenyl–phenylazonium salt (INT) reduction at 510 nm for the superoxide detection. The reaction mixture contained 8.5 × 10\(^{-3}\) M xanthine and 1.5 × 10\(^{-4}\) M INT in 0.05 M phosphate buffer solution at pH 7.8. The reaction was started by the addition of xanthine oxidase in the amount needed to yield an absorbance change of 0.03–0.04 units per minute at 510 nm in the absence of the copper complex. The SOD mimetic activity of the copper complex at 25 °C was evaluated from the absorbance decrease at 510 nm comparing to the blank (the reaction mixture without the copper complex). A unit SOD activity is the concentration of the complex or enzyme which causes 50% inhibition reduction of INT (the IC\(50\) value). The IC\(50\) value for each complex was obtained from the plot of percentage of inhibition versus the complex concentration.

3. Results and discussion

3.1. Spectroscopic and magnetic characterization

Complexes 1 and 2 are the product of the slow reaction of binuclear copper (II) aspirinate [Cu2(asp)4], with methylimidazole derivatives (Scheme 1). During the reaction and/or re-crystallization the acetoxy group of the aspirinate ligand undergoes hydrolysis to give the salicylate ligand. The stretching frequency of the acetoxy group of the aspirinate ligand occurs near 1750 cm\(^{-1}\) for mononuclear copper (II) aspirinate complexes and at 1758 and 1725 cm\(^{-1}\) for the binuclear copper (II) aspirinate [36]. The complexes do not exhibit the C=O stretching frequency in this region, suggesting that the acetoxy group has been lost. This is confirmed by the solid state structure for complex 1 (vide infra).

The antisymmetric \(v_{as}(\text{COO})\) and symmetric \(v_{s}(\text{COO})\) carboxylate stretching vibrations for the coordinated di-anion salicylate (Hsal\(^{-}\)) in 1 appear as doublets occurring at 1601 and 1585 cm\(^{-1}\) and at 1414 and 1392 cm\(^{-1}\), respectively. For complex 2 the \(v_{as}(\text{COO})\) and \(v_{s}(\text{COO})\) frequencies for the coordinated di-anion salicylate(sal\(^{-}\))

<table>
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<tr>
<th>Chemical formula</th>
<th>C24H26N4O6Cu</th>
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<tr>
<td>fw</td>
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</tr>
<tr>
<td>Space group</td>
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</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>(a (\text{Å}))</td>
<td>10.522(5)</td>
</tr>
<tr>
<td>(b (\text{Å}))</td>
<td>23.761(10)</td>
</tr>
<tr>
<td>(c (\text{Å}))</td>
<td>9.709(5)</td>
</tr>
<tr>
<td>(\alpha (°))</td>
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<tr>
<td>(\beta (°))</td>
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<tr>
<td>(\gamma (°))</td>
<td>90.00</td>
</tr>
<tr>
<td>(V (\text{Å}^3))</td>
<td>2426(2)</td>
</tr>
<tr>
<td>Radiation, (\lambda (\text{Å}))</td>
<td>Mo: 0.71073</td>
</tr>
<tr>
<td>Temp. (°C)</td>
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</tr>
<tr>
<td>(\text{abs coeff. (cm}^{-1}))</td>
<td>9.45</td>
</tr>
<tr>
<td>(R%)</td>
<td>4.46</td>
</tr>
<tr>
<td>(R_{wp}%)</td>
<td>5.93</td>
</tr>
<tr>
<td>GOF</td>
<td>1.82</td>
</tr>
</tbody>
</table>

\( R = \sum |F_o| - |F_c| / \sum |F_o|\)
\( R_{wp} = \sum [w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}\).
occur at 1601 and 1408 cm$^{-1}$, respectively. The positions of these carboxylate stretching vibrations and the separation between $\nu_{as}(\text{COO})$ and $\nu_{sy}(\text{COO})$, $\Delta \nu$, of 187–193 cm$^{-1}$ in 1 and of 193 cm$^{-1}$ in 2, are within the range expected for carboxylate groups that act as "unsymmetrical" bidentate or as monodentate coordination ligand [34,37]. This coordination mode in complex 1 is borne out by the solid-state structure (see below). The $\nu(\text{C–C})$ stretching vibrations of the salicylate aromatic ring occur at 1613 and 1556 cm$^{-1}$ in complex 1 and at 1562 cm$^{-1}$ in complex 2. The $\nu(\text{C–O})$ of the phenolic group occurs at 1254 in 1 and 2 and the bending frequency of the phenyl ring–O–H, $\delta$(Ph–O–H), occurs at 1344 cm$^{-1}$ in complex 1, but this frequency is absent in complex 2 which indicates coordination of phenolic oxygen to copper atom [38,39]. This coordination also may explain the change in the $\nu(\text{C–C})$ ring vibrations in 2, compare to those for 1, due to change in the Ph–O bond order and change in charge density distribution on the benzene ring [39].

The d–d transitions for 1 and 2 in methanol solutions occur at 690 nm ($\epsilon_M = 85$) and 656 nm ($\epsilon_M = 75$), respectively. A band between 400 and 450 nm previously reported for mononuclear copper (II) salicylate compounds was ascribed to a ligand-to-metal charge transfer transition [34,40]. The spectra of complexes 1 and 2 exhibit shoulders at ca. 400 nm. The $\lambda_{\text{max}}$ of the d–d transition of 1 at 690 nm is in the range expected for mononuclear copper (II) complexes that contain the chromophore CuN$_2$O$_2$–O$_2$ [36,41,42] and thus is consistent with the formation of [Cu(1,2-Melm)$_2$(Hsal)$_2$] complex which has the CuN$_2$O$_2$–O$_2$ chromophore. The $\lambda_{\text{max}}$ for the d–d transition in complex 2 occurs at higher energy than that of complex 1, which indicates a stronger ligand field in the Cu (II) plane. A survey of the electronic data of copper (II) complexes that contain nitrogen and oxygen donor atoms in square planar or tetragonally distorted octahedral geometry, studied in the same solvent, indicated that as the number of nitrogen donors increases the energy of the d–d transition increases. This is attributed to stronger ligand field for nitrogen donor ligands compare to oxygen donor ligands. Spectroscopic results as well as X-ray structural determination (see below) indicated that complex 1 has two imidazole nitrogen atoms and two carboxylate oxygen atoms in the copper (II) plane. The electronic results indicated that there are more than two nitrogen atoms in the plane of Cu (II) in complex 2. And since electronic spectra for complexes which have four imidazole nitrogen atoms in the Cu (II) plane, such as hexakis (N-methylimidazole) copper (II) bis (salicylate) [20], and tetrakis (imidazole or N-methylimidazole) bis (aspirinato) copper (II) complexes [36] exhibit $\lambda_{\text{max}}$ at about 630 nm in methanol solutions, complex 2 is expected to have three imidazole nitrogen atoms in the Cu (II) plane showing $\lambda_{\text{max}}$ at 656 nm. These electronic results for complex 2 are supported by electron spin resonance (ESR) spectroscopy studies of this complex as discussed below.

The room temperature X-band ESR spectrum of a polycrystalline sample of complex 2 is shown in Fig. 1A. The spectrum is clearly that of a rhombic system with $g_1 = 2.194$, $g_2 = 2.081$, and $g_3 = 2.032$. These results suggest that there is a pronounced distortion form square planar symmetry. Such spectra are characteristic of a distorted trigonal–bipyramidal or a distorted square–pyramidal geometry [43]. The polycrystalline ESR spectrum is slightly temperature-dependent with $g_1 = 2.192$, $g_2 = 2.066$, $g_3 = 2.035$ at $-196 \, ^\circ\text{C}$. The spectrum is consistent with a copper (II) complex that has a distorted-square base arrangement. The room-temperature ESR spectrum of 2 in methanol is isotropic and consists of the four equally-spaced lines expected for hyperfine coupling of the unpaired electron with the

Fig. 1. X-band ESR spectrum of [Cu(2-Melm)$_3$(sal)]$^2$ as: (A) powder at room temperature and (B) frozen solution at $-196 \, ^\circ\text{C}$.  

copper (II) ion. The spectral parameters are \( g_s = 2.126 \), and \( A_\theta = 66 \times 10^{-4} \text{ cm}^{-1} \). The frozen-solution spectrum, Fig. 1B, is that of an axial system with \( g_{\parallel} = 2.254, g_s = 2.061, g_{\perp} = 2.013 \), and \( A_{\perp} = 177 \times 10^{-4} \text{ cm}^{-1} \), suggesting a \( d_{x^2-y^2} \) or \( d_{xy} \) ground state that is characteristic of square symmetry [43,44]. In addition to the hyperfine structure of copper (II) in the \( g_{\parallel} \) region, the \( g_s \) signals and the lowest-field component of the \( g_{\perp} \) signal exhibit \( ^{14} \text{N} \) super-hyperfine structure that consists of seven lines with \( A_{\parallel} \) (N) = \( 14 \times 10^{-4} \text{ cm}^{-1} \) and \( A_{\perp} \) (N) = \( 11.5 \times 10^{-4} \text{ cm}^{-1} \). The seven-line pattern is attributed to the interaction of the unpaired electron with three 2-methylimidazole nitrogen donor atoms in the plane of the copper (II) ion.

The room temperature (298 K) solid-state magnetic moments for the two adducts are 1.88 and 1.85 BM for complexes 1 and 2, respectively. These values are consistent with the presence of one unpaired electron in a mononuclear copper (II) complexes.

Collectively these spectral and magnetic results along with analytical data indicate that Cu (II) ion in complex 2 is coordinated to three 2-methylimidazole ligands and one doubly deprotonated salicylate ion (\( \text{sal}^{2-} \)), which is chelated to Cu (II) ion through one of its carboxylate oxygen atoms and the deprotonated hydroxyl oxygen atom to form Cu(2-Melm)_3(sal) complex which has distorted square pyramidal CuN_3O_O chromophore (Scheme 1).

3.2. X-ray crystal structure of complex 1

The structure of complex 1 with the atomic labeling is illustrated in Fig. 2. The complex crystallizes with four close donor atoms in a distorted cis-square plane and two weakly coordinating atoms above and below the plane. The four closest donor atoms consist of two nitrogen atoms from the two 1,2-dimethylimidazole ligands with Cu–N distances of 1.979 Å and two carboxylate oxygen atoms from the two salicylate ions with Cu–O distances of 1.981 Å. The remaining two carboxylate oxygen atoms are weakly coordinated to Cu (II) in the axial positions with Cu–O distances of 2.590 Å. The bond distances in 1 are comparable with the analogous distances in other mononuclear copper (II) carboxylates with 1,2-dimethylimidazole ligand which have cis:italic>/ce:italic>-Cu-N\textsubscript{3}O\textsubscript{+}O characteristic of square symmetry [43,44]. The Cu–N distances in this adduct compare to 2.86 Å [34], the Cu–O distances of the weakly coordinated carboxylate oxygen atoms of the copper (II) plane will have more space to come nearer to Cu (II) atom and Cu–O distances become shorter (1.981 Å) compared with 2.042 Å for the imidazole adduct. The Cu–O distances of the weakly coordinated carboxylate oxygen atoms in the axial positions for the imidazole adduct are 2.86 Å compared with 2.59 Å in the 1,2-dimethylimidazole adduct (1). The N1–Cu–O1 angle is 92.5° (Fig. 2); however, the least squares planes defined by N1–Cu–N1A and O1–Cu–O1A have a dihedral angle of 38.6° as a result of distortion from square symmetry. Since there is a methyl substituent on the uncoordinated nitrogen atom of each imidazole ligands, there is no intermolecular hydrogen bonding involving the imidazole ligand and hydroxyl groups of salicylate ligands of neighboring molecules. But because the hydroxyl group lines on the same side of the salicylate ring as the weakly coordinating carboxylate oxygen atom Fig. 2, intramolecular hydrogen bondings are formed between these oxygen atoms of the salicylate ligand. The carboxylate distances C1–O1 and C1–O2 are the same (about 1.265 Å). The carboxylate function and the six carbon member ring of the salicylate ligand are twisted about the C1–C2 bond by only 2.2°; thus, the salicylate ion is essentially planar.

3.3. Superoxide dismutase activity

The superoxide dismutase mimetic activities of the complexes 1, 2 and 3 (the copper salicylate imidazole mixture, Cu(Im)_n(Hsal)_2, where \( n = 2, 5, 6 \)), were determined with an indirect method using the xanthine–xanthine oxidase – INT method [16,20]. The activity is expressed as IC\textsubscript{50} which is the concentration (\( \mu \text{M} \)) of the complex or enzyme required to dismutate 50% of the evolved superoxide radical anion (\( \text{O}_2^– \)). Fig. 3 shows the percentage inhibition of INT reduction plotted against the concentration of the complex Cu(1,2-Melm)_3(sal)_2(1). Table 2 shows the IC\textsubscript{50} values of the complexes under investigation along with the corresponding values of the copper (II) complexes with salicylate type ligands with or without imidazoles and of the native Cu, Zn–SOD enzyme. The table contains also, for comparison purposes, the activities of other copper (II) complexes of anti-inflammatory drugs such as Cu(Indo)_2(H_2O)_2 [where IndoH = indomethacin] which is considered to be an excellent SOD mimic [12] and is used therapeutically as an oral anti-inflammatory drug in veterinary medicine [2].

All copper (II) salicylate imidazoles complexes we tested in the present work or previously [20] exhibited significant activities with IC\textsubscript{50} values in the range of 0.17–0.65 \( \mu \text{M} \) and their activities decrease in the order: Cu[N-Melm]_6(Hsal)_2(4) > Cu(Im)_n(Hsal)_2(3) > Cu(2-Melm)_3(sal)(2) > Cu(1,2-Melm)_3(sal)(2). (The lower the IC\textsubscript{50} value the higher complex activity). It appears that inclusion of the imidazol nitrogen donor atoms in the plane of the Cu (II) atom increases the SOD activity. The relatively high SOD activities of the mixture complexes 3 and 4, with four imidazole nitrogen atoms in Cu (II) plane, compared to the activities of complexes 2 and 1 with three and two imidazole nitrogen atom, respectively, in the Cu (II) plane, may be attributed to the similarity of coordination site in the former complexes to that for the native Cu, Zn–SOD enzyme which have four imidazole nitrogen atoms in its Cu (II) equatorial plane [11].

The dismutation of superoxide anion, by both the native enzyme SOD or the copper complexes mimics, is involving redox cycling of Cu (II) ion as following [11]:

![Fig. 2. View of the molecular structure of [Cu(1,2-Melm)_3(Hsal)_2(1)]. Hydrogen atoms have been omitted for clarity. Selected bond distances and angles are: Cu-N1 = 1.979 Å, Cu-O1 = 1.981 Å, Cu-O2 = 2.590 Å, C1–O1 = C1–O2 = 1.265 Å, N1–Cu–O1 = 92.5 Å, N1A–Cu–O1 = 151.8°.]](image)
Cu(II) + O_2^− → Cu(I) + O_2
Cu(I) + O_2^− + 2H_2 → Cu(II) + H_2O_2

Hydrogen peroxide formed in this reaction is destroyed *in vivo* by the enzyme catalase. The electron transfer between Cu(II) and O_2 occurs through direct binding, and the axial site of the copper (II) complexes is most likely the coordination site of O_2 to Cu(II) ion. Thus for the copper complex to act as good mimics for superoxide dismutase the following requirements are proposed and may in-clude: (1) the O_2^− anion must gain direct access to the metal ion. A limited steric hindrance to the approach of superoxide anion to coordination site. In these complexes which contain the Cu-N_2O_2 + O_2 (complex 1, CuN_2O + O (complex 2), CuN_2 + N, CuN_2O + O_2 (for the mixture complex 3) or CuN_2 + N_2 (complex 4) chromophores, the axial atoms are the weakly coordinated oxygen atoms from salicylate ions or the imid-azole nitrogen atoms, which are readily dissociated to provide sites on Cu(II) for O_2 bonding. The dissociation would also facilitate any necessary geometrical changes induced by O_2 bonding during catalysis as in the native SOD [11]. The presence of salicylate hydroxyl group (in complexes 1 and 3) and the free N–H group in imidazole (complex 3) and 2-methylimidazole (complex 2) which are capable of forming hydrogen bonds with the O_2 anion that may assist its induction and stabilize its coordination to copper ion, which will result in SOD activity enhancement for these complexes [28,33,45].

The SOD-like activities which are measured by IC_{50} values of the complexes under investigations are comparable with those IC_{50} values reported for the most active SOD mimics [12,15,29–32,45–48]. The IC_{50} for complex 1 is comparable with that reported for the trans-bis (benzimidazole) bis (salicylato) copper (II) complex (Table 2) [15]. The IC_{50} values for complexes 2–4 were of the same order or better than those obtained for copper complexes showing pharmacological properties associated with the dismutation of O_2 radical, such as those for copper complexes of non-steroidal anti-inflammatory drugs, showing enhanced anti-inflammatory effects [2,5,12,15,16].

### 4. Conclusions

The results obtained from the present study and from our previous studies [20,34] demonstrated the ability of copper to form di verse geometries with the same or similar ligands. Mononuclear complexes with two, three, five and six coordinated imidazole or its methyl derivatives and salicylate ion have been formed from the interaction of the imidazole ligands with the copper (II) aspirine dimer, where aspirine ligand was hydrolyzed during the reaction to salicylate mono-anion or di-anion. While the interaction of 1,2-dimethylimidazole and 2-methylimidazole with binuclear copper (II) aspirinate produced the ce:italic>ce:italic>-bis (1,2-dimethylimidazole) bis (salicylato) copper (II) adduct (1) and the tris (2-methylimidazole) (salicylato) copper (II) adduct (2) respectively, the imidazole and N-methylimidazole interactions produced a mixture of trans-bis, pentakis-, and hexakis (imidazole) adducts (3) [34], and hexakis (N-methylimidazole) adduct (4) [20] as we reported previously.

The complexes (1–4) showed significant SOD mimetic activities with IC_{50} values in the range of 0.17–0.65 μM. Although these IC_{50} values are still larger than the value reported for native Cu, Zn-SOD (0.04 M) but are comparable with the IC_{50} values reported for the best copper complex mimics [12,15,29–32,45–48]. These complexes are considered potent SOD mimics considering their very low molecular weights when compared to that of the native Cu, Zn–SOD enzyme. Further, the complexes are easily formed with

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**Table 2**

Superoxide dismutase mimetic activity of copper (II) complexes.

<table>
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<tr>
<th>Copper complex</th>
<th>IC_{50} (μM)</th>
<th>References</th>
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<td>[Cu(1,2-MeIm)_2(Hsal)_2]</td>
<td>0.65</td>
<td>This work</td>
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<td><a href="2">Cu(2-MeIm)_2(sal)</a></td>
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<td>[20]</td>
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<td>[Cu(Hsal)_2(BZDH)_2]</td>
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<td>[Cu(2,5-DTBS)_2(phen)_2]</td>
<td>0.23</td>
<td>[12]</td>
</tr>
<tr>
<td>[Cu(2,5-DTBS)_2(Eth)_2]</td>
<td>0.17</td>
<td>[20]</td>
</tr>
<tr>
<td>Native Cu, Zn–SOD</td>
<td>0.042</td>
<td>[31]</td>
</tr>
</tbody>
</table>

Where H_{sal} = salicylic acid; MeIm = methylimidazole; Im = imidazole; BZDH = benzimidazole; phen = 1,10-phenanthroline; en = ethylenediamine; D MF = dimethylformamide; tol = tolmanic acid; dic = diclofenac acid; 3,5-DTBS = 3,5-dimethyl-thiobutyl salicylate; Eth = ethanol.

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**Fig. 3.** Percentage of inhibition of INT reduction versus copper complex concentra-

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biologically active salicylate and imidazole ligands, and they are promising antioxidant agents for preventing pathologies in which free superoxide anion is implicated.

References