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Mononuclear copper(ll) aspirinate or salicylate complexes with methylimidazoles as biomimetic catalysts for oxidative dealkylation of a hindered phenol, oxidation of catechol and their superoxide scavenging activities

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ABSTRACT

Mononuclear complex bis(aspirinato) bis(2-methylimidazole) copper(II), $Cu(asp)_2$ $(2\text{-MeIm})_2$ (**1**), has been synthesized and spectroscopically characterized. The biomimetic catalytic activities of this complex and our previously characterized complexes, $Cu(asp)_2$ $(1,2\text{-MeIm})_2$ (**2**), $Cu(Hsal)_2$ $(1,2\text{-MeIm})_2$ (**3**), and Cu(sal)$(2\text{-MeIm})_3$, (**4**) [H_2sal = salicylic acid and MeIm = methylimidazole], for the oxidation of 3,5-di-tert-butylcatechol to the corresponding *o*-quinone and the oxidative dealkylation of 2,4,6-tri-tert-butylphenol to 2,6-di-tert-butyl-1,4-benzoquinone and 4,6-di-tert-butyl-1,2-benzoquinone as the main products are reported. Complexes **1** and **2** are found to be potent SOD mimics and their SOD activities are compared with those obtained previously for complexes **3** and **4**.

Salicylic acid and its derivatives including aspirin (acetylsalicylic acid) are non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs. Copper complexes of anti-inflammatory drugs have been found to be more potent and desirable drugs than their parent ligands themselves [1,2]. In addition, these complexes are found to have several pharmacological effects, which include anti-inflammatory, anti-convulsant, anti-ulcer and anti-cancer activities [1–5]. Some of these pharmacological activities are enhanced in the presence of ancillary nitrogen donor ligands such as imidazoles, diimines and pyridines [6–9].

Copper is one of the most ubiquitous transition metal (in addition to Iron and Zinc) present in several metalloenzymes and is involved in a large number of functions and processes [10]. Copper containing enzymes are utilized for electron transfer (galactose oxidase, azurins, and laccases), for oxidation and oxygenation reactions (polyphenol oxidase, ascorbate oxidase, and hemocyanin) and for superoxide dismutation (Cu,Zn-superoxide dismutase). Binary and ternary copper complexes of anti-inflammatory drugs, such as aspirin and other salicylate derivatives, have been used as biomimetics of some copper containing enzymes [3,6–9,11–13]. In continuation of our work on copper complexes biomimetics, we report here the synthesis and spectral characterization of bis(aspirinato)bis(2-methylimidazole)copper(II),$Cu(asp)_2(2\text{-MeIm})_2$(**1**) and studied the biomimetic activities of this complex and our previously characterized complexes (Scheme I), $Cu(asp)_2(1,2\text{-MeIm})_2$ (**2**) [11a], $Cu(Hsal)_2(1,2\text{-MeIm})_2$ (**3**) and Cu(sal)$(2\text{-MeIm})_3$ (**4**) [12a] (H_2sal = salicylic acid), as catalysts for oxidation of 3,5-di-tert-butylcatechol ($DTBCH_2$) to corresponding *o*-benzoquinone (DTBQ) and for oxidative dealkylation of a hindered 2,4,6-tri-tert-butylphenol (TTBP). In addition, superoxide dismutase (SOD) mimetic activities of copper(II) aspirinate complexes **1** and **2** were measured and compared to those activities obtained previously for copper(II) salicylate complexes **3**, **4** and for Cu (II) complexes with other anti-inflammatory drugs.

The mononuclear complex (**1**) [14] was prepared by interacting of 2-methylimidazole with binuclear $Cu_2(aspirinate)_4$ [15]. Its magnetic and spectral measurements results are summarized as follows: Magnetic moment = 1.89 BM, Uv–visible spectrum in methanol solution showed the d–d transitions at 684 nm ($\varepsilon = 95\ L\ mol^{-1}\ cm^{-1}$), IR spectrum showed stretching frequencies of the acetoxy carbonyl moiety of the aspirinate ligand at about 1765 cm^{-1} and those of the anti-symmetric ν_{asy} (COO) and symmetric ν_{sy} (COO) of carboxylate group at 1595 and at 1390 cm^{-1}, respectively. The ESR spectral data for methanol–toluene solution at 77 K are $g_{//} = 2.27$, $g\perp = 2.05$ and $A_{//} = 158 \times 10^{-4}\ cm^{-1}$. These magnetic and spectral data are in the range expected for mononuclear copper(II) carboxylate complexes that contain the $CuN_2O_2\ldots O_2$ chromophore in a tetragonally distorted geometry [8,9,11–13]. In complex **1** two nitrogen atoms from two 2-methylimidazole molecules and two caboxylate oxygen atoms from two aspirinato molecules coordinated in Cu(II) plane. The second aspirinato carboxylate oxygen atoms interact weakly in the axial positions to form $CuN_2O_2\ldots O_2$ chromophore. These spectral data are also comparable with those obtained for the bis (salicylato) bis (1,2-dimethylimidazole) copper(II) complex (**3**) [12a] and bis(valproato) bis(2-methylimidazole) [11c] whom X-ray structures were determined and have $CuN_2O_2\ldots O_2$ chromophore.

The catalytic activities of the complexes for the air oxidation of 3,5-di-tert-butylcatechol ($DTBCH_2$) to corresponding *o*-quinone (DTBQ)

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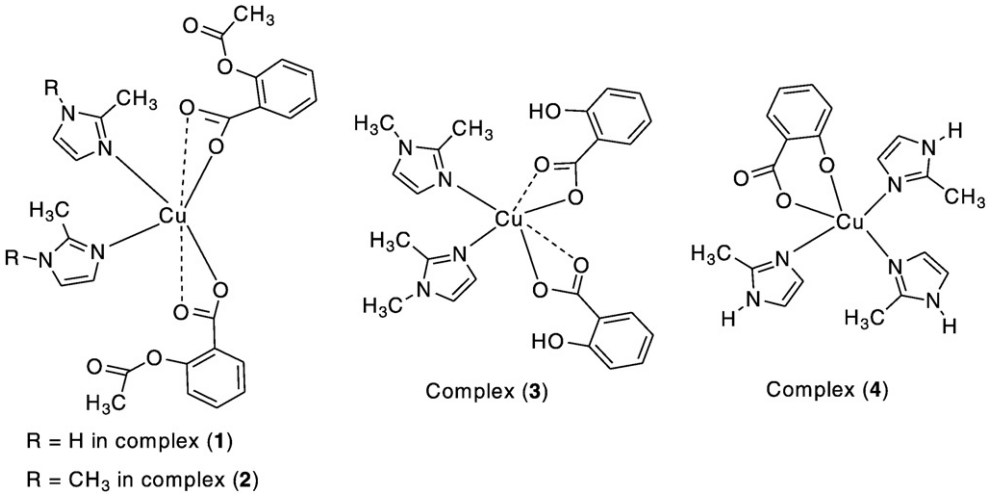


Scheme I. Chemical structures of mononuclear copper(II) complexes.

were followed spectrophotometrically by monitoring the absorbance increase of DTBQ formation at 400 nm ($\varepsilon = 1800\ M^{-1}\,cm^{-1}$) as function of time. Methanol solution of copper complex (0.3 mL of 0.001 M) previously saturated with oxygen and 2.0 mL of a methanol solution (0.1 M) of $DTBCH_2$ were combined in a 1 cm quartz cell at room temperature and the absorbance changes at 400 nm were recorded for the first 15 min of the reaction. Complexes **1**–**4** catalyze the oxidation of $DTBCH_2$ to corresponding *o*-benzoquinone(DTBQ). The oxidation activities of the complexes were measured as micromoles of substrate (DBPQ) produced per mg catalyst per min. They are: 0.58 for **1**, 0.57 for **2**, 0.58 for **3** and 0.69 for **4**.

It has been accepted now that the catecholase activity of mononuclear copper(II) complexes follows the mononuclear pathway as we and other researchers showed previously [12b,13,16,17]. $DTBCH_2$ binds to Cu(II) after its dehydrogenation to form Cu(II)–DTBC complex followed by an internal electron transfer to form Cu(I)-o-semiquinone intermediate species. Oxidation by aerobic oxygen occurs to produce `o-benzoquinone (DTBQ) and Cu(II) complex as shown in the following equations:

$$\text{Cu(II) complex} + \text{DTBCH}_2 \rightarrow \left[\text{Cu(II)}\ (\text{DTBC})^{-2}\right]\text{complex} \quad (1)$$

$$\left[\text{Cu(II)}\ (\text{DTBC})^{-2}\right] \underset{\longleftarrow}{\overset{\text{electron transfer}}{\longrightarrow}} \left[\text{Cu(I)}\ (\text{DTBSQ})^{-}\right] \quad (2)$$

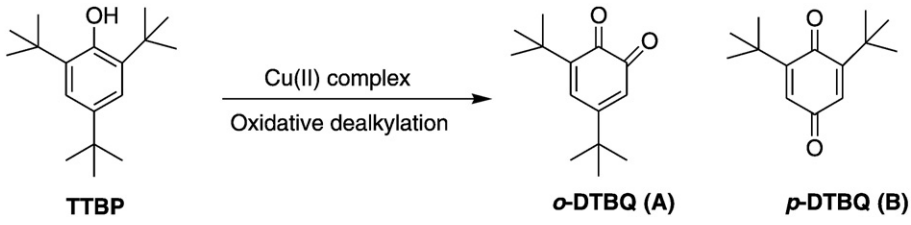
$$\left[\text{Cu(I)}\ (\text{DTBSQ})\right] \xrightarrow{\text{oxidation}} \text{Cu(II) complex} + \text{DTBQ} \quad (3)$$

In complexes under investigation the aspirinate or salicylate ligands dissociate and provide sites on the copper(II) plane for catecholate bonding . Catecholate is a stronger ligand than carboxylate and replacement occurs by dehydrogenating the $DTBCH_2$ hydroxyl groups (Eq. (1)). Optimal intramolecular electron transfer rates would require equatorial coordination to copper(II) in order to maximize overlap between the catecholate donor and the half empty dx^2–y^2 copper(II) orbital to form a $[Cu(II)(DTBC)^{-2}]$ complex. An intramolecular electron transfer from the coordinated ligand $DTBC^{-2}$ to copper(II) resulting in Cu(I)-*o*-semiquinone intermediate species $[Cu(I)\ (DTBSQ)^{-}]$ which is in equilibrium with $[Cu(II)\ (DTBC)^{-2}]$ complex (Eq. (2)). The copper (I) semiquinone species is oxidized by air oxygen to produce *o*-benzoquinone (DTBQ) and Cu(II)complex (Eq. (3)). The identification of the oxidation product (DTBQ) and the formation of copper(I)- 3,5-di-t-butyl o-semiquinone intermediate during the oxidation process was demonstrated in this study by following the Uv–visible spectral changes of the catalytic reaction mixture as we described previously [13].

Complexes **1**–**4** were used to catalyze the oxidative dealkylation reaction of 2,4,6- tri-tert-butylphenol (TTBP) to 4,6-di-tert-butyl-1,2-benzoquinone (*o*-TTBQ) (A) and 2,6-di-tert-butyl-1,4-benzoquinone (*p*-TTBQ) (B) as major products (Scheme II).

It has been found that the oxidative dealkylation of TTBP by transition metal complexes proceed through the formation of TTBP radical followed by formation of metal-superoxo intermediate species which is used to oxygenate the TTBP radical [18–20]. For copper(II) complexes (**1**–**4**) under investigations this is presented by Eqs. (4)–(6) described below. The oxygenation reaction of TTBP through the initial formation of the 2,4,6-tri-tert-butylphenoxyl radical was followed spectrophotometrically. An oxygen saturated methanol or CH_2Cl_2 solution of copper(II) complex (0.3 mL of 1×10^{-3} M) was mixed with 2 mL (0.05 M) of TTBP dissolved in methanol or CH_2Cl_2 and the formation of phenoxyl radical was followed at 400 nm, since TTB phenoxyl radical showed bands in visible region at about 634 nm, 400 nm and 382 nm [18,21].

The first step of the reaction may involve deprotonation of relatively weak O—H phenolic group of TTBP by the aspirinate or salicylate groups of the Cu(II) complex and the coordination of the deprotonated $TTBP^{-}$ to Cu (II) complex (Eq. (4)). An internal electron



Scheme II. Oxidative dealkylation reaction of TTBP catalyzed by copper(II) complex.

transfer from $TTBP^-$ to Cu(II) occurs and Cu(I)-phenoxyl radical species is formed (Eq. (5)). Oxidation of Cu(I)-species with oxygen produces Cu(II)-superoxo intermediate species (Cu(II)—O_2^{-}•) which is used to oxygenate the rearranged TTB phenoxyl radical at ortho and at para-positions along with a rapidly elimination of t-BuOH molecules to form 4,6-di-tert-butyl-1,2-benzoquinone (*o*-TTBQ) (A) and 2,6-di-tert-butyl-1,4-benzoquinone (*p*-TTBQ) (B) as major products (Eq. (6)). The formation of Cu(II)-superoxo species has been recently demonstrated which is able to effect oxygenation, including TTBP and hydroperoxylation of phenols, by incorporation oxygen atom derived from the Cu(II)—O_2^{-}• moiety[20].

$$\text{Cu(ll) complex} + \text{TTBP} \rightarrow [\text{Cu(ll)}\ (\text{TTBP}^-)\,] \quad (4)$$

$$[\text{Cu(ll)}\ (\text{TTBP}^-)] \underset{\longleftarrow}{\xrightarrow{\text{electron transfer}}} [\text{Cu(I)TTBP}^{\cdot}]\text{radicalspecies} \quad (5)$$

$$[\text{Cu(I)TTBP}^{\cdot}] \xrightarrow{\text{oxygenation, } O_2,\ H^+} \text{Cu(ll) complex} + o-\text{TTBQ} + p-\text{TTBQ} + 2\text{t}-\text{BuOH} \quad (6)$$

It has been recently shown that the ortho and para resonance forms of the TTB phenoxyl radical are the predominate forms with para resonance is the largest contributor [21b]. This may explain that the main products of the oxidative dealkylation of TTBP by the copper (II) complexes are the *o*-TTBQ (A) and the *p*-TTBQ (B) in about 20% and 35%, respectively. These products [A and B] are obtained in larger scale, separated and characterized by IR, Uv–visible and NMR spectroscopy [22].

The catalytic activities of the mononuclear Cu(II) complexes **1**–**4** were determined as micromoles TTB phenoxyl radical produced per mg catalyst per minute by monitoring the absorbance increase of radical formation at 400 nm (ε in methanol = 2000 $M^{-1}\,cm^{-1}$) [21c] of the above reaction mixture for the first 15 min. These values are: 0.879 for **1**; 0.595 for **2**; 0.601 for **3**; and 1.134 for **4**.

The catecholase oxidation of DTBC and the TTB phenoxyl radical production activities for complex **4** are higher than those for complexes **1**–**3** which showed comparable catecholase activities, with an activity of complex **1** for TTBP phenoxyl radical production is little higher than those for complexes **2** and **3**. This may be attributed to similarities in structures of complexes **1**–**3** having distorted tetragonal $CuN_2O_2...O_2$ chromophore while complex **4** has distorted square pyramidal geometry with $CuN_3O + O$ chromophore. One of the axial positions at this complex is free and can initially accommodate the incoming catechol or phenol ligands faster than in complexes **1**–**3**. In addition, the salicylate dianion chelate in complex **4** is a stronger base than the aspirinate or salicylate monoanions in complexes **1**–**3** and can dehydrogenate the incoming catechol or phenol faster and this will result in higher catalytic activities for this complex.

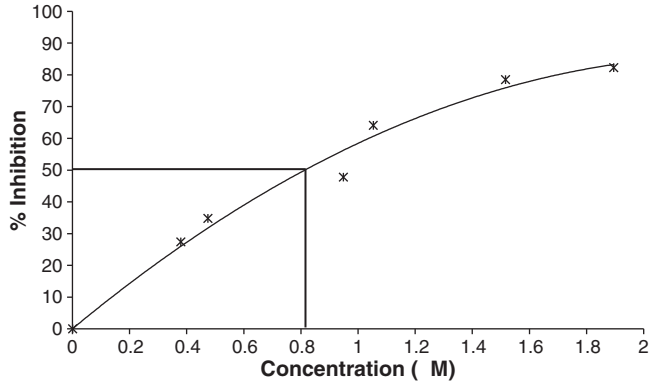


Fig. 1. Percentage of inhibition reduction of INT against concentration of complex **1**.

Table 1
Superoxide dismutase mimetic activity of copper(II) complexes.

Copper complex	IC_{50}	References
$Cu(asp)_2(2\text{-Melm})_2$ (**1**)	0.81	This work
$Cu(asp)_2(1,2\text{-Melm})_2$ (**2**)	0.95	This work
$Cu(Hsal)_2(1,2\text{-Melm})_2$ (**3**)	0.65	11a
$Cu(sal)(2\text{-Melm})_3$ (**4**)	0.53	11a
$Cu(Hsal)_2(benzimidazole)_2$	0.74	9
Cu(sal)(phenanthroline)	1.01	9
$Cu_2\ (Hsal)_4$	1.30	2
$Cu_2\ (asp)_4$	2.13	2
$Cu_2(Indomethacin)_4(DMF)_2$	0.23	24
$Cu_2(Tolfenamate)_4(DMF)_2$	1.97	25
Cu,Zn-SOD enzyme	0.04	2

Superoxide dismutase activity was assayed, as described previously [7], using the xanthine–xanthine oxidase for the production of superoxide and iodophenyl–nitrophenyl–phenyltrazolium salt (INT) reduction at 510 nm for the superoxide detection. A 50% inhibition reduction of INT (the IC_{50} value) for complexes **1** and **2** was obtained from the plot of percentage of inhibition versus the complex concentration as shown in Fig. 1 for complex **1**. The IC_{50} values are summarized in Table 1 along with other IC_{50} values obtained previously for copper(II) complexes with other ant-inflammatory drugs [2,9,11a, 23–25]. The SOD-like activity of copper(II) complexes is a function of several factors which we recently discussed [7,12]. Among them is the presence of groups in the active site of Cu(II) complex which are capable to have electrostatic interactions or to form hydrogen bonding with the coordinated superoxide radical which will result in an increase of SOD activity [12,23]. This may explain the relatively higher SOD activities (lower IC_{50} values) of copper(II) salicylate complexes **3** and **4** compare to those for the aspirinate complexes **1** and **2**. The presence of salicylate hydroxyl group (in complexes **3** and **4**) which is capable of forming hydrogen bonding with the O_2•$^-$ anion that may stabilize its coordination to copper ion, which will result in SOD activity enhancement for these complexes. This may also explain higher SOD activity exhibited by binary $Cu_2(salicylate)_4$ complex compared with that of binary $Cu_2(aspirinate)_4$ complex, Table 1. The little higher SOD activity exhibited by 2-methylimidazole adduct **1** compared to corresponding activity exhibited by 1,2-methylimidazole adduct **2** may be attributed to the presence of free polar N—H group of 2-methylimidazol ligand in the former adduct. The group is capable to have electrostatic interaction with the O_2•$^-$ anion that may assist in its induction to copper ion active site which will result in SOD activity enhancement for this complex. The IC_{50} values exhibited by complexes **1** and **2** (Table 1) fall in the lower end of the range (0.17–29 μM) previously reported for copper(II) complexes with salicylate derivatives [2,7,9]. This IC_{50} range was used therapeutically for anti-inflammatory agents in human and veterinary medicine [2,9,24]. In addition, complexes **1** and **2** are potent SOD mimics considering their low molecular weight when compared to that of the native Cu,Zn-SOD enzyme. They are easily formed with biologically active aspirinate and methylimidazole ligands.

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