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Transition metal complexes bearing flexible N_3 or N_3O donor ligands: Reactivity toward superoxide radical anion and hydrogen peroxide

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ABSTRACT

Mononuclear complexes of *N*-methylpropanoate-*N*,*N*-*bis*-(2-pyridylmethyl)amine (MPBMPA) and *N*-propanoate-*N*,*N*-*bis*-(2-pyridylmethyl)amine (HPBMPA) with first row transition metals from Mn to Cu were synthesized and characterized by spectroscopy (infrared, UV–visible), electrochemistry (cyclic voltammetry), microanalysis and in four cases X-ray crystallography. Structure of the complexes revealed high flexibility of these ligands that can adopt facial (Fe) and meridional (Cu) geometry. Activity in the degradation of reactive oxygen species (superoxide radical anion: superoxide dismutase (SOD)-like activity and hydrogen peroxide: catalase-like activity) was tested throughout the complex series in aqueous solutions. In connection with the catalytic dismutation of H_2O_2, bleaching tests with morin were also conducted in water. Comparison of the two ligands helped in elucidating the possible role of the carboxylate moiety in the different catalytic reactions. Although no general trends could be revealed between reactivity and constitution of the first coordination sphere, plausible explanations for differences are discussed individually for SOD like, catalase-like and bleaching activity.

1. Introduction

During metabolic processes O_2 can readily accept unpaired electrons to give rise to superoxide ($O_2^{\bullet -}$) that is harmful to cells at low levels. Superoxide impacts the production of further reactive metabolites associated with oxidative stress, H_2O_2, OOH, $ONOO^-$, CO_3^-, OH, lipid peroxyl (ROO) and alkoxyl (RO) radicals (Scheme 1) that have been entitled as reactive oxygen species (ROS). ROS are produced during normal metabolism, in pathophysiological processes as well as UV light or ionizing radiation. In suppressing ROS *in vivo*, antioxidants play a key role, such as the enzymes that metabolize ROS: superoxide dismutases (SODs) [1,2], by accelerating the dismutation of $O_2^{\bullet -}$, catalases, by catalyzing the disproportionation of H_2O_2, peroxidases, by using H_2O_2 to oxidize substrates, or non-enzymatic antioxidants (ascorbic acid, glutathione, polyphenols, *etc.*) that are very efficient scavengers of ROS. The above enzyme families help sustain the reactive species at a tolerable level and considered among the most important pillars of a very complex homeostatic equilibrium system including other reactive species like those of nitrogen (RNS), sulfur (RSS), carbon (RCS) and selenium (RSeS), and their regulation [3].

Pathological conditions, such as neurodegenerative diseases, excessive inflammatory responses, cardiovascular conditions, diabetes and cancer [4,5] have been widely associated with any increase in oxidative stress, *e.g.* the imbalanced production of reactive species [6]. It has become an obvious effort to find exogenous antioxidants for medical purposes, for example synthetic mimics of SOD or catalase enzymes can assist efficiently the endogenous counterparts in suppressing the levels of reactive species. Since SODs represent the first line of defense against oxidative stress, their mimics have become the primary target of extensive research [7,8].

Artificial mimics with various metal ions (Mn, Fe, Cu) have been prepared and tested for both SOD and catalase enzymes. Out of these, Mn seems to be the most suitable transition metal for pharmaceutical applications as artificial SOD mimic due to its relatively low toxicity [9], but Fe complexes would be also attractive because of their higher kinetic and thermodynamic stability. However, transition metal complexes were also studied to help elucidate structure/activity relationships and other properties influencing the SOD- or catalase-like activity.

The inspiration for such studies comes from the fact that life forms express structurally versatile forms of SODs. Depending on the metal cofactor Fe- [10,11], CuZn- [12], Mn- [13,14] and NiSODs [15] are distinguished. The schematic structures of the active sites are shown in Scheme 2. The majority of these enzymes show very high metal-specificity. Nevertheless, a recent review on Mn- and FeSODs (both active sites have trigonal–bipyramidal N_3O_2 core with three histidines, a monodentate aspartate and an aqua or hydroxide ligand [13]) points out that "there is a continuum from Mn-specific through cambialistic to Fe-specific activity among these enzymes" [16]. The structural homology of the differently behaving Mn-, Fe- and cambialistic SODs and model complexes [17] underlines that besides structure and flexibility of the ligand framework [14], other properties also influence

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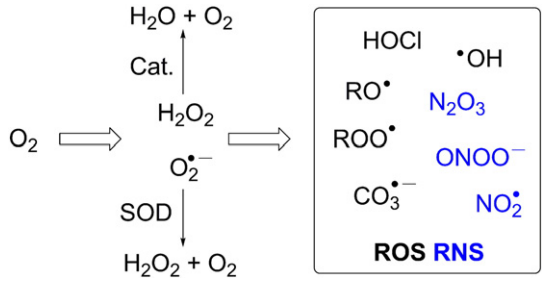


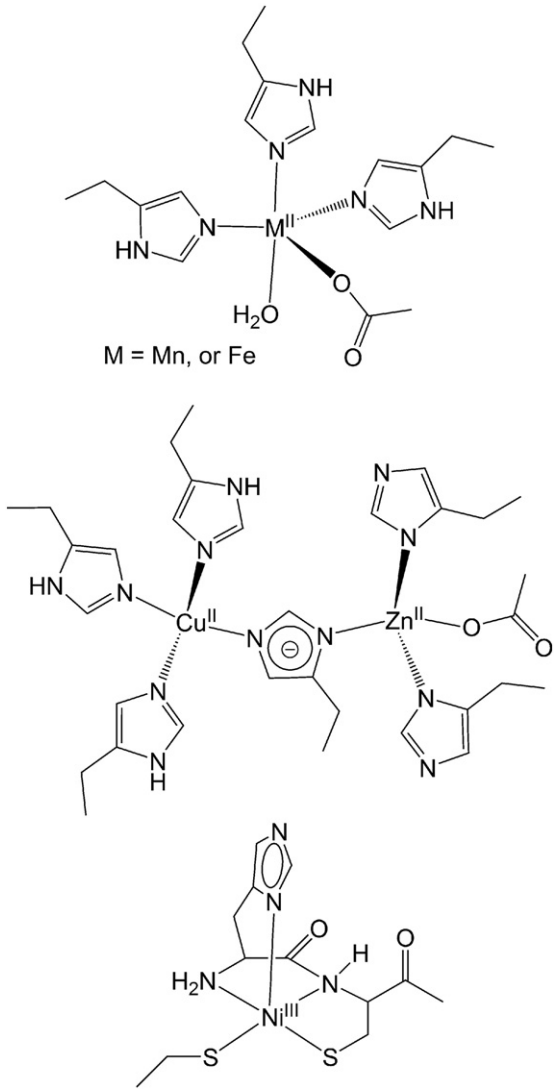
Scheme 1. Role of SOD and catalase enzymes in the elimination of superoxide and peroxide that helps prevent secondary reactive metabolites (in frame).

the SOD activity. Extensive research was done on elucidating the role of metal-centered redox potential [17–21] and more distant electrostatic contributions [17,22]. Studies on systematically modified ligands that fine-tune the redox properties of the metal ions, or alter the geometry while providing similar stability for the complexes can be very helpful in elucidating the factors for efficient superoxide scavenging.

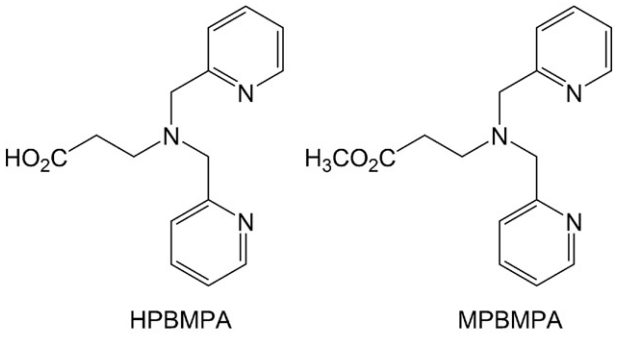
Catalases that disproportionate hydrogen peroxide into H_2O and O_2, are also structurally versatile enzymes. Besides heme type catalases, there is a class of manganese catalases which has been isolated from several bacterial organisms, recent examples are *Thermus* sp. YS 8–13 [23], and *Pyrobaculum calidifontis* VA1 [24]. The structural aspects of catalysis are of great current interest, moreover, synthetic catalytic scavengers of H_2O_2 just like artificial SOD mimics, would be clinically desirable. Mimics exhibiting dual functions, *i.e.* SOD- and catalase-mimetic activities also seem promising [25].

Recently, we investigated a series of isoindoline-based ligands with N_3 donor set that was capable of altering the redox potential for the metal(II) centers. It was shown for their Mn [26], Fe [27], Co [28] and Cu complexes [29] the redox potentials are in the suitable range for superoxide scavenging. At the same time, Mn-complexes with some isoindolines were also demonstrated to be good catalase mimics [30,31]. As a continuation of these studies we wished to apply homologous ligands with which the N_3, or N_3O donor sets are both attainable. Here we report a series of metal complexes with the ligands *N*-methylpropanoate-*N*,*N*-*bis*-(2-pyridylmethyl)amine (MPBMPA) and *N*-propanoate-*N*,*N*-*bis*-(2-pyridylmethyl)amine (HPBMPA) that are shown in Scheme 3. With these ligands we prepared Mn-, Fe-, Co-, Ni- and Cu-complexes, which have been listed in Scheme 3.

The main inspiration for this work was that HPBMPA can provide a flexible N_3O donor environment that makes it very similar to the metal binding site of Mn- and FeSODs. In MPBMPA, on the other hand, the carboxylate is methylated removing it from the coordination sphere. In addition, complexes with these aminoacid-based ligands may serve as good artificial mimics of catalase and dioxygenase enzymes, too, since in these enzymes the N_3 or N_3O donor sets often occur as the basis of the metal-binding site. We also wanted to initiate studies on a wide spectrum of metal–ligand combinations with biologically relevant metals (Mn, Fe, Co, Ni, Cu) that may lead to the



Scheme 2. Schematic structure of the active sites of the various SODs.



M(L)X_n

M	L	X	n	Complex
Mn^{II}	$PBMPA^-$	Cl^-	1	**1**
Mn^{II}	MPBMPA	Cl^-	2	**1-Me**
Fe^{III}	$PBMPA^-$	ClO_4^-	2	**2**
Fe^{III}	MPBMPA	ClO_4^-	3	**2-Me**
Fe^{II}	$PBMPA^-$	Cl^-	1	**2r**
Fe^{II}	MPBMPA	Cl^-	2	**2r-Me**
Co^{II}	$PBMPA^-$	Cl^-	1	**3**
Co^{II}	MPBMPA	Cl^-	2	**3-Me**
Ni^{II}	$PBMPA^-$	Cl^-	1	**4**
Ni^{II}	MPBMPA	Cl^-	2	**4-Me**
Cu^{II}	$PBMPA^-$	Cl^-	1	**5**
Cu^{II}	MPBMPA	Cl^-	2	**5-Me**

Scheme 3. Structure of the applied ligands, composition and numbering of the prepared complexes.