Journal of Molecular Catalysis A: Chemical 365 (2012) 154–161

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Functional model for catecholase-like activity: A mechanistic approach with manganese(III) complexes of salen type Schiff base ligands

Piya Seth[a,1], Michael G.B. Drew[b], Ashutosh Ghosh[a,*]

[a] Department of Chemistry, University College of Science, University of Calcutta, 92, A.P.C. Road, Kolkata 700009, India
[b] School of Chemistry, The University of Reading, P.O. Box 224, Whiteknights, Reading RG6 6AD, UK

ARTICLE INFO

Article history:
Received 3 April 2012
Received in revised form 23 August 2012
Accepted 25 August 2012
Available online 1 September 2012

Keywords:
Manganese(III)
Schiff base
Crystal structure
Catecholase activity

ABSTRACT

Three new Mn(III) complexes $[MnL^1(OOCH)(OH_2)]$ (**1**), $[MnL^2(OH_2)_2][Mn_2L_2{}^2(NO_2)_3]$ (**2**) and $[Mn_2L_2{}^1(NO_2)_2]$ (**3**) (where $H_2L^1 = H_2Me_2Salen$ = 2,7-bis(2-hydroxyphenyl)-2,6-diazaocta-2,6-diene and $H_2L^2 = H_2Salpn$ = 1,7-bis(2-hydroxyphenyl)-2,6-diazahepta-1,6-diene) have been synthesized. X-ray crystal structure analysis reveals that **1** is a mononuclear species whereas **2** contains a mononuclear cationic and a dinuclear nitrite bridged (μ-1κO:2$\kappa O'$) anionic unit. Complex **3** is a phenoxido bridged dimer containing terminally coordinated nitrite. Complexes **1**–**3** show excellent catecholase-like activity with 3,5-di-*tert*-butylcatechol (3,5-DTBC) as the substrate. Kinetic measurements suggest that the rate of catechol oxidation follows saturation kinetics with respect to the substrate and first order kinetics with respect to the catalyst. Formation of bis(μ-oxo)dimanganese(III,III) as an intermediate during the course of reaction is identified from ESI-MS spectra. The characteristic six line EPR spectra of complex **2** in the presence of 3,5-DTBC supports the formation of manganese(II)-semiquinonate as an intermediate species during the catalytic oxidation of 3,5-DTBC.

1. Introduction

Metalloenzymes that activate molecular oxygen have received great attention as potential catalysts for specific oxidation reactions and also for the development of efficient small molecule catalysts [1–6]. The oxidation of organic substrates with molecular oxygen under mild conditions is of growing interest for industrial and synthetic processes [7]. As a result synthesis and reactivity studies of transition metal complexes, as model compounds for metalloenzymes with oxidase activity have been undertaken by various groups in order to develop bio-inspired catalysts for oxidation reactions [8–10]. One of the major enzymes that play a key role in these reactions is catechol oxidase (CO), a lesser known member of the type-III copper proteins. This enzyme belongs to the polyphenol oxidases which oxidize phenolic compounds to the corresponding quinones in the presence of oxygen. Quinones are highly reactive compounds that autopolymerize to brown polyphenolic catechol melanins. Some higher plants utilize this process to resist diseases and to protect themselves from pathogens or insects.

Most abundant functional mimics of CO are mono- or dinuclear Cu(II) complexes [9,10] as the native form of this enzyme consists of a hydroxo-bridged dicopper(II) center. Therefore, structure–activity relationships for the catechol oxidation reaction are mainly investigated with Cu(II) complexes [11]. From this survey, it can be said that the rate of catechol oxidation reactions catalyzed by Cu(II) complexes is a composite effect of several parameters such as: M–M distance, flexibility of the ligand, type of exogenous ligand and coordination geometry around the metal ion. Besides the Cu(II) containing species, some complexes of Mn(II) [12–14], Mn(III) [15,16], Mn(IV) [17,18] have also being reported to perform catecholase mimicking activity. In these complexes different types of ligands e.g. tetra-dentate tripodal ligands, several pyridine derivatives, azametallacrown and compartmental ligands have been utilized. However, the number of such studies is far less in comparison to Cu(II) complexes, although the manganese(III) complexes play very important roles in biological systems e.g. in many metalloenzymes, redox and non-redox proteins [19,20], and are used as catalysts in olefin epoxidation reactions [21].

In order to have clearer insight into the catecholase activity of manganese complexes we have chosen complexes of salen-type Schiff base ligands (Scheme 1), and synthesized three new Mn(III) complexes, $[MnL^1(OOCH)(OH_2)]$ (**1**), $[MnL^2(OH_2)_2][Mn_2L_2{}^2(NO_2)_3]$ (**2**) and $[Mn_2L_2{}^1(NO_2)_2]$ (**3**). Their characterization, crystal structure and catecholase activity are reported in this paper. All three complexes exhibit substantial catechol oxidation with 3,5-di-*tert*-butylcatechol (3,5-DTBC) as the substrate in acetonitrile solvent. The phenoxido bridged dinuclear

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* Corresponding author. Tel.: +91 9433344484; fax: +91 3323519755.
E-mail address: ghosh_59@yahoo.com (A. Ghosh).
[1] Tel.: +91 9433344484; fax: +91 33 2351 9755.

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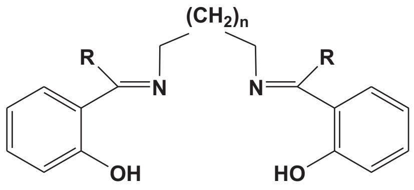
http://dx.doi.org/10.1016/j.molcata.2012.08.024



H_2L^1 (n=0, R=CH_3)
H_2L^2 (n=1, R=H)

Scheme 1. Schiff base ligand H_2L.

Mn(III) compounds with this kind of N_2O_2 donor Schiff base ligands are well known for their interesting magnetic properties [22] specially for their potential use as single molecule magnets [23]. A nitrito bridged complex of such ligand also exhibited the sign of SMM behavior [24]. However, the catecholase activity of Mn(III) complexes with salen type di-Schiff bases have not been explored till date. We show here that these complexes are very good catalysts for catechol oxidation reaction and try to explain the plausible mechanisms for the same. A manganese(II)-semiquinonate intermediate which is identified through EPR measurements is thought to be responsible for this oxygenation reaction. ESI-MS positive spectra also signify the presence of a bis(μ-oxo)dimanganese(III,III) intermediate during the aerobic oxidation of catechol.

2. Experimental

2.1. Synthesis of the complexes

o-Hydroxy acetophenone, 1,2-ethanediamine, salicylaldehyde and 1,3-diaminopropane were purchased from Lancaster and were of reagent grade. They were used without further purification.

2.1.1. Synthesis of the Schiff base ligands, H_2L^1 and H_2L^2

The two di-Schiff-base ligands, H_2L^1 and H_2L^2 (Scheme 1), were prepared by standard methods [25]. Briefly, 2 mM of diamine {1,2-ethanediamine (0.12 mL) or 1,3-diaminopropane (0.16 mL)} was mixed with 4 mM of the required aldehyde {*o*-hydroxy acetophenone (0.48 mL) or salicylaldehyde (0.41 mL)} in methanol solvent. The resulting mixture was refluxed for ~1.5 h, and allowed to cool. The yellow solutions were used directly for complex formation.

2.1.2. Synthesis of complex $[MnL^1(OOCH)(OH_2)]$ (**1**)

A methanolic solution (10 mL) of H_2L^1 (2 mM) was added to a methanolic solution (5 mL) of $Mn(ClO_4)_2 \cdot 6H_2O$ (0.722 g, 2 mM) with constant stirring. After ~10 min an aqueous solution of HCOONa (0.136 g, 2 mM) was added to the solution, followed by triethyl amine (0.56 mL, 4 mM). The solution was further stirred for half an hour. A dark brown crystalline compound separated on stirring. It was filtered. On slow evaporation of the solvent from the filtrate dark brown, X-ray quality single crystals were obtained.

Complex 1: Yield: 0.313 g (78%) Anal Calc. for $C_{19}H_{21}Mn_1N_2O_5$: C, 55.35; H, 5.13; N, 6.79; Found: C, 55.47; H, 5.07; N, 6.62. IR (KBr pellet): ν(C=N), 1590 cm^{-1}, ν_{as}(C=O), 1537 cm^{-1}, ν_s(C=O), 1328 cm^{-1}. UV–vis (CH_3CN) λ_{max} (nm), ε(M^{-1} cm^{-1}): 396 (9491).

2.1.3. Synthesis of the complexes $[MnL^2(OH_2)_2][Mn_2L_2{}^2(NO_2)_3]$ (**2**) and $[Mn_2L_2{}^1(NO_2)_2]$ (**3**)

A methanolic solution (10 mL) of the required ligand H_2L^1 or H_2L^2 (2 mM) was added to a methanolic solution 5 mL of $MnCl_2 \cdot 4H_2O$ (0.394 g, 2 mM) with constant stirring. To this solution triethylamine (0.56 mL, 4 mM) was added. After ca. 15 min a H_2O–MeOH mixture of $NaNO_2$ (0.169 g, 2 mM) was added to the mixture and stirred. The dark brown compound of both **2** and **3** started to separate on stirring; the solids were filtered after about 2 h and washed with diethyl ether, and then redissolved in CH_3CN. Layering of these brown solutions with Et_2O gave well formed X-ray quality single crystals.

Complex 2: Yield: 0.846 g (72%) Anal Calc. for $C_{51}H_{52}Cl_{0.38}Mn_3N_{8.62}O_{13.23}$: C, 51.92; H, 4.44; N, 10.68; Found: C, 51.76; H, 4.31; N, 10.51. IR (KBr pellet): ν(C=N), 1612 cm^{-1}, $\nu_s(NO_2)$, 1295 cm^{-1}, $\nu_{as}(NO_2)$, 1213 cm^{-1}, $\nu(H_2O)$, 3395 cm^{-1}. UV–vis (CH_3CN) λ_{max} (nm), ε(M^{-1} cm^{-1}): 388 (17,549).

Complex 3: Yield: 0.584 g (75%) Anal Calc. for $C_{36}H_{36}Cl_{1.02}Mn_2N_{4.98}O_{5.96}$: C, 54.69; H, 4.59; N, 10.63; Found: C, 54.52; H, 4.69; N, 10.47. IR (KBr pellet): ν(C=N), 1589 cm^{-1}, $\nu_s(NO_2)$, 1313 cm^{-1}, $\nu_{as}(NO_2)$, 1234 cm^{-1}. UV–vis (CH_3CN) λ_{max} (nm), ε(M^{-1} cm^{-1}): 397 (9013).

2.2. Physical measurements

Elemental analyses (carbon, hydrogen and nitrogen) were performed using a Perkin-Elmer 240C elemental analyzer. IR spectra in KBr (4000–500 cm^{-1}) were recorded using a Perkin-Elmer RXI FT-IR spectrophotometer. Electronic spectra in acetonitrile (600–300 nm) were recorded in a Hitachi U-3501 spectrophotometer. The electro spray ionization mass (ESI-MS positive) spectra were recorded on a MICROMASS Q-TOF mass spectrometer. The X-band (9.1 GHz) EPR spectra were recorded using a JEOL JES-FA 200 instrument at liquid nitrogen temperature (77 K) in acetonitrile solvent.

2.2.1. Catalytic oxidation of 3,5-DTBC

In order to examine the catecholase activity of the complexes, a 10^{-5} M solution of **1**–**3** in acetonitrile solvent was treated with 100 equiv. of 3,5-di-*tert*-butylcatechol (3,5-DTBC) under aerobic conditions at room temperature. Absorbance vs. wavelength (wavelength scans) of these solutions were recorded at a regular time interval of 5 min in the wavelength range 300–500 nm. To determine the dependence of rate on substrate concentration and various kinetic parameters, a 10^{-5} M solution of these complexes was treated with at least 10 equiv. of substrate so as to maintain the pseudo first order condition. The reaction was followed spectrophotometrically by monitoring the increase in the absorbance at 400 nm (Quinone band maxima) as a function of time (time scan).

2.3. Crystallographic data collection and refinement

Crystal data for the three complexes **1**–**3** are given in the supporting information, Table ST1. 4021, 14044 independent reflections data were collected with MoKα radiation for **1** and **2** at 150 K using the Oxford Diffraction X-Calibur CCD System. The crystals were positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10 s. Data analyses were carried out with the CrysAlis program [26]. 2556 independent reflections data for **3** were collected with MoKα radiation at room temperature using the Bruker-AXS SMART APEX II diffractometer equipped with a graphite monochromator and MoKα (λ = 0.71073 Å) radiation. The crystal was positioned at 60 mm from the CCD. 360 frames were measured with a counting time of 10 s. All three structures were solved using direct methods with the Shelxs97 program [27]. Both **2** and **3** showed some disorder between one terminal nitrite and chloride ions. In **2** this was treated via population parameters x and $1 - x$, respectively with x refined to 0.62(1). In **3** similar refinement converged to 0.49(3) and was subsequently fixed at 0.5. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times (or 1.5 times for methyl groups) those of the atom to which they were attached. The hydrogen atoms of the water molecules in **1** and