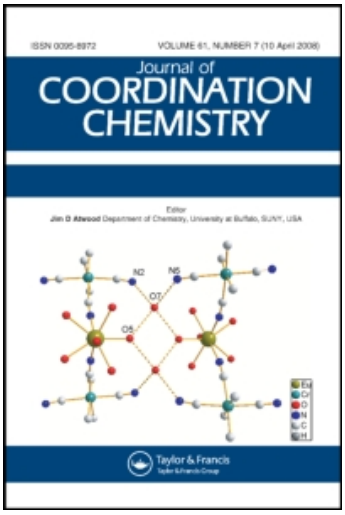

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Catalase-like catalytic reaction of the dinuclear manganese–salen complex

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Catalase-like activity of a dinuclear manganese-salen (Mn–salen) complex, $[Mn(salen)(H_2O)]_2(ClO_4)_2$ (salen = *N*,*N*′-*bis*(salicylidene)-1,2-diaminoethane), was investigated. The dinuclear Mn–salen complex exhibits higher catalase-like activity than that of the mononuclear Mn–salen compound, and its activity can be enhanced by an external base. Different reaction intermediates in the presence and absence of an external base were observed, and the catalytically active species was dimeric as evidenced by UV-Vis spectroscopic studies and mass spectrometry data.

Keywords: Dinuclear Mn–salen complex; Catalase-like activity; Catalytic reaction mechanism; Mn–salen

1. Introduction

Manganese–salen (Mn–salen) complexes exhibited promising features as scavengers of reactive oxygen species (ROS) due to their dual activities, i.e., superoxide dismutase (SOD) and catalase-mimetic activities [1–3]. Therefore, improving their enzymatic activities is a subject of interest for the development of candidate clinical drugs for ROS-associated diseases [4–6]. Their catalase catalytic activities were extensively investigated along with their SOD activities. Doctrow *et al*. [7] reported that the catalase activity of the mononuclear Mn–salen compounds varies widely in their ability to scavenge hydrogen peroxide with this activity, most influenced by the salen ring alkoxy substitution and aromatic bridge modifications. Mn–salen complex bearing an auxiliary structure fused to the salen ligand exhibited considerably higher catalase-like activity than the original Mn–salen [8]. The catalase catalytic mechanism of Mn–salen compounds was proposed through theoretical calculation [9]. These studies along with other works indicated that Mn–salen compounds are the subject of interest for catalase mimic-development of candidate clinical drugs for ROS-associated diseases

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and sophisticated catalyst design [10–13]. However, the catalase-like activity of dinuclear Mn–salen complexes was barely explored. Several dinuclear Mn–salen compounds were reported, but only their structures and magnetic properties were investigated [14–17]. A dimeric Mn–salpn complex, in which salpn is structurally very similar to salen, can be easily converted to an efficient catalase mimic $[Mn^{IV}(salpn)(\mu\text{-}O)]_2$, indicating the potential of dimeric Mn–salen complexes as catalase mimics [18]. Dinuclear Mn–salen complex is structurally close to the active site of manganese catalase in terms of metal center and should be a more effective mimic than mononuclear Mn–salen complexes [4]. Recently, different metal complexes with Schiff bases involving N_2O_2 donors like salen were reviewed [19, 20], and many focused on structures and biological activities [21–24]. The activity and reaction differences between the dinuclear and mononuclear complexes were explored. Several basic questions, such as whether a dinuclear Mn–salen complex has a higher catalytic activity than that of mononuclear Mn–salen compounds, and do they share a common reaction pathway, have not been answered.

We reported here the catalase-like activity and the reaction pathway of the dinuclear Mn–salen complex $[Mn(salen)(H_2O)]_2(ClO_4)_2(H_2O)_2$ ($[Mn–salen]_2$ for simplicity) as a model compound with UV-Vis spectroscopy, mass spectrometry, and catalytic activity assay. The catalase activity of $[Mn–salen]_2$ in the presence of a base was also explored and the results were compared with the mononuclear Mn–salen to understand the functional role of the base and catalytic pathway difference between the mononuclear and dinuclear Mn–salen complexes.

2. Experimental

All reagents were of analytical grade and used as received from SinoPharm Chemical Reagent Co., Ltd without purification. Electronic absorption spectra were recorded on a Cary 50 spectrophotometer (VARIAN, USA). Elemental analyses were performed with an Elementar Vario ELIII analyzer (Germany). X-ray crystallographic data of $[Mn–salen]_2$ were collected on a SMART diffractometer (Bruker, USA) using Mo-Kα radiation ($\lambda = 0.71$ Å). Mass spectrometry data were acquired with Esquire 3000 (Bruker, USA).

2.1. *Preparation of $[Mn(salen)(H_2O)]_2(ClO_4)_2$*

Caution: Although no problems have occurred during our work, perchlorates are potentially explosive and should be treated in small quantities with care and suitable precautionary measures should be taken when handled.

Manganese perchlorate (0.9 g, 2.5 mmol L^{-1}) was added to a stirring solution of salicylaldehyde (1.2 g, 10 mmol L^{-1}) in 50 mL methanol and 1,2-diaminoethane (0.3 g, 5 mmol L^{-1}) was then added to the mixture [25]. Dark brown precipitate was formed after 2 h of stirring at room temperature. The precipitate was filtered off and washed twice with methanol and diethyl ether, and dried under vacuum. Yield, 1.71 g (78%). Elemental Anal. (%), Found: C, 42.15; H, 3.87; N, 6.05. Calcd for $C_{32}H_{36}N_4O_{14}Mn_2Cl_2$: C, 42.08; H, 3.97; N, 6.13. Dark brown single crystals suitable

for X-ray diffraction were obtained by crystallization from methanol upon exposure to air at room temperature for several days.

2.2. *Catalase-like activity assay*

Catalase activity was assayed using a volumetric method [26]. Dioxygen evolution was measured as a function of reaction time. Due to poor solubility in water, $[Mn–salen]_2$ was first dissolved in a small quantity of acetonitrile and then dispersed into Milli Q water. All samples were incubated at 30°C for 10 min to reach equilibrium before the measurement. The addition of H_2O_2 to the reaction system initiated the reaction. In general, total reaction volume is 2 mL. The reaction vial was directly connected to a home-made soap bubble flow meter. The volume of the generated dioxygen by the reaction mixture was recorded according to the time. Initial dioxygen evolution rates were obtained by linear regression of the first 10–20 s of data.

3. Results and discussion

3.1. *Crystal structure*

The crystal structure of $[Mn–salen]_2$ is identical to the literature reported (figure S1) [17]. Two manganese ions are bridged through oxygens from two salen ligands, forming a *bis*(μ-phenoxo)dimanganese core. The half structure of $[Mn–salen]_2$ is almost identical to a mononuclear Mn–salen. The bridged Mn–O bond (2.483(4) Å) is longer than the other Mn–O bond length. The latter and Mn–N bond lengths are all similar to that of the mononuclear Mn–salen complexes.

3.2. *Electronic property*

The electronic spectrum of $[Mn–salen]_2$ in acetonitrile exhibits three strong absorption bands, 240, 277, and 308 nm, which are transitions of the salen ligands. The absorption at 393 nm with moderate intensity is from charge transfer between salen and manganese (ligand–metal charge transfer (LMCT)). The spectrum is almost identical to that of the mononuclear Mn–salen compound [27].

3.3. *Catalytic activity and base enhancement*

UV-Vis absorption of $[Mn–salen]_2$ provides a spectral handle to monitor its catalase catalytic reaction. Figure 1(a) shows the spectral changes of the reaction of $[Mn–salen]_2$ with H_2O_2 as a function of reaction time. The catalytic activity was further examined by O_2 evolution during the reaction as shown in figure 2, which exhibits the time course of O_2 evolution in the presence of $[Mn–salen]_2$ and H_2O_2. These results indicate that $[Mn–salen]_2$ can disproportionate H_2O_2 to H_2O and O_2. The H_2O_2 disproportionation proceeded in two steps according to the UV-Vis spectra evolution, a fast step followed by a gradual process (inset of figure 1a), which is analogous to mononuclear [Mn(salen)Cl] [28]. However, in the mononuclear [Mn(salen)Cl], the fast process was

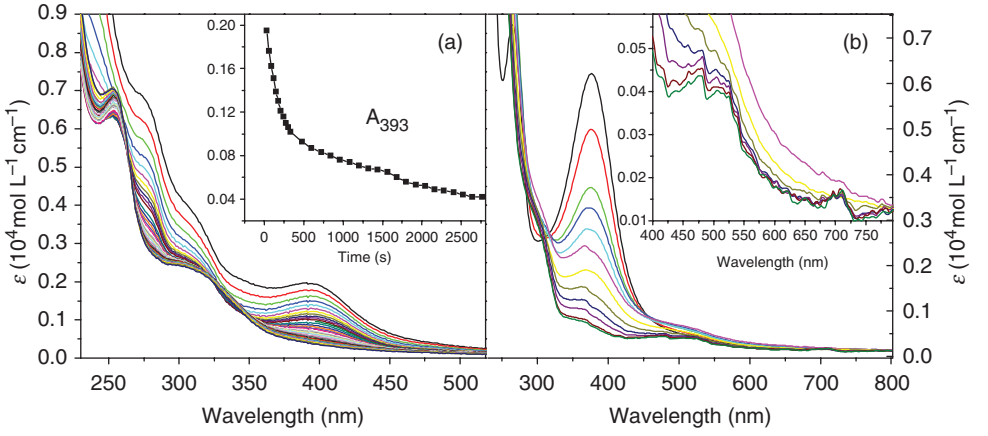

Figure 1. (a) UV-Vis spectra of the reaction of $[Mn–salen]_2$ ($0.1\,mmol\,L^{-1}$) with H_2O_2 ($10\,mmol\,L^{-1}$) at room temperature as a function of time (inset: the UV-absorption changes monitored at 393 nm during the reaction) and (b) UV-Vis spectra under the same conditions except for the presence of $1\,mmol\,L^{-1}$ NaOH (inset: the spectra at the high wavelength region).

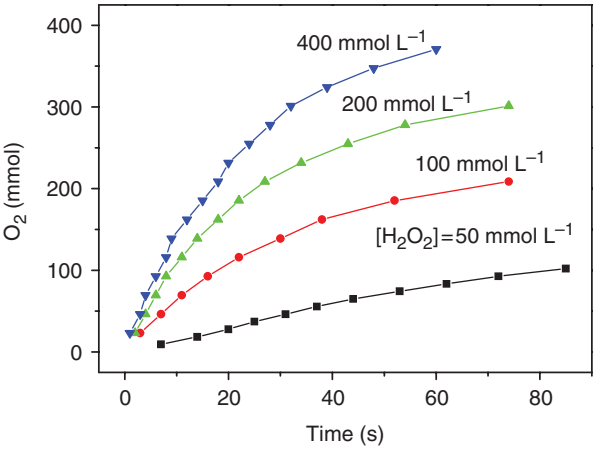

Figure 2. Time dependence of dioxygen evolution catalyzed by $[Mn–salen]_2$ with different H_2O_2 concentration.
$[Mn–salen]_2 = 1\,mmol\,L^{-1}$, $[H_2O_2] = 50–400\,mmol\,L^{-1}$, and $T = 303\,K$.

proposed as fast equilibrium of Mn^{III} with Mn^{IV}–OH, which has an intense absorption in the 500–600 nm range. In contrast, no such absorption was observed in the dinuclear $[Mn–salen]_2$, suggesting that the dinuclear complex likely undergoes a different reaction intermediate.

To further understand H_2O_2 disproportionation by the dinuclear $[Mn–salen]_2$, we carried out H_2O_2 disproportionation in the presence of sodium hydroxide. It was reported that the base could enhance the catalase activity of mononuclear Mn–salen [28]. At a high H_2O_2 concentration, the initial velocity increased with increasing base, and finally reached a constant. At lower H_2O_2 concentration, the initial rate was linear to the second order of the base concentration [28]. Similar to [Mn(salen)Cl], the initial reaction rates of $[Mn–salen]_2$ increased with increasing NaOH concentration, with a

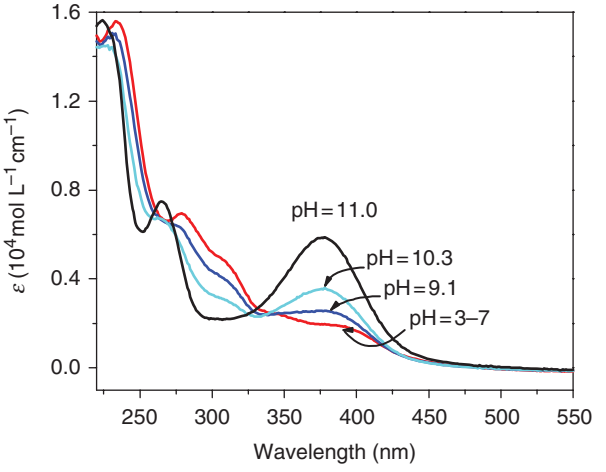

Figure 3. The pH dependence of the UV-Vis spectra of $[Mn–salen]_2$ (0.1 mmol L^{-1}).

maximum rate with 15 equivalents of base, and started to decrease when the base was increased further (figure S2). Interestingly, the base enhancement was not stoichiometrically proportional to NaOH concentration, suggesting that they may not only coordinate to manganese.

Figure 1(b) illustrates the UV-Vis spectral changes of the reaction in the presence of NaOH as a function of time. When compared to figure 1(a), the reaction in the absence of base had noticeable differences. The reaction in the presence of base proceeded in one phase instead of two, and two weak absorption bands at ~500 and ~700 nm were observed during the reaction (inset of figure 1b). The latter was remarkably different from that of the [Mn(salen)Cl] in which, with excess NaOH, Mn^{IV}=O species with absorption at 520 nm, assigned to $\nu(Mn^{IV}=O)$ coupled to the LMCT band, was observed. In the presence of equimolar NaOH, there was no such absorption observed [28]. Weak absorption at ~500 nm was observed in the di-μ-oxo dimanganese(IV) complexes, which was contributed by manganese orbital changes owing to the oxidation [17]. Therefore, the species with weak bands at high wavelength, ~500 and ~700 nm in the $[Mn–salen]_2$ is tentatively assigned as a high valent intermediate. We infer that H_2O_2 disproportionation reactions catalyzed by $[Mn–salen]_2$ in the presence of an external base proceed *via* different reaction pathways.

External base functions as an assistant in H_2O_2 deprotonation in many catalase-mimic dinuclear manganese complexes [29–34]. If this is also the case for $[Mn–salen]_2$, we expect that the UV-Vis spectra of the $[Mn–salen]_2$ itself should remain unchanged under different pH as in most dinuclear manganese compounds. However, the titration of $[Mn–salen]_2$ with sodium hydroxide was accompanied by a shift in LMCT (from 393 to 375 nm) with a concomitant increase in intensity, and another band shift from 278 to 267 nm with first an increase and then a decrease in the intensity as depicted in figure 3. The spectral changes of $[Mn–salen]_2$ differ from either the ligand or $[Mn–salen]_2$ itself at neutral pH, suggesting that the external base in this case may not only function as an assistant in H_2O_2 disproportionation as reported in the literature. LMCT band shift had been reported in dinuclear copper complex, when two water molecules were replaced by two OH^- ions under basic conditions [33]. Hence, it is very

likely that OH^- coordinates to manganese as proposed in some dinuclear manganese compounds [29–34]. Unfortunately, X-ray crystal diffraction of the product formed with NaOH was not successful because of poor crystal quality. Electron paramagnetic resonance (EPR) spectroscopy for Mn(III) compound was not very informative.

3.4. *ESI–MS analysis*

Electrospray ionization–mass spectrometry (ESI–MS) analysis was used to further determine the catalytic species of the $[Mn–salen]_2$ in the presence and absence of base. In $[Mn–salen]_2$ methanol solution, peaks at m/z 321.0 $[Mn(salen)]^+$, 741.1 $\{[Mn(salen)]_2(ClO_4)\}^+$ were observed (figure S3a). The appearance of $\{[Mn(salen)]_2(ClO_4)\}^+$ suggested that the dinuclear core of the complex does persist in the solution, and is the active species in the catalysis. To further confirm this result, the catalytic reactions with the equal molar dinuclear and mononuclear Mn–salen compounds under the same reaction condition were compared as shown in figure 4(a). The higher initial reaction rates of the $[Mn–salen]_2$ clearly indicated that it has different reaction species, comparing with the mononuclear Mn–salen. To prove that such a difference is not caused by the decomposition of one $[Mn–salen]_2$ into two mononuclear Mn–salen, the initial rates *versus* the concentrations of both compounds were plotted as shown in figure 4(b). It is obvious that the curves of the concentrations *versus* the initial reaction rates of the two compounds were different (slope is 2.86 for $[Mn–salen]_2$ and 0.87 for Mn–salen). This result is consistent with our MS result.

After incubating with five equivalent NaOH for 2 h, ESI–MS spectrum of the reaction mixture was complicated, but a peak exists at m/z 721.2, which tentatively can be assigned as $\{Na_2[Mn_2(salen)_2(O)(OH)]\}^+$ (figure S3b) [35]. The presence of [Mn(O)Mn(OH)] suggested that OH^- may coordinate to manganese, based on pH titration and UV-Vis studies in the presence and absence of an external base. However, the MS was carried out with the reaction mixture and several peaks such as 687, 689, and 355 were not able to be determined in this case. Different reaction conditions such as temperature and lower concentration are under testing to trap the intermediates.

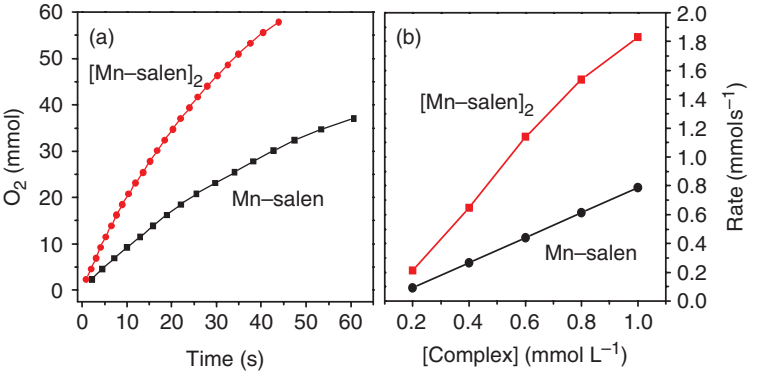

Figure 4. (a) Comparison of the reactions of dinuclear and mononuclear Mn–salen complexes under the same reaction conditions. [complex] = 1 mmol L^{-1}, $[H_2O_2]$ = 50 mmol L^{-1}, and T = 303 K. (b) Plots of the initial reaction rates *vs*. concentrations of dinuclear and mononuclear compounds.

Considering that the base enhancement is not stoichiometrically proportional to the NaOH concentration, we believe that the external base has dual functions, coordination to manganese centers and deprotonation of H_2O_2 during the catalytic reaction.

4. Conclusion

$[Mn–salen]_2$ exhibits higher catalase-like activity than mononuclear Mn–salen and its activity can be enhanced by an external base. UV-Vis spectra and MS data indicate that the catalytically active species of $[Mn(salen)]_2$ is dinuclear. The catalytic pathways of the dinuclear and the mononuclear Mn–salen complexes are different. Long wavelength UV-Vis absorbances observed for the catalytic intermediate with $[Mn(salen)]_2$ in the presence of external base, and the base enhancement that is not stoichiometrically proportional to NaOH concentration, suggested that OH^- coordination to manganese enhances the activity of the $[Mn(salen)]_2$, and uncoordinated OH^- may function as a base to assist H_2O_2 deprotonation. $[Mn(salen)]_2$ is more active under the basic conditions due to these two reasons. The results provide valuable information for improving or optimizing the catalase activity of the Mn(salen) complexes.

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