Synthesis, Crystal Structure and Superoxide Dismutase (SOD) Activity of Novel Seven-Coordinated Manganese(II) Complex with Multidentate Di-Schiff Base Ligands

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A novel hepta-coordinated mononuclear manganese(II) complex, $[Mn(L)_2(H_2O)](ClO_4)_2\cdot 2.5H_2O$ [L = 1,2-bis(2′-pyridylmethyleneamino)propane], was obtained by assembly reaction of a di-Schiff base ligand L with manganese(II) perchlorate. The crystal structure shows that one of the L ligand acts as a quadridentate ligand, while the other one serves as a bidentate. The Mn(II) complex was found to have activity of dismutation of superoxide ($O_2^{\cdot -}$) in the riboflavin-methionine-nitro blue tetrazolium assay.

Some human diseases, such as Alzheimer, Parkinson etc, are considered to be associated with the overproduction of superoxide radical anion ($O_2^{\cdot -}$), an undesired and toxic metabolic by-product, that inflicts cell damage.[1] The superoxide dismutase (SOD) enzymes containing either Cu/Zn, Fe or Mn at the active site catalyze the dismutation of the superoxide radical to hydrogen peroxide and oxygen and protect living cells against the toxicity of hyperoxia.[2] Therefore the rational design and synthesis of mimics of the SOD enzyme has potential for the treatment and prevention of some diseases. Recently Mn complexes have been often selected in the synthetic catalysts for pharmaceutical use because of their less toxicity in vivo.[3]

The Mn complexes of Schiff base, porphyrin and their derivatives have been studied as Mn-SOD mimics in the past decades. Five-coordinated Mn(II) complexes with trigonal-bipyramidal coordination geometry and structural similarities to the native Mn-SOD have been reported to exhibit SOD activity.[4] While the reported seven-coordinated Mn(II) complexes are principally with macrocyclic ligands. For example, a Mn(II) complex with bis(cyclohexylpyridine)-substituted macrocyclic ligand shows high SOD activity,[5] and Mn(II) complexes with 1,4,7,10,13-pentaazacyclopentadecane ligands are excellent functional mimics of the native Mn-SOD and probed the effects of substituents on the SOD activity.[6,7] However, few reports are known for seven-coordinated Mn(II) complex with noncyclic Schiff base ligand.[8] We report herein a novel seven-coordinated Mn(II) complex with a new di-Schiff base ligand, 1,2-bis(2′-pyridylmethyleneamino)propane (L), and its SOD activity.

The complex $[Mn(L)_2(H_2O)](ClO_4)_2\cdot 2.5H_2O$ was readily prepared by reaction of new ligand L with $MnClO_4\cdot 6H_2O$.[9] The X-ray crystal structure analysis indicates that the complex contains one mononuclear Mn(II) cation, two perchlorate anions and two and half uncoordinated water molecules.[10] The cationic structure of the complex is illustrated in Figure 1.

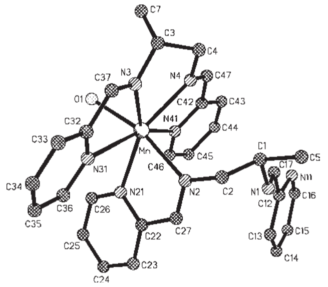

Figure 1. Cationic structure of $[Mn(L)_2(H_2O)](ClO_4)_2\cdot 2.5H_2O$, hydrogen atoms were omitted for clarity. Selected bond lengths (Å) and angles (°): Mn-O1 = 2.153(3), Mn-N2 = 2.274(4), Mn-N3 = 2.282(5), Mn-N4 = 2.289(4), Mn-N21 = 2.288(3), Mn-N41 = 2.509(4), Mn-N31 = 2.599(4), N2-Mn-O1 = 164.96(12), N2-Mn-N21 = 72.92(14), N2-Mn-N3 = 99.46(17), N2-Mn-N41 = 93.97(12), O1-Mn-N3 = 88.62(15), O1-Mn-N21 = 92.97(13), N3-Mn-N21 = 142.79(19), O1-Mn-N4 = 98.31(14), N3-Mn-N4 = 71.5(2), N21-Mn-N4 = 144.39(17), N3-Mn-N41 = 137.7(2), N21-Mn-N41 = 79.49(14), O1-Mn-N41 = 88.36(12), N4-Mn-N41 = 67.27(16), N2-Mn-N4 = 96.29(16).

Each Mn(II) atom is seven-coordinated with a N_6O donor set. The coordination environment of the Mn(II) atom can be regarded as a distorted pentagonal bipyramid. Four N atoms (N31, N3, N4 and N41) of one L ligand, one N21 atom from a pyridine group of another L ligand form the equatorial plane. The Mn atom is almost at the equatorial plane since the deviation of the Mn atom from the N21, N31, N3, N4 and N41 plane is less than 0.1 Å. One O1 atom of water molecule and a N2 atom from ethylenediimine unit of another L ligand occupy the apical positions with a bond angle N2-Mn-O1 of 164.96(12) °. The angle is similar to the Cl-Mn-Cl angle [169.7(1) °] in the reported Mn(II) complex [Mn(2,2,3,3-tetramethyl-1,4,7,10,13-pentaazacyclopentadecane)Cl_2].[11] It is interesting that in the title complex only one of two L ligands coordinates to the Mn(II) atom in a quadridentate manner, and the other one is in a bidentate manner. Two uncoordinated N atoms from the pyridine group and the ethylenediimine unit in the L ligand participate in formation of two O-H· · ·N hydrogen bonds [O2B-H39B· · ·N11: $r_{O2B\text{-}N11} = 2.849(5)$; O3A-H41A· · ·N1: $r_{O3A\text{-}N1} = 2.845(5)$ Å] with the solvate water molecule [Figure 2(a)]. In addition to these two O-H· · ·N hydrogen bonds, there are three O-H· · ·O hydrogen bonds [O1A-H37A· · ·O3A: $r_{O1A\text{-}O3A} = 2.676(4)$; O1E-H38E· · ·O2B: $r_{O1E\text{-}O2B} = 2.709(4)$; O3A-H40A· · ·O4A: $r_{O3A\text{-}O4A} = 2.847(8)$ Å] linked the cation part of the complex to generate a 2D network as shown in Figure 2(a). The perchlorate anions occupy the channels formed between two adjacent sheets and held there by O-H· · ·O hydrogen bonds. Figure 2(b) shows the O(water)-H· · ·O(perchlorate) hydrogen bonds indicated by dash lines. Although the hydrogen atoms attached to the water molecule of O4 could not be found from the difference maps, the distances of 2.85 (2) Å between O4A and O24A and 2.92 Å between O4C and O22A indicate the presence of O(water)-H· · ·O(perchlorate) hydrogen bonds. Such hydrogen bonds make the complex a 3D network [Figure 2(b)]. The results show that the formation of hydrogen bonds plays important roles in the crystal engineering of 1D, 2D and 3D supramolecular frameworks.[12] In addition to the hydrogen bonds, the structure is also stabilized by face to face π-π interactions. The nearest centroid-centroid distance between two pyridine rings with a dihedral angle of 18 ° is 3.94 Å.

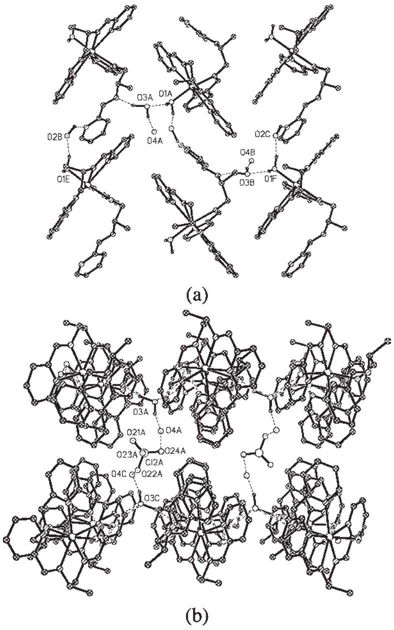

Figure 2. (a) Cationic 2D network of the complex linked by O-H···O and O-H···N hydrogen bonds (dashed lines). (b) O(water)-H···O(perchlorate) hydrogen bonds linked the 2D network to form a 3D structure.

The SOD activity of the title complex was studied by indirect method using the nitro blue tetrazolium (NBT) assay.[13] The reaction mixture contained 4.3×10^{-6} M riboflavin, 0.01 M methionine, 4.6×10^{-5} M NBT and 0.05 M potassium phosphate at pH 7.8, and the illumination of the reaction mixture at 303 K caused an increase in absorbance at 560 nm in aerobic solutions.[4] The rate of increase was reduced when the Mn(II) complex was added to the above reaction mixture. The correlation between the inhibition and concentration of the complex is shown in Figure 3. The result indicates that the complex has an IC_{50} value of 2.85 μM which implies that the complex has activity of dismutation of superoxide.

The mononuclear structure of the Mn(II) complex in solution was confirmed by electrospray mass (ES-MS) spectral measurement. Only mononuclear species of $[Mn(L)_2]^{2+}$ at m/z 279.7, $[Mn(L)(ClO_4)]^+$ at m/z 406.1 and $[Mn(L)_2(ClO_4)]^+$ at m/z 657.8 were observed in the ES-MS spectrum of the Mn(II) complex in acetonitrile. The reported Mn complexes with various organic ligands showed IC_{50} values ranging from 0.70 to 35 μM.[4] The IC_{50} value reported here is smaller than the 6.5 μM for the complex $Mn(PA)_2(PAH)(H_2O)$ (PAH = picolinic acid) obtained by the same NBT method,[14] but larger than those of Mn(II) complexes with benzoate tris(pyrazolyl)borate (0.75 μM) and tris(benzimidazol-2-ylmethyl)amine ligands (0.70 μM).[4] Riley and his co-workers studied the SOD activity for various substituted pentaaza macrocyclic Mn(II) complexes and found that the number, position and stereochemistry of the substituents have influence on the SOD activity.[7,11] However, the detail of the structure-reactivity relationship in the SOD activity is not well established to now because the SOD activities of reported Mn(II)-SOD mimics were assayed in different ways, and the catalytic mechanisms need further investigations.

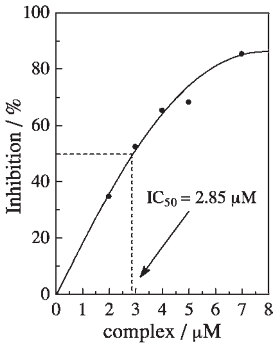

Figure 3. The SOD activity of the complex in the riboflavin-methionine-nitro blue tetrazolium assay.

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9 Preparation of title compound. A deionized aqueous solution (5 ml) of $MnClO_4 \cdot 6H_2O$ (19.9 mg, 0.05 mmol) was added dropwise to a stirred aqueous solution (5 ml) of the L (12.6 mg, 0.05 mmol). Pale yellow single crystals suitable for X-ray diffraction were obtained with a yield of 70% by slow evaporation of the reaction mixture for several days. Anal. Found: C, 43.61; H, 4.71; N, 13.67%. Calcd for $C_{30}H_{39}Cl_2N_8MnO_{11.5}$: C, 43.86; H, 4.79; N, 13.64%. CAUTION: Although no problems were encountered in the present study, perchlorate salts of Mn(II) complex with organic ligands are potentially explosive and should be handled with care.

10 Crystal data for $[Mn(L)_2(H_2O)](ClO_4)_2 \cdot 2.5H_2O$: $M = 821.53$, monoclinic, space group C2/c, $a = 39.724(2)$, $b = 11.4393(7)$, $c = 16.8332(7)$ Å, $\beta = 102.0350(10)$ °, $V = 7481.1(7)$ Å^3, $Z = 8$, $Dc = 1.459$ g/cm^3, $\mu = 5.64$ cm^{-1}, $T = 200$ K. The data collection were performed on a Rigaku RAXIS-RAPID Imaging Plate diffractometer using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods with SIR92 and expanded using Fourier techniques. All data were refined anisotropically by the full-matrix least-squares method for non-hydrogen atoms. 15893 reflections were collected of which 8533 are independent ($R_{int} = 0.0924$). The final weighting scheme was $w = 1/[\sigma^2(Fo^2)+(0.0200P)^2]$ where $P = (Fo^2 + 2Fc^2)/3$; $R1 = 0.0635$ and $wR2 = 0.0792$. max. min. residual density: $+0.324$, -0.287 e Å^{-3}. One of the perchlorate anion Cl2 is at special position, and Cl3 is disordered in two positions. The atoms O11, O12, O13, O14 [s.o.f.: 0.54(3) and 0.46(3)], O4, O21, O22, O24 (s.o.f.: 0.50 and 0.50), and C6, C7 [s.o.f.: 0.501(10) and 0.499(10)] have two positions with site occupancy factors (s.o.f.) given in the brackets.

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