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# Carboxylate-bridged dinuclear manganese systems – From catalases to oxidation catalysis

Johannes W. de Boer<sup>a</sup>, Wesley R. Browne<sup>a</sup>, Ben L. Feringa<sup>a</sup>, Ronald Hage<sup>b,\*</sup><sup>a</sup> Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands<sup>b</sup> Unilever R&D Vlaardingen, Olivier van Noortlaan 120, 3133 AT, Vlaardingen, The Netherlands

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## Abstract

Dinuclear manganese based enzymes engage in processes as diverse as amino acid hydrolysis and hydrogen peroxide disproportionation. Despite the mechanistic diversity displayed by this class of enzymes, a common feature is the presence of carboxylate residues, which serve to bridge the manganese centres and of hemi-labile oxo-, hydroxyl- and aqua-bridge, which shows considerable redox state dependence on their lability. The role of carboxylate-bridged dinuclear manganese complexes in the disproportionation of hydrogen peroxide is reviewed both in enzymatic and biomimetic systems. The lability of the carboxylate bridge and bridging oxo, hydroxyl and aqua ligands during the catalase cycle is discussed in relation to the redox cycle, which the dinuclear manganese centres undergo. The relationship between catalase activity and catalytic oxidation is discussed briefly with regard to understanding the nature of catalytically active species present during oxidation catalysis. **To cite this article : Johannes W. de Boer et al., C. R. Chimie 10 (2007).**

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## Résumé

Les enzymes possédant des complexes binucléaires de manganèse sont engagées dans des proces biologiques aussi divers que l'hydrolyse d'acides aminés ou encore la décomposition du peroxyde d'hydrogène. Malgré la richesse des mécanismes mis en jeu, ces enzymes se caractérisent toutes par la présence de résidus carboxylates, dont le rôle est de complexer le manganèse, et de ligands oxo-, hydroxyl- et aqua- hémi-labiles, dont l'état redox influence considérablement la labilité. Le rôle du complexe binucléaire carboxylate–manganèse dans la dégradation du peroxyde d'hydrogène, aussi bien d'un point de vue enzymatique que biomimétique, est présenté dans cette revue. De même, la labilité des ligands pontants carboxylate, oxo-, hydroxyl- et aqua- durant le cycle catalytique est discutée, en rapport avec le cycle redox du complexe binucléaire de manganèse. Enfin, la relation entre

*Abbreviations:* PS II, photosystem II; TTC, *Thermus thermophilus* manganese catalase; LPC, *Lactobacillus plantarum* manganese catalase; tacn, 1,4,7-triazacyclononane; tmtacn, *N,N',N''*-trimethyl-1,4,7-triazacyclononane; L, *N,N',N'',N'''*-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol; SALPN, 1,3-bis(salicylideneamino)propane; 2-OH-SALPN, *N,N'*-disalicylidene-2-hydroxypropanediamine; bpia, bis(picoly)(*N*-methylimidazol-2-yl)amine; bpea, *N,N'*-bis(2-pyridylmethyl)-ethylamine; tptn, *N,N',N'',N'''*-tetrakis(2-pyridylmethyl)-1,3-propanediamine; N2PyMePhOH, 2-[[di(2-pyridyl)methyl](methylamino)methyl]phenol.

\* Corresponding author.

*E-mail addresses:* [j.w.de.boer@rug.nl](mailto:j.w.de.boer@rug.nl) (J.W. de Boer), [w.r.browne@rug.nl](mailto:w.r.browne@rug.nl) (W.R. Browne), [b.l.feringa@rug.nl](mailto:b.l.feringa@rug.nl) (B.L. Feringa), [ronald.hage@unilever.com](mailto:ronald.hage@unilever.com) (R. Hage).

l'activité de la catalase et l'oxydation catalytique est abordée, dans le but de comprendre la nature des espèces catalytiques actives présentes lors de l'oxydation. **Pour citer cet article :** Johannes W. de Boer et al., *C. R. Chimie 10 (2007)*.

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**Keywords:** Dinuclear manganese; Oxidation catalysis; Catalase; Biomimetic; Carboxylate

**Mots-clés:** Manganèse binucléaire ; Catalyse oxydative ; Catalase ; Biomimétique ; Carboxylate

## 1. Introduction

By virtue of its non-singlet spin state, oxygen, in the form of  $^3\text{O}_2$ , is kinetically inert despite being an energetically very potent oxidant. Its oxidizing power is realized through the formation of 'active oxygen' species, i.e. singlet oxygen ( $^1\text{O}_2$ ) and its reducing equivalents, the superoxide radical anion ( $\text{O}_2^-$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and hydroxyl radical ( $\text{OH}^\cdot$ ). Handling active oxygen is a major challenge both in vivo [1a] and in oxidation catalysis [1b], a challenge which frequently employs catalytic mediators to control the expression of their oxidizing power.

In vivo, the ability to deal with all forms of active oxygen is central to cellular protection. Indeed any imbalance in the decomposition of active oxygen species leads to oxidative cellular stress and, ultimately, loss of cellular viability. The mechanisms by which nature diffuses active oxygen safely involve the disproportionation of the active species to the inert oxygen species  $^3\text{O}_2$  and  $\text{H}_2\text{O}$ , through a range of superoxide dismutases and hydrogen peroxide catalase enzymes or through reduction to  $\text{H}_2\text{O}$  with ascorbate or glutathione [2]. Several of these catalase enzymes utilize dinuclear manganese active sites to effect these reactions, a key feature of which is the presence of carboxylate groups, which form bridges between the manganese centres [3,4]. Furthermore, manganese plays a key role in several other important biological processes and other manganese-containing enzymes include the oxygen evolving complex of photosystem II (PS II) [5,6], manganese superoxide dismutase [3,7] and arginase [8]. In this review, the nature and role of carboxylate bridging ligands in several of these enzymes, including dinuclear manganese based catalases [9,10] and arginases, and in structural and functional mimics will be explored. The role of carboxylate bridging ligands both in maintaining the dinuclear nature and in controlling the redox and hence ligand exchange chemistry of the complexes and enzyme active sites is discussed. The systems will be compared to related dinuclear manganese complexes employed in the catalytic oxidation of organic substrates, with regard to mechanistic aspects of the catalysis.

## 2. Dinuclear manganese catalase enzymes

Although the majority of known catalase enzymes are iron-heme based enzymes, several organisms utilize dinuclear manganese-containing enzymes to disproportionate hydrogen peroxide [9,10]. Two crystal structures at atomic resolution have been obtained for enzymes isolated from *Thermus thermophilus* (TTC) [11,12] and *Lactobacillus plantarum* [13]. The enzymes originating from both species consist of six identical subunits, each containing a manganese dimer in the active site. In *T. thermophilus* [12] two conformations (forms I and II) of the enzyme can be distinguished. The manganese ions are bridged by a  $\mu$ -carboxylate ligand (Glu70) and  $\mu$ -oxygen bridges (either aqua, hydroxo or oxo ligands). The Mn ions are each coordinated to one His residue and one Glu residue. For Mn(2) the Glu is bound via one oxygen, resulting in penta-coordination, while Mn(1) is coordinated to a (labile) terminal molecule of water also, rendering the Mn ion hexa-coordinated. The crystal structure for the dinuclear manganese catalase enzyme from *L. plantarum* [13] reveals a similar 1st coordination sphere (Fig. 1). The manganese ions are bridged by a  $\mu$ -carboxylate from Glu66 and contain two more oxygen bridges, most probably one  $\mu$ -oxo and one  $\mu$ -hydroxo (in the resting,  $\text{Mn}_2^{\text{III}}$ , state). Furthermore, one of the Mn ions is bound to one His181 and a chelating Glu148 carboxylate, while the second Mn ion is bound to one His69 and a monodentate Glu35 carboxylate, with the sixth coordination site again being occupied by a (labile) water molecule.

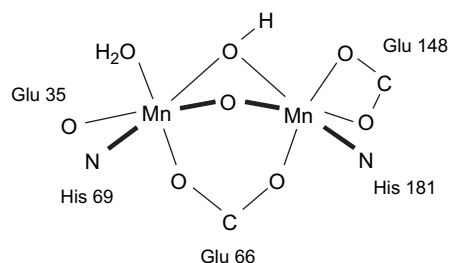


Fig. 1. The active site of *L. plantarum* catalase [13].

Four oxidation states are accessible in the dinuclear manganese catalase enzymes ( $\text{Mn}_2^{\text{II}}$ ,  $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$ ,  $\text{Mn}_2^{\text{III}}$  and  $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$ ) [14,15]. The majority of the as-isolated enzyme was in the  $\text{Mn}_2^{\text{III}}$  state, although residual  $\text{Mn}_2^{\text{II}}$  species and the inactive superoxidized  $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$  state (vide infra) were also present [16,17].

The activity of these enzymes is dependent on both the pH [10,18] and the oxidation state of the dinuclear manganese centre. During the catalytic decomposition of  $\text{H}_2\text{O}_2$  the enzyme cycles between the  $\text{Mn}_2^{\text{III}}$  and  $\text{Mn}_2^{\text{II}}$  states [14,15] and shows similar activity when starting either in the  $\text{Mn}_2^{\text{II}}$  and  $\text{Mn}_2^{\text{III}}$  redox states [15,20]. Treatment with  $\text{NH}_2\text{OH}$  [16,19,69], which serves either as one or as two-electron reductant, depending on local pH [14], in the presence of  $\text{H}_2\text{O}_2$  leads to complete conversion of the enzyme to the inactive  $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$  state (via  $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$ ). In contrast, reduction with  $\text{NH}_2\text{OH}$  in the absence of  $\text{H}_2\text{O}_2$  of either the  $\text{Mn}_2^{\text{III}}$  enzyme or the inactive  $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$  superoxidized form yields the  $\text{Mn}_2^{\text{II}}$  state, with full restoration of activity [16]. The interconversion between the different redox states is summarized in Fig. 2.

When the enzyme is in the  $\text{Mn}_2^{\text{II}}$  state it can be inhibited by the (reversible) binding of several anions (e.g.  $\text{Cl}^-$ ,  $\text{F}^-$ ,  $\text{HPO}_4^-$ ) [11,20] and consequently, when  $\text{H}_2\text{O}_2$  decomposition is performed in the presence of either  $\text{Cl}^-$  or  $\text{F}^-$  the enzyme is trapped in  $\text{Mn}_2^{\text{II}}$  state [15]. Inhibition by chloride has been confirmed by X-ray crystallography to be due to the replacement of a bridging  $\mu$ -oxygen ligand by a bridging  $\mu$ - $\text{Cl}^-$  ligand [11,12]. In contrast, azide binds to the terminal position of Mn(1) (in the  $\text{Mn}_2^{\text{III}}$  state, Fig. 1) by displacing the terminal labile water molecule from the native enzyme in a mode, which is, possibly, similar to the (initial) binding of  $\text{H}_2\text{O}_2$  [13].

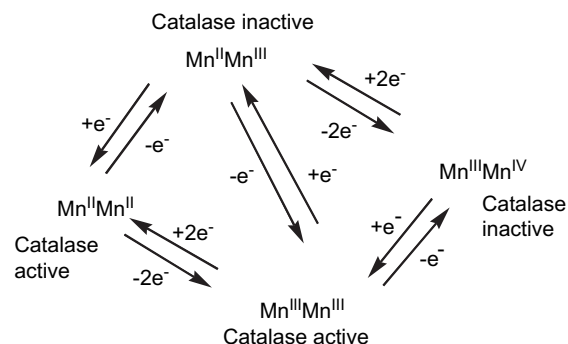


Fig. 2. Interconversion between the different redox states of the manganese catalase enzymes.  $\text{H}_2\text{O}_2$  acts both as a two-electron oxidant and reductant, whereas  $\text{NH}_2\text{OH}$  acts, predominantly, as a one-electron reductant [16,69].

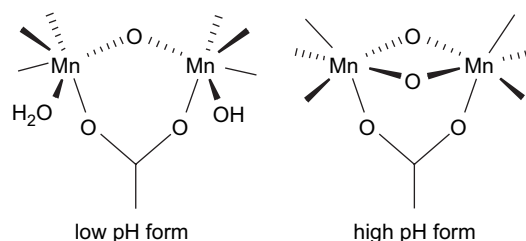


Fig. 3. Proposed pH-dependent equilibrium between open and closed  $\text{Mn}_2^{\text{III}}$  catalase enzyme active site [22].

As mentioned above, the active site of manganese catalase enzymes contains three distinct solvent molecules. From X-ray crystallographic analysis (on the native  $\text{Mn}_2^{\text{III}}$  enzyme), two solvent molecules bridge between the two Mn centres, while the third water molecule occupies a terminal position on one of the Mn ions. The lability of both the terminal water and the oxygen bridges (either being  $\mu$ -aqua,  $\mu$ -hydroxo or  $\mu$ -oxo) is central to the catalytic activity as exemplified by both  $\text{Cl}^-$  and  $\text{N}_3^-$  inhibition (vide supra). This lability is dependent on the oxidation state of the manganese centres, the Mn–Mn separation and protonation state of the oxygen bridges [10,13,21]. For the  $\text{Mn}_2^{\text{III}}$  state, it has been proposed that the solvent bridges are  $\mu$ -hydroxo (*trans*-His) and  $\mu$ -oxo (*trans*-Glu), while for the  $\text{Mn}_2^{\text{II}}$  state the solvent bridges are believed both to be singly protonated, i.e. both are  $\mu$ -hydroxo [12,13]. The protonation of the  $\mu$ -oxo bridges increases their lability and may play a role in governing the differences in the interaction of  $\text{H}_2\text{O}_2$  with the  $\text{Mn}_2^{\text{II}}$  and  $\text{Mn}_2^{\text{III}}$  states [13,14]. Based upon magnetization studies (on TTC) two different pH-dependent bridging modes  $\{(\text{Mn}_2^{\text{III}}(\mu\text{-O})(\text{OH}_2)(\text{OH}))$  (open) and  $\text{Mn}_2^{\text{III}}(\mu\text{-O})_2$  (closed)} for the  $\text{Mn}_2^{\text{III}}$  state have been proposed (Fig. 3) [22].

During catalytic turnover the dinuclear manganese catalase enzymes cycle between  $\text{Mn}_2^{\text{III}}$  and  $\text{Mn}_2^{\text{II}}$  and one molecule of  $\text{H}_2\text{O}_2$  is oxidized to  $\text{O}_2$ , while another molecule is being reduced to  $\text{H}_2\text{O}$  (Fig. 4) [10,11,14]. For the oxidative and reductive half-reactions several different coordination modes for  $\text{H}_2\text{O}_2$  have been proposed. During the oxidative half-reaction  $\text{H}_2\text{O}_2$  replaces the terminal  $\text{H}_2\text{O}$  ligand on one of the Mn centres in the  $\text{Mn}_2^{\text{III}}$  complex, and protonates the  $\mu$ -oxo bridge.<sup>1</sup> Subsequent reduction of the Mn-dimer results in the formation and release of  $\text{O}_2$ . The second equivalent of  $\text{H}_2\text{O}_2$  binds to the  $\text{Mn}_2^{\text{II}}$  as a bridging  $\mu_{1,1}$ -hydroperoxo (either

<sup>1</sup> Before the crystal structures of the (native,  $\text{Cl}^-$  and  $\text{N}_3^-$ ) inhibited enzymes were known, a similar catalytic mechanism was proposed, however, here initial  $\mu$ -oxygen bridge opening is required to gain labile water ligand, e.g. Ref. [9].

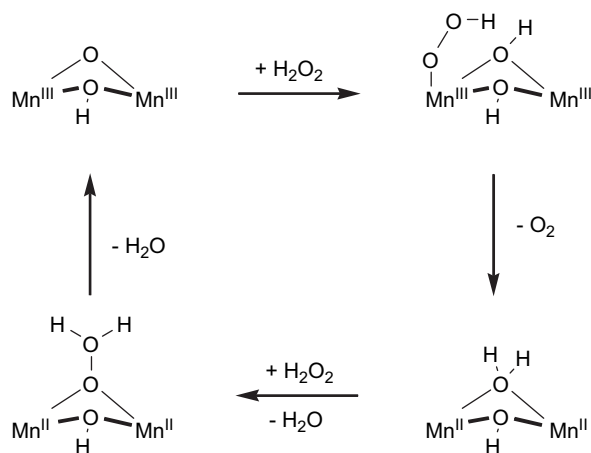


Fig. 4. Catalytic cycle for a dinuclear manganese catalase enzyme showing two different coordination modes for H<sub>2</sub>O<sub>2</sub> during the oxidative and reductive steps [14].

associatively via initial terminal coordination weakening the bridging water, or dissociatively via initial loss of labile H<sub>2</sub>O). The  $\mu_{1,1}$ -bridging mode polarizes the O–O bond and may even be polarized further by *gem*-protonation of hydrogen peroxide, thus facilitating heterolytic O–O bond cleavage, closing the catalytic cycle by reoxidation to Mn<sup>III</sup><sub>2</sub> with loss of water.

It is worth noting that, in addition to the manganese catalase enzymes, several other manganese-containing enzymes have been tested for catalase activity and, although their biological role is different from that of catalases, they are nevertheless active [26]. An example is arginase, whose physiological role is to cleave L-arginine to L-ornithine hydrolytically and thus plays an important role in mammalian nitrogen metabolism [3,23]. The active site consists of a Mn<sup>II</sup><sub>2</sub> dimer (which does not undergo redox change during the hydrolytic catalysis), bridged by two aspartates and one  $\mu$ -H<sub>2</sub>O (Fig. 5). It has been

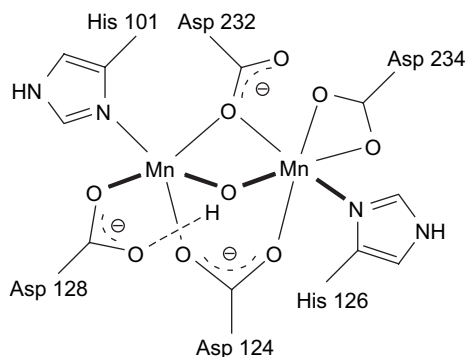


Fig. 5. Active site of arginase enzyme containing a Mn<sup>II</sup><sub>2</sub> dimer [25,26].

proposed recently that upon binding of arginine to one of the Mn centres, the  $\mu$ -H<sub>2</sub>O bridge is opened. Deprotonation of the H<sub>2</sub>O ligand provides a nucleophilic hydroxide, which then attacks the substrate [24].

The catalase activity ( $k_{\text{cat}}/K_M$ ) of arginase is five orders of magnitude lower than the catalase enzymes, however, its ability to exhibit catalase activity demonstrates the importance of the dinuclear manganese core [26]. The reason for the lower catalase activity of arginase may be due either to the lack of a suitable proton donor/acceptor near the active site (e.g. Lys162 in TTC), which facilitates proton-transfer or the difference in the third bridging ligand (for arginase a  $\mu_{1,1}$ -carboxylate bridge and for manganese catalases a  $\mu$ -oxo bridge) in stabilizing the Mn<sup>II</sup><sub>2</sub> redox state or both.

Overall it is apparent that the dinuclear  $\mu$ -carboxylate bridge structural motif is key to the activity of these enzymes in addition to the availability of labile coordination site(s). Importantly, the catalytic activity of these enzymes does not involve loss or partial dissociation of the carboxylate bridge, although in other dinuclear manganese or iron enzymes a carboxylate shift has been found to play an important role in enzyme function (e.g. MMO) [27,28].

### 3. Structural, functional and spectroscopic models for catalase enzymes

Modeling the active site of dinuclear manganese catalase enzymes both in terms of structure and function has, over the last two decades, focused on the use of multidentate ligand systems, most notably in the systems described by the groups of Dismukes [29,30], Wieghardt [31,32], Pecoraro [33], Sakiyama [34–37] and others [38]. In the present review we will focus on the functional and structural models for the catalase enzymes, which present similar dinuclear carboxylate-bridged cores<sup>2</sup> [39]. The majority of systems reported are based on a relatively few, albeit structurally diverse, set of non-bridging ligands, in particular phenols [34,37,40], polypyridyl ligands [41–43], tris(pyrazoyl)-borates [44] and tris(imidazolyl)-phosphines [45]. Overall, four remarkable aspects regarding the diversity in the ligand systems employed in modeling catalase enzymes are (i) that structurally very similar complexes can exhibit remarkably different behaviours with respect to both catalase activity and in oxidation catalysis, (ii) that the

<sup>2</sup> The phenol based systems of Sakiyama et al., despite containing carboxylate bridges, will not be discussed in detail, since their catalase activity is proposed to go via a Mn<sup>III</sup><sub>2</sub>/Mn<sup>IV</sup><sub>2</sub> cycle and thus do not resemble the natural enzymes (see Refs. [34–37]).

lability of ligands, in particular water, is central to activity and decreases with increasing oxidation state of the manganese ions, (iii) that whereas in enzymatic systems the carboxylate bridging ligand is generally accepted to be stable and oxo, aquo and aqua ligands to be labile with respect to dissociation during catalysis, in biomimetic studies (vide infra) the reverse is frequently perceived to be the case, and (iv) while  $\mu$ -oxygen bridges generally facilitate communication between two Mn centres, carboxylate bridges both increase the Mn–Mn separation and electronically shield the Mn centres, thus promoting two-electron processes instead of two subsequent one-electron processes to occur<sup>3</sup> (e.g.  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  instead of  $\text{Mn}_2^{\text{II}}/\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}/\text{Mn}_2^{\text{III}}$ ).

### 3.1. TACN-based structural models

A structurally and electronically diverse series of mono-, di-, tri- and tetranuclear manganese complexes can be obtained with both the tacn (1,4,7-triazacyclononane) and tmtacn (*N,N',N''*-trimethyl-1,4,7-triazacyclononane) family of ligands (Fig. 6) [46–52]. For the dinuclear complexes a series of redox states ( $\text{Mn}_2^{\text{II}}$  to  $\text{Mn}_2^{\text{IV}}$ ) are accessible containing  $\mu$ -carboxylate bridges and/or  $\mu$ -oxygen bridges. The solid-state (i.e. X-ray crystallography) and solution chemistry of these different dinuclear manganese (carboxylate) complexes have been examined in detail and demonstrate the propensity for dinuclear manganese systems to undergo rearrangement of their bridging ligands in response to changes in redox state [53–58]. Indeed, the lower oxidation states of the complexes described favour carboxylate and aquo bridging ligands whereas the higher oxidation states favour  $\mu$ -oxo bridging ligands.

Bis-carboxylate  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2\text{L}_2]^{2+}$  complexes (with  $\text{L} = \text{tacn}$  or  $\text{tmtacn}$ ) exhibit dynamic solution chemistry [31]. For example,  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})_2]^{2+}$  can exhibit the  $\text{Mn}_2^{\text{IV}}/\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}/\text{Mn}_2^{\text{II}}/\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$  redox couples in (anhydrous) acetonitrile, retaining the mono- $\mu$ -oxo/di- $\mu$ -carboxylate core. The same holds for  $[\text{Mn}_2^{\text{II}}(\mu\text{-OH})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})_2]^+$ , which can be oxidized by two separate, reversible one-electron processes:  $\text{Mn}_2^{\text{III}}/\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}/\text{Mn}_2^{\text{II}}$ . On the other

hand, in aqueous solutions disproportionation reactions can occur resulting in the formation of for example  $[\text{Mn}_4^{\text{IV}}(\mu\text{-O})_6(\text{tacn})_4]^{4+}$  and  $[\text{Mn}_2^{\text{IV}}(\mu\text{-O})_3(\text{tmtacn})_2]^{2+}$  [46,31].

The latter complex  $[\text{Mn}_2^{\text{IV}}(\mu\text{-O})_3(\text{tmtacn})_2]^{2+}$ , although kinetically stable towards ligand exchange, can undergo electrochemically induced ligand exchange reactions of the  $\mu$ -oxo bridges in carboxylate containing buffer systems, forming carboxylate-bridged  $[\text{Mn}_2^{\text{III}}(\text{O})(\mu\text{-RCO}_2)_2(\text{tmtacn})_2]$  complexes [59]. Mixing equimolar amounts of  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})_2]^{2+}$  and  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tacn})_2]^{2+}$  results in slow formation of mixed ligand species  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})(\text{tacn})]^{2+}$  [60] as shown by <sup>1</sup>H NMR spectroscopy [61]. The lability of both the  $\mu$ -oxo and  $\mu$ -acetate bridges is demonstrated further by the formation of mononuclear complexes of the type  $[\text{Mn}^{\text{III}}(\text{X})_3(\text{tmtacn})]$  ( $\text{X} = \text{N}_3^-$ ,  $\text{Cl}^-$  or  $\text{NCS}^-$ ) when  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\text{CH}_3\text{CO}_2)(\text{tmtacn})_2]^{2+}$  is reacted with the corresponding anion in ethanol [31,62].

$[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tacn})_2]^{2+}$ , under aerobic conditions in acidified aqueous media, forms the mixed-valent  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)(\text{tacn})_2]^{2+}$  complex (in which one of the acetates is replaced by  $\mu$ -oxo bridge). By contrast  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})_2]^{2+}$  retains both acetate bridges to form  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2(\text{tmtacn})_2]^{3+}$  in (anaerobic) acidic aqueous solution [31,63]. Subsequent replacement of the  $\mu$ -acetate in  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)(\text{tacn})_2]^{2+}$  by either two chloride or fluoride ligands yields  $[\text{Mn}_2^{\text{IV}}(\mu\text{-O})_2(\text{tacn})_2(\text{X})_2]^{2+}$  ( $\text{X} = \text{F}^-$ ,  $\text{Cl}^-$ ) with a terminal bound halide anion on each Mn centre upon (aerobic) reaction in water with either  $\text{NaBF}_4$  or conc.  $\text{HCl}$ , respectively [63].

Surprisingly, despite their structural diversity the catalase activity of this family of complexes has received relatively little attention, in part due to its remarkable catalytic activity with respect to oxidation of organic compounds with hydrogen peroxide (vide infra). Indeed, considerable effort has been expended on suppressing catalase activity.<sup>4</sup> Nevertheless a Mn-tmtacn dinuclear complex has been reported, the first to contain a  $\mu$ -peroxo bridge. The complex  $[\text{Mn}_2^{\text{IV}}(\text{O})_2(\mu\text{-O}_2)(\text{tmtacn})_2]$  releases  $\text{O}_2$  at room temperature, yielding, initially, a  $\text{Mn}_2^{\text{III}}$  complex which undergoes rapid disproportionation to the  $\text{Mn}^{\text{II}}$  and  $\text{Mn}_2^{\text{IV}}$  states [64]. The observation of this bridging mode is of particular relevance to the oxidation of  $\text{H}_2\text{O}_2$  during catalase activity.

Mixed ligand complexes based upon Mn-tmtacn were also prepared: both  $[(\text{tmtacn})\text{Mn}^{\text{IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)]$

<sup>3</sup> The latter is important, at least for the natural enzyme, since formation of the  $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$  state in the presence of  $\text{H}_2\text{O}_2$  eventually yields the kinetically inert superoxidized  $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$ . In other words, suppression of the formation of the mixed-valent  $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$  state is essential for proper functioning of the enzymes. Hence, in addition to acting as a bridging ligand, the carboxylate bridge seems to play a key role in the enzyme by inhibiting one-electron processes and ensuring two-electron processes taking place under physiological conditions (see for example Ref. [9]).

<sup>4</sup> See for example Refs. [85,86].

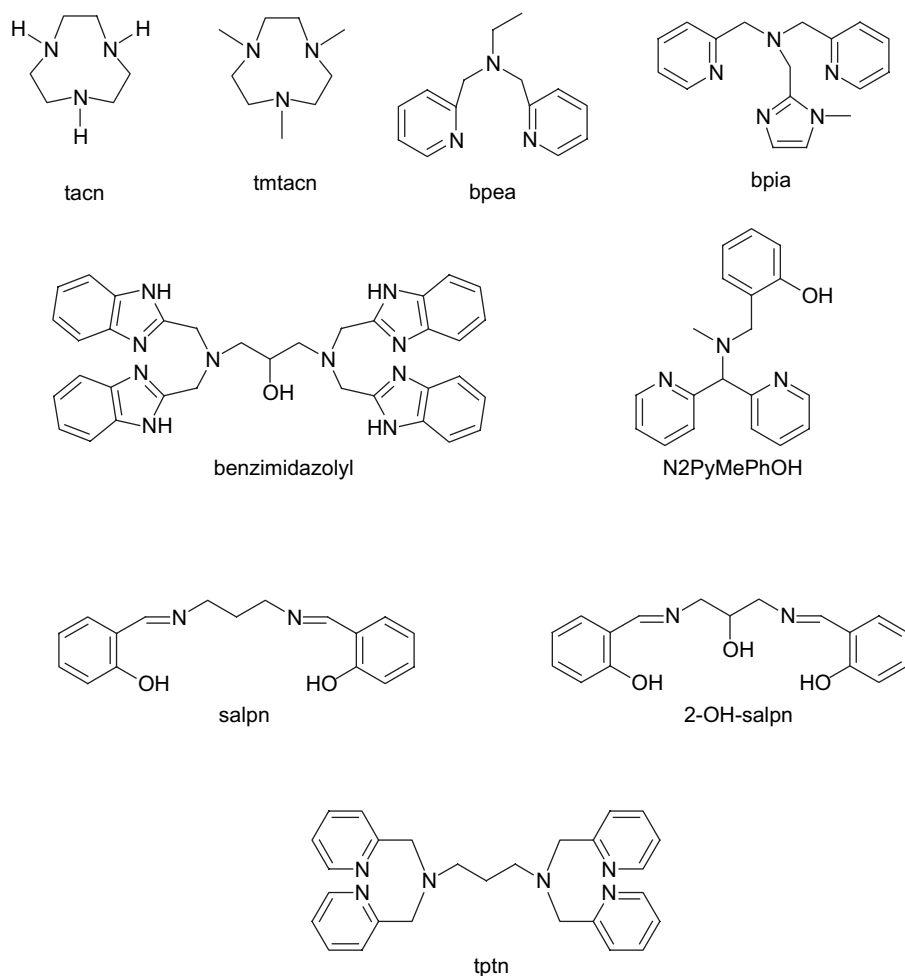


Fig. 6. Ligands discussed in the text.

$\text{Mn}^{\text{III}}(\text{CH}_3\text{CO}_2)_2]$  and  $[(\text{tmtacn})\text{Mn}^{\text{IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)\text{Mn}^{\text{III}}(\text{bipy})(\text{MeOH})]^{2+}$  [32]. Both complexes showed catalase activity in aqueous acetate buffer and the activity was approximately five orders of magnitude lower than the natural enzymes.

### 3.2. Bpea-based catalase mimics

As for the tacn and tmtacn family of ligands, the bpea (*N,N'*-bis(2-pyridylmethyl)-ethylamine, Fig. 6) ligand allows the preparation of a diverse range of dinuclear manganese complexes in several oxidation states and bridging modes, including  $\text{Mn}_2^{\text{II}}(\mu\text{-CH}_3\text{CO}_2)_3$ ,  $\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)_2$ ,  $\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)$  and  $\text{Mn}_2^{\text{IV}}(\mu\text{-O})_2(\mu\text{-CH}_3\text{CO}_2)$  cores which show electrochemically induced interconversion [65]. As for the catalase enzymes, the catalytic cycle for the catalase activity exhibited by these types of complexes is proposed to involve a  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  couple as depicted in Fig. 7,

with ‘opening’ of the  $\mu\text{-oxo}$  bridge of the  $\text{Mn}_2^{\text{III}}$  complex being central to allow ligand exchange with  $\text{H}_2\text{O}_2$ . For  $[(\text{bpea})_2\text{Mn}_2^{\text{II}}(\mu\text{-CH}_3\text{CO}_2)_3]^+$  catalase activity was found to decrease with increasing acetate concentration (the measured  $\text{O}_2$  evolution rate decreases from 1.8 to 0.9 to 0.5 ml/min in the presence of 0, 1 and 5 equiv. of NaOAc with respect to complex, respectively), assigned to the stabilization of the tris-acetate bridged complex in which the labile sites are ‘blocked’ to  $\text{H}_2\text{O}_2$  coordination. However, it should be noted also that the addition of acetate leads to a change in pH, which favours the formation of the  $\mu\text{-oxo}$  bridged  $\text{Mn}_2^{\text{III}}$  complex, and thereby may prevent ligand exchange with  $\text{H}_2\text{O}_2$ .

### 3.3. Bpia-based catalase mimics

A series of (mono- and dinuclear) manganese complexes based on the ligand bpia (bis(picolyl)(*N*-methylimidazol-2-yl)amine, Fig. 6) with various oxidation

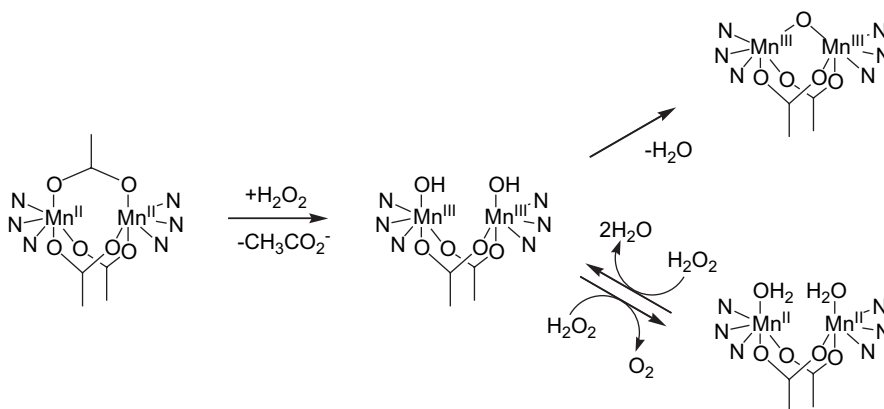


Fig. 7. Catalase activity by  $[(\text{bpea})_2\text{Mn}_2^{\text{II}}(\text{CH}_3\text{CO}_2)_3]^{2+}$  [65].

states and bridging modes have been reported by Krebs and Pecoraro [66], e.g.  $[\text{Mn}_2^{\text{II}}(\mu\text{-CH}_3\text{CO}_2)_2(\text{bpia})_2]^{2+}$ ,  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)(\text{bpia})_2]^{3+}$ ,  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\text{bpia})_2]^{3+}$  and  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\text{bpia})(\text{Cl})_2]^{2+}$ . Although  $\text{H}_2\text{O}_2$  is an efficient reductant of the chloride complex, containing a single  $\mu$ -oxo bridge and a terminal chloride on each Mn centre, it is incapable of reoxidising the reduced complex, and hence this complex does not exhibit catalase activity. By contrast,  $[\text{Mn}_2^{\text{II}}(\mu\text{-CH}_3\text{CO}_2)_2(\text{bpia})_2]^{2+}$  is a very efficient manganese catalase model with a  $k_{\text{cat}}/K_{\text{M}}$  of only two to three orders of magnitude lower than that of the manganese catalase enzymes. Similarly,  $[\text{Mn}_2^{\text{III}}(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)(\text{bpia})_2]^{3+}$  showed catalase activity and was converted to the  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\text{bpia})_2]^{3+}$  complex in the presence of  $\text{H}_2\text{O}_2$ .<sup>5</sup>

### 3.4. Benzimidazolyl-based catalase mimics

In a series of reports, Dismukes and coworkers described the redox chemistry and catalase activity of a series of binuclear manganese complexes based on chelating heptadentate, benzimidazolyl based ligand (L) (*N,N',N'',N'''*-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol, Fig. 6) [67]. The complexes isolated initially were  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-Cl})(\text{Cl})_2]$  and  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-OH})(\text{Br})_2]$ , containing a  $\mu$ -chloride bridge and a  $\mu$ -hydroxo bridge, respectively, in addition to a  $\mu$ -alkoxy bridge from the ligand. The complexes were isolated in the  $\text{Mn}_2^{\text{II}}$  oxidation state, however, during  $\text{H}_2\text{O}_2$  decomposition (typically up to 200 t.o.n.) the predominant oxidation state was found to be  $\text{Mn}_2^{\text{III}}(\mu\text{-O})$ , determined by UV–vis and IR spectroscopy, suggesting

<sup>5</sup> Although  $[\text{Mn}_2^{\text{III,IV}}(\mu\text{-O})_2(\text{bpia})_2]$  is a structural model for the inactive  $\text{Mn}_2^{\text{III,IV}}$  state of the catalase enzyme, it does show catalase activity.

that a  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  cycle was in operation, i.e. similar to that observed for the manganese catalase enzymes.

Three separate redox processes were observed for  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-OH})(\text{Br})_2]$  complex (i.e.  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{III}}\text{Mn}_2^{\text{IV}}$ ), while for the  $\mu\text{-Cl}$  bridged complex a one electron, followed by a two-electron oxidation was observed ( $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{III}}\text{Mn}_2^{\text{IV}}$ ) [67]. However, upon replacement of the halide by an acetate ligand, i.e.  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]^{2+}$  (Fig. 8), the first oxidation becomes a two-electron process followed by an one electron oxidation, i.e.  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  and  $\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{III}}\text{Mn}_2^{\text{IV}}$  [68]. The effect of the acetate bridge in the series of complexes based upon L is intriguing. While for both the related  $\mu\text{-Cl}$  and the  $\mu\text{-OH}$  complexes a  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  couple is observed (vide supra;  $E_{1/2} = 0.49$  and  $0.54$  V vs. SCE respectively), the  $\mu$ -acetate complex shows a two-electron  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  process at  $0.81$  V [68,69]. Thus introduction of a  $\mu$ -acetate bridge induces a two-electron process in place of two sequential one electron processes, thus circumventing the mixed-valent  $\text{Mn}_2^{\text{II}}\text{Mn}_2^{\text{III}}$  state. The behavior of the  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]$  complex with water, hydroxide and oxygen (in acetone) was studied by several techniques (electrochemistry,  $^1\text{H}$  NMR, ESR, FT-IR and MS

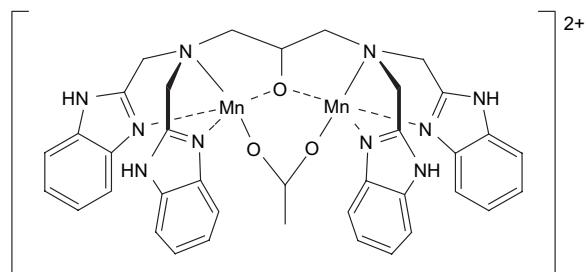


Fig. 8.  $[\text{Mn}_2^{\text{II}}(\text{CH}_3\text{CO}_2)(\text{L})]^{2+}$  complex as a functional model for catalase [68].

spectroscopies) [2]. The penta-coordinate dinuclear manganese complex  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]^{2+}$  shows a two-electron  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  process (in acetone), while addition of one equivalent of hydroxide changes this to two single electron processes ( $\text{Mn}_2^{\text{II}}/\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}/\text{Mn}_2^{\text{III}}$ ), attributed to the formation of hexa-coordinate  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$ . Addition of another equivalent of hydroxide is proposed to yield  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\text{OH})_2]$  with two terminal hydroxides, leading to the (re-)appearance of a two-electron processes ( $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}/\text{Mn}_2^{\text{IV}}$ ). Overall, the redox behavior suggests that the acetate remains bound as a bridging ligand and the changes (from  $2e^-$  to  $1e^-$  processes, and vice versa) can be rationalized by the differing coordination modes of the oxygen ligands (i.e. hydroxide), with  $\mu\text{-O}/\mu\text{-OH}$ ,  $\mu\text{-Cl}$  and  $\mu\text{-Br}$  ligands facilitating electronic communication between the manganese centres. By contrast the acetate bridges serve to reduce electronic communication and allow for two-electron redox processes to take place.

From UV–vis and EPR spectroscopies and kinetic studies the catalase activity of the acetate bridged complex was determined to involve a  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  cycle [29]. Two notable observations with respect to water and acetate content of the reaction mixture were made: i.e. the use of up to 2 v/v% of water (in MeOH) resulted in a decrease in the lag-time observed normally, while above 2 v/v% water,<sup>6</sup> a lower catalase rate was observed. Addition of (tetra-*n*-ethylammonium) acetate resulted in a decrease in the rate of  $\text{H}_2\text{O}_2$  decomposition (4-fold reduction in rate for 20 equiv. of acetate). These results were initially interpreted as shown in the following mechanistic scheme (Fig. 9) [29]. Acetate inhibition was thought to arise from coordination of a second  $\mu$ -acetate bridge to the five-coordinate manganese centres, while replacement of the single  $\mu$ -acetate bridge by two terminally bound water molecules was proposed to be responsible for the lag-time observed (while at higher water concentration binding of water competes with peroxide). Alternatively, the binding mode of the acetate might simply change from bridging to terminal monodentate.

The kinetics of the catalytic decomposition of  $\text{H}_2\text{O}_2$  by  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]^{2+}$  in MeOH and MeOH/ $\text{H}_2\text{O}$  (98:2 and 11:89) was studied by monitoring the rate of  $\text{O}_2$ -evolution in a more recent study. The species present during and after catalysis were characterized by UV–vis and  $^1\text{H}$  NMR spectroscopies and structural assignments made, primarily by comparison with species assigned in

earlier studies [30]  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]^{2+}$  is an efficient catalase mimic, reaching  $> 2000$  t.o.n. with no detectable catalyst decomposition. As for the related catalase enzyme,  $\text{H}_2\text{O}_2$  disproportionation proceeds via a  $\text{Mn}_2^{\text{II}}/\text{Mn}_2^{\text{III}}$  cycle. The lag-phase normally observed for this reaction was shown to either decrease upon pre-equilibration with water (vide supra) or was completely eliminated upon pretreatment with one equivalent of hydroxide (and the steady state rate of  $\text{H}_2\text{O}_2$  decomposition increases linearly with up to 5 equiv. of hydroxide). Addition of one equivalent of hydroxide converts  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)]^{2+}$  to  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$  (based upon electrochemistry). While the effect of water was rationalized by the formation of equal amounts of the (active)  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$  species (via deprotonation of  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-H}_2\text{O})]^{2+}$  formed initially) and (inactive) protonated complex  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-H}_2\text{O})]^{3+}$  (observed by ESR as an uncoupled  $\text{Mn}_2^{\text{II}}$  species). The catalase rate shows saturation kinetics at high  $\text{H}_2\text{O}_2$  concentrations, indicating peroxide/catalyst complex formation.

Two species appeared to be important precursors (i.e.  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$  and  $[\text{Mn}_2^{\text{III}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^{3+}$ ) to the catalytically active species [2,30]. The reactivity of  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$  is increased by either addition of hydroxide or water (the non-coordinating base 2,6-di-*t*-butylpyridine has no effect) and upon reaction with  $\text{H}_2\text{O}_2$   $[\text{Mn}_2^{\text{III}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^{3+}$  undergoes a change to a species proposed to be  $[\text{Mn}_2^{\text{III}}(\text{L})(\text{CH}_3\text{CO}_2)(\text{OH})(\mu\text{-O})]^+$ , in which the acetate bridge has changed its coordination mode to a terminal position (Fig. 10). During catalytic turnover,  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-CH}_3\text{CO}_2)(\mu\text{-OH})]^+$  is proposed to be in equilibrium with ‘open’ species  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-OH})(\text{CH}_3\text{CO}_2)(\text{H}_2\text{O})]^+$  in which the acetate has shifted to a terminal position. The terminal water undergoes ligand exchange with  $\text{H}_2\text{O}_2$  and the terminal peroxo ligand subsequently exchanges with the  $\mu\text{-OH}$  to form a  $\mu,\eta_2$ -peroxo bridge. In the next step the O–O bond of the peroxide is cleaved and the complex undergoes two-electron oxidation to  $[\text{Mn}_2^{\text{III}}(\text{L})(\text{CH}_3\text{CO}_2)(\text{OH})(\mu\text{-O})]^+$ . Binding of a second  $\text{H}_2\text{O}_2$  yields a terminally bound peroxide and subsequently  $\text{O}_2$  is released together with reduction of the complex to reform  $[\text{Mn}_2^{\text{II}}(\text{L})(\mu\text{-OH})(\text{CH}_3\text{CO}_2)(\text{H}_2\text{O})]^+$  and closing the catalytic cycle.

### 3.5. SALPN-based catalase mimics

Carboxylate shifts, although implicit in the conclusions of Dismukes and coworkers, are not suspected as to play a significant role in effecting  $\text{H}_2\text{O}_2$

<sup>6</sup> However, in the presence of 5 equiv. of hydroxide, an increase of the rate was observed with increasing water content of the reaction, see Ref. [30].



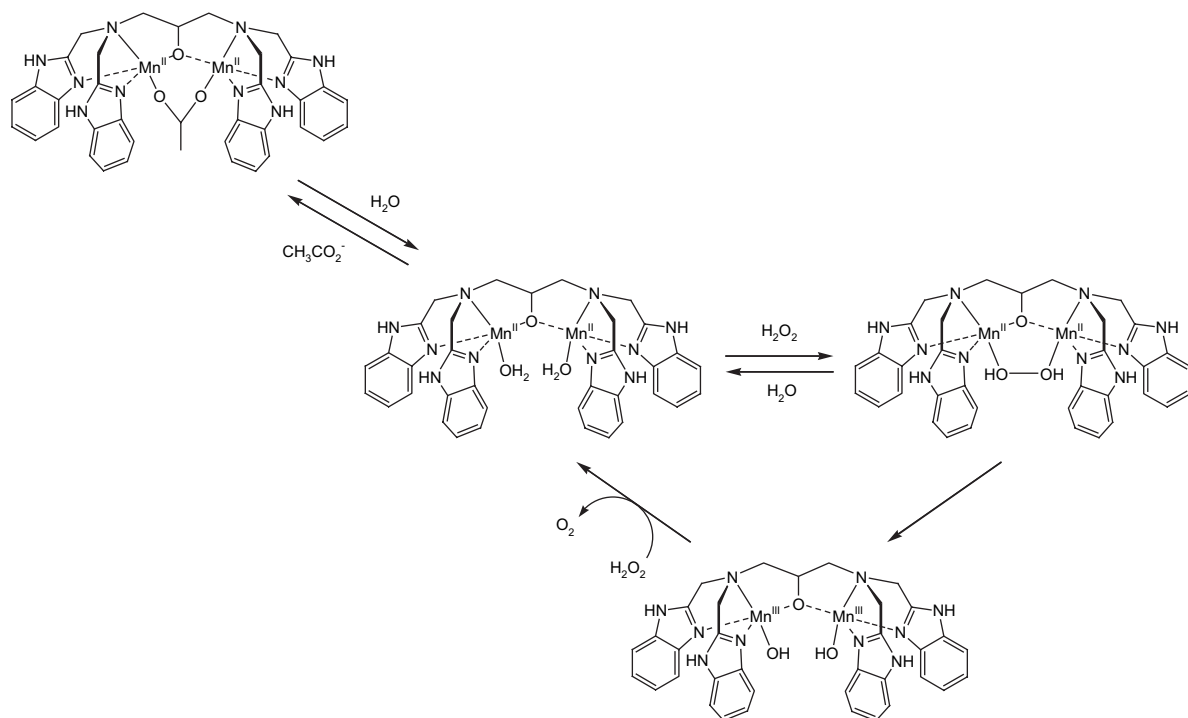


Fig. 9. Proposed mechanistic scheme [29].

disproportionation in the catalase enzymes themselves. Indeed in the SALPN (1,3-bis(salicylideneamino)propane, Fig. 6) based series of catalase mimics, carboxylate bridging ligands are not present, yet they have shown catalase type activity also. The dinuclear manganese complexes based on SALPN ligands operate as binuclear catalysts through a Mn<sup>II</sup>/Mn<sup>III</sup> redox cycle, reminiscent of the redox cycle of the catalase enzymes<sup>7</sup> [70–73]. The SALPN ligands react with manganese(III) acetate to form a large variety of complexes depending upon reaction conditions, including mono- and dinuclear complexes and polymeric chains [74,75]. Reaction of these ‘Mn<sup>III</sup>(SALPN)’ complexes with H<sub>2</sub>O<sub>2</sub> yields dinuclear [Mn<sub>2</sub><sup>IV</sup>(SALPN)(μ-O)<sub>2</sub>] complexes [76,77].

Modification of the SALPN ligand by incorporation of an alcohol functional group into the propane bridge, i.e. 2-OH-SALPN (1,3-bis(salicylideneamino)-2-propanol,

Fig. 6), allows similar dinuclear complexes to be obtained. Dinuclear [Mn<sub>2</sub><sup>III</sup>(2-OH-SALPN)<sub>2</sub>] acts as an efficient functional model for manganese catalase enzymes and the corresponding Na<sub>2</sub>[Mn<sub>2</sub><sup>II</sup>(2-OH-SALPN)<sub>2</sub>]·2MeOH has been prepared under anaerobic conditions also [78]. The catalytic cycle for H<sub>2</sub>O<sub>2</sub> decomposition is proposed to involve a Mn<sup>II</sup>/Mn<sup>III</sup> cycle and, as for the manganese catalase enzymes, the combination of H<sub>2</sub>NOH and H<sub>2</sub>O<sub>2</sub> results in the formation of a catalytically inactive Mn<sup>III</sup>Mn<sup>IV</sup> dimer. Reactivity can be restored by reaction with H<sub>2</sub>NOH in the absence of H<sub>2</sub>O<sub>2</sub>.

Kinetic studies on a series of [Mn<sub>2</sub><sup>II</sup>(2-OH-X-SALPN)<sub>2</sub>]<sup>2-</sup> (X = 5-OCH<sub>3</sub>, H, 5-Cl, 3,5-diCl, or 5-NO<sub>2</sub>) complexes with electron donating and electron withdrawing substituents showed that these systems are effective functional mimics of dinuclear manganese catalase enzymes [33,79]. The 2-OH-SALPN based dinuclear manganese complexes are bridged by two alkoxides and each of the manganese dimers is further coordinated to two oxygen and two nitrogen atoms from the 2-OH-SALPN ligands. As with catalase, the catalytic cycle involves the Mn<sup>II</sup>/Mn<sup>III</sup> couple. An inactive Mn<sup>III</sup>Mn<sup>IV</sup> is formed when oxygen is present at high concentration during H<sub>2</sub>O<sub>2</sub> decomposition, however, reactivity can be restored upon reaction with H<sub>2</sub>NOH. The catalyst can undergo at least 5000 t.o.n. Upon binding of H<sub>2</sub>O<sub>2</sub> to [Mn<sub>2</sub><sup>III</sup>(2-OH-(X)-SALPN)<sub>2</sub>], one of the

<sup>7</sup> While a mixture of [Mn<sub>2</sub><sup>IV</sup>(SALPN)<sub>2</sub>(μ-O)<sub>2</sub>] and [Mn<sub>2</sub><sup>IV</sup>(3,5-Cl<sub>2</sub>-SALPN)<sub>2</sub>(μ-O)<sub>2</sub>] does not give rise to the formation of mixed ligands, however, when a mixture of both catalysts is used to decompose H<sub>2</sub>O<sub>2</sub>, mixed ligand species [Mn<sub>2</sub><sup>IV</sup>(SALPN)(3,5-Cl<sub>2</sub>-SALPN)(μ-O)<sub>2</sub>] is formed. This, together with the observation that only <sup>18</sup>O<sub>2</sub> is formed for the decomposition of H<sub>2</sub><sup>18</sup>O<sub>2</sub> using [Mn<sub>2</sub><sup>IV</sup>(-SALPN)<sub>2</sub>(μ-<sup>16</sup>O)<sub>2</sub>], indicates that the μ-oxo bridges are quite labile and monomers might be involved in the catalytic cycle (proposed to be via a Mn<sup>IV</sup>/Mn<sup>III</sup> cycle).

alkoxide bridges changes its coordination mode from bridging to monodentate (alkoxide shift), thus facilitating terminal coordination of the peroxide to the other Mn ion (Fig. 11). Subsequent reduction of the Mn-dimer and release of O<sub>2</sub> is the rate limiting step. A second H<sub>2</sub>O<sub>2</sub> molecule oxidizes the Mn<sub>2</sub><sup>II</sup> to Mn<sub>2</sub><sup>III</sup>, closing the proposed catalytic cycle.

#### 4. From catalase to catalysis – dinuclear carboxylate-bridged manganese catalysts

Whereas during catalase activity the dinuclear manganese complexes act as both an alternating 2e<sup>-</sup> reductant and oxidant of H<sub>2</sub>O<sub>2</sub>, for these manganese complexes to act as oxidation catalysts it is required that the oxidized state of the catalyst oxidizes the organic substrate instead of oxidizing H<sub>2</sub>O<sub>2</sub>. Indeed carboxylate-bridged dinuclear complexes based on a range of multi-dentate pyridyl, phenolate and amine based ligands, most notably those based on tmtacn [80–90], and tptn (*N,N',N'',N'''*-tetrakis(2-pyridylmethyl)-1,3-propanediamine, Fig. 6) [91–94], have proven to be effective oxidation catalysts over the last several decades (Fig. 12) [95–100].

This change in reactivity frequently involves only minor changes to the coordination environment of the

dinuclear manganese core, exemplified in two different dinuclear complexes based on the same pyridyl/phenolate ligand (Fig. 13) [101,102]. Both complexes share similar coordination chemistry with a N2PyMePhOH ligand (2-[[[di(2-pyridyl)methyl](methyl)amino]methyl]phenol, Fig. 6) coordinating to each manganese centre and a bridging carboxylate ligand. However, if the phenolate ligands act as μ-O bridges between the manganese centres then the complex shows strong catalase activity whereas if the phenolates coordinate to only one of the metal centres and the manganese centres are bridged by a μ-hydroxy bridge then no catalase activity is observed, but instead the complex engages in the catalytic oxidation of organic substrates. The role of the carboxylate as a stable bridging ligand rather than a hemi-labile ligand has been demonstrated [102].

Mn–tmtacn complexes have been employed extensively as oxidation catalyst for bleaching of laundry and for oxidative transformation of a wide range of organic substrates: epoxidation, *cis*-dihydroxylation, sulfoxidation, C–H activation and alcohol oxidation [96–98]. In many of these applications carboxylic acids are present in the reaction mixture (either as additive or as anion in the Mn-salt used). Although, to date a detailed understanding of the mechanism(s) by which these Mn–tmtacn catalysts operate is not available, it is apparent from recent work that the carboxylic acid additives are important as bridging ligands in the dinuclear [Mn<sub>2</sub><sup>III</sup>(O)(RCO<sub>2</sub>)<sub>2</sub>(tmtacn)<sub>2</sub>]<sup>n+</sup> complexes [80]. Indeed in this latter example the ligating role of the carboxylate ligand serves to control both reactivity and selectivity of the catalyst. Importantly with respect to the dinuclear manganese based catalase enzymes, for the tmtacn-based complexes the quantitative formation of bis-μ-carboxylate dinuclear complexes and the efficient consumption of H<sub>2</sub>O<sub>2</sub> during catalysis suggest that the difference between catalase and oxidation catalysis activity may rest in very slight electronic differences.

#### 5. Conclusions

Perhaps the most sweeping conclusion that may be drawn from the very many examples of carboxylate-bridged dinuclear manganese complexes that have been described to date is that the perception of the carboxylate bridging ligand simply as a labile/hemi-labile ligand, which can be conveniently displaced by hydrogen peroxide during both catalase activity and oxidation catalysis, is perhaps unwise. Indeed studies of enzymatic active sites provide strong support for the counter view that bridging carboxylate ligands serve to stabilize

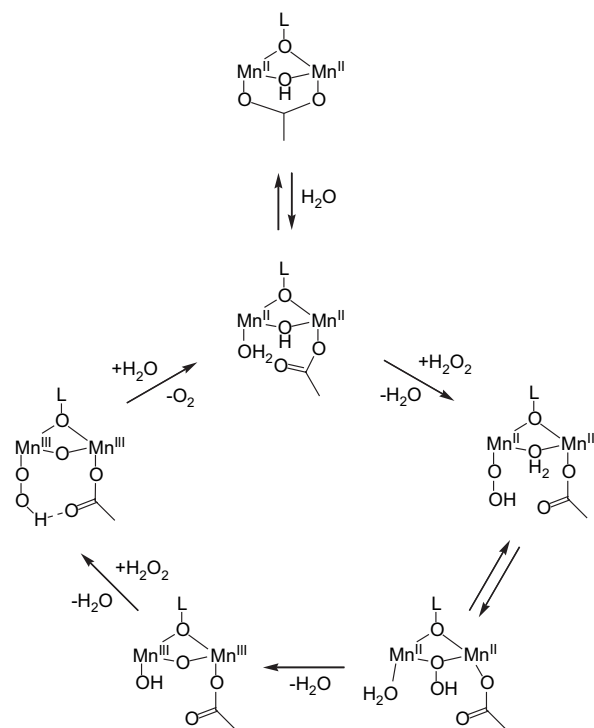


Fig. 10. Proposed catalytic cycle for catalase activity of [Mn<sub>2</sub><sup>II</sup>(L)(μ-CH<sub>3</sub>CO<sub>2</sub>)]<sup>2+</sup> [30].

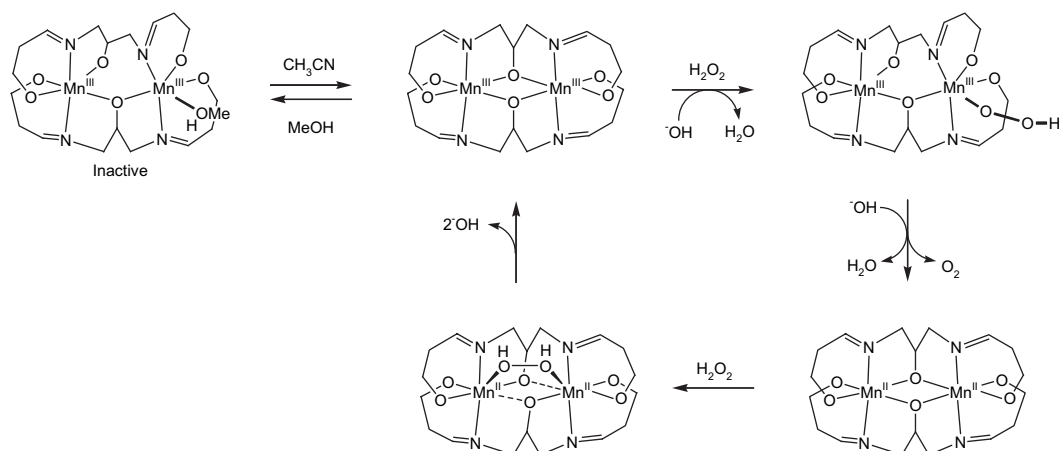


Fig. 11. Proposed catalytic cycle for H<sub>2</sub>O<sub>2</sub> decomposition by Mn–SALPN [33].

the dinuclear complexes during catalysis. In contrast to enzymatic and biomimetic catalase systems, the role of carboxylates in oxidation catalysis is at best unclear and in particular the nature of the active states in many manganese carboxylate based catalytic systems has proven somewhat elusive, in part, due to the reluctance to

recognize the close relationship between catalase activity and hydrogen peroxide activation. It is apparent then that in order to understand the catalytic activity of manganese carboxylate oxidation systems, the role of the carboxylate as a non-labile bridging unit both in the resting and active states should be considered in

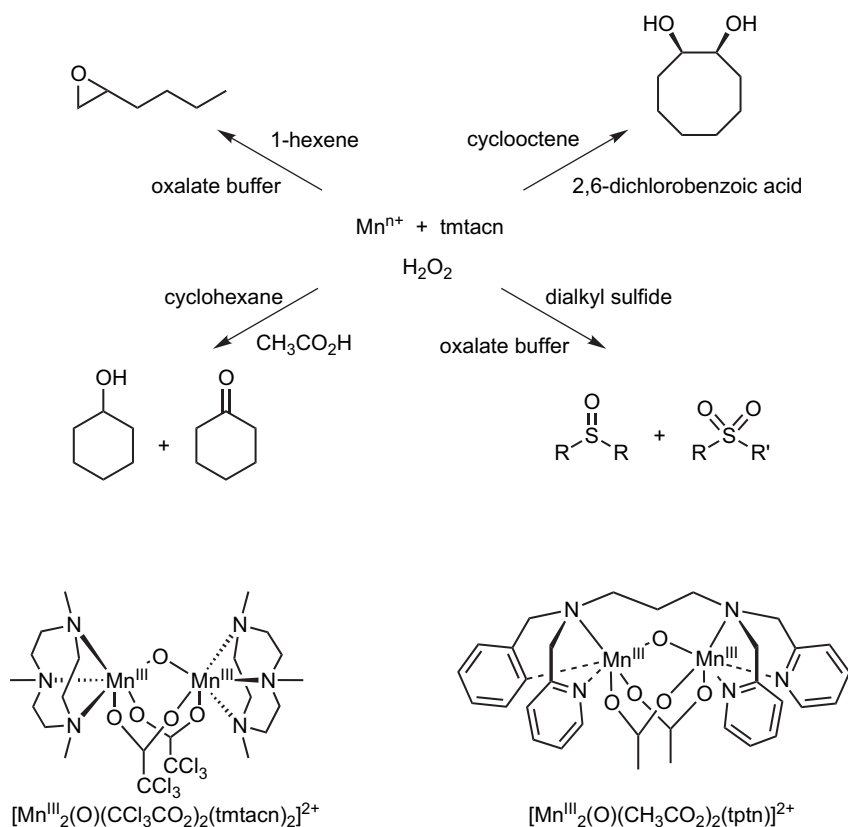


Fig. 12. Examples of catalytic oxidation reactions.

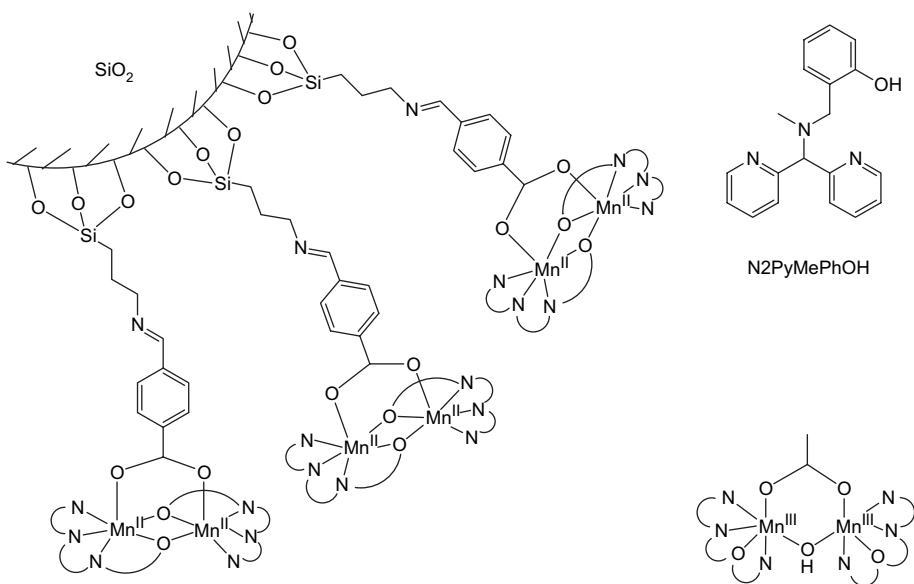


Fig. 13. Surface bound catalase active Mn-dimers (left) and dinuclear  $[\text{Mn}^{\text{III}}(\mu\text{-OH})(\text{N}2\text{PyMePhO})_2]^{2+}$  active in epoxidation of styrene (right) [101,102].

addition to the more commonly postulated mononuclear high valent manganese-oxo species.

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