

Mimicking class Ib Mn₂-ribonucleotide reductase: a Mn^{II}₂ complex and its reaction with superoxide

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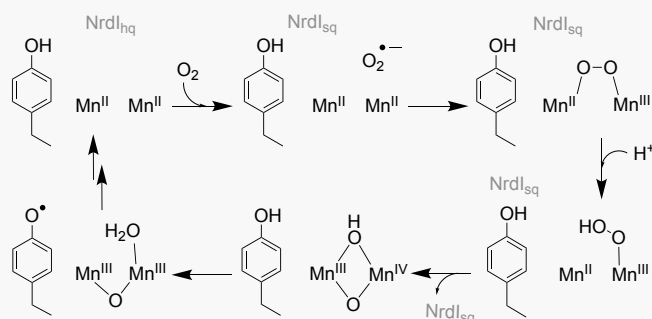
Abstract: A fascinating discovery in ribonucleotide reductase's (RNRs) Chemistry has been the identification of a dimanganese (Mn₂) active site in class Ib RNRs that requires superoxide anion (O₂^{•-}), rather than dioxygen (O₂), to access a high-valent Mn₂ oxidant. Complex **1** ([Mn₂(O₂CCH₃)(N-Et-HPTB)](ClO₄)₂, N-Et-HPTB = N,N,N',N'-tetrakis(2-(1-ethylbenzimidazolyl))-2-hydroxy-1,3-diaminopropane) was synthesised in high yield (90%). **1** was reacted with O₂^{•-} at -40 °C resulting in the formation of a metastable species (**2**). **2** displayed electronic absorption features (λ_{max} = 460, 610 nm) typical of a Mn-peroxide species, and a 29 line EPR signal typical of a Mn^{III}Mn^{IV} entity. Mn K-edge X-ray absorption near-edge spectroscopy (XANES) suggested a formal oxidation state change of Mn^{II}₂ in **1** to Mn^{III}Mn^{IV} for **2**. Electrospray ionisation mass spectrometry (ESI-MS) suggested **2** was a Mn^{III}Mn^{IV}-peroxide complex. **2** was capable of oxidizing ferrocene and weak O–H bonds upon activation with proton donors. Our findings provide support for the postulated mechanism of O₂^{•-} activation at class Ib Mn₂ RNRs.

Ribonucleotide reductases (RNRs) are essential enzymes that convert ribonucleotides to their corresponding deoxyribonucleotides, providing the precursors required for DNA synthesis and repair in all organisms.^[1] Three different RNR classes (I, II, III) have been reported, with class I further divided into sub-classes Ia, Ib, and Ic. All three classes use different metallo-cofactors.^[2] In sub-classes Ia and Ib, through O₂^{•-} activation, the metallo-cofactor is postulated to oxidize a tyrosine group, forming a tyrosyl radical which mediates the generation of a cysteine (thiyl) radical. The thiyl radical in turn initiates nucleotide reduction.

Inspired by a recent study on class Ib dimanganese (Mn₂) RNRs,^[3] we became interested in the role of superoxide anion (O₂^{•-}, Scheme 1). Stubbe and colleagues demonstrated that the Mn₂ cofactor showed no reaction with O₂.^[3d] However, in the

presence of a flavodoxin protein (NrdI_{hq}, flavodoxin hydroquinone) O₂ was reduced to O₂^{•-}. The O₂^{•-} was proposed to react with the Mn^{II}₂ core yielding a Mn^{III}Mn^{IV}-peroxide entity.^[3a] Subsequent cleavage of the O–O bond to generate a Mn^{III}(μ-OH)(μ-O)Mn^{IV} species that oxidizes tyrosine was also proposed.^[3d] EPR spectroscopy supported the formation of a Mn^{III}Mn^{IV} intermediate from the Mn^{III}Mn^{IV}-peroxide, but no insight into the initial species was obtained.^[3d]

Synthetic Mn₂ model complexes that mimic some of the intermediates in Scheme 1 have been prepared.^[4] A series of mononuclear Mn^{III}-peroxide and -hydroperoxide species have been reported.^[5] These species were generated by treating mononuclear Mn^{II} precursors with a variety of oxidants including O₂,^[5g, 5k] O₂^{•-},^[5d, 5i] and H₂O₂.^[5b, 5c, 5e, 5f, 5h–j] Model compounds that feature bis-μ-oxo-Mn^{III}Mn^{IV} cores that could serve as potential mimics of the Mn^{III}(μ-OH)(μ-O)Mn^{IV} species in RNRs have also been reported.^[6a, 6b, 4a, 6c, 5g] These high-valent complexes formed upon treatment of mononuclear Mn^{II} complexes with O₂ or H₂O₂.^[4a, 6c] Jackson and co-workers recently reported the formation of a bis(μ-oxo)Mn^{III}Mn^{IV} species using O₂^{•-} as an oxidant from mononuclear Mn^{II} precursors.^[7] Initially a mononuclear peroxomanganese(III) adduct formed which subsequently reacted with the mononuclear Mn^{II} precursor forming the bis(μ-oxo)Mn^{III}Mn^{IV} species. To the best of our knowledge, however, a Mn^{III}Mn^{IV}-peroxide complex has not been previously reported. Furthermore, no investigations into the reaction between Mn^{II}₂ complexes and O₂^{•-} have been reported. In order to probe the above mechanistic postulates, herein we explore the interaction between a synthetic Mn^{II}₂ complex and O₂^{•-}.



Scheme 1. Proposed catalytic cycle for class Ib Mn₂ RNRs in *B. subtilis* (NrdI_{hq} = Flavodoxin hydroquinone, NrdI_{sq} = Flavodoxin semiquinone).^[8, 3d]

[Mn₂(O₂CCH₃)(N-Et-HPTB)](ClO₄)₂ (**1**, N-Et-HPTB = N,N,N',N'-tetrakis(2-(1-ethylbenzimidazolyl))-2-hydroxy-1,3-diaminopropane^[9]) was synthesised using a slight modification of the procedure reported for the preparation of [Mn₂(O₂CCH₃)(HPTB)](ClO₄)₂ (**1'**, HPTB = N,N,N',N'-tetrakis(2-

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(benzimidazolyl))-2-hydroxy-1,3 diaminopropane).^[10] Elemental analysis and matrix assisted laser desorption ionisation time of flight (MALDI-TOF) mass spectrometry confirmed the elemental composition of **1**. The electron paramagnetic resonance (EPR) spectra of complexes **1** and previously reported **1'** showed very similar signals ($g = 2.0$, Figures S1-S2, supporting information). The obtained EPR signal was assigned to axially distorted Mn^{II} sites, as described by Boelrijk *et al.* for complex **1'**.^[11]

Crystals of **1** suitable for X-ray diffraction measurements were grown from acetonitrile (CH_3CN) by diethyl ether (Et_2O) vapour diffusion. **1** was found to consist of two five-coordinate Mn^{II} atoms both with a distorted trigonal-bipyramidal geometry (Figure 1). The average $\text{Mn-N}_{\text{amine}}$ and $\text{Mn-N}_{\text{benz}}$ bond lengths of **1** were shorter than those of **1'**,^[10] presumably as a result of the higher basicity of the alkylated ligand (N-Et-HPTB) in **1**. **1'** displayed a $\text{Mn}\cdots\text{Mn}$ separation of 3.5 Å versus 3.6 Å for **1**. Interestingly, the $\text{Mn}^{2+}\cdots\text{Mn}^{2+}$ distance in the X-ray crystal structure reported for class Ib Mn_2 RNRs from *E. coli* was 3.7 Å,^[3a] from *B. subtilis* 3.9 Å, while from *C. ammoniagenes* a $\text{Mn}^{3+}\cdots\text{Mn}^{3+}$ separation was 3.3 Å.^[3c] For all three structures of Mn_2 RNRs the Mn active sites displayed either at least one vacant site on the metal, or a labile ligand, presumably the location of $\text{O}_2\bullet^-$ binding. Importantly in **1**, the Mn ions were similarly not coordinatively saturated. The structural data obtained for **1** thus compares favourably with these enzymes suggesting that **1** is a good structural mimic for class Ib Mn_2 RNRs.

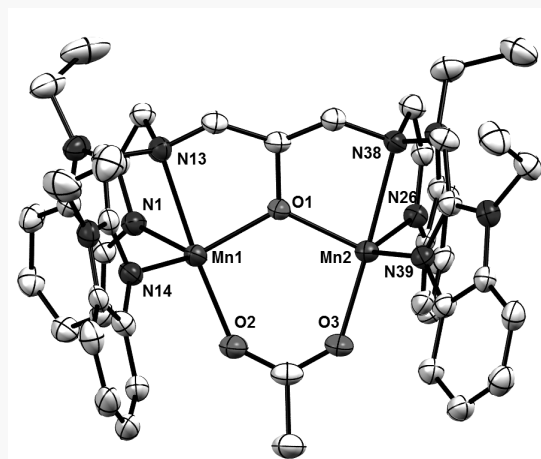
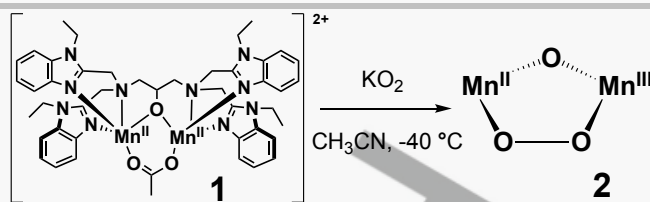


Figure 1. ORTEP plot of **1**. Hydrogen atoms and perchlorate anions have been omitted for clarity. Ellipsoids are shown at 50% probability. Selected bond distances (Å): Mn1-Mn2: 3.6; Mn1-O1: 2.05, Mn1-O2: 2.08, Mn1-N13: 2.42, Mn1-N1: 2.12, Mn1-N14: 2.13, Mn2-O1: 2.04, Mn2-O3: 2.07, Mn2-N38: 2.41, Mn2-N26: 2.13, Mn2-N39: 2.13.

To a CH_3CN solution containing complex **1** (1 mM, 2 mL) cooled to -40°C was added a N,N-dimethylformamide (DMF, 0.3 mL) solution containing 3 equiv. KO_2 (20 mM in DMF solution) and 18-crown-6 (59 mM in DMF solution) (Scheme 2). An immediate reaction occurred (complete in 35 s) resulting in the formation of a new species (**2**), as evidenced by electronic absorption spectroscopy (Figure 2). The electronic absorption spectrum of **2** displayed low-intensity features at $\lambda_{\text{max}} = 460$ and 610 nm (Figure 2), whereas **1** displayed limited absorptivity above 300 nm. At higher concentrations of **1**, lower yields of **2** were obtained (Figure S3). This is presumably as a result of intermolecular interactions preventing the formation of or accelerating the decay of **2** at higher concentrations of **1**.^[12]



Scheme 2. Reaction of **1** with $\text{O}_2\bullet^-$ forming a $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$ -peroxide complex, **2**.

We noted that the electronic absorption features for **2** were characteristic of Mn^{III} -peroxide complexes.^[13, 7] Previously reported Mn^{III} -peroxide complexes $[\text{Mn}^{\text{III}}(\text{O}_2)(\text{TMC})]^+$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), $[\text{Mn}^{\text{III}}(\text{O}_2)(13\text{-TMC})]^+$ (13-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclotridecane), and $[\text{Mn}^{\text{III}}(\text{O}_2)(\text{Tp}^{\text{iPr}})]^+$ (Tp^{iPr} = tris(3,5-diisopropylpyrazolyl)borate), all exhibited an absorption band at around 460 nm attributed to peroxide-to-metal charge transfer^[14] and a broader band in the 560–620 nm range, derived from $d-d$ transitions.^[14] In addition, Mn^{III} -peroxides supported by other polydentate amine ligands exhibited a prominent band at $\lambda_{\text{max}} = 430\text{--}445$ nm and a weaker band at $\lambda_{\text{max}} = 590\text{--}610$ nm.^[15] We therefore concluded that **2** contained a Mn-peroxide core.

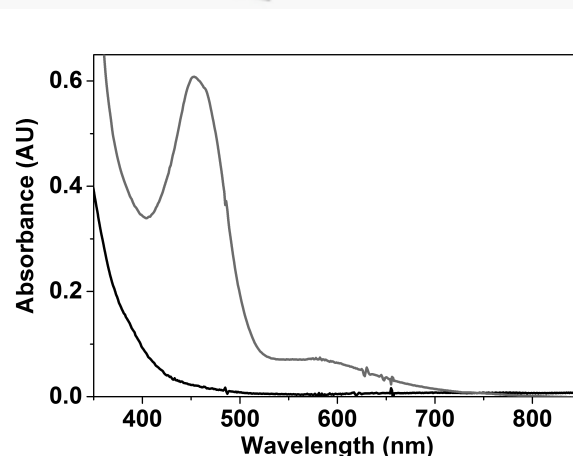


Figure 2. Electronic absorption spectra of **1** (black trace, 1 mM) and **2** (grey trace, from **1** (1 mM) + KO_2) at -40°C in CH_3CN .

Cold injection electrospray ionisation mass spectrometry (ESI-MS) experiments on a just-thawed CH_3CN solution of **2** revealed ion peaks consistent with **2** being a $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$ -peroxide complex. A mass peak ($m/z = 431.54$) consistent with the formulation of the di-cation $[\text{Mn}_2(\text{O}_2)(\text{N-Et-HPTB})]^{2+}$ (Figure 3, left) was obtained. When **2** was prepared with K^{18}O_2 , cold injection ESI-MS of the ^{18}O -labelled **2** resulted in a mass peak at $m/z = 433.48$, a mass that can be ascribed to the di-cation $[\text{Mn}_2(^{18}\text{O}_2)(\text{N-Et-HPTB})]^{2+}$ (Figure 3, right). These results led us to define **2** as a $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}$ -peroxide complex derived from $\text{O}_2\bullet^-$.

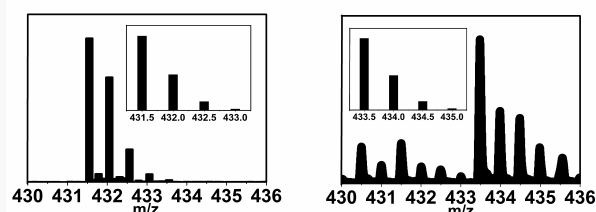


Figure 3. ESI-MS spectra of **2** prepared using KO_2 (left) and K^{18}O_2 (right). Insets: simulated mass spectra.

Raman and infra-red spectroscopy studies on **2** were attempted, but failed to provide any insight. In contrast, Kovacs and co-workers were successful in observing the $\nu_{\text{O-O}}$ and the $\nu_{\text{Mn-O}}$ of a thiolato-Mn^{III}₂-peroxide complex by resonance Raman spectroscopy,^[5k] while Nam and Solomon reported the $\nu_{\text{O-O}}$ of a Mn^{IV}-peroxo complex.^[16] These are the only two examples of a vibrational analysis of Mn-dioxygen species.^[5e, 5h, 5j]

2 displayed a 29-line EPR signal at 2 K (Figure 4), resembling those observed for several Mn^{II}Mn^{III} complexes.^[17] This group includes a recent example reported by Borovik and co-workers to have a Mn^{II}-(μ -OH)-Mn^{III} core.^[18] The signal is typical of a Mn^{II}Mn^{III} species with an effective $S = 1/2$ ground state ($g \sim 1.96$).^[17d] The observation of multiple lines derives from hyperfine interactions with the two non-equivalent Mn ions. The yield of **2**, as determined by EPR integration, was $\sim 80\%$ (see supporting information, Figure S4). The broad signal at ~ 1000 G has been seen in previously reported Mn^{II}Mn^{III} complexes and was assigned by those groups to an $S = 3/2$ spin state.^[17b, 17c, 19] The similarities in EPR data between the previously reported Mn^{II}Mn^{III} complexes and that obtained for **2** lead us to assign **2** as a Mn^{II}Mn^{III} complex.

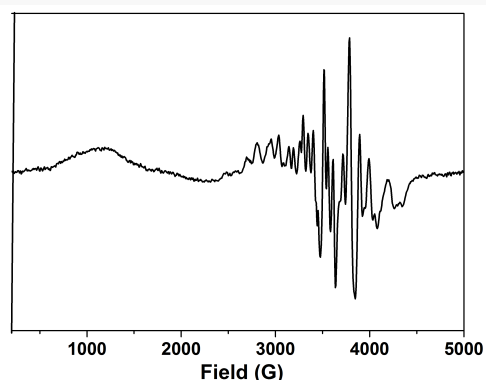


Figure 4. Perpendicular mode EPR spectrum of **2** at 2 K (obtained from the reaction of 1 mM **1** and KO₂ in CH₃CN) (9.64 GHz, 0.2 mW microwave power, 1 mM of **1**).

In order to further understand the Mn oxidation states in **2** we performed Mn K-edge X-ray absorption near-edge spectroscopy (XANES) on frozen solutions of **1** and **2**. The first inflection of the rising edge was found to be 6547.7 eV for **1** (Figure 5), consistent with assignment to the Mn^{II} state. **2** exhibited an increase in edge energy of ~ 1 eV, to 6548.7 eV, relative to **1**. Notably, the 1s-to-3d pre-edge transition was found at identical energy (6540.4 eV) for both complexes. Previous reports suggest that each integer change in Mn oxidation state was accompanied by a 2–4 eV blue-shift in Mn K-edge energy, while the pre-edge energies were largely invariant for the Mn^{II} and Mn^{III} states.^[20] Our observation of a 1-eV blue-shift in edge energy and unchanged pre-edge energy is consistent with a half-integer change in average Mn valence, and assignment of **2** as a Mn^{II}Mn^{III} complex. Extended X-ray absorption fine structure (EXAFS) measurements were not performed because we were unable to obtain **2** in sufficiently high concentration (optimal yield obtained at 1 mM of **1**) to allow accurate EXAFS analyses.

2 decayed very slowly at low temperatures (-40 °C, $t_{1/2} \sim 4$ hours) but it decayed within 4 minutes upon warming to room temperature. At -40 °C the electronic absorption spectrum of **2** was unaffected by the addition of triphenylphosphine (PPh₃), cyclohexene, or substrates containing weak C–H bonds (all added in 60-fold excess, including TEMPO-H (2,2,6,6-tetramethyl-piperidine-1-ol, C–H bond dissociation energy (BDE)

= 70.6 kcal/mol),^[21] 1-methyl-1,4-cyclohexadiene (BDE_{C–H} = 77 kcal/mol),^[22] and dihydroanthracene (BDE_{C–H} = 78 kcal/mol)^[23]). The lack of any reaction with this group of substrates demonstrated that **2** was not a capable electrophilic oxidant. Furthermore, **2** was unreactive towards aldehydes, indicating it was also a poor nucleophilic oxidant.^[5, 14, 24, 15] **2** was also not reduced by ferrocene. We thus concluded that the Mn^{II}Mn^{III}-peroxide unit in **2** was unreactive at -40 °C.

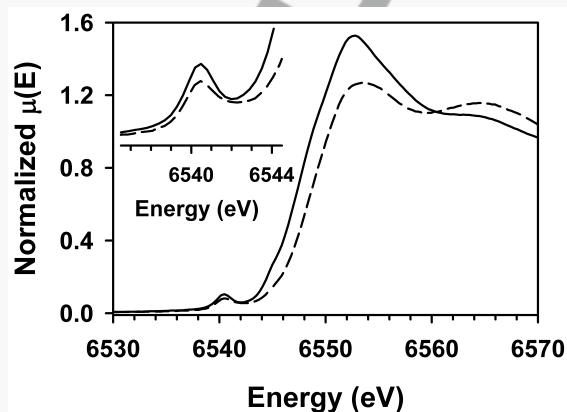


Figure 5. Normalized XANES spectra of **1** (—) and **2** (---). The inset shows an expansion of the pre-edge region.

2 reacted readily with proton donors (*para*-toluenesulfonic acid (TsOH), HBF₄) resulting in the immediate disappearance/bleaching of the electronic absorption features associated with **2** (Figure S5). The addition of HBF₄ to **2** in the presence of ferrocene likewise caused the immediate decay of the features associated with **2**, alongside the appearance of electronic absorption features attributed to the ferrocenium cation (Figure 6). The yield of ferrocenium formed was calculated to be $\sim 20\%$ with respect to the concentration of **1** in the initial reaction mixture through electronic absorption spectroscopy. Ferrocene was not oxidised under the same reaction conditions in the absence of **1** or **2**, demonstrating that H⁺-donor mediated activation of **2** yielded a capable Mn oxidant. Furthermore, ferrocene did not react with KO₂ or H₂O₂ under the same conditions. Similarly, when **2** was reacted with HBF₄ in the presence of TEMPO-H we identified TEMPO radical as a product of the reaction using EPR spectroscopy (Figures 6, S5, S6). Although TEMPO-H did not react with KO₂, it did react with H₂O₂ under the same reaction conditions, suggesting that the oxidation of TEMPO-H could be caused by either a Mn₂ oxidant or released H₂O₂. We also observed the formation of free Mn^{II} ions, as evidenced by a 6-line EPR signal, which can be ascribed to de-complexation, although the mechanism for this event is not as yet clear.

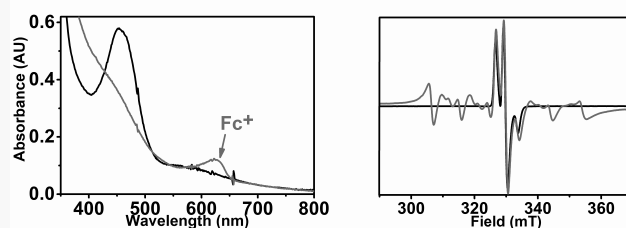


Figure 6. Electronic absorption spectra (left) showing formation of ferrocenium (Fc⁺, $\lambda_{\text{max}} = 620$ nm, grey trace) from the reaction of **2** (black trace) with H⁺ in the presence of ferrocene; normalised EPR spectrum (right) exhibiting the reference TEMPO radical (black trace) and TEMPO radical formation (grey trace) from the reaction of **2** with H⁺ in the presence of TEMPO-H.

We surmise that the H⁺-donor activated the Mn^{II}Mn^{III}-peroxide core of **2**, yielding an oxidant that was capable of electron transfer (ferrocene) and hydrogen atom transfer (TEMPO-H). This mimics the postulated role of proton donors in class Ib Mn₂ RNRs, where protonation of the metal-bound peroxide is postulated to precede formation of the tyrosine-oxidising high-valent Mn₂ oxidant.^[3d]

We have provided experimental insight into Stubbe's proposed mechanism of O₂•⁻ activation at Mn₂ RNRs. The Mn₂ complex **1** reacted with O₂•⁻, yielding a Mn^{II}Mn^{III}-peroxide complex (**2**). **2** was further shown to be activated by proton donors, yielding an unidentified species capable of electron transfer and oxidative activation of O–H bonds, presumably through hydrogen atom transfer. This provides experimental insight into the postulated biochemistry of Mn₂ RNRs, where both a proton and O₂•⁻ are postulated to be required to access a high-valent oxidant via a Mn^{II}Mn^{III}-peroxide intermediate. Work continues in our labs to probe this mechanism further and trap the putative high-valent oxidant.

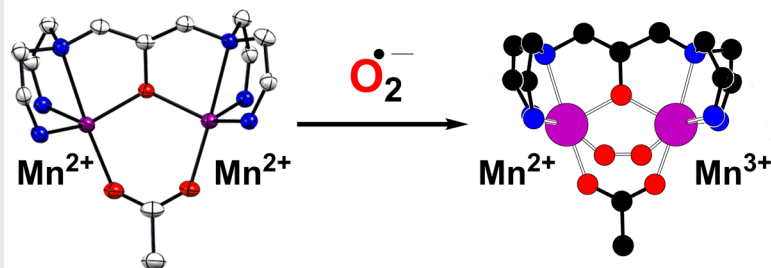
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Keywords: bioinorganic chemistry • ribonucleotide reductases • dimanganese complex • dioxygen/superoxide activation • oxidation reaction

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Entry for the Table of Contents

COMMUNICATION

Mimicking Class Ib Mn₂ RNRs

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Mimicking class Ib Mn₂
ribonucleotide reductase: a Mn^{II}₂
complex and its reaction with
superoxide

Superoxide activation: The chemistry of Class Ib Mn₂ ribonucleotide reductases was mimicked by probing the reaction between a synthetic Mn^{II}₂ complex and superoxide. The reaction yielded a Mn^{II}Mn^{III}-peroxide species. Proton donors activated the Mn^{II}Mn^{III}-peroxide core facilitating electron transfer and hydrogen atom transfer reactivity. These observations provide experimental support for the postulated mechanism in Class Ib Mn₂-ribonucleotide reductases.