Mimicking class Ib Mn_2-ribonucleotide reductase: a Mn^{II}_2 complex and its reaction with superoxide

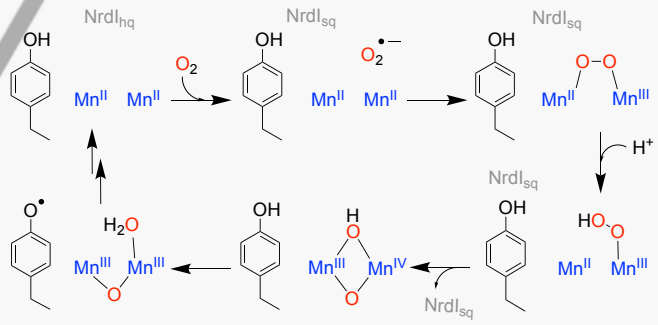
Adriana M. Magherusan,[a] Ang Zhou,[b] Erik R. Farquhar,[c] Max García-Melchor,[a] Brendan Twamley,[a] Lawrence Que, Jr.,[b] Aidan R. McDonald*[a]

Abstract: *A fascinating discovery in ribonucleotide reductase's (RNRs) Chemistry has been the identification of a dimanganese (Mn_2) active site in class Ib RNRs that requires superoxide anion (O_2•$^-$), rather than dioxygen (O_2), to access a high-valent Mn_2 oxidant. Complex **1** ($[Mn_2(O_2CCH_3)(N\text{-}Et\text{-}HPTB)](ClO_4)_2$, 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 O_2•$^-$ 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 $Mn^{II}Mn^{III}$ entity. Mn K-edge X-ray absorption near-edge spectroscopy (XANES) suggested a formal oxidation state change of Mn^{II}_2 in **1** to $Mn^{II}Mn^{III}$ for **2**. Electrospray ionisation mass spectrometry (ESI-MS) suggested **2** was a $Mn^{II}Mn^{III}$-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 O_2•$^-$ activation at class Ib Mn_2 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 class Ia and Ib, through O_2-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 (Mn_2) RNRs,[3] we became interested in the role of superoxide anion (O_2•$^-$, Scheme 1). Stubbe and colleagues demonstrated that the Mn_2 cofactor showed no reaction with O_2.[3d] However, in the presence of a flavodoxin protein ($NrdI_{hq}$, flavodoxin hydroquinone) O_2 was reduced to O_2•$^-$. The O_2•$^-$ was proposed to react with the Mn^{II}_2 core yielding a $Mn^{II}Mn^{III}$-peroxide entity.[3a] Subsequent cleavage of the O–O bond to generate a $Mn^{III}(\mu\text{-}OH)(\mu\text{-}O)Mn^{IV}$ species that oxidizes tyrosine was also proposed.[3d] EPR spectroscopy supported the formation of a $Mn^{III}Mn^{IV}$ intermediate, but no insight into the initial species was obtained.[3d]

Synthetic Mn_2 model complexes that mimic some of the intermediates in Scheme 1 have been prepared.[4] A series of mononuclear Mn^{III}-peroxide species have been reported.[5] Model compounds that feature bis-μ-oxo-$Mn^{III}Mn^{IV}$ cores that could serve as potential mimics of the $Mn^{III}(\mu\text{-}OH)(\mu\text{-}O)Mn^{IV}$ species have also been reported.[6a, 6b, 4a, 6c, 5g] Jackson and co-workers recently reported the formation of a $Mn^{III}Mn^{IV}$ species using O_2•$^-$ as an oxidant from mononuclear Mn^{II} precursors.[7] To the best of our knowledge, however, a $Mn^{II}Mn^{III}$-peroxide complex has not been previously reported. Furthermore, no investigations into the reaction between Mn^{II}_2 complexes and O_2•$^-$ have been reported. In order to probe the above mechanistic postulates, herein we explore the interaction between a synthetic Mn^{II}_2 complex and O_2•$^-$.



Scheme 1. Proposed catalytic cycle for class Ib Mn_2 RNRs in B. *subtilis* ($NrdI_{hq}$ = Flavodoxin hydroquinone , $NrdI_{sq}$ = Flavodoxin semiquinone). [8, 3d]

$[Mn_2(O_2CCH_3)(N\text{-}Et\text{-}HPTB)](ClO_4)_2$ (**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 $[Mn_2(O_2CCH_3)(HPTB)](ClO_4)_2$ (**1'**, HPTB **=** N,N,N',N'-tetrakis(2-(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, Figure S1-S2, supporting information).

[a] Adriana M. Magherusan, Max García-Melchor , Brendan Twamley, Aidan R. McDonald
School of Chemistry and CRANN/AMBER Nanoscience Institute, Trinity College Dublin, The University of Dublin, College Green, Dublin 2, Ireland
E-mail: aidan.mcdonald@tcd.ie
[b] Ang Zhou, Lawrence Que, Jr.
Department of Chemistry and Centre for Metals in Biocatalysis, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455, USA
[c] Erik R. Farquhar
Case Western Reserve University Centre for Synchrotron, Biosciences, National Synchrotron Light Source II, Brookhaven, National Laboratory, Upton, NY 11973, USA

Supporting information for this article is given via a link at the end of the document.

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 diethylether (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 Mn-N_{amine} and Mn-N_{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 Mn···Mn separation of 3.5 Å versus 3.6 Å for **1**. Interestingly, the $Mn^{2+}\cdots Mn^{2+}$ 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 $Mn^{3+}\cdots Mn^{3+}$ 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 $O_2^{\bullet-}$ 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.

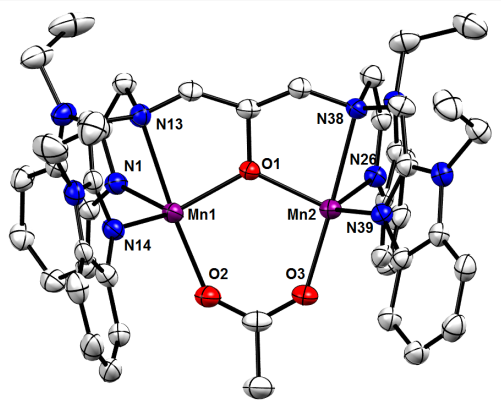
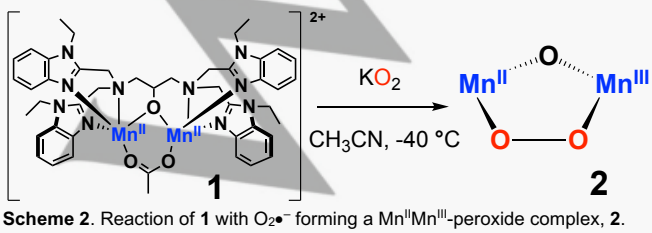


Figure 1. ORTEP plot of **1.** Hydrogen atoms and perchlorate anions have been omitted for clarity. Ellipsoids are shown at 50% probability. Selected bond distances (Å): Mn1-Mn2: 3.6; Mn1-O1: 2.05, Mn1-O2: 2.08, Mn1-N13: 2.42, Mn1-N1: 2.12, Mn1-N14: 2.13, Mn2-O1: 2.04, Mn2-O3: 2.07, Mn2-N38: 2.41, Mn2-N26: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

To a CH_3CN solution containing complex **1** (1 mM, 2 mL) cooled to -40 °C was added an N,N-dimethylformamide (DMF, 0.3 mL) solution containing KO_2 (20 mM) and 18-crown-6 (59 mM) (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 λ_{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 or accelerating the decay of **2** at higher concentrations of **1**.[12]



Scheme 2. Reaction of **1** with $O_2^{\bullet-}$ forming a $Mn^{II}Mn^{III}$-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 $[Mn^{III}(O_2)(TMC)]^+$, (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), $[Mn^{III}(O_2)(13\text{-TMC})]^+$, (13-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclotridecane) and $[Mn^{III}(O_2)(Tp^{iPr})]^+$, ($Tp^{iPr}$ = 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 λ_{max} = 430-445 nm and a weaker band at λ_{max} = 590-610 nm.[15] We therefore concluded that **2** contained a Mn-peroxide core.

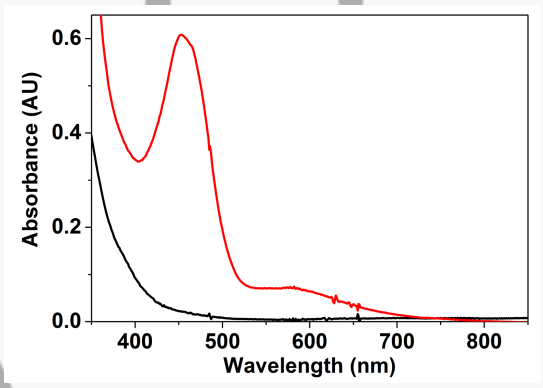


Figure 2. Electronic absorption spectra of **1** (black trace, 1 mM) and **2** (red trace, from **1** (1 mM) + KO_2) at -40 °C in CH_3CN.

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 $Mn^{II}Mn^{III}$-peroxide complex. A mass peak (*m/z* = 431.54) consistent with the formulation of the di-cation $[Mn_2(O_2)(N\text{-Et-HPTB})]^{2+}$ (Figure 3 right) 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 $[Mn_2(^{18}O_2)(N\text{-Et-HPTB})]^{2+}$ (Figure 3, left). These results led us to define **2** as a $Mn^{II}Mn^{III}$-peroxide complex derived from $O_2^{\bullet-}$.

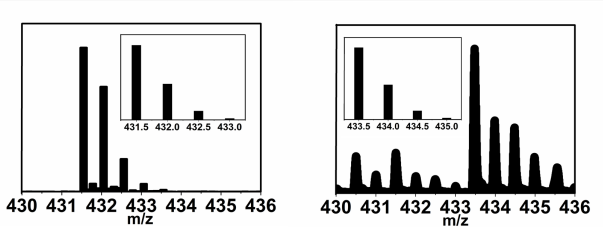


Figure 3. ESI-MS spectra of **2** prepared using KO_2 (left) and $K^{18}O_2$ (right). Insets: simulated mass spectra.

Raman and infra-red spectroscopy studies on **2** were attempted, but failed to provide any insight. Kovacs and co-workers have successfully determined the $\nu_{O\text{-}O}$ and the $\nu_{Mn\text{-}O}$ of a thiolato-Mn^{III}_2-peroxide complex by resonance Raman spectroscopy.[5k] However, this is the only successful example of a vibrational analysis of Mn-dioxygen species.[5e, h, j]

2 displayed a 29-line EPR signal at 2 K (Figure 4), resembling those observed for several $Mn^{II}Mn^{III}$ complexes.[16] This group includes a recent example reported by Borovik and co-workers to have a Mn^{II}-(μ-OH)-Mn^{III} core.[17] The signal is

typical of a $Mn^{II}Mn^{III}$ species with an effective $S = ½$ ground state ($g \sim 1.96$).[16d] 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 ~80% (see supporting information, Figure S4). The broad signal at ~1000 G has been seen in previously reported $Mn^{II}Mn^{III}$ complexes.[16b, 16c, 18] 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.

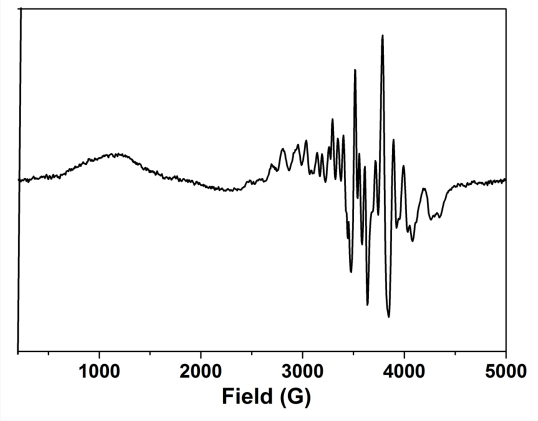


Figure 4. Perpendicular mode EPR spectrum of **2** at 2 K (9.64 GHz, 0.2 mW microwave power).

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 every 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.[19] 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.

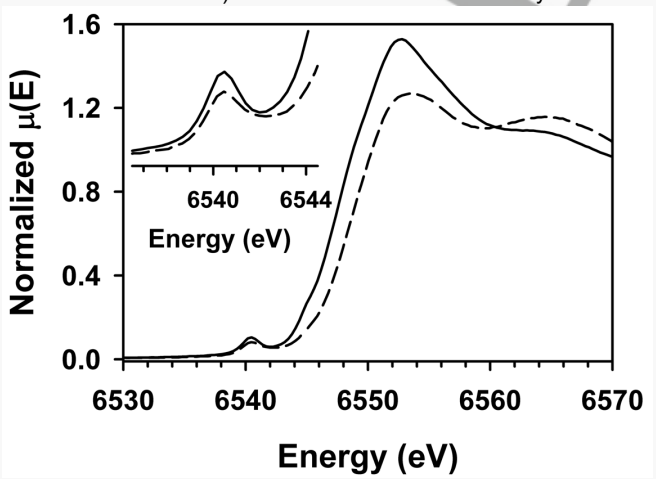


Figure 5. Normalized XANES spectra of **1** (—) and **2** (---). The inset shows an expansion of the pre-edge region.

Efforts to model the structural and electronic properties of **2** using DFT methods are ongoing in our labs, and will be communicated in a later manuscript.

2 was stable 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 (PPh_3), 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),[20] 1-methyl-1,4-cyclohexadiene ($BDE_{C–H}$ = 77 kcal/mol),[21] and dihydroanthracene ($BDE_{C–H}$ = 78 kcal/mol)[22]). 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.[5j, 14, 23, 15] **2** was also unreactive towards ferrocene. We thus concluded that the $Mn^{II}Mn^{III}$-peroxide unit in **2** was stable and unreactive at -40 °C.

2 reacted readily with proton donors (*para*-toluenesulfonic acid (TsOH), HBF_4) resulting in the immediate disappearance/bleaching of the electronic absorption features associated with **2** (Figure S5). The addition of HBF_4 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 ~ 20% with respect to the concentration of **1** in the initial reaction mixture through electronic absorption spectroscopy. Similarly, when **2** was reacted with HBF_4 in the presence of TEMPO-H we identified TEMPO radical as a product of the reaction using EPR spectroscopy (Figures 6, S5, S6). 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 of this event is as not yet clear.

We surmise that the proton 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 Mn_2 RNRs, where protonation of the metal-bound peroxide is postulated to precede formation of the tyrosine-oxidising high-valent Mn_2 oxidant.[3d]

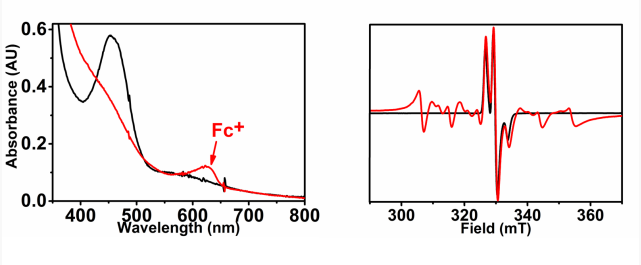


Figure 6. Electronic absorption spectra (left) showing formation of ferrocenium (Fc^+, λ_{max} = 620 nm, red trace) from the reaction of **2** (black trace) with H^+ in the presence of ferrocene; normalised EPR spectrum (right) exhibiting the reference TEMPO radical (black trace) and TEMPO radical formation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

We have provided experimental insight into Stubbe's proposed mechanism of superoxide activation at Mn_2 RNRs. The Mn_2 complex **1** reacted with $O_2^{\bullet-}$, 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 oxidative

activation of O–H bonds, presumably through hydrogen atom transfer. This provides experimental insight into the postulated biochemistry of Mn_2 RNRs, where both a proton and $O_2\bullet^-$ 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.

Acknowledgements: This publication has emanated from research supported by the Irish Research Council (IRC) under Grant Number GOIPG/2014/942 to A. Magherusan. Research in the McDonald lab is supported in part by the European Union (FP7-333948, ERC-2015-STG-678202) and a research grant from Science Foundation Ireland (SFI/12/RC/2278, SFI/15/RS-URF/3307). Support for research in the Que lab is provided by the US National Institutes of Heath (GM38767). XAS data collection at SSRL BL 9-3 was made possible by support from the National Institutes of Health (P30-EB-009998 and P41-GM-103393) and Department of Energy (Contract DE-AC02-76SF00515 to SLAC National Accelerator Laboratory from the Office of Science, Office of Basic Energy Sciences). We thank the DJEI/DES/SFI/HEA Irish Centre for High-End Computing (ICHEC) for the provision of computational facilities and support. We are grateful to Mr. Paolo Pirovano for assistance with EPR measurements.

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

[1] a) A. Willing, H. Follmann, G. Auling, *Eur. J. Biochem.* **1988**, *175*, 167-173; b) M. Bennati, F. Lendzian, M. Schmittel, H. Zipse, *Biol. Chem.* **2005**, *386*, 1007-1022.

[2] M. Kolberg, K. R. Strand, P. Graff, K. K. Andersson, *Biochim. Biophys. Acta* **2004**, *1699*, 1-34.

[3] a) A. K. Boal, J. A. Cotruvo, Jr., J. Stubbe, A. C. Rosenzweig, *Science* **2010**, *329*, 1526-1530; b) J. A. Cotruvo, Jr., J. Stubbe, *Biochemistry* **2010**, *49*, 1297-1309; c) N. Cox, H. Ogata, P. Stolle, E. Reijerse, G. Auling, W. Lubitz, *J. Am. Chem. Soc.* **2010**, *132*, 11197-11213; d) J. A. Cotruvo, Jr., T. A. Stich, R. D. Britt, J. Stubbe, *J. Am. Chem. Soc.* **2013**, *135*, 4027-4039.

[4] a) S. Mukhopadhyay, S. K. Mandal, S. Bhaduri, W. H. Armstrong, *Chem. Rev.* **2004**, *104*, 3981-4026; b) A. J. Wu, J. E. Penner-Hahn, V. L. Pecoraro, *Chem. Rev.* **2004**, *104*, 903-938.

[5] a) R. B. VanAtta, C. E. Strouse, L. K. Hanson, J. S. Valentine, *J. Am. Chem. Soc.* **1987**, *109*, 1425-1434; b) K. Fujisawa, M. Tanaka, Y. Moro-oka, N. Kitajima, *J. Am. Chem. Soc.* **1994**, *116*, 12079-12080; c)U. P. Singh, A. K. Sharma, S. Hikichi, H. Komatsuzaki, Y. Moro-oka, M. Akita, *Inorg. Chim. Acta* **2006**, *359*, 4407-4411; d) S. Groni, G. Blain, R. Guillot, C. Policar, E. Anxolabehere-Mallart, *Inorg. Chem.* **2007**, *46*, 1951-1953; e) M. S. Seo, J. Y. Kim, J. Annaraj, Y. Kim, Y. M. Lee, S. J. Kim, J. Kim, W. Nam, *Angew. Chem. Int. Ed.* **2007**, *46*, 377-380; f) S. Groni, P. Dorlet, G. Blain, S. Bourcier, R. Guillot, E. Anxolabehere-Mallart, *Inorg. Chem.* **2008**, *47*, 3166-3172; g) R. L. Shook, W. A. Gunderson, J. Greaves, J. W. Ziller, M. P. Hendrich, A. S. Borovik, *J. Am. Chem. Soc.* **2008**, *130*, 8888-8889; h) J. Annaraj, J. Cho, Y. M. Lee, S. Y. Kim, R. Latifi, S. P. de Visser, W. Nam, *Angew. Chem. Int. Ed.* **2009**, *48*, 4150-4153; i) R. A. Geiger, S. Chattopadhyay, V. W. Day, T. A. Jackson, *J. Am. Chem. Soc.* **2010**, *132*, 2821-2831; j) R. A. Geiger, S. Chattopadhyay, V. W. Day, T. A. Jackson, *Dalton Trans.* **2011**, *40*, 1707-1715; k) M. K. Coggins, X. Sun, Y. Kwak, E. I. Solomon, E. Rybak-Akimova, J. A. Kovacs, *J. Am. Chem. Soc.* **2013**, *135*, 5631-5640.

[6] a) M. J. Baldwin, V. L. Pecoraro, *J. Am. Chem. Soc.* **1996**, *118*, 11325-11326; b) K. Wang, J. M. Mayer, *J. Am. Chem. Soc.* **1997**, *119*, 1470-1471; c) C. S. Mullins, V. L. Pecoraro, *Coord. Chem. Rev.* **2008**, *252*, 416-443.

[7] D. F. Leto, S. Chattopadhyay, V. W. Day, T. A. Jackson, *Dalton Trans.* **2013**, *42*, 13014-13025.

[8] a) J. A. Cotruvo, J. Stubbe, *Annu. Rev. Biochem.* **2011**, *80*, 733-767; b) J. A. Cotruvo, Jr., J. Stubbe, *Metallomics* **2012**, *4*, 1020-1036.

[9] a) V. McKee, M. Zvagulis, J. V. Dagdigian, M. G. Patch, C. A. Reed, *J. Am. Chem. Soc.* **1984**, *106*, 4765-4772; b) L. Westerheide, F. K. Müller, R. Than, B. Krebs, J. Dietrich, S. Schindler, *Inorg. Chem.* **2001**, *40*, 1951-1961.

[10] P. J. Pessiki, S. V. Khangulov, D. M. Ho, G. C. Dismukes, *J. Am. Chem. Soc.* **1994**, *116*, 891-897.

[11] A. E. M. Boelrijk, S. V. Khangulov, G. C. Dismukes, *Inorg. Chem.* **2000**, *39*, 3009-3019.

[12] a) *It is common that such Mn_2 clusters form larger tetranuclear clusters,[12] and we postulate that at higher concentrations of **1** such larger clusters form and prevent a reaction with KO_2 to form **2***; b) M. K. Chan, W. H. Armstrong, *J. Am. Chem. Soc.* **1989**, *111*, 9121-9122; c) F. B. Larsen, A. Boisen, K. J. Berry, B. Moubaraki, K. S. Murray, V. McKee, R. C. Scarrow, C. J. McKenzie, *Eur. J. Inorg. Chem.* **2006**, *19*, 3841-3852.

[13] a) D. R. Gamelin, M. L. Kirk, T. L. Stemmler, S. Pal, W. H. Armstrong, J. E. Penner-Hahn, E. I. Solomon, *J. Am. Chem. Soc.* **1994**, *116*, 2392-2399; b) J. Cho, R. Sarangi, W. Nam, *Acc. Chem. Res.* **2012**, *45*, 1321-1330.

[14] H. Kang, J. Cho, K. B. Cho, T. Nomura, T. Ogura, W. Nam, *Chem. Eur. J.* **2013**, *19*, 14119-14125.

[15] N. Saravanan, M. Sankaralingam, M. Palaniandavar, *RSC Advances* **2014**, *4*, 12000.

[16] a) H. Diril, H. R. Chang, X. Zhang, S. K. Larsen, J. A. Potenza, C. G. Pierpont, H. J. Schugar, S. S. Isied, D. N. Hendrickson, *J. Am. Chem. Soc.* **1987**, *109*, 6207-6208; b) R. M. Buchanan, K. J. Oberhausen, J. F. Richardson, *Inorg. Chem.* **1988**, *27*, 971-973; c) H. Diril, H. R. Chang, M. J. Nilges, X. Zhang, J. A. Potenza, H. J. Schugar, S. S. Isied, D. N. Hendrickson, *J. Am. Chem. Soc.* **1989**, *111*, 5102-5114; d) N. Cox, W. Ames, B. Epel, L. V. Kulik, L. Rapatskiy, F. Neese, J. Messinger, K. Wieghardt, W. Lubitz, *Inorg. Chem.* **2011**, *50*, 8238-8251.

[17] Y. Sano, A. C. Weitz, J. W. Ziller, M. P. Hendrich, A. S. Borovik, *Inorg. Chem.* **2013**, *52*, 10229-10231.

[18] L. Dubois, D. F. Xiang, X. S. Tan, J. Pecaut, P. Jones, S. Baudron, L. Le Pape, J. M. Latour, C. Baffert, S. Chardon-Noblat, M. N. Collomb, A. Deronzier, *Inorg. Chem.* **2003**, *42*, 750-760.

[19] a) T. C. Weng, W. Y. Hsieh, E. S. Uffelman, S. W. Gordon-Wylie, T. J. Collins, V. L. Pecoraro, J. E. Penner-Hahn, *J. Am. Chem. Soc.* **2004**, *126*, 8070-8071; b) F. Farges, *Phys. Rev. B* **2005**, *71*; c) R. E. Schreiber, H. Cohen, G. Leitus, S. G. Wolf, A. Zhou, L. Que, Jr., R. Neumann, *J. Am. Chem. Soc.* **2015**, *137*, 8738-8748.

[20] J. J. Warren, T. A. Tronic, J. M. Mayer, *Chem. Rev.* **2010**, *110*, 6961-7001.

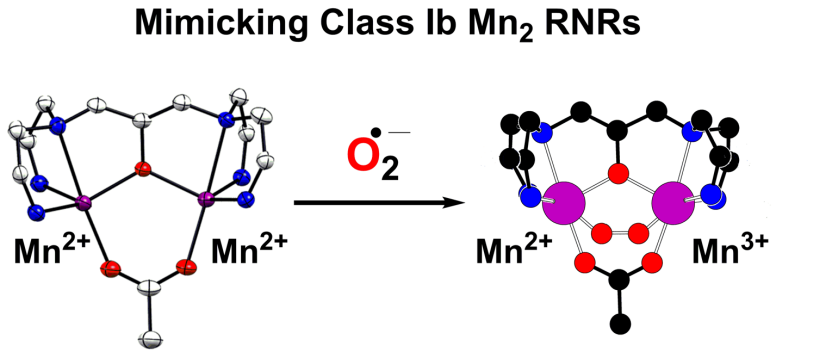
[21] T. Matsumoto, K. Ohkubo, K. Honda, A. Yazawa, H. Furutachi, S. Fujinami, S. Fukuzumi, M. Suzuki, *J. Am. Chem. Soc.* **2009**, *131*, 9258-9267.

[22] C. Arunkumar, Y. M. Lee, J. Y. Lee, S. Fukuzumi, W. Nam, *Chem. Eur. J.* **2009**, *15*, 11482-11489.

[23] P. Pirovano, A. M. Magherusan, C. McGlynn, A. Ure, A. Lynes, A. R. McDonald, *Angew. Chem. Int. Ed.* **2014**, *53*, 5946-5950.

Entry for the Table of Contents

COMMUNICATION



Adriana M. Magherusan,[a] Ang Zhou,[b] Erik R. Farquhar,[c] Max García-Melchor,[a] Brendan Twamley,[a] Lawrence Que, Jr.,[b] Aidan R. McDonald[a]*

Page No. – Page No.

Mimicking class Ib Mn_2 ribonucleotide reductase: a Mn^{II}_2 complex and its reaction with superoxide

Superoxide activation: We mimicked the chemistry of Class Ib Mn_2-ribonucleotide reductases 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 Mn_2-ribonucleotide reductases.