# High-valent manganese(v)–oxo porphyrin complexes in hydride transfer reactions†

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**Hydride transfer from dihydronicotinamide adenine dinucleotide (NADH) analogues to *trans*-dioxomanganese(v) porphyrin complexes proceeds *via* proton-coupled electron transfer, followed by rapid electron transfer.**

High-valent metal–oxo complexes are involved in a variety of oxygenation reactions by metalloenzymes, such as cytochromes P450 (CYP 450).[1] Although high-valent iron–oxo species have never been identified in CYP 450,[2] a number of high-valent iron(IV)–oxo porphyrin complexes have been synthesized, characterized with various spectroscopic techniques, and extensively investigated in the oxygenation of various organic substrates, such as alkane hydroxylation and olefin epoxidation.[3] Thus, reactivities of iron(IV)–oxo complexes are well understood in biomimetic reactions.

High-valent manganese(v)–oxo porphyrin complexes have also been implicated as reactive intermediates in the catalytic oxidation of organic substrates by manganese(III) porphyrins and terminal oxidants.[4] In contrast to the iron–oxo porphyrin intermediates, the nature of manganese(v)–oxo porphyrins has been ambiguous until Groves and co-workers reported the UV-Vis and $^1$H NMR spectra of manganese(v)–oxo porphyrins in aqueous solution.[5] Subsequently, Mn(v)–oxo porphyrins have been synthesized in organic solvents in the presence of base and characterized with resonance Raman and X-ray absorption spectroscopy/extended X-ray absorption fine structure spectroscopy (XAS/EXAFS).[6] The spectroscopic data from $^1$H NMR, resonance Raman, and EXAFS suggested that the Mn(v)–oxo species are diamagnetic with a low-spin ($S = 0$) state and with double-bond character between the Mn(v) ion and the oxygen atom.[5,6] More recently, re-evaluation of the $^1$H NMR and resonance Raman data revealed that the Mn(v)–oxo porphyrins are *trans*-dioxomanganese(v) species [O=Mn$^V$=O].[7]

Since it is only recently that the synthesis of Mn(v)–oxo porphyrins has become well established, only a few reactivity studies have been performed with *in situ*-generated Mn(v)–oxo species in oxidation and halogenation reactions.[5,8–11] As our ongoing efforts to elucidate the chemical properties of high-valent metal–oxo species, we have generated *trans*-dioxomanganese(v) porphyrins and investigated their reactivities in hydride-transfer reactions.[12] In this communication, we report the first example of hydride transfer from dihydronicotinamide adenine dinucleotide (NADH) analogues to Mn(v)–oxo porphyrins.

*trans*-Dioxomanganese(v) porphyrins, [Mn(v)(O)$_2$(TPFPP)]$^+$ (**1**) (TPFPP = *meso*-tetrakis(pentafluorophenyl)porphinato dianion), [Mn(v)(O)$_2$(TDFPP)]$^+$ (**2**) (TDFPP = *meso*-tetrakis(2,6-difluorophenyl)porphinato dianion), and [Mn(v)(O)$_2$(TDCPP)]$^+$ (**3**) (TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphinato dianion) (see structures in Chart 1, *Mn(v)(O)$_2$(Porp) Complexes*), were prepared by the published method;[6,7] manganese(III) porphyrin chlorides were reacted with *m*-chloroperbenzoic acid (*m*-CPBA, 5 equiv.) in the presence of base (tetrabutylammonium hydroxide (TBAH), 20 equiv.) in a solvent mixture of $CH_3CN$ and $CH_2Cl_2$ (1 : 1) at 25 °C. The UV-Vis spectrum of **1** exhibits a strong Soret band at 431 nm and a Q-band at 551 nm, characteristic of Mn(v)–oxo porphyrins (Fig. 1a).[5–8] **1** was quite stable at 25 °C ($t_{1/2} \approx 3.5$ h). The reactivity of **1** was then investigated with NADH analogues, 10-methyl-9,10-dihydroacridine ($AcrH_2$), 1-benzyl-1,4-dihydronicotinamide (BNAH), and their derivatives (see Chart 1, *Hydride Donors*). Upon addition of substrates to a solution of **1**, the intermediate reverted to the starting manganese(III) porphyrin complex, showing isosbestic points at 403, 439, and 558 nm (Fig. 1a). First-order rate constants, determined by the pseudo-first-order fitting of the kinetic data for the decay of **1**, increased linearly with the increase in the substrate concentration, leading us to determine the second-order rate constants of 1.5(2) × 10 $M^{-1}$ $s^{-1}$ for $AcrH_2$ and 1.3(2) × $10^3$ $M^{-1}$ $s^{-1}$ for BNAH (Fig. 1b). By using dideuterated compounds, $AcrD_2$ and BNAH-4,4′-$d_2$ (see Chart 1, *Hydride Donors*), large kinetic isotope effect (KIE) values, such as KIE of 15(2) for the reaction of $AcrH_2$ and KIE of 10(2) for the reaction of BNAH, were determined (Fig. 1b). The large KIE values indicate that the C–H bond activation of NADH analogues is

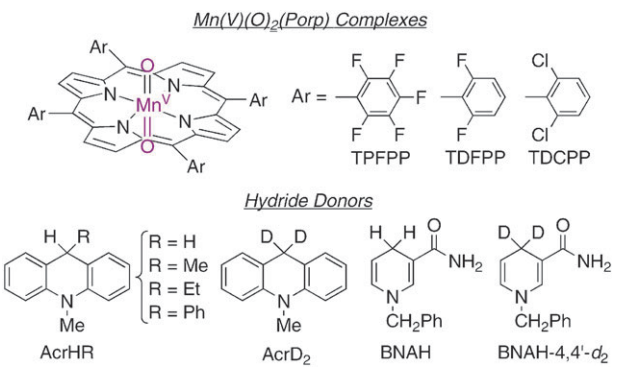


**Chart 1**

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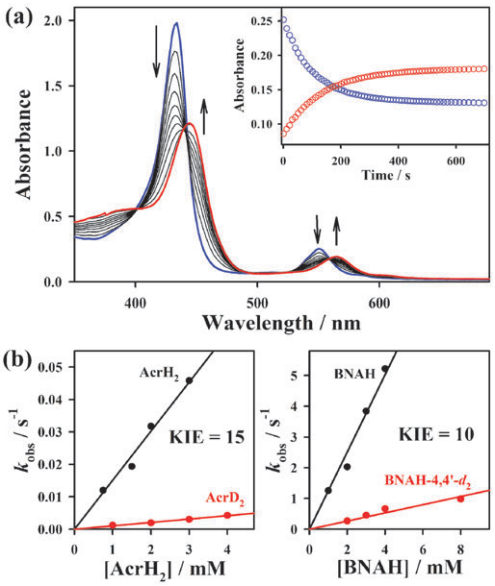



**Fig. 1** (a) UV-Vis spectral changes of **1** ($1 \times 10^{-2}$ mM, blue line) upon addition of $AcrH_2$ ($3 \times 10^{-1}$ mM). Inset shows time course of the decay of **1** monitored at 551 nm (blue) and the formation of $[Mn^{III}(TPFPP)]^+$ species monitored at 569 nm (red). (b) Plot of $k_{obs}$ against the concentration of $AcrH_2$ and $AcrD_2$ (left panel) and BNAH and BNAH-4,4′-$d_2$ (right panel) to determine second-order rate constants. Black circles indicate the oxidation of $AcrH_2$ and BNAH; red circles indicate the oxidation of $AcrD_2$ and BNAH-4,4′-$d_2$.

involved as a rate-determining step in the hydride-transfer reactions by **1**. The hydride-transfer reaction was also investigated with other $AcrH_2$ derivatives bearing a substituent R at the C-9 position, such as AcrHMe, AcrHPh, and AcrHEt (see the structure of AcrHR in Chart 1, *Hydride Donors*), and it was found that the reaction rates are significantly affected by the substituent R in the AcrHR (ESI, Table S1†). Interestingly, the reactivity of AcrHR bearing an electron-donating R group is lower than that of $AcrH_2$, suggesting that the hydride-transfer reaction does not occurs *via* an one-step hydride-transfer mechanism (*vide infra*).[12]

The porphyrin ligand effect on the reactivity of *trans*-dioxomanganese(v) complexes in hydride-transfer reactions was also investigated, and second-order rate constants of 15(2), 3.9(3), and 1.3(2) $M^{-1}$ $s^{-1}$ were determined in the oxidation of $AcrH_2$ by **1**, **2** and **3**, respectively. These results indicate that a Mn(v)–oxo complex bearing an electron-deficient porphyrin ligand is more reactive in the hydride-transfer reaction. The reactivity order of **1** > **2** > **3** is the same as that observed in the olefin epoxidation and C–H activation by Mn(v)–oxo complexes.[9a] In iron porphyrin systems, a high-valent iron–oxo complex with an electron-deficient porphyrin ligand is more reactive in electrophilic oxidation reactions, including C–H activation and hydride-transfer reactions.[13,14] The reactivity order of **1** > **2** > **3** was also observed in the oxidation of other NADH analogues (ESI, Table S1†). Further, as observed in the reaction of **1**, large KIE values of 6–20 were obtained in the reactions of $AcrH_2$, BNAH, and their deuterated compounds by **2** and **3** (ESI, Table S1†).

It has been reported previously that hydride transfer from $AcrH_2$, BNAH, and their derivatives to hydride acceptors,

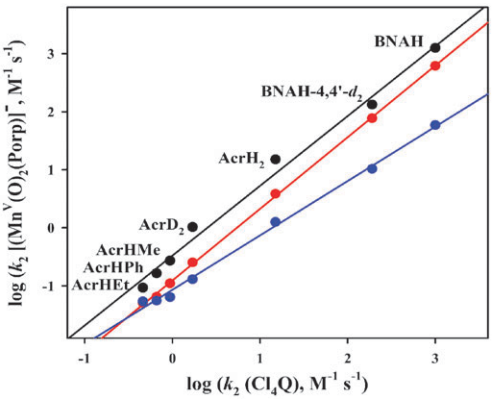
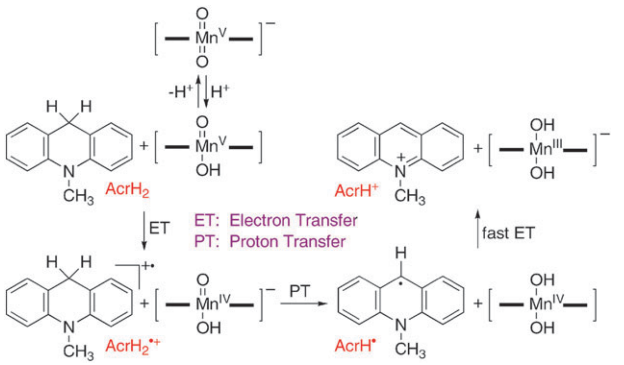


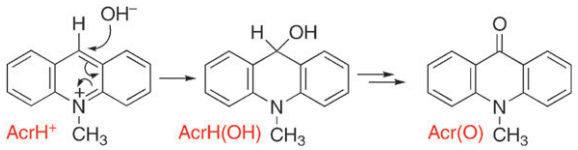

**Fig. 2** Plots of log $k_2$ for hydride transfer from NADH analogues to $[Mn^V(O)_2(TPFPP)]^-$ (black circles), $[Mn^V(O)_2(TDFPP)]^-$ (red circles), and $[Mn^V(O)_2(TDCPP)]^-$ (blue circles) *vs.* log $k_2$ for hydride transfer from the same series of NADH analogues to $Cl_4Q$ in MeCN at 298 K.

such as *p*-chloranil ($Cl_4Q$) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, occurs *via* proton-coupled electron transfer (PCET), followed by rapid electron transfer.[14,15] Also, the reactivity comparison of high-valent metal–oxo complexes and $Cl_4Q$ was used as indirect evidence for proposing the PCET mechanism in hydride transfer reactions.[14] We therefore compared $k_2$ values of the hydride transfer from NADH analogues to Mn(v)–oxo complexes and $Cl_4Q$. As shown in Fig. 2, there is a good linear correlation between the $k_2$ values of $[Mn(v)(O)_2(Porp)]^-$ and the corresponding values of $Cl_4Q$. Such a linear correlation implies that hydride transfer from NADH analogues to $[Mn(v)(O)_2(Porp)]^-$ follows the hydride-transfer mechanism of $Cl_4Q$. That is the PCET, followed by rapid electron transfer.[15] In addition, the $k_2$ values of hydride transfer from NADH analogues to $Cl_4Q$ are similar to that of hydride transfer from NADH analogues to **1**, indicating that the reactivities of **1** and $Cl_4Q$ are similar in the hydride-transfer reactions (compare the data in the columns of $k_2$ ($[Mn^V(O)_2(TPFPP)]^-$) and $k_2$ ($Cl_4Q$) in ESI, Table S1†). We have also observed that the $k_2$ values of hydride transfer from NADH analogues to $[Mn(v)(O)_2(Porp)]^-$ are well correlated with the rate constants of deprotonation of radical cations of NADH analogues ($k_d$) (ESI, Fig. S1†), indicating that the proton transfer from $AcrHR^{\bullet+}$ to Mn(IV)(O)(OH)(Porp) is involved as a rate-determining step (Scheme 1, pathway PT).[12,16] The latter was further supported by the large KIE values determined in the oxidation of $AcrH_2$, BNAH, and their deuterated compounds by Mn(v)–oxo complexes. Further, as we have discussed above, the significant decrease in the reactivity by the introduction of a substituent R at the C-9 position can hardly be reconciled by a one-step hydride transfer mechanism.[12] Based on the results of the mechanistic studies discussed above, we propose the following mechanism: the hydride transfer from NADH analogues to Mn(v)–oxo porphyrins occurs *via* an uphill electron transfer from NADH analogues to Mn(v)(O)(OH)(Porp),[17] followed by the rate-limiting proton transfer from the radical cations of NADH analogues to $[Mn(IV)(O)(OH)(Porp)]^-$ (Scheme 1). Then, rapid electron transfer from the deprotonated radicals to the $Mn(IV)(OH)_2(Porp)$ species affords the final products, such as the corresponding $NAD^+$ analogues and the starting Mn(III) porphyrins.




**Scheme 1** Proposed mechanism of the hydride transfer from $AcrH_2$ to a manganese(v)–oxo porphyrin complex.

Scheme 1 shows that the final products formed in the hydride transfer from $AcrH_2$ to $[Mn(v)(O)_2(Porp)]^-$ are $[Mn(iii)(OH)_2(Porp)]^-$ and 10-methylacridinium ion ($AcrH^+$). Although we have observed the conversion of **1** to the starting manganese(iii) complex in the reaction of **1** and $AcrH_2$, we did not observe the formation of $AcrH^+$, which should exhibit an absorption band at 357 nm in the UV-Vis spectrum (Fig. 1).[12,18] Since no detection of $AcrH^+$ might be due to the instability of the $AcrH^+$ ion in the presence of $OH^-$, we carried out a control reaction by adding $OH^-$ to a solution containing $AcrH^+$. As we expected, the $AcrH^+$ ion was converted to AcrH(OH) immediately with a rate of $> 10^8\ s^{-1}$ (ESI, Fig. S2a†), followed by the slow conversion of AcrH(OH) to Acr(O) (ESI, Fig. S2b) [eqn (1)].[19] Thus, we carried out the reaction of **1** and $AcrH_2$ and confirmed that Acr(O) was formed as the final product by analyzing product(s) with $^1H$ NMR after column chromatography (ESI, Fig. S3†).[19]




(1)

In conclusion, we have reported the first example of the oxidation of NADH analogues by manganese(v)–oxo porphyrin complexes. We have demonstrated that hydride transfer from a series of NADH analogues to Mn(v)–oxo species proceeds *via* PCET, followed by rapid electron transfer, rather than one-step hydride transfer. Other mechanistic aspects, such as porphyrin ligand effect and KIE, have also been discussed in the oxidation of NADH analogues by Mn(v)–oxo porphyrin complexes.

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