Proton-Coupled Electron Transfer

International Edition: DOI: 10.1002/anie.201611709
German Edition: DOI: 10.1002/ange.201611709

A Chromium(III)-Superoxo Complex as a Three-Electron Oxidant with a Large Tunneling Effect in Multi-Electron Oxidation of NADH Analogues

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Abstract: *Metal-superoxo species are involved in a variety of enzymatic oxidation reactions, and multi-electron oxidation of substrates is frequently observed in those enzymatic reactions. A Cr^{III}-superoxo complex, $[Cr^{III}(O_2)(TMC)(Cl)]^+$ (**1;** TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), is described that acts as a novel three-electron oxidant in the oxidation of dihydronicotinamide adenine dinucleotide (NADH) analogues. In the reactions of **1** with NADH analogues, a Cr^{IV}-oxo complex, $[Cr^{IV}(O)(TMC)(Cl)]^+$ (**2**), is formed by a heterolytic O–O bond cleavage of a putative Cr^{II}-hydroperoxo complex, $[Cr^{II}(OOH)(TMC)(Cl)]$, which is generated by hydride transfer from NADH analogues to **1**. The comparison of the reactivity of NADH analogues with **1** and p-chloranil (Cl_4Q) indicates that oxidation of NADH analogues by **1** proceeds by proton-coupled electron transfer with a very large tunneling effect (for example, with a kinetic isotope effect of 470 at 233 K), followed by rapid electron transfer.*

Metal–oxygen intermediates, such as high-valent metal-oxo, metal-superoxo, and metal-(hydro)peroxo species, are involved in the activation of dioxygen and the oxygenation of organic substrates by metalloenzymes and their model compounds.[1–3] Among them, high-valent metal-oxo species have been extensively investigated in a variety of oxidation reactions over several decades, and especially in heme and nonheme iron systems and water oxidation in photosystem II.[4–10] Recently, metal-superoxo species have attracted much attention in the communities of bioinorganic and biological chemistry, since the intermediates have been invoked as reactive species in the C–H bond activation and oxygen atom transfer reactions by nonheme iron and copper enzymes.[11,12] In biomimetic studies, a number of metal-superoxo complexes have been successfully synthesized and characterized structurally and spectroscopically, and their reactivities have been investigated in both electrophilic and nucleophilic oxidative reactions.[13–19] However, the chemical properties of metal-superoxo species are less clearly understood and remain elusive in many respects. For example, although mechanisms of hydride transfer from dihydronicotinamide adenine dinucleotide (NADH) analogues to high-valent metal-oxo complexes have been discussed recently,[20] hydride-transfer reactions by metal-superoxo complexes have never been explored previously. Additionally, although it has been shown that metal-superoxo complexes ($M\text{-}O_2^{\bullet-}$) are capable of abstracting a hydrogen atom (H-atom) from substrates (that is, a one-electron oxidant),[21–23] there has been no example showing that metal-superoxo complexes ($M\text{-}O_2^{\bullet-}$) can be a three-electron oxidant without a change in the oxidation state of metal ions.

We report herein the first example of hydride transfer from NADH analogues to a nonheme Cr^{III}-superoxo complex, $[Cr^{III}(O_2)(TMC)(Cl)]^+$ (**1**, see the structure in Scheme 1 A; TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane).[21,22] Compound **1** acts as a novel three-electron oxidant in the oxidation of NADH analogues[23,24] to produce a Cr^{III}-hydroxo complex and two- or four-electron oxidized products of NADH analogues (Scheme 1 B). Mechanisms of the multi-electron oxidation of NADH analogues by **1** are proposed based on the kinetics and mechanistic studies, including the characterization of intermediates and their involvement in the NADH oxidation reactions. The rate constants of hydride transfer from NADH analogues to **1** are also compared with those of hydride transfer from the same NADH analogues to an iron(IV)-oxo complex, $[Fe^{IV}(O)(TMC)]^{2+}$, and *p*-chloranil;[20a] leading us to propose that the hydride-transfer reaction by **1** occurs by a rate-determining concerted proton-coupled electron transfer (PCET) from NADH analogues to **1**, followed by a rapid electron transfer. Interestingly, a very large deuterium kinetic isotope effect (KIE) is observed in the reactions of **1** with 10-methyl-9,10-dihydroacridine ($AcrH_2$) and a deuterated compound ($AcrD_2$; for example, KIE = 470 at 233 K).

The Cr^{III}-superoxo complex, $[Cr^{III}(O_2)(TMC)(Cl)]^+$ (**1**), was synthesized and characterized according to the published methods.[21,22] When **1** was reacted with 1 equiv of 1-benzyl-

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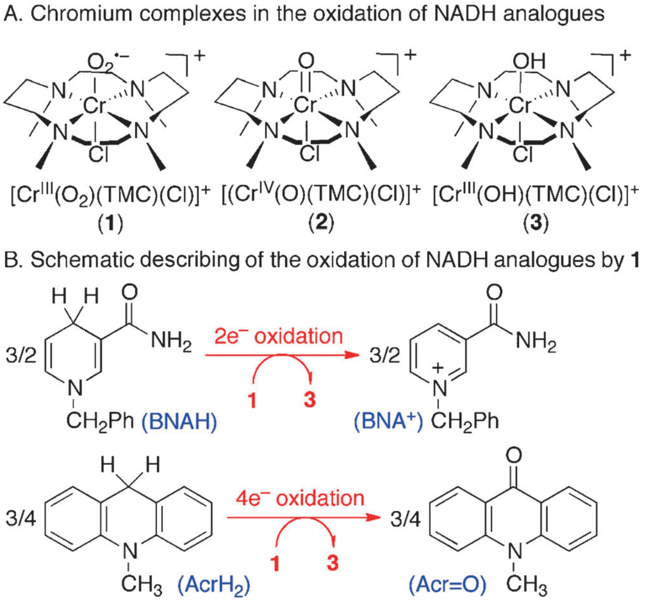


Scheme 1. A) Schematic structures of Cr^{III}-superoxo (**1**), Cr^{IV}-oxo (**2**), and Cr^{III}-hydroxo (**3**) complexes. B) Reactions showing the oxidation of NADH analogues by a Cr^{III}-superoxo complex (**1**).

1,4-dihydronicotinamide (BNAH; frequently used as an NADH analogue)[23,24] in deaerated acetonitrile (MeCN) at 253 K, the absorption bands at 470, 550, 645, and 675 nm arising from **1** disappeared within 4 min and bands at 605 and 960 nm corresponding to [Cr^{IV}(O)(TMC)(Cl)]$^+$ (**2**)[21,22] appeared simultaneously (Figure 1; see the structure of **2** in Scheme 1). The formation of **2** along with BNA$^+$ was confirmed with electrospray ionization mass spectrometry (ESI-MS) of the reaction solution (Supporting Information, Figure S1). The stoichiometry of the reaction of BNAH with **1** was determined to be 1:1 from the spectral titration experiments (Figure 1b). Thus, an overall reaction is summarized in [Eq. (1)].

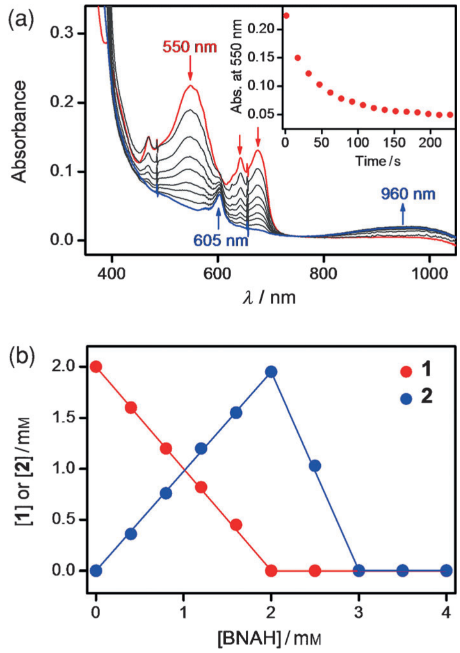
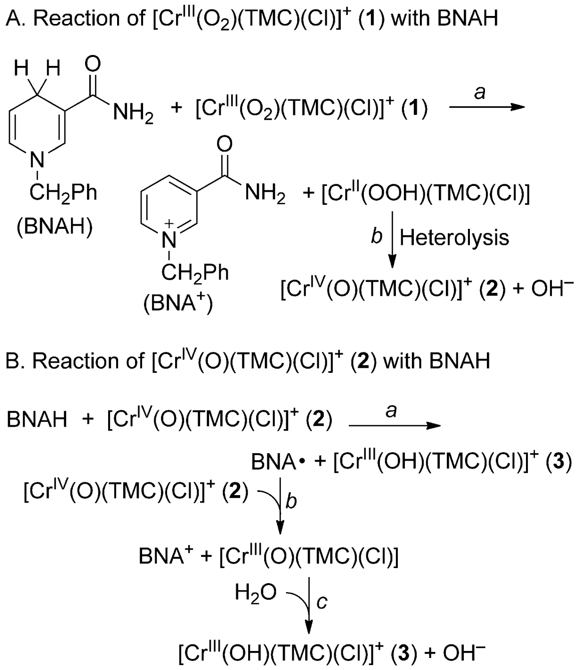


Figure 1. a) UV/Vis spectral changes observed in the oxidation of BNAH (1.0 mм) by **1** (1.0 mм) in deaerated MeCN at 253 K. Inset shows the time profile monitored at 550 nm arising from the decay of **1**. b) Titration experiments performed with **1** and BNAH in deaerated MeCN at 253 K.

$$\begin{aligned}&\mathrm{BNAH}+[\mathrm{Cr^{III}(O_2)(TMC)(Cl)}]^+\ (\mathbf{1})\rightarrow\\&\qquad\mathrm{BNA^+}+[\mathrm{Cr^{IV}(O)(TMC)(Cl)}]^+\ (\mathbf{2})+\mathrm{OH^-}\end{aligned}\tag{1}$$

A mechanism is proposed as follows: in the 1:1 reaction of **1** and BNAH, the first step is a hydride transfer from BNAH to **1**, resulting in the formation of BNA$^+$ and [Cr^{II}(OOH)(TMC)(Cl)] (Scheme 2A, reaction *a*). Subsequently, the hydroperoxo O–O bond of the putative [Cr^{II}(OOH)(TMC)(Cl)] intermediate is cleaved heterolytically to form **2** and OH$^-$ (Scheme 2A, reaction *b*). Recently, we have shown that a nonheme Fe^{II}-OOH species, [Fe^{II}(OOH)(TMC)]$^+$, cleaves its hydroperoxo O–O bond heterolytically, resulting in the formation of iron(IV)-oxo complex [Fe^{IV}(O)(TMC)]$^{2+}$ and OH$^-$.[25] It was also confirmed that no reaction occurred between BNA$^+$ and OH$^-$ in deaerated MeCN (Supporting Information, Figure S2b) when BNA$^+$ was produced in the oxidation of BNAH by H_2O_2 in the presence of Fe(ClO$_4$)$_3$ (Supporting Information, Figure S2a). This is explained by the resonance structures of the amide group in BNA$^+$ (Supporting Information, Figure S3), in which the negative charge on the amide oxygen prohibits the addition of OH$^-$ at the 4-position of BNA$^+$.



Scheme 2. Proposed mechanisms for the oxidation of BNAH by **1** (A) and **2** (B).

In the reaction of **1** with an excess amount of BNAH, [Cr^{IV}(O)(TMC)(Cl)]$^+$ (**2**), which was formed in the reaction of **1** and BNAH (Scheme 2 A), reacted further with a second molecule of BNAH to produce BNA$^{\cdot}$ and [Cr^{III}(OH)(TMC)(Cl)]$^+$ (**3**; Scheme 1) by hydrogen atom (H-atom) transfer (Scheme 2 B, reaction *a*). Subsequently, a fast electron transfer occurred from BNA$^{\cdot}$ ($E_{ox} = -1.1$ V vs. SCE)[24] to another molecule of **2** to give BNA$^+$ and [Cr^{III}(O)(TMC)(Cl)] (Scheme 2 B, reaction *b*). The latter species, [Cr^{III}(O)(TMC)(Cl)], was unstable and thus hydrolyzed to give [Cr^{III}(OH)(TMC)(Cl)]$^+$ and OH$^-$ (Scheme 2 B, reaction *c*). The formation of the BNA$^+$ and [Cr^{III}(OH)(TMC)(Cl)]$^+$ products in the oxidation of BNAH with 2/3 equiv of **1** [Eq. (2)] was analyzed

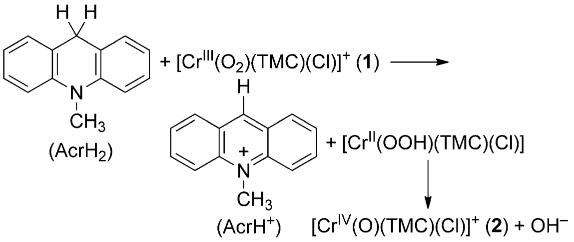
$$\begin{aligned}&3\,\mathrm{BNAH}{+}2\,[\mathrm{Cr^{III}(O_2)(TMC)(Cl)}]^+\ (\mathbf{1}) + \mathrm{H_2O} \rightarrow\\ &\qquad 3\,\mathrm{BNA}^+ + 2\,[\mathrm{Cr^{III}(OH)(TMC)(Cl)}]^+\ (\mathbf{3}) + 3\,\mathrm{OH}^-\end{aligned} \tag{2}$$

by ESI-MS and electron paramagnetic resonance (Supporting Information, Figure S4 for UV/Vis and ESI-MS, Figure S5 for EPR). The amount of the [Cr^{III}(OH)(TMC)(Cl)]$^+$ (**3**) product was determined to be 93(5) % by comparing the double integration of the EPR signal of **3**—which was produced in the oxidation of BNAH by **1**—with that of an authentic **3** reference complex prepared independently (Supporting Information, Figure S5 and Table S1). Thus, in the reaction of **1** and an excess amount of BNAH, **1** acts as a three-electron oxidant that oxidizes BNAH to BNA$^+$ [Eq. (2)].

In a separate study, we synthesized **2** according to the published method[21] and reacted it with BNAH under pseudo first-order reaction conditions (Supporting Information, Figure S6); a second-order rate constant of 16 $\mathrm{M^{-1}s^{-1}}$ at 253 K was determined in the reactions of **2** with different amounts of BNAH (Supporting Information, Figure S7b). Similarly, a second-order rate constant of 27 $\mathrm{M^{-1}s^{-1}}$ at 253 K was obtained in the reaction of **1** with different amounts of BNAH (Supporting Information, Figure S7a), indicating that the reactivity of **1** is slightly greater than that of **2** in this hydride-transfer reaction. We have shown recently that **1** is much more reactive than **2** in oxygen atom transfer reactions (for example, oxidation of thioanisole derivatives by **1** and **2**).[26]

When BNAH was replaced by AcrH$_2$, four-electron oxidation of AcrH$_2$ by **1** occurred to produce 10-methylacridone (Acr=O)[27] and **3** (Supporting Information, Figure S8 for cold-spray ionization mass spectrometry (CSI-MS)). The ^{18}O-labeling experiments were performed to confirm that the oxygen atoms in Acr=O were derived from **1**. [Cr^{III}(O$_2$)(TMC)(Cl)]$^+$ (**1**-^{18}O) was synthesized by reacting [Cr^{II}(TMC)(Cl)]$^+$ with ^{18}O$_2$ (98 % ^{18}O-enriched), as reported previously.[21,22] In the hydride-transfer reaction from AcrH$_2$ to **1**-^{18}O, Acr=^{18}O was obtained quantitatively together with [Cr^{III}(^{18}OH)(TMC)(Cl)]$^+$ (**3**-^{18}O), as shown in Figure S8c (Supporting Information), clearly demonstrating that the oxygen atoms in the Acr=O product were derived from **1**. The stoichiometry of the reaction of AcrH$_2$ and **1** was determined to be 3:4 (Supporting Information, Figure S9), where the concentration of Acr=O was 75 % of the initial concentration of **1** (Supporting Information, Figure S9c). Such a unique stoichiometry also indicates that **1** acts as a three-electron oxidant in the four-electron oxidation of AcrH$_2$ to Acr=O. In the 3:4 stoichiometry, three molecules of AcrH$_2$ (4-electron reductant) are oxidized by four molecules of **1** (3-electron oxidant; Scheme 1 B).

A mechanism for the reaction of **1** and AcrH$_2$ is proposed as follows. Hydride transfer from AcrH$_2$ to **1** forms 10-methylacridinium ion (AcrH$^+$) and [Cr^{II}(OOH)(TMC)(Cl)], followed by heterolytic O−O bond cleavage of [Cr^{II}(OOH)(TMC)(Cl)] to give **2** and OH$^-$; as described by [Eq. (3)] and Scheme 2 A. Subsequently, OH$^-$ is added to AcrH$^+$ to produce AcrH(OH) [Eq. (4)];[27,28] the observation of the reaction of OH$^-$ with AcrH$^+$ is in sharp contrast to the case of BNA$^+$ (see earlier), in which no reaction occurs between OH$^-$ and BNA$^+$ (Supporting Information, Figure S2b). Indeed, the reaction of AcrH$^+$ and OH$^-$ was confirmed independently by adding tetramethylammonium hydroxide (Me$_4$NOH) to a deaerated MeCN solution of AcrH$^+$, in which addition of OH$^-$ at the 9-position of AcrH$^+$ afforded the formation of AcrH(OH) (Supporting Information, Figure S10).[27,28] Subsequently, a second hydride transfer from AcrH(OH) to **1** yields Acr=O, **2**, and H$_2$O [Eq. (5)]. Furthermore, H-atom transfer from AcrH(OH) to **2** produces AcrOH$^{\cdot}$ and **3** [Eq. (6)],[29] and a subsequent H-atom transfer from AcrOH$^{\cdot}$ to **2** produces Acr=O and **3** [Eq. (7)]. The formation of Acr=O in the hydride transfer from AcrH(OH) to **1** [Eq. (5)] and the H-atom transfer from AcrH(OH) to **2** [Eq. (6) and (7)] were confirmed by carrying out independent reactions of AcrH(OH) with **1** and **2** (Supporting Information, Figure S11a and S11b, respectively). Notably, **2** predominantly reacts with AcrH(OH), rather than AcrH$_2$, because the oxidation of AcrH$_2$ by **2** produces AcrH$^+$ (Supporting Information, Figure S12), which was not produced in the oxidation of AcrH$_2$ by **1**. The yield of **3** was also determined to be 91(4) % by comparing the EPR signal of **3** produced with that of an authentic reference (Supporting Information, Table S1 and Figure S13). Thus, the overall stoichiometry is shown in [Eq. (8)], which agrees well with the stoichiometry



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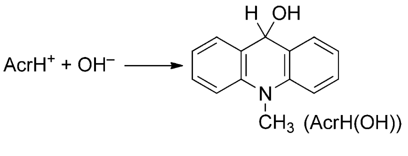

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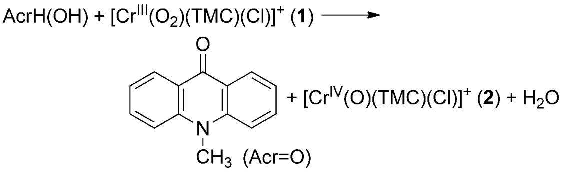

(5)

determined spectroscopically (Supporting Information, Figure S9).

$$\mathrm{AcrH(OH)}+[\mathrm{Cr^{IV}(O)(TMC)(Cl)}]^{+}\ (\mathbf{2}) \rightarrow \mathrm{AcrOH^{\bullet}} + [\mathrm{Cr^{III}(OH)(TMC)(Cl)}]^{+}\ (\mathbf{3}) \tag{6}$$

$$\mathrm{AcrOH^{\bullet}} + [\mathrm{Cr^{IV}(O)(TMC)(Cl)}]^{+}\ (\mathbf{2}) \rightarrow \mathrm{Acr{=}O} + [\mathrm{Cr^{III}(OH)(TMC)(Cl)}]^{+}\ (\mathbf{3}) \tag{7}$$

Yielding the overall reaction [Eq. (8)]: 3 × [Eq. (3)] + 3 × [Eq. (4)] + [Eq. (5)] + 2 × [Eq. (6)] + 2 × [Eq. (7)].

$$3\,\mathrm{AcrH_2} + 4\,[\mathrm{Cr^{III}(O_2)(TMC)(Cl)}]^{+}\ (\mathbf{1}) \rightarrow 3\,\mathrm{Acr{=}O} + 4\,[\mathrm{Cr^{III}(OH)(TMC)(Cl)}]^{+}\ (\mathbf{3}) + \mathrm{H_2O} \tag{8}$$

The hydride transfer from $AcrH_2$ to **1** obeyed pseudo first-order kinetics in the presence of an excess amount of $AcrH_2$, and the second-order rate constant (k_2) of 2.0 at 253 K was determined from the slope of the plot of pseudo first-order rate constants (k_1) versus concentration of $AcrH_2$ (Figure 2a). The k_2 values of other dihydroacridine derivatives (AcrHR, R = Me and Et) were determined as well (Supporting Information, Table S2 and Figure S14). Interestingly, a large KIE value of 74 ± 5 was determined at 253 K in the reaction of $AcrH_2$ and a deuterated compound ($AcrD_2$; Figure 2a). The large KIE can be ascribed to the involvement of H-atom tunneling in the hydride-transfer reaction.[30,31] Since it is the curvature of the Arrhenius plot that demonstrates incidence of tunneling experimentally, there are two criteria for the recognition of the tunneling effect: 1) the difference in activation energy ($E_D - E_H$) > 6 kJ mol^{-1} and 2) the ratio of the pre-exponential factor (A_H/A_D) < 0.6.[30,31] To study the involvement of H-tunneling, we examined the temperature dependence of the second-order rate constants (k_2) in the hydride-transfer reactions from both $AcrH_2$ and $AcrD_2$ to **1** over the temperature range from 253 K to 233 K (Supporting Information, Table S3); the Arrhenius plots are shown in Figure 2b. The activation energies (E_H and E_D) and the pre-exponential factors (A_H and A_D) were determined from the Arrhenius plots (Supporting Information, Table S4). The large difference between E_D and E_H ($E_D - E_H = 45$ kJ mol^{-1}) and the extremely small ratio of $A_H/A_D = 4.1 \times 10^{-8}$ demonstrate a large tunneling effect in the hydride-transfer reactions from $AcrH_2$ and $AcrD_2$ to **1**. To the best of our knowledge, the KIE value of 470 ± 30 at 233 K is the largest ever reported in the oxidation reactions by metal–oxygen intermediates. The second largest KIE value was reported in the C−H bond activation of benzyl alcohol by an iron(IV)-oxo porphyrin π-radical cation, $[(\mathrm{TMP})^{+\bullet}\mathrm{Fe^{IV}(O)}][\mathrm{ClO_4}^{-}]$ (TMP^{2-} = 5,10,15,20-tetramesitylporphyrin dianion), with a KIE of 360 ± 20 in MeCN at 243 K.[32] The large tunneling effect in the hydroxylation of xanthene and 1,2,3,4-tetrahydronaphthalene by $[(\mathrm{TMP})^{\bullet+}\mathrm{Fe^{IV}(O)}]^{+}$ has also been confirmed by the non-linear Arrhenius plots in dichloromethane in a wide range of temperatures.[33]

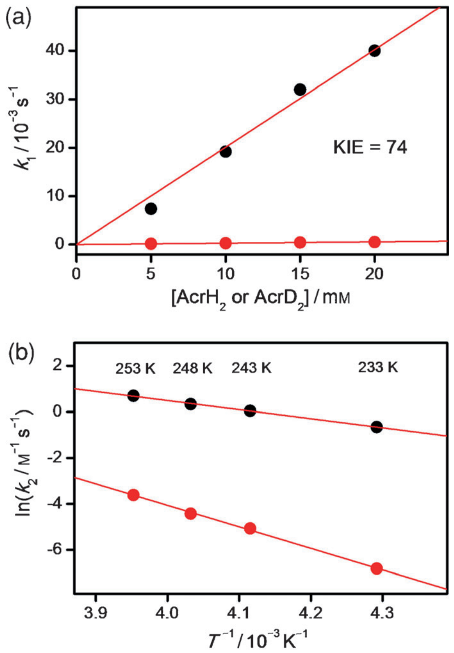

Figure 2. a) Plots of pseudo first-order rate constants against concentrations of $AcrH_2$ and $AcrD_2$ for hydride transfer from $AcrH_2$ (●) and $AcrD_2$ (●) to **1** (0.50 mM) in MeCN at 253 K. b) Arrhenius plots of the second-order rate constants for hydride transfer from $AcrH_2$ (●) and $AcrD_2$ (●) to **1** in deaerated MeCN (Supporting Information, Table S3).

When $AcrH_2$ was replaced by 9-methyl-10-methyl-9,10-dihydroacridine (AcrHMe), the stoichiometry of the reaction of **1** and AcrHMe was also 3:4 and the yield of Acr=O was 75(5) % based on the amount of **1** used (Supporting Information, Figure S15). The 3:4 stoichiometry entails removal of 12 electrons from three molecules of AcrHMe (4-electron reductant) by four molecules of **1** (3-electron oxidant). When AcrHMe was replaced by AcrHEt, the same stoichiometry was obtained (Supporting Information, Figure S16). The yields of **3** produced in the oxidation of AcrHMe and AcrHEt by **1** were also determined to be 92(4) % and 90(4) % by EPR, respectively (Supporting Information, Table S1).

As reported previously, hydride transfer from NADH analogues to hydride acceptors, such as *p*-chloranil (Cl_4Q) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, occurs by a concerted PCET mechanism followed by a rapid electron transfer.[17] Since a reactivity comparison between high-valent metal–oxo complexes and Cl_4Q was used as evidence supporting the concerted PCET mechanism in hydride-transfer reactions,[20] the rate constants of hydride transfer from NADH analogues to **1** were also compared with those of hydride transfer from the same NADH analogues to Cl_4Q (Supporting Information, Table S2), as shown in Figure 3. There is a good linear correlation between the k_2 values of **1** and the corresponding values of Cl_4Q, implying that hydride transfer from NADH analogues to **1** occurs by a concerted PCET, followed by a rapid electron transfer.

In conclusion, we have reported the first example of a hydride-transfer reaction by a synthetic metal-superoxo complex (that is, Cr^{III}-superoxo complex, $[\mathrm{Cr^{III}(O_2)(TMC)(Cl)}]^{+}$). We have shown that the Cr^{III}-superoxo complex acts as a three-electron oxidant in multi-electron oxidation of NADH analogues (up to four electrons). We have also shown that a very large KIE is obtained in the hydride transfer from NADH analogues to a metal-superoxo complex. The present

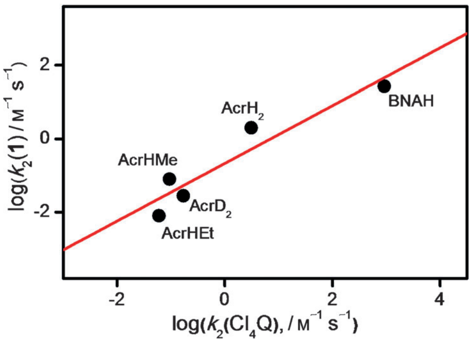

Figure 3. Plot of logk_2(**1**) for hydride transfer from NADH analogues to $[Cr^{III}(O_2)(TMC)(Cl)]^+$ (**1**) in MeCN at 253 K vs. log $k_2(Cl_4Q)$ for hydride transfer from the same series of NADH analogues to Cl_4Q in deaerated MeCN at 253 K.

study paves a new way to utilize metal-superoxo complexes as novel three-electron oxidants.

Acknowledgements

This work was supported by a SENTAN project from Japan Science and Technology Agency (JST) and JSPS KAKENHI (No. 16H02268) from MEXT, Japan to S.F. and NRF of Korea through the CRI (NRF-2012R1A3A2048842) and GRL (NRF-2010-00353) programs to W.N.

Conflict of interest

The authors declare no conflict of interest.

Keywords: chromium(III)-superoxo complexes · hydride transfer · hydrogen atom transfer · NADH analogues · three-electron oxidant

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Manuscript received: December 1, 2016
Revised: January 15, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Proton-Coupled Electron Transfer

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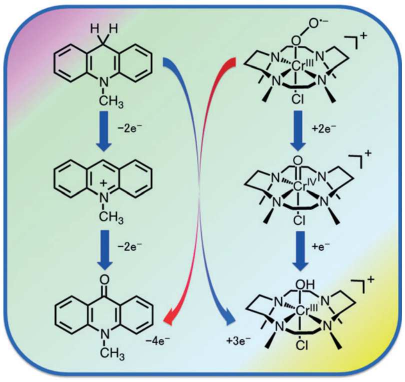
A Chromium(III)-Superoxo Complex as a Three-Electron Oxidant with a Large Tunneling Effect in Multi-Electron Oxidation of NADH Analogues



A Cr^{III}**-superoxo complex** involved in the oxidation of dihydronicotinamide adenine dinucleotide analogues functions as a novel three-electron oxidant with a very large tunneling effect. The hydride-transfer reaction occurs by a concerted proton-coupled electron transfer mechanism.