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C−H Bond Activation of External Substrates with a Bis(*μ*-oxo)dicopper(III) Complex

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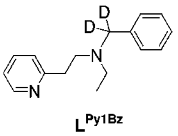
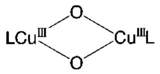
C−H bond activation by metal−oxo species has long been one of the most important and attractive research objectives not only in bioinorganic chemistry but also in numerous and diverse array of catalytic oxidation reactions for organic synthesis.[1] Reactivity of iron−oxo complexes of both heme and non-heme systems in various oxidation states has so far been studied extensively to provide valuable insight into the catalytic mechanisms of iron-dependent oxygenases as well as of Fenton-type and Gif-type reactions.[1−3] Much attention has recently been focused on the dinuclear copper−oxo species such as bis(μ-oxo)dicopper(III), since it is considered as a possible active oxygen intermediate in the aliphatic hydroxylation by dinuclear copper monooxygenases.[4] Structural and spectroscopic characterizations of the bis(μ-oxo) species have been well-documented,[5] and their decomposition processes leading to intramolecular aromatic and aliphatic ligand hydroxylation as well as oxidative *N*-dealkylation of the ligand sidearm have been investigated as functional models for copper monooxygenases.[6,7] However, little is known about mechanistic details on the reactions of bis(μ-oxo)dicopper(III) complexes and external substrates.[8]



L^Py1Bz



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We report herein the mechanistic studies on the C−H bond activation of external substrates such as 10-methyl-9,10-dihydroacridine (AcrH$_2$) and 1,4-cyclohexadiene (CHD) with a bis(μ-oxo)dicopper(III) complex supported by bidentate ligand $\mathbf{L}^{\mathbf{Py1Bz}}$ ($\mathbf{L}^{\mathbf{Py1Bz}}$ = *N*-ethyl-*N*-[2-(2-pyridyl)ethyl]-α,α-dideuterio-benzylamine).[9] An unusual kinetic behavior observed in the present reactions implicates the existence of a new copper-active oxygen intermediate that is responsible for the C−H bond activation of the external substrates.

Introduction of dry O$_2$ gas into an acetone solution of $[\mathrm{Cu^I}(\mathbf{L}^{\mathbf{Py1Bz}})(\mathrm{CH_3CN})]\mathrm{PF_6}$ at −94 °C resulted in a spectral change, where a characteristic absorption band at 400 nm (ϵ = 17400 M^{-1} cm^{-1}) readily developed (see Supporting Information, S1). The resulting acetone solution was ESR silent, and the resonance Raman spectrum of the oxygenated intermediate in frozen acetone-d_6 (λ_{ex} = 457.9 nm) exhibited a characteristic peak at 604 cm^{-1} (S2).[10] These spectral features together with the observed stoichiometry of Cu:O$_2$ = 2:1 demonstrate the formation of a bis(μ-oxo)dicopper(III) intermediate (**1**).[10] The bis(μ-oxo)dicopper(III) complex supported by the deuterated ligand $\mathbf{L}^{\mathbf{Py1Bz}}$ was stable enough to examine the reactivity toward external substrates at the low temperature.

Addition of the substrates into an acetone solution of **1** (5.0×10^{-5} M) at −94 °C under Ar atmosphere resulted in a color change from dark brown to green. Figure 1A shows the spectral change for the reaction with AcrH$_2$ as a typical example, where the characteristic absorption band at 400 nm due to **1** decreases with a concomitant increase in the absorption bands at 358, 395, 415, and 440 nm due to the oxidation product AcrH$^+$ (*N*-methylacridinium ion). From the absorption intensity at 440 nm (ϵ = 2150 M^{-1} cm^{-1})[11] is determined the yield of AcrH$^+$ as 100% based on **1**. Oxidation of CHD also proceeded smoothly to produce the corresponding oxidation products, i.e., benzene.[12] The nearly quantitative formation was confirmed by GC−MS. Thus,

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(10) Because of low intensity of the Raman bands of the ^{18}O-derivative, the amount of the isotope shift could not be determined accurately. Although the Raman evidence for the bis(μ-oxo)dicopper(III) core is not as strong as in earlier instances,[9] the structural similarity of this molecule to others in the series[7] and great similarities of the UV−vis and the ^{16}O-Raman data to those of the other bis(μ-oxo)dicopper(III) complexes[5] are strong enough arguments for the presence of the diamond core intermediate.

(11) Itoh, S.; Kumei, H.; Nagatomo, S.; Kitagawa, T.; Fukuzumi, S. *J. Am. Chem. Soc*. **2001**, *123*, 2167−2175.

(12) Stack and co-workers reported that the bis(μ-oxo)dicopper(III) complex supported by *N,N,N′,N′*-tetramethyl-1,3-propanediamine did not react with 1,4-cyclohexadine and 9,10-dihydroanthracene.[8b]

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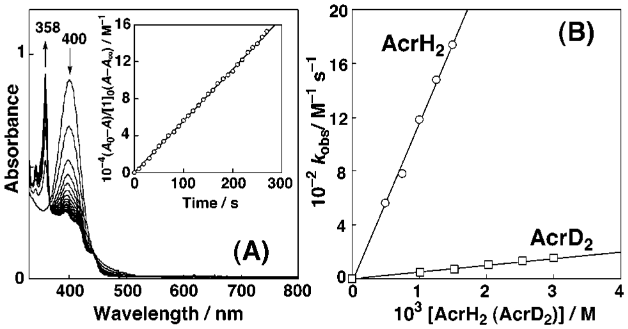


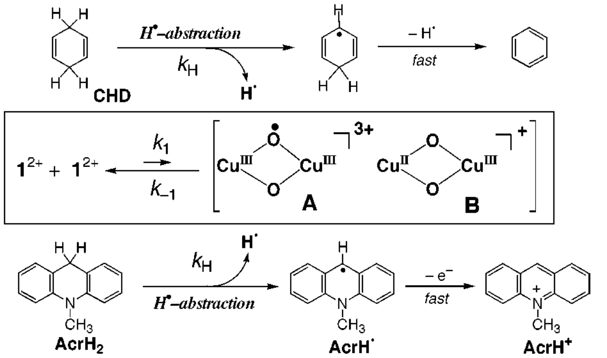
Figure 1. (A) Spectral change (20 s interval) observed upon addition of 10-methyl-9,10-dihydroacridine (5.0×10^{-4} M) into an acetone solution of **1** (5.0×10^{-5} M) at −94 °C under Ar. (Inset) Second-order plot based on the decrease of the absorption at 400 nm. (B) Plots of k_{obs} vs substrate concentration for the reaction of **1** with AcrH$_2$ (○) and AcrD$_2$ (□) under the same experimental conditions.

the present system gives us an excellent opportunity to examine the C−H bond activation mechanism of external substrates with the bis(μ-oxo)dicopper(III) species.

To our surprise, the decrease of the absorption band at 400 nm due to **1** obeys *second-order kinetics* even in the presence of a large excess substrate as shown in the inset of Figure 1A, where the second-order rate constant k_{obs} was obtained as a slope of the linear second-order plot $[(A_0 - A)/\{(A - A_\infty)[\mathbf{1}]_0\}$ vs time]. The second-order dependence on the bis(μ-oxo)dicopper(III) intermediate (**1**) has also been confirmed by the result that the k_{obs} values obtained at various initial concentrations of **1** were inversely proportional to the initial concentration of **1** as expected from the equation of the second-order plot: $(A_0 - A)/\{(A - A_\infty)\cdot[\mathbf{1}]_0\} = k_{obs}t$. The second-order rate constant k_{obs} was then plotted against the substrate concentration to demonstrate the first-order dependence of k_{obs} on [substrate] (Figure 1B, line AcrD$_2$), from which the third-order rate constant k_3 was determined as 1.2×10^6 M^{-2} s^{-1} from the slope. The same kinetic behavior (the second-order dependence on **1** and the first-order dependence on [substrate]) was observed in the reaction with CHD, and the k_3 values at −94 °C was determined as 1.5×10^4 M^{-2} s^{-1}. In addition, a large primary kinetic deuterium isotope effect ($k_3^H/k_3^D = 22.7$) was obtained at −94 °C when AcrD$_2$ (AcrD$_2$ = the 9,9-dideuterated analogue of AcrH$_2$) was used in place of AcrH$_2$ (Figure 1B, line AcrD$_2$). The overall activation energies were determined from their temperature dependence as $E_{3(H)} = 8.9 \pm 0.6$ kcal mol^{-1} and $E_{3(D)} = 10.0 \pm 0.2$ kcal mol^{-1} (S3).[13] The k_3^H/k_3^D value is significantly larger than the primary kinetic deuterium isotope effect (3.0) reported for the hydrogen abstraction from AcrH$_2$ by hydroperoxyl radical (HO$_2^\bullet$).[14] Such a large primary kinetic deuterium isotope effect indicates that a tunneling hydrogen-transfer process is involved in the rate-determining step of the C−H bond activation by **1**. However, the direct reaction between **1** and AcrH$_2$ would afford a first-order dependence of the rate with respect to the concentration of each reactant, contrary to the present experimental observation.

One of the possible explanations for such an unusual kinetic behavior (the *second-order* dependence on **1**) is following. Disproportionation of two molecules of the bis(μ-oxo)dicopper(III) complexes may afford one molecule of (μ-oxo)(μ-oxyl radical)dicopper(III) (**A**) and one molecule of bis(μ-oxo)Cu(II)-Cu(III) (**B**), the former of which is a real active species for the C−H bond activation (hydrogen atom abstraction) of the substrates (Scheme 1).[15] In such a case, the reaction is second-order with respect to **1** as experimentally observed.[16] Unfortunately, however, we could not obtain any direct evidence for such an intermediate, since the equilibrium of the disproportionation reaction may lie far to the left, that is, to the starting material [bis(μ-oxo)dicopper(III) complex].

Scheme 1



Alternatively two molecules of the bis(μ-oxo)dicopper(III) intermediate may function in unison (e.g., via a tetranuclear copper−oxo complex) to oxidize the substrate. At present, however, it is extremely difficult to distinguish between the disproportionation complex in Scheme 1 and a tetranuclear copper−oxo complex, since such a complex could not be detected because of the facile dissociation of the complex ($k_{-1} \gg k_1$ in Scheme 1).[17]

In conclusion, we present the first example of the C−H bond activation of external noncoordinative substrates such as AcrH$_2$ and CHD with a bis(μ-oxo)dicopper(III) complex, where participation of a new copper-active oxygen species such as a (μ-oxo)(μ-oxyl radical)dicopper(III) or a tetranuclear copper−oxo complex is suggested by the kinetic data. The present results will provide important insight into the C−H bond activation mechanism of copper monooxygenases, since such a (μ-oxo)(μ-oxyl radical)dicopper unit has been suggested as an actual active oxygen intermediate in the reaction of particulate methane monooxygenase.[18]

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Supporting Information Available: Experimental details including synthetic procedures, resonance Raman spectra (S2), product analysis, manometry, and kinetic measurements (S1 and S3) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The activation energy for the reaction with CHD was also determined from the temperature dependence of k_3 as $E_3 = 6.4 \pm 0.1$ kcal mol^{-1} (S3).

(14) Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1037−1045.

(15) The reaction rate was not influenced even when it was carried out in the presence of excess O$_2$. This may indicate that the subsequent hydrogen-atom transfer and the electron transfer from the radical intermediates (C$_6$H$_7^\bullet$ and AcrH$^\bullet$) are much faster than the initial hydrogen abstraction from the substrates.

(16) According to Scheme 1, the observed rate constant k_3 is given by $k_H(k_1/k_{-1})$, when the overall activation energy (E_3) consists of the activation enthalpy of each process: $\Delta H_H^\ddagger + \Delta H_1^\ddagger - \Delta H_{-1}^\ddagger$. The overall activation entropies ($\Delta S_3^\ddagger = \Delta S_H^\ddagger + \Delta S_1^\ddagger - \Delta S_{-1}^\ddagger$) were also determined from the temperature dependence of k_3 as −35, −35, and −13 cal K^{-1} mol^{-1} for AcrH$_2$, AcrD$_2$, and CHD, respectively (see Supporting Information S3).

(17) The observed negative activation entropies[16] are consistent with formation of an associative complex (a disproportionation complex or a tetranuclear complex).

(18) Elliott, S. J.; Zhu, M.; Tso, L.; Nguyen, H.-H. T.; Yip, J. H.-K.; Chan, S. I. *J. Am. Chem. Soc.* **1997**, *119*, 9949−9955.