Thermal Stability of Mononuclear Hydroperoxocopper(II) Species. Effects of Hydrogen Bonding and Hydrophobic Field

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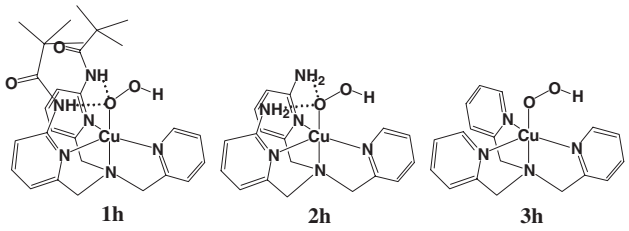
The effects of hydrogen bonding and hydrophobic field on the thermal stabilities of Cu(II)–OOH complexes have been studied using tripodal tetradentate ligands with their functional groups on the basis of UV–vis, ESR, ESI-mass, and resonance Raman spectroscopies.

Hydroperoxocopper(II) complexes are very important as active intermediates in biological oxygenases such as dopamine β-hydroxylase (DβH) and peptidylglycine α-hydroxyling monooxygenase (PHM).[1–4] In recent detailed researches on DβH, it has been reported that the hydroperoxide ion binds to Cu(II) ion and is activated through hydrogen bond between noncoordinating hydroperoxo oxygen and Tyr–OH hydrogen.[3,4] From the structural interest of hydroperoxocopper(II) intermediate, the preparations and characterizations of some hydroperoxocopper(II) complexes have been studied by many bioinorganic chemists.[5–11] We also challenged preparation of Cu(II)–OOH species, and succeeded in obtaining a stable hydroperoxocopper(II) complex with a tripodal tetradentate ligand, bis(6-pivalamido-2-pyridylmethyl)(2-pyridylmethyl)amine (BPPA) (**1h**).[5] The crystal structure and spectroscopic characterization of the hydroperoxocopper(II) complex, where the hydroperoxide ion has occupied the axial position of the Cu(II) ion with a trigonal bipyramidal geometry, revealed that it must have been stabilized by a combination of the hydrophobic field of bulky *tert*-butyl groups and the hydrogen bonding interactions between two pivalamido NH hydrogens and coordinating hydroperoxide oxygen (Scheme 1). In order to clarify the respective contribution of the effects of hydrogen bonding and hydrophobic field, the spectroscopic properties and thermal stability of hydroperoxocopper(II) complex (**2h**) have been studied using the ligand BAPA (bis(6-amino-2-pyridylmethyl)(2-pyridylmethyl) amine)[12] without hydrophobic *tert*-butyl groups, which has been compared with those of hydroperoxocopper(II) complexes (**1h** and **3h**) of BPPA and TPA (tris(2-pyridylmethyl)amine)[13] without both interaction groups (Scheme 1).

The starting copper(II) complex, [Cu(bapa)(OH)]ClO_4 (**2a**),[14] has been prepared from reaction of $Cu(ClO_4)_2 \cdot 6H_2O$ with BAPA and successive addition of KOH in MeCN. The copper(II) complex, [Cu(tpa)(H_2O)](ClO_4)$_2$ (**3a**),[15] has been prepared from reaction of $Cu(ClO_4)_2 \cdot 6H_2O$ with TPA in MeCN.

Addition of H_2O_2 (10 equiv.) to an acetonitrile solution of **2a** at $-40\,^{\circ}C$ generated a pale green colored species (**2h**), whose absorption spectrum gave an intense band at 380 nm ($\varepsilon = 700\,M^{-1}cm^{-1}$) assignable to LMCT($OOH^- \rightarrow Cu$). The ESR spectrum of **2h** exhibited typical spectrum suggesting the formation of trigonal bipyramidal mononulear copper(II) complex with a hydroperoxide ion in an end-on mode; $g_{//} = 1.95$, $g_{\perp} = 2.16$, $|A_{//}| = 84$ G, $|A_{\perp}| = 91$ G in acetonitrile. The resonance



Scheme 1.

Raman spectrum of **2h** in acetonitrile measured at $-40\,^{\circ}C$ (using 406.7 nm laser excitation) gave a resonance-enhanced Raman band at 850 cm^{-1}, which shifted to 801 cm^{-1} ($\Delta\nu = 49\,cm^{-1}$) when ^{18}O-labeled H_2O_2 was used. That of **2h** in methanol measured at $-80\,^{\circ}C$ (using 406.7 nm laser excitation) gave Raman bands at 854 and 492 cm^{-1}, assignable to ν(O–O) and ν(Cu–O), respectively. The formation of **2h** was also confirmed from ESI mass spectrum measured in acetonitrile at $-20\,^{\circ}C$; a parent peak cluster was observed at m/z 416 corresponding to the positive ion $[Cu(bapa)(OOH)]^+$.

As comparison with the spectroscopic properties of **1h** and **2h**, the preparation and characterization of $[Cu(tpa)(OOH)]^+$ species have also been performed (Table 1). Addition of H_2O_2 (10 equiv.) to an acetonitrile solution of **3a** containing Et_3N (2 equiv.) at $-40\,^{\circ}C$ also afforded a pale green colored species (**3h**). The UV–vis spectrum of **3h** in an acetonitrile gave an LMCT band at 379 nm ($\varepsilon = 1700\,M^{-1}cm^{-1}$). The ESR spectrum of **3h** exhibited typical one suggesting the formation of trigonal bipyramidal mononulear copper(II) complex with a hydroperoxide ion in an end-on fashion; $g_{//} = 2.01$, $g_{\perp} = 2.19$, $|A_{//}| = 83$ G, $|A_{\perp}| = 95$ G in acetonitrile. The resonance Raman spectra of methanol solution of **3h** measured at $-80\,^{\circ}C$ (using 406.7 nm laser excitation) showed a resonance-enhanced Raman band at 847 and 512 cm^{-1}, which are assigned to ν(O–O) and ν(Cu–O), the former of which shifted to 792 cm^{-1} ($\Delta\nu = 55\,cm^{-1}$) when ^{18}O-labeled H_2O_2 was employed. The formation of **3h** was also confirmed from ESI mass spectrum measured in acetonitrile at –40 °C; a parent peak cluster was observed at m/z 386 corresponding to the positive ion $[Cu(tpa)(OOH)]^+$.

Interestingly, the effects of hydrogen bonding and hydrophobic field on the thermal stabilities of Cu–OOH species, when their decomposition rates were followed using decrease in the absorption intensities of LMCT bands, was dramatically found out in the stability of these hydroperoxocopper(II) complexes. Complex **3h**, as measured at $-40\,^{\circ}C$, decomposed according to a good first order kinetics ($k_{obs} = 1.55 \times 10^{-3}\,s^{-1}$, $t_{1/2} = 7.5$ min), although the other two complexes, **1h** and **2h** with hydrogen bonding interaction sites, are very stable at $-40\,^{\circ}C$. However, **2h** showed a decomposition at 25 °C, whose rate also

Table 1. Summary of several spectral data of Cu–L–OOH species

L (Hydroperoxo -complexes)	UV–vis[a] (−40 °C) LMCT ($HOO^- \rightarrow Cu$) λ_{max}/nm	ESR[a] (77 K) $g_{//}$	$g_{\perp}$	$\lvert A_{//}\rvert$/G	$\lvert A_{\perp}\rvert$/G	Resonance Raman[b] (−80 °C) ν(O–O)/cm^{-1}	ν(Cu–O)/cm^{-1}
BPPA (**1h**)[c]	380(890)	2.00	2.21	109	75	863	481
BAPA (**2h**)	380(700)	1.95	2.16	84	91	854	492
TPA (**3h**)	379(1700)	2.01	2.19	83	95	847	512

[a]in MeCN. [b]in MeOH. [c]Ref. 5, 11c.

obeyed a good first order kinetics ($k_{obs} = 3.37 \times 10^{-4}\,s^{-1}$, $t_{1/2} = 34.3$ min), although another complex **1h** with sterically-bulky hydrophobic *tert*-butyl groups was extremely stable even at 25 °C.[5] Therefore, the order of the thermal stabilities of these hydroperoxocopper(II) complexes is determined as follows; **1h** ≫ **2h** > **3h**. These findings clearly indicate that the hydrogen bond stabilizes the hydroperoxo species, and the additional introduction of sterically-bulky hydrophobic *tert*-butyl group makes it more stable.

The thermal stabilities of hydroperoxocopper(II) complexes are closely correlated with Raman shifts of ν(O–O) and ν(Cu–O) (Table 1); the stable hydroperoxo species has a stronger O–O bond, but it makes the Cu–O bond weaken. The strengths of Cu–O bonds may also be reflected in $|A_{//}|$ values; the formation of stronger Cu–O bond in the *z*-axis direction causes the permeation of spin density to increase onto the d_{z^2}-orbital of copper ion to give smaller $|A_{//}|$ value (Table 1). Thus the hydrogen bonding interaction with the proximal α-oxygen of the hydroperoxo species makes the Cu–O and O–O bonds weaken and strengthen, respectively, because its interaction makes the electron density on the α-oxygen atom reduced.

Previously we reported that the hydrogen bonding interaction with non-coordinating β-oxygen of the hydroperoxo species activates the peroxide,[11a] in contrast with the above result that the interaction with the proximal α-oxygen stabilizes it. These facts include the following biological implication; the hydroperoxocopper(II) species is stabilized by the interaction with α-oxygen but activated by that with β-oxygen, which coincides well with the case of DβH.[3,4]

In conclusion, in order to elucidate the contributions of hydrogen bonding and hydrophobic field on the stability of hydroperoxocopper(II) species, the hydroperoxocopper(II) complexes with and without their interaction sites was systematically studied by the use of spectroscopic and kinetic methods. As was expected, the complexes with amide (**1h**) or amine NH group (**2h**) as the hydrogen bonding site have obviously been stabilized as compared with **3h** not having hydrogen bonding site. The hydrogen bonding interaction is quite critical for the stability, although there may be a slight difference in the strengths of hydrogen bonding interactions between amide and amine NH groups. And the hydroperoxocopper(II) species with *tert*-butyl group (**1h**) was also undoubtedly stabilized as compared with **2h** and **3h** bearing the *tert*-butyl groups. This must be due to significant contribution of the hydrophobic field, although of course it is due to the stabilization by the protection of the hydroperoxo species from the attack of solvent molecules by *tert*-butyl group (Figure S1). Recently, the X-ray crystal structure of the precatalytic PHM enzyme with both of *N*-acetyl-diiodo-tyrosyl-D-threonine (IYT) and dioxygen, which has been soaked as a substrate and has been bound to one of coppers with an end-on mode, respectively, has been reported.[16] In this complex, it has been described that the dioxygen adduct is stabilized in the presence of IYT, suggesting that IYT plays as a hydrophobic field to protect the dioxygen molecule bound to copper. This report supports our results described here, although it is very difficult to demonstrate the effect of hydrophobic field on the stability of peroxo species.

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16 Elemental analysis for **3a**: Found: C, 36.36; H, 3.88; N, 9.41%. Calcd for **3a**· 1.5 H_2O ($C_{18}H_{20}Cl_2CuN_4O_9 \cdot 1.5H_2O$) C, 36.16; H, 3.88; N, 9.37%.
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