Synthesis and Characterization of Novel Alkylperoxo Mononuclear Iron(III) Complexes with a Tripodal Pyridylamine Ligand: A Model for Peroxo Intermediates in Reactions Catalyzed by Non-Heme Iron Enzymes

Akira Wada,[†] Seiji Ogo,[‡] Yoshihito Watanabe,*[,‡] Masahiro Mukai,[‡] Teizo Kitagawa,[‡] Koichiro Jitsukawa,*[,†] Hideki Masuda,*[,†] and Hisahiko Einaga[†]

Department of Applied Chemistry, Nagoya Institute of Technology, Showa-ku, Nagoya 466-8555, Japan, and Institute for Molecular Science, Myodaiji-cho, Okazaki 444-8585, Japan

Received January 6, 1999

Peroxo−iron species are frequently implicated as potential intermediates in many biological oxidations[1] catalyzed by mononuclear non-heme iron enzymes such as lipoxygenase, α-keto acid dependent enzymes, isopenicillin N synthase, catechol dioxygenase, and bleomycin. It has recently been suggested that treatment of the iron(II) site of lipoxygenase[2] with excess ROOH converts it to an alkylperoxo−iron(III) species which corresponds to the metastable purple one found during the oxygenation process of polyunsaturated fatty acids. Thus, alkylperoxo−iron(III) complexes particularly deserve attention as models for the elucidation of the proposed intermediates in these reactions. However, only a few spectroscopic characterizations of mononuclear alkylperoxo−iron(III) complexes[3,4] that were prepared from the mononuclear iron(II) and μ-oxo dinuclear iron(III) complexes have been reported because of their instabilities.

Previously, by the use of a tripodal pyridylamine ligand, tris(6-neopentylamino-2-pyridylmethyl)amine (TNPA), we first succeeded in the preparation of [Fe(tnpa)(OH)(PhCOO)]ClO_4 as a model complex for an active form of soybean lipoxygenase-1, in which stable formation of the hydroxo−iron(III) complex was accomplished by intramolecular hydrogen bonds.[5] We also achieved the isolation of [Cu(bppa)(OOH)]ClO_4 having Cu(II)−OOH species by employing a similar tripodal pyridylamine ligand, bis(6-pivalamido-2-pyridylmethyl)(2-pyridylmethyl)amine (BPPA).[6] Here, in order to understand the coordination environment of peroxo intermediates in reactions catalyzed by non-heme iron enzymes, we have tried to synthesize stable alkylperoxo mononuclear iron(III) complexes using BPPA ligand and to examine the physicochemical properties.

Treatment of BPPA with equimolar amounts of $Fe(ClO_4)_3 \cdot 10H_2O$ and sodium trimethylacetate (*t*-BuCOONa) in MeCN/MeOH followed by vapor diffusion of toluene afforded red crystals of [Fe(bppa)(*t*-BuCOO)]$(ClO_4)_2$ (**1**) suitable for X-ray diffraction measurement.[7] The structure of **1** reveals seven-coordinate monocapped octahedral geometry around the iron(III) ion, with the tertiary amine nitrogen in the axial position, the three pyridine nitrogens in the bottom trigonal plane, and the two pivalamido oxygens and a *t*-BuCOO oxygen in the top trigonal plane. The *t*-BuCOO oxygen, as the seventh exogenous ligand, is coordinated in the end-on fashion with a Fe−O(3) bond length of 1.984(6) Å.

The addition of aqueous solutions containing excess amounts of *tert*-butyl hydroperoxide (TBHP, 69 w/w%) or cumene hydroperoxide (CHP, 80 w/w%) to a MeCN solution containing complex **1** at room temperature generated a blue (**2**) ($\lambda_{max} = 613$ nm, $\epsilon = 2000$ M^{-1} cm^{-1}) (Figure 1A) or a purple species (**3**) ($\lambda_{max} = 585$ nm, $\epsilon = 2200$ M^{-1} cm^{-1}), respectively, both of which are stable at room temperature for ∼5 h. The spectral changes in visible region for these complexes agree well with those for the enzyme system.[2] Especially, the absorption band in complex **3** is extremely similar to LMCT in the lipoxygenase cycle (585 nm).[2]

The resonance Raman spectra of a MeCN solution containing the complex **2** which were measured at room temperature by using 600 nm laser excitation[8] revealed strong resonance-enhanced Raman features at 873, 838, 629, and 469 cm^{-1} (Figure 1B), while that of **3** exibited features at 878, 838, 639, 548, and 493 cm^{-1}. The Raman features normally observed at ca. 800 cm^{-1} are in the range characteristic for ν(O−O) vibrations of peroxide species[9] and are insensitive upon the addition of $H_2{}^{18}O$. Since these vibrational data were in agreement with those observed for the terminal η^1-alkylperoxo species obtained from the reaction of Fe(II)−(6-Me_3TPA) complexes with alkylperoxides,[3b] we deduced that the alkylperoxo moiety is retained on the iron(III) ion in an end-on fashion and the intense absorption bands near 585 and 613 nm for complexes **2** and **3**, respectively, are thus assignable to the alkylperoxo-to-iron(III) charge transfer transition.

[†] Nagoya Institute of Technology.
[‡] Institute for Molecular Science.

(1) (a) Feig, A. L.; Lippard, S. J. *Chem. Rev.* **1994**, *94*, 759. (b) Que, L., Jr.; Ho, R. Y. N. *Chem. Rev.* **1996**, *96*, 2607. (c) Nivorozhkin, A. L.; Girerd, J.-J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 609.
(2) (a) Nelson, M. J. *Biochemistry* **1988**, *27*, 4273. (b) Zang, Y.; Gan, Q.; Pavel, E. G.; Sigal, E.; Solomon, E. I. *J. Am. Chem. Soc.* **1995**, *117*, 7422 and references therein. (c) Minor, W.; Steczko, J.; Bolin, J. T.; Otwinowski, Z.; Axelrod, B. *Biochemistry* **1993**, *32*, 6320. (d) Boyington, J.; Gaffney, B.; Amzel, L. M. *Science* **1993**, *260*, 1482. (e) Gillmor, S. A.; Villasenor, A.; Fletterick, R.; Sigal, E.; Browner, M. F. *Nature Struct. Biol.* **1997**, *4*, 1003.
(3) (a) Zang, Y.; Elgren, T. E.; Dong, Y.; Que, L. *J. Am. Chem. Soc.* **1993**, *115*, 811. (b) Zang, Y.; Kim, J.; Dong, Y.; Wilkinson, E. C.; Appelman, E. H.; Que, L. *J. Am. Chem. Soc.* **1997**, *119*, 4197.
(4) (a) Menage, S.; Wilkinson, E. C.; Que, L., Jr.; Fontecave, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 203. (b) Kim, J.; Larka, E.; Wilkinson, E. C.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2048.
(5) Ogo, S.; Wada, S.; Wada, Y.; Iwase, M.; Wada, A.; Harata, M.; Jitsukawa, K.; Masuda, H.; Einaga, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2102.
(6) (a) Wada, A.; Harata, M.; Hasegawa, K.; Jitsukawa, K.; Masuda, H.; Mukai, M.; Kitagawa, T.; Einaga, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 798. (b) Harata, M.; Hasegawa, K.; Jitsukawa, K.; Masuda, H.; Einaga, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1031.
(7) X-ray analysis: red crystal of [Fe(bppa)(*t*-BuCOO)]$(ClO_4)_2 \cdot CH_3CN$ (**1**) from a MeCN/MeOH solution, $FeCl_2O_{12}N_7C_{35}H_{46}$, MW 883.54, monoclinic, space group *Cc*, $a = 23.632(4)$ Å, $b = 11.158(1)$ Å, $c = 18.680(2)$ Å, $\beta = 121.18(1)°$, $V = 4214.0(1)$ Å^3, $Z = 4$, $D_c = 1.393$ g cm^{-3}, μ(Mo Kα) = 5.50 cm^{-1}, $T = 226$ K, number of reflections used 3538 ($I > 3\sigma(I_o)$), $R = 0.069$, and $R_w = 0.074$.
(8) Although Raman measurements using of other laser excitations, 514 and 580 nm, were also performed, any characteristic spectral changes were not detected in the range 400−1000 cm^{-1}. Further examination is in progress.
(9) (a) Kitajima, N.; Tamura, N.; Amagai, H.; Fukui, H.; Moro-oka, Y.; Mizutani, Y.; Kitagawa, T.; Mathur, R.; Heerwegh, K.; Reed, C. A.; Randall, C. R.; Que, L., Jr.; Tatsumi, K. *J. Am. Chem. Soc.* **1994**, *116*, 9071. (b) Hayashi, Y.; Kayatani, T.; Sugimoto, H.; Suzuki, M.; Inomata, K.; Uehara, A.; Mizutani, Y.; Kitagawa, T.; Maeda, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11220. (c) Kim, K.; Lippard, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 4914.

10.1021/ic9900298 CCC: $18.00
Published on Web 07/13/1999

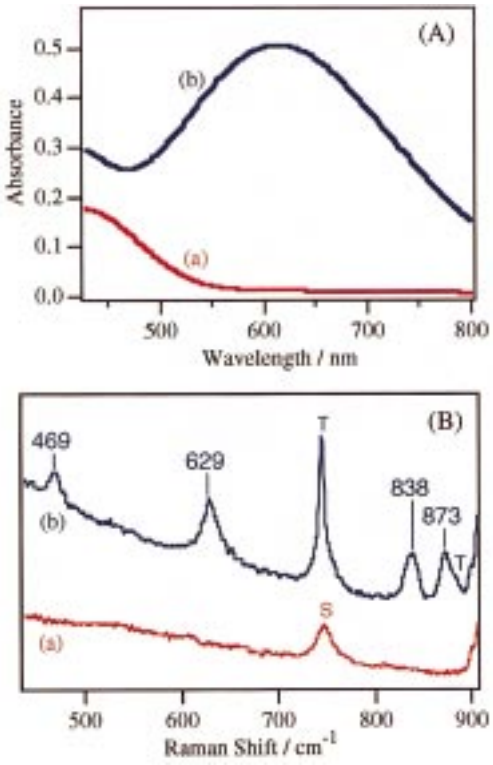

Figure 1. Electronic (A) and resonance Raman (B), spectra of the species **2** (b) obtained in the reaction of **1** (a) with TBHP in MeCN at room temperature.

The ESI mass spectra of a MeCN solution of complex **1** treated with excess amounts of TBHP at room temperature afforded positive- and negative-ion spectra with prominent peak clusters at *m*/*z* 316.5 and 932 (Figure 6S, Supporting Information), respectively. These observed masses and isotope patterns corresponded to the ions, $[Fe(bppa)(OO\text{-}t\text{-}Bu)]^{2+}$ and $\{[Fe(bppa)(OO\text{-}t\text{-}Bu)](ClO_4)_3\}^-$, demonstrating that complex **1** has completely reacted with TBHP at room temperature without decomposition. The use of CHP made these features shift to *m*/*z* 347.5 and 994, respectively, which are consistent with the increased mass of C_6H_5 relative to CH_3. These intense colors of **2** and **3** remained intact in the course of the mass spectrometry experiment, suggesting that the complexes are very stable as described above. It is thus clear from these facts that **2** and **3** could be commonly best formulated as $[Fe(bppa)(OOR)]^{2+}$.

The frozen solution ESR spectra of these reaction products demonstrated a typical high-spin state of iron(III) sites with small rhombic distortion (**2**, $g = 7.58, 5.81, 4.25, 1.82$, $E/D = 0.067$; **3**, $g = 7.76, 5.65, 4.20, 1.78$, $E/D = 0.070$ at 77 K in MeCN),[10] which are distinct from the greater rhombic ESR signals of high-spin alkylperoxo mononuclear iron(III) complexes[3,4] reported previously, reflecting that the above products **2** and **3** form an axially symmetric seven-coordination structure similar to **1** after exchange of an alkylperoxide for *t*-BuCOO. This observation may suggest that the Fe(III)−OOR bond is elongated due to steric interactions between *tert*-butyl groups of BPPA and results in a lowering of the electron donor ability of the alkylperoxide to the iron site, which induces a higher stability of the complexes even at room temperature and prevents the decomposition of the Fe(III)−OOR species by a Haber−Weiss process.[11]

These electronic absorption, resonance Raman, ESI mass, and ESR spectral data acquired at room temperature represent the evidence that the stable alkylperoxo mononuclear iron(III) complexes are synthetically prepared in solution. In order to elucidate the cause of stable formation of the alkylperoxo complexes, the redox potential of the iron(III) site was examined. Complex **1** displayed a quasi-reversible redox wave with $E_{1/2}$ values at +700 mV vs NHE related to the Fe^{III}/Fe^{II} couple, indicating that **1** favors the iron(II) oxidation state more than other mononuclear iron(III) complexes.[3b,12] This potential is in fair agreement with that in lipoxygenase ($E_{1/2} \sim 0.6$ V vs NHE).[2a] The introduction of electron-withdrawing substituents, two 6-pivalamide groups, on the pyridine rings should make the basicity of pyridine nitrogens lower enough and make the redox potential of the iron center shift to more positive side, which may contribute to thermodynamic stabilization of the alkylperoxo mononuclear iron(III) complexes.

Fortunately, the alkylperoxide iron(III) complexes have successfully been isolated as powder precipitates by addition of Et_2O to an acetone solution of **1** treated with CHP/TBHP at −78 °C, although they were accompanied by slight decomposition. After removing excess CHP/TBHP by dry Et_2O, the electronic absorption, ESR, and ESI mass measurements of acetone solutions of the powder precipitates demonstrated almost the same spectra as the peroxide adducts prepared in solutions described above.

In conclusion, we have first succeeded in the preparation of thermodynamically stable iron(III) complexes with alkylperoxide in the end-on fashion, whose spectral behaviors are comparable to those of lipoxygenases.[2] The above findings strongly suggest that the ligand BPPA with some noncovalent interaction groups contributes to the formation of the extremely stable iron(III)−alkylperoxide complexes and the coordination environment of the peroxo intermediate in lipoxygenase[2] may be seven-coordinate. This is attributable to the success of the functional ligand, BPPA, that enables electronical and/or structural control.[6] Furthermore, we believe these results will provide important information for further studies on metal−oxygen interactions and become a starting point for catalytic oxidation chemistry by activated mononuclear non-heme iron complexes.

Acknowledgment. We are grateful to Dr. Shigenori Nagatomo for his useful discussion for resonance Raman spectra. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (Y.W., K.J., and H.M.) and the Sumitomo Foundation (H.M.), for which we express our thanks.

Supporting Information Available: ORTEP drawing of **1** (Figure 1S) and UV−vis, ESR, resonance Raman, ESI-mass, and FT-IR spectral data for complexes **2** and **3** (Figures 2S−8S). This material is available free of charge via the Internet at http://pubs.acs.org.

IC9900298

(10) The intense resonances at $g = \sim 7$ that appeared after the reaction of complex **1** with CHP indicate that at least two paramagnetic species are present.

(11) Willing, C. *Acc. Chem. Res.* **1975**, *8*, 125.
(12) Norman, R. E.; Holz, R. C.; Menage, S.; O'Connor, C. J.; Zhang, J. H.; Que, L., Jr. *Inorg. Chem.* **1990**, *29*, 4629.