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Cite this: DOI: 10.1039/c0xx00000x

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Biomimic O_2 Activation Hydroxylates a *meso*-Carbon of the Porphyrin Ring Regioselectively under Mild Condition

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The reaction site of the Co(II) porphyrin created by an amide group and coordinating 1,2-dimethylimidazole at the fifth site activated an O_2 molecule, and then hydroxylated the *meso*-carbon of the ligand. The biomimic O_2 activation under mild condition is described.

Proximal and distal histidine residues provide the coordination environment for stable O_2 fixation[1] at the heme site of hemoglobin (Hb) and myoglobin (Mb), while proximal and distal-polar residues create a reaction environment for O–O bond activation[2,3] at the heme sites of some metalloenzymes such as cytochrome *c* peroxidase (C*c*P), cytochrome P450 (CYPs), and heme oxygenase (HO) (Fig. 1). HO activates O_2 at the active site, and then hydroxylates the *meso*-carbon of heme, yielding hydroxy heme in the initial step (Fig. 1c). For activation of the O–O bond at the acctive sites, the so-called "push–pull" mechanism[3] has been proposed. This is a cooperative effect by electron donation from the proximal residue at the fifth site (push effect) and associations from distal-polar residues to the coordinating substrate (pull effect).

Although various porphyrin complexes that mimic the microenvironments have been designed and synthesized,[4-6] model complexes that activate O_2 molecules under mild conditions are still rare. As an important example, Chang and co-workers have shown that their complex [Co^{II}(npca-por)] (H_2npca-por = naphthoic acid porphyrin), having a carboxyl group that interacts with O_2 bound at the metal center, activates O_2 and then oxidizes itself to the oxaporphyrin cation.[4] Because this reaction did not need coordination of a proximal base, the O_2 activation of this system would be caused by the carboxyl group (pull effect).

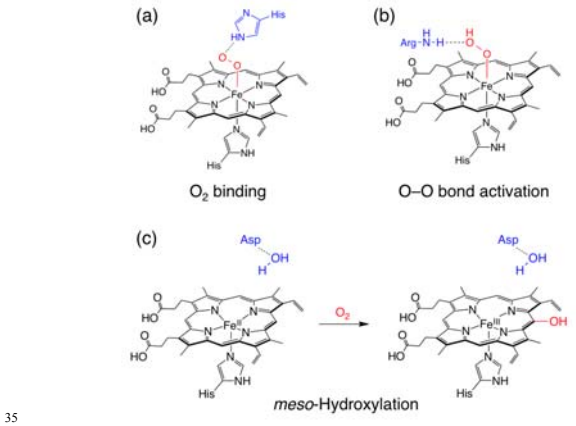
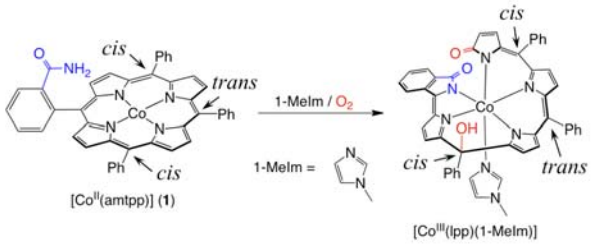


Fig. 1 (a) Proximal and distal histidine for stable O_2 fixation observed in active sites of Hb and Mb. (b) Active site of C*c*P created by proximal and distal-polar residues for "push-pull" O–O bond activation. (c) The hydroxylation of *meso*-carbon of heme at the initial step in the catalytic reaction by HO.

We have recently designed a new porphyrin ligand, amtpp, that has an amide group at the *ortho*-position of a phenyl group of tetraphenylporphyrin (TPP) to mimic the microenvironment created by a distal-polar residue observed in the heme-containing metalloproteins. In a recent report, we have shown that [Co^{II}(amtpp)] (**1**) converted to new Co(III) complexes bearing an acyclic pentapyrrole-type ligand, lpp, under air in the presence of nitrogen bases (Scheme 1).[6] The structure of lpp is shown in this Scheme.



Scheme 1 Conversion of **1** to [Co^{III}(lpp)(1-MeIm)] by reaction with O_2 in the presence of 1-MeIm.

We have continued studies on the conversion reaction by using other types of nitrogen bases. Through this work, we have found

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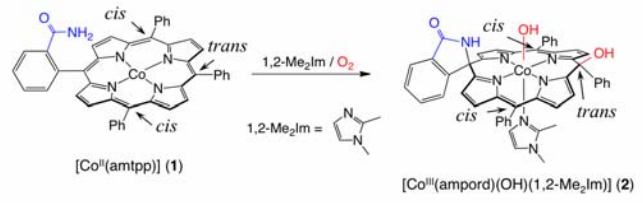
† Electronic supplementary information (ESI) available: Experimental procedures and physical properties. CCCDC 908587 (**2**) and 908586 (**3**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

that treatment of **1** with 1,2-dimethylimidazole (1,2-Me_2Im) under air yielded a new Co(III) complex **2** bearing a porphodimethene-type ligand, ampord, whose structure is illustrated in Scheme 2. We report herein the new conversion reaction from **1** to **2** by "push–pull" O_2 activation, which mimics the initial step of the catalytic reaction by HO.

A chloroform solution of **1** led to a dramatic color change from red to brown in a few hours by addition of 1,2-Me_2Im. Diffusion of *n*-hexane into the solution afforded single crystals of [Co^{III}(ampord)(OH)(1,2-Me_2Im)] (**2**) in 32% yield after a few days. As byproduct, [Co(amtpp)(1,2-Me_2Im)$_2$]Cl was isolated in 28% yield (Scheme S1 in ESI†).



Scheme 2 Conversion of **1** to **2** by reaction with O_2 in the presence of 1,2-Me_2Im.

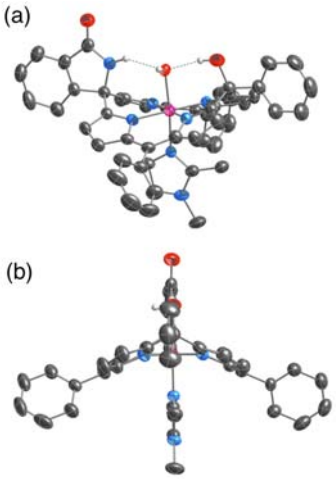


Fig. 2. (a) Thermal ellipsoid plot of **2** at 30% probability. (b) This view shows the bent structure of **2**. Hydrogen bonds formed by the coordinating OH^- with NH and OH groups are illustrated by broken lines. Color code: pink, cobalt; red, oxygen; blue, nitrogen; black, carbon; gray, hydrogen.

The structure of **2** was determined by a single-crystal X-ray diffraction study[8] (Fig. 2). The *meso*-carbon atoms in the positions *cis* and *trans* to the benzamide group of amtpp are designated as *cis*-*meso*-carbon and *trans*-*meso*-carbon atoms, respectively, in this paper (Scheme 1, 2). The amide nitrogen atom of **1** forms a C–N bond with the *meso*-carbon atom of amtpp to yield an oxoisoindoline ring in **2**, while a hydroxyl group is added to the *trans*-*meso*-carbon atom of **1**. The hydroxyl group is regioselectively introduced to the same side of the porphyrin framework where the amide group existed. This is the opposite side from the one that 1,2-Me_2Im occupies. The coordinating OH^- at the Co(III) center forms hydrogen bonds with an NH site of the oxoisoindoline ring (O···N = 2.788(6) Å) and the hydroxyl group at the *meso*-carbon (O···O = 2.704(5) Å).

As shown in Fig. 2b, the porphodimethene framework is remarkably bent at the two sp^3 carbons. The angle defined by the two conjugating dipyrrin rings is about 118°. The Co(III) ion is in the plane defined by the four coordinating nitrogen atoms of ampord. The average of the four Co–N bond distances is 1.93 Å. These bond distances are slightly shorter than those of Co–N and Co–O formed between the Co(III) ion and 1,2-Me_2Im and the coordinating OH^- (2.030(4) Å and 2.007(3) Å). Complex **2** shows characteristic absorptions at 470 and 502 nm, which are ascribed to the π–π* transition of their polypyrrole parts. Charts of absorption spectra of **1** and **2** are shown in Figs. S18 and S19 in the ESI.

We confirmed that OH^- at the Co(III) center and a hydroxyl group at the *meso*-carbon of **2** come from O_2 molecules by $^{18}O_2$-labeling experiments. Fig. 3 shows the electrospray ionization–time of flight (ESI–TOF) mass spectrum charts of **2** obtained by reaction of **1** with $^{16}O_2$ or $^{18}O_2$ in the presence of 1,2-Me_2Im. Complex **2** obtained under $^{16}O_2$ showed an isotope cluster at *m*/*z* 844.2, assigned to [H^+·**2**], while **2** obtained under $^{18}O_2$ showed the corresponding isotope cluster at *m*/*z* 848.3. The isotope shift clearly shows that both of the OH^- and hydroxyl groups in **2** originate from the O_2 molecules.

When the reaction was carried out in tetrahydrofuran containing 2,000 equiv of $H_2{}^{18}O$ under $^{16}O_2$, ^{18}O was not incorporated into the obtained **2** (Fig. S12 in the ESI†), showing that the water molecule is not a source of the OH^- and hydroxyl group in **2**. This result is consistent with the above isotope-labeling experimental results.

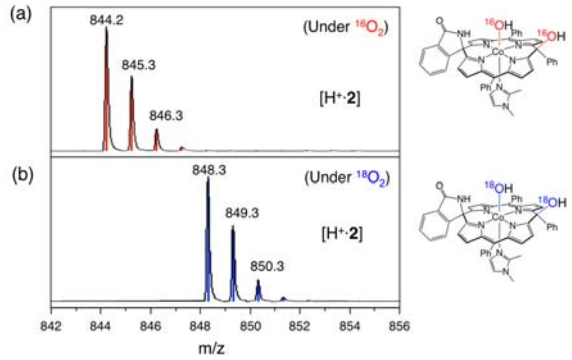


Fig. 3. ESI–TOF mass spectrum charts of **2** obtained by treatment of **1** with 1,2-Me_2Im under $^{16}O_2$ (a) and $^{18}O_2$ (b). Each simulation pattern is illustrated by red and blue lines.

Scott and co-workers have reported that porphyrins that have two carboxyl groups near two different *meso*-carbon atoms that are located in the *trans* position converted to porphodimethene-type compounds by chemical or electrochemical oxidation.[7] The metal ions are not necessary in this conversion system. We characterized the electrochemical behavior of **1** in the presence of 1,2-Me_2Im using cyclic voltammetry (CV). The oxidation wave was observed at 1063 mV (vs. SCE), which is extremely positive compared with those of Scott's compounds (286–516 mV). Moreover, in contrast to the case of Scott's system, treatment of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in MeOH did not yield Co(III)-ampord-type compounds (page 18 in the ESI†),

showing that the formation of **2** from **1** is not the result of the simple oxidation of the amtpp framework by O_2 molecules without O–O bond activation.

The nitrogen base 1,2-Me_2Im has a stronger electron-donating ability than other nitrogen bases that yielded Co(III)-lpp-type complexes by treatment with **1** (Fig. S22 in the ESI†). To examine whether or not the conversion of **1** to **2** is due to the strong electron-donating ability of the axial ligand, we studied the reaction of **1** with 1,5-dicyclohexylimidazole (1,5-Cy_2Im), which has a similar strong electron-donating ability compared with that of 1,2-Me_2Im. Single-crystal X-ray analysis and elemental analysis clearly showed that the reaction product is not a Co(III)-amperd-type complex, but [Co^{III}(lpp)(1,5-Cy_2Im)] (**3**) (page 5 and Figs. S3-S5 in the ESI†). This result means that the formation of **2** in this system is not due to stronger electron donation from the axial ligand, but would likely be due to the steric effect of the methyl groups of 1,2-Me_2Im.

To obtain insight into the steric effects of the 1,2-Me_2Im on the reactivity of **1** toward O_2, structures of [Co^{II}(amtpp)B] (**1**·B) (B = 1-MeIm and 1,2-Me_2Im) were estimated by density functional theory (DFT) calculations at the B3LYP/6-31G* level.[9] Their optimized structures are shown in Fig. S29. For **1**·1-MeIm, although the phenyl group in the position *trans* to the benzamide bends down slightly, the conjugating porphyrin framework including four *meso*-carbon atoms remains planar. In contrast, for **1**·1,2-Me_2Im, the porphyrin framework significantly deviates from planarity because of the steric repulsion from the methyl group of 1,2-Me_2Im in the 2-position. The two *cis*-*meso*-carbon atoms bend down from the porphyrin plane, while the *trans*-*meso*-carbon site bends up from the plane. Selective hydroxylation at the *trans*-*meso*-carbon atom induced by 1,2-Me_2Im in this system would be due to the approach of the *trans*-*meso*-carbon atom to the activated O_2 species, and the separation of the *cis*-*meso*-carbon atom from the activated O_2 species. It is likely that terminal oxygen of the activated O_2 molecule is a source of hydroxyl group which was introduced to the *meso*-carbon, and the residual oxygen would be the source of OH^- bound at the Co(III) site.

In summary, reaction of air-stable Co(II) complex **1** with O_2 in the presence of 1,2-Me_2Im was studied. The reaction site, which is created by the amide group and 1,2-Me_2Im at the fifth position, activated the O_2 molecule under mild condition, and then yielded a new Co(III)-porphodimethene-type complex **2**. Isotope-labeling experiments showed that OH^- at the Co(III) center and a hydroxyl group at the *meso*-carbon of **2** originate from the O_2 molecule. This reaction mimics the "push–pull" O_2 activation observed in heme-containing metalloenzymes. The effects of 1,2-Me_2Im on the selective hydroxylation at the *trans*-*meso*-carbon were preliminary studied by using DFT calculation. The further studies of the reaction mechanism are currently undergone.

This work was supported by JSPS Fellowship for Young Scientists. We thank K. Terasaki and A. Yamamoto of the Center for Instrumental Analysis in Shizuoka University for support in obtaining the elemental analysis data.

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8 Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCCDC 908587 (**2**) and 908586 (**3**)) and can be obtained via www.ccdc.cam.ac.uk/ data_request/cif. Single Crystal Data; **2**·2$CHCl_3$: $C_{52}H_{40}Cl_6CoN_7O_3$, M = 1082.58, monoclinic, $P2_1/n$, a = 10.7642(5) Å, b = 20.7043(12) Å, c = 22.5542(12) Å, β = 96.087(3)º, V = 4998.2(5) Å^3, T = 293 K, reflections collected/unique reflections/parameters refined: 31876/8708/757, R_{int} = 0.0556, final R_1 = 0.0777 ($I > 2\sigma$ (I)), wR_2 = 0.1395 (all data); **3**·3.25$CHCl_3$: $C_{63.25}H_{55.25}Cl_{9.75}CoN_7O_3$, M = 1366.03, triclinic, $P\bar{1}$, a = 12.8053(7) Å, b = 12.8800(6) Å, c = 21.7874(17) Å, α = 87.958(6)º, β = 80.671(6)º, γ = 62.793(4), V = 3150.6(4) Å^3, T = 173 K, reflections collected/unique reflections/parameters refined: 20445/10799/1018, R_{int} = 0.0364, final R_1 = 0.0538 ($I > 2\sigma$ (I)), wR_2 = 0.1138 (all data).

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