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Formation of Superoxide Anion on Aerial Oxidation of Cu(II)–Porphyrinogen in the Synthesis of Tetrakis(cyclohexyl)porphyrinogenCu(III) Anion

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Tetraethylammonium–tetrakis(cyclohexyl)porphyrinogenCu(II) (**1**) is spontaneously oxidized by aerial oxygen to the corresponding Cu(III) (**2**) species, producing 1 equiv of O_2^-. Steric crowding of the peripheral hydrogens in **1** prevented any direct Cu−O_2 bond formation in the oxidation process, which suggests an outer-sphere electron transfer reaction.

Copper plays a crucial role in the sustenance of aerobic life.[1,2] It also prevents tissue damage by catalyzing the disproportionation of toxic superoxide in superoxide dismutase.[3] These events involve direct oxygen binding to at least one copper(I) center as the first step for initiating further chemical reactions to occur. In synthetic and model copper−oxygen chemistry, the structure−reactivity in $Cu(I)_n-O_2$ (n = no of copper) interaction is founded on the ligand coordination of the Cu(I) ion.[4] More commonly, it is the dicopper(I) center which responds to oxygenation to form a dicopper(II) moiety with an oxo-bridged bond. Such a reaction may involve the formation of dicopper(III) species at low temparatures.[5] Unlike Cu(I), Cu(II) normally remains stable in the air but curiously reacts in a hot pyridine medium with corrole in the air to yield Cu(III)–corrole.[6] The fate of oxygen in such an oxidation process has not yet been studied. Porphyrins and porphyrinogens having an $\{N_4\}$ donor site similar to corrole generally form stable $\{Cu(II)(N_4)\}$ cores even in the air.

Thus Cu(II)−porphyrinogen complex, $[Et_8N_4Cu^{II}Li_2(THF)_4]$, synthesized from the anion, $Et_8N_4^{4-}$, of octaethylporphyrinogen ($Et_8N_4H_4$) is stable in the air. However, excess $CuCl_2$ neatly changes it to the corresponding Cu(III) species.[7]

More intriguing is its solvent-dependent redox stability, as in benzene it is reverted back to Cu(II) along with ligand oxidation. Such a disproportionation reaction has been prevented by adding 12-crown-4 ether, which coordinates with the lithium present[7] in the complex to form $[Li(12\text{-Crown-}4)]^+[Et_8N_4Cu^{III}]^-$. The $[Li(THF)_2]^+$ cation in $[Et_8N_4Cu^{II}Li_2(THF)_4]$ remains η^3-bonded to the pyrrolyl ring of coordinated porphyrinogen via π bonding.[7] Recently, a synthesis of Cu(II)−porphyrinogen based on the preattachment of four ruthenocenes to the four pyrrole segments of the porphyrinogen has been described. This complex responds to reversible reduction, suggesting the stability of Cu(I) in a porphyrinogen environment.[8] Thus, the reactivity of Cu(II)−porphyrinogen systems may be controlled by changing the electronic population of the pyrrolyl ring of

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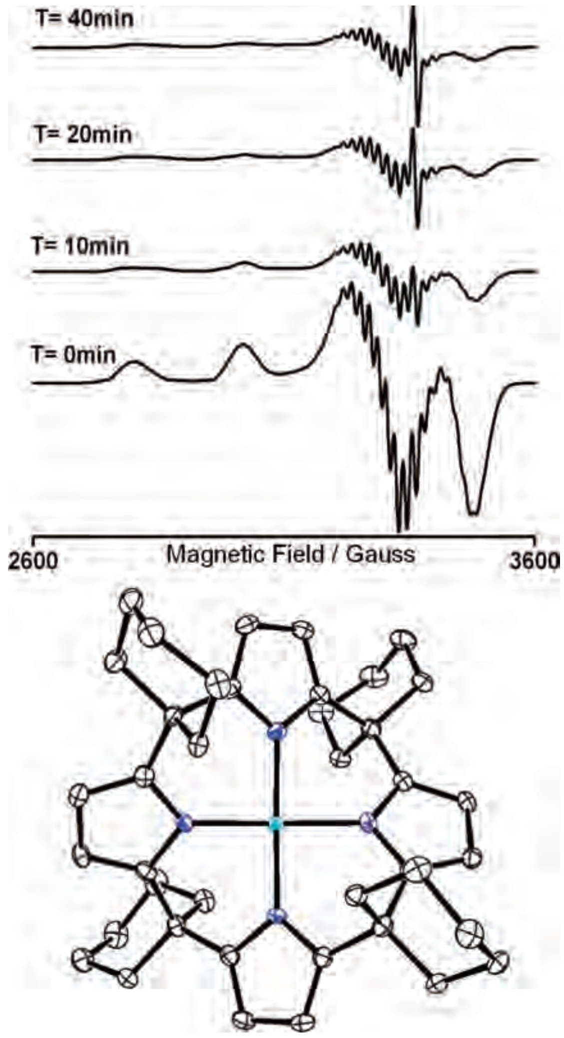

Figure 1. Time-dependent EPR spectral changes of a 10^{-2} M solution of **1** in dichloromethane by thawing in the air and refreezing after a desired time interval at 120 K (top) and an ORTEP view for the anionic part of complex **2** (showing 50% probability thermal ellipsoids) isolated from such a reaction (bottom; colors: cyan, Cu; blue, N; gray, C; H atoms omitted for clarity).

coordinated porphyrinogen. Direct incorporation of a trivalent metal ion in porphyrinogen remains difficult. The use of a quaternary ammonium countercation was shown to facilitate such an incorporation of the Fe(III) ion in a porphyrinogen system.[9]

Similarly, the authors were interested in isolating a Cu(II)−porphyrinogen complex using tetraalkyammonium as the countercation to minimize any special role of the pyrrolyl ring present in porphyrinogen. A complex, tetraethylammonium−tetrakis(cyclohexyl)porphyrinogen Cu(II),$[Et_4N]_2[LCu^{II}]$ (LH_4 = tetrakis(cyclohexyl)porphyrinogen) (**1**), was thus readily synthesized as a red brown solid (see the Supporting Information). However, **1** was found to be very susceptible to air.

Upon aerial exposure, the brown dichloromethane solution of **1** rapidly changed to deep blue under ambient conditions. A blue diamagnetic complex, isolated from such a reaction, was structurally characterized as $[Et_4N][LCu^{III}]$, **2** (Figure 1, bottom).[10] Cu−N bonds present in **2** are comparable to those reported in other Cu(III) complexes[7b] but fall shorter than those reported for similar Cu(II) complexes.[11] The course of aerial oxidation of **1** to form **2** was followed by electron paramagnetic resonance (EPR) spectroscopy to monitor the gradual diminution of the Cu(II) signal in light of the formation of diamagnetic Cu(III) species. Interestingly enough, concomitant to the gradual reduction in intensity of the Cu(II) EPR signal, the appearance of another EPR signal characteristic to O_2^- was observed during the time-dependent progress of the reaction (Figure 1, top). Quantification of O_2^- generated from the reaction as in eq 1 by the EPR method using a known concentration of $[Me_4N][O_2]$ as a standard showed an average of 70% conversion. Such an analysis is reasonable considering the difficulty in handling O_2^- in solution. The O_2^- formation was further quantified[12] chemically by monitoring the reduction of nitrobluetetrazolium (NBT)[13] to monoformazan dye at 560 nm at 25 °C. Both of the methods used here with their respective inherent error limits complement the stoichiometry of the reaction (eq 1).

$$[Et_4N]_2[LCu^{II}] + O_2 \rightarrow [Et_4N][LCu^{III}] + [Et_4N]^+[O_2]^- \qquad (1)$$

The cyclic voltammetric response of **1** under an oxidative scan displayed a reversible oxidation process at $E_{1/2} = -0.46$ V (vs Ag/AgCl in acetonitrile, Figure 2a) for the Cu^{III}/Cu^{II}

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(10) Detailed syntheses of **1** and **2** are available in the Supporting Information. Crystal data for **2**: $C_{51}H_{74}Cl_6CuN_5$, formula weight 1033.40, orthorhombic, space group *P*212121, $a = 13.619$ (5) Å, $b = 18.299$ (5) Å, $c = 20.249$ (5) Å, $\alpha = \beta = \gamma = 90°$, $V = 5046$ (3) Å^3, $Z = 4$, $T = 100$ K, $D_{calc} = 1.360$ g cm^{-3}. Of a total of 34 061 reflections collected, 12 549 were independent ($R_{int} = 0.0475$). The structure was solved by direct methods and refined by full-matrix least squares on F^2. Final R1 [$I > 2\sigma(I)$] = 0.0449 and wR2 = 0.0903 R indices (all data), R1 = 0.0569, wR2 = 0.0952, GOF = 0.992. Data were collected on a Bruker-AXS smart APEX CCD diffractometer.

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(12) Solutions of $[Me_4N][O_2]$ in different concentrations (details in the Supporting Information) were prepared in acetonitrile and evaporated under reduced pressure and, when dried, were mixed with a fixed volume of NBT (4 mL) solution prepared in an aqueous phosphate buffer. A calibration plot was made from the optical density of the blue formazan formed against the concentration of $[Me_4N][O_2]$ used. A total of 0.012g of $[Et_4N][LCu^{II}]$ (**1**) dissolved in 4 mL of acetonitrile under a slow air jet was stirred for 5 min, whereupon the color of the solution changed from brown to blue. The solvent was removed under reduced pressure using the Schlenk line technique. A total of 4 mL of buffered aqueous NBT solution was added into it. The mixture was stirred for 1 min and centrifuged in the cold, and the centrifugate was transferred; the residue was washed thrice with 4 mL of a fresh buffer solution each time, and the original centrifugate and washed buffer solutions were mixed, and the volume of mixed solution was made up to 1 L with a phosphate buffer. The optical density of this blue-colored stock solution was measured. From the calibration plot, the amount of superoxide formed was calculated and found to be 61 ± 5% on the basis of the average of five determinations. The time taken to dry the superoxide solution from organic solvent and the temperature of the reaction were maintained the same in each experiment to average out the spontaneous decomposition of the superoxide ion under such conditions.

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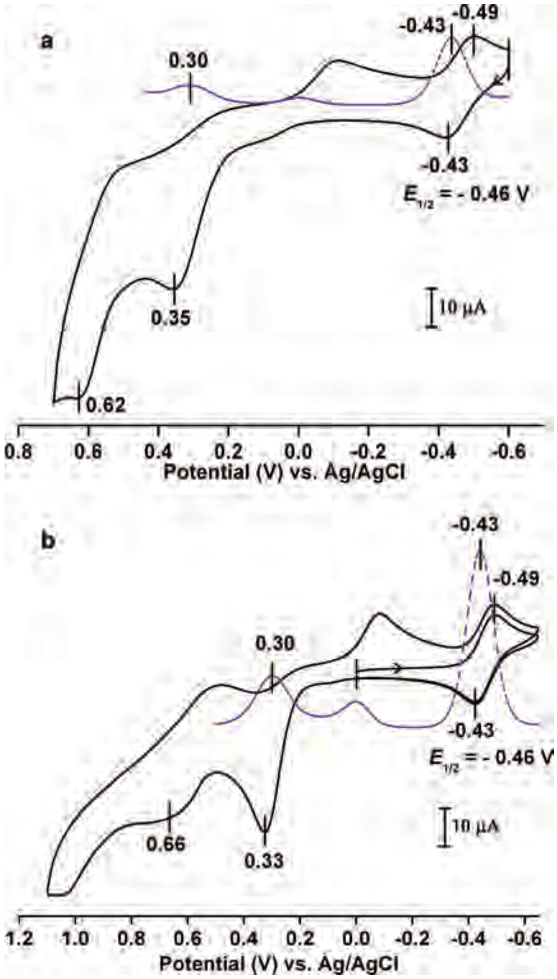

Figure 2. Cyclic voltammogram traces (black line) and DPPs (blue line) of a 10^{-3} M solution of (a) **1** and (b) **2** in acetonitrile containing 0.1 M Bu_4NClO_4 (scan rate 100 mV s^{-1}; for DPP, pulse width, 50 ms; pulse period, 200 ms; and pulse amplitude 50 mV). For the direction of these scans, see the text.

couple. As a check, the reductive scan of **2** displayed its reversible reduction process at an identical $E_{1/2}$ of −0.46 V (Figure 2b). Such a cyclic voltammetric response is fully compatible with the oxidation of **1** in the air. For both of the complexes, there are irreversible oxidation processes around +0.3 V and +0.6 V which are related to the irreversible oxidations of the coordinated porphyrinogen ligand.

The possibility of direct metal−oxygen adduct formation in the oxidation of **1** to **2** following eq 1 was checked by a space-filling model of the anion of **1**, which showed that the approach of any oxygen molecule toward the central copper atom is blocked by steric crowding of the hydrogens of the porphyrinogen ligand, and O_2 may reach nearest to the central copper at a distance around 6 Å (Figure 3). This suggests that there is no possibility of any direct bond formation between copper and oxygen. Thus, the oxidation of Cu(II) in **1** to Cu(III) in **2** by aerial oxygen may involve an outer-sphere electron-transfer reaction.

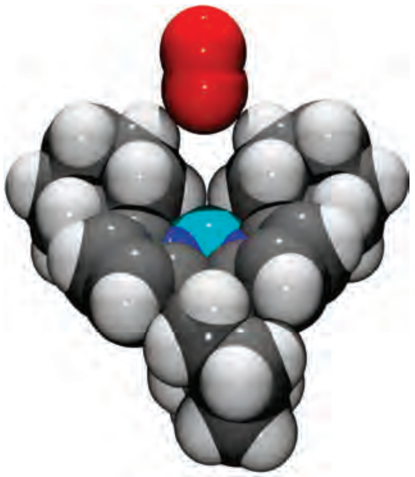

Figure 3. Space-filling representation of the anion of **1** showing the closest possible distance (~6 Å) of oxygen (red) to copper (cyan).

In summary, the hitherto unknown production of a superoxide anion by the {Cu(II)(N_4)} moiety under aerial exposure has been demonstrated. Identification of such a type of reaction, as described herein, may have implications in complementing the generation of reactive oxygen species.

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Supporting Information Available: Details of the synthesis and analytical, electrochemical, and spectral data of **1** and **2**; X-ray crystallographic data in CIF format for **2**; and experimental details of the NBT test. This material is available free of charge via the Internet at http://pubs.acs.org.

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