of the two $-NH_3^+$ groups to the [18]-N_3O_3 macrocyclic subunits. The shifts observed provide information about the location of the included substrate with respect to the aromatic residues.

As for macrotricycles,[4,12] complexation with chain length discrimination among $^+H_3N-(CH_2)_n-NH_3^+$ substrates was observed. Whereas **1** binds the $n = 5$ and $n = 6$ species, no complexes were formed with the $n = 4$ and $n = 8$ dications in the same conditions.

Binding of two $A-NH_3^+$ substrates by receptors **1-4** may in principle yield three types of *dinuclear monohapto*[1] species, depending on whether the two substrates are both inside the central molecular cavity, one in and one out, or both outside. Which form predominates depends on toposelective factors which direct substrate binding either into or out of the central cavity. Steric repulsions between the A group of $A-NH_3^+$ and the bridges in **1-4** hinder inside binding, whereas inside orientation of the nitrogen sites (which are the strongest binding sites)[13] and eventual attractive interactions between A and the bridges favor inside binding. The balance between these effects rests on the nature of the macrocycles, the bridges, and group A. For compound **4**[1] and other macrotricycles,[3,4] NMR data indicated that internal complexation occurs but external binding could not be exluded.[1,14] The tighter internal cavity of **1** and **2** should hinder inside binding more than with **4**. When $CH_3NH_3^+$ picrate was added to **1** or **2**, complexation occurred and peaks appeared at high field in the 0.7-1.7-ppm region in the ^1H NMR spectrum at -55 °C.[10] It is not possible at present to decide which species were formed, but the marked high field shifts indicate that internal binding presumably occurs to some extent. $A-NH_3^+$ substrates where A is larger than CH_3, gave transprotonation under the same conditions.

The complexation data described above indicate that substrate binding is more restricted for **1** and **2** than for **4**, implying that these macrotetracycles display *very high selecticity* of complexation at the expense, of course, of the ability to bind a broader range of substrates. There is probably a close to total discrimination against internal binding of a more bulky derivative of $^+H_3N-(CH_2)_5-NH_3^+$ or $CH_3NH_3^+$ by receptor **1**.

Information about substrate exchange rates and relative stabilities of the complexes was obtained from competition experiments. Addition of 1 equiv of **1** to the [$^+H_3N-(CH_2)_5-NH_3^+\subset$ **4**] cryptate or addition of 1 equiv of **4** to the [$^+H_3N-(CH_2)_5-NH_3^+\subset$ **1**] cryptate gave the same ^1H NMR spectrum, displaying the high field signals of the substrates in *both* complexes.[10] The equilibrium mixture [S$\subset$ **1**] + **4** $\rightleftharpoons$ **1** + [S$\subset$ **4**] contained about 40% and 60% of the cryptates of **1** and **4**, respectively.

Thus, substrate exchange was slow on the NMR time scale, and the two complexes have about the same stability. The tighter cavity of **1** probably causes larger steric interactions between the substrate and the bridges as compared to **4**, thus compensating the expected stronger binding of $-NH_3^+$ groups by the [18]-N_3O_3 subunit **5** of **1** as compared to the [18]-N_2O_4 ring of **4**.[7]

Further studies are required to ascertain the precise structure of the complexes formed by the macrotetracyclic receptors **1** and **2**, as well as the nature of the binding scheme (tentatively represented by **16**). The triply bridged nature of these systems provides a closer control of cavity properties; bent bridges (as in **14**) open up the cavity, presumably expanding the range of complexable substrates. Comparison of systems like **1**, **4**, and **14** should allow delineating the respective properties of "closed" and "open" macropolycycles (complexation stability, selectivity, exchange rates, etc.).

Acknowledgment. We thank Pierre Plumerē for the preparation of macrocycle **6**[8] used in the present work.

(12) Kintzinger, J. P.; Kotzyba-Hibert, F.; Lehn, J. M.; Pagelot, A.; Saigo, K., *J. Chem. Soc., Chem. Commun.*, in press.

(13) In the crystal structure of the tricycle 4, all four nitrogen sites are found to be oriented toward the interior of the molecule: Arnoux, B.; Pascard-Billy, C., unpublished results.

(14) Low-temperature NMR measurements on the complexes of **4** with $CH_3NH_3^+$ or $CH_3CH_2NH_3^+$ point to the presence of more than one species, indicating that both internal and external binding occurs; work in progress.

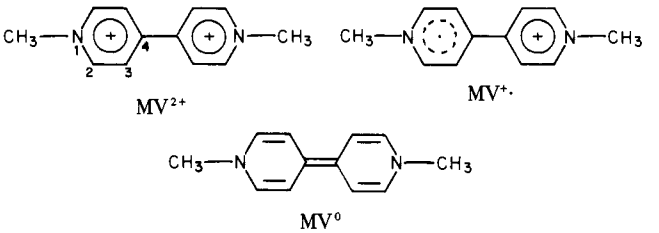
Oxygen Activation by Radical Coupling between Superoxide Ion and Reduced Methyl Viologen

Edward J. Nanni, Jr., Charles T. Angelis, Jon Dickson, and Donald T. Sawyer*

Department of Chemistry, University of California Riverside, California 92521

Received August 4, 1980
Revised Manuscript Received March 26, 1981

Superoxide ion, $O_2^{-}\cdot$, has been cited as a major factor in the toxicity of methyl viologen (1,1′-dimethyl-4,4′-bipyridinium ion (MV^{2+}) or paraquat).[1,2] The methyl viologen radical cation



MV^{2+} $MV^{+}\cdot$ MV^{0}

($MV^{+}\cdot$) reacts with O_2 rapidly ($k_2 = 7.7 \times 10^8 M^{-1}\ s^{-1}$) to generate $O_2^{-}\cdot$.[3] MV^{2+} augments the production of $O_2^{-}\cdot$ by chloroplasts,[4,5] lung microsomes,[6] and homogenates of lung, liver, and kidney;[7] and O_2 augments the toxicity of MV^{2+} in plants,[8-10] rats,[11] and *E. coli*.[2] However, the role of $O_2^{-}\cdot$, if any, in paraquat toxicity remains unclear.[12] To propose that $O_2^{-}\cdot$ is the penultimate toxin in paraquat toxicity is unverified and may be falacious; the studies to data indicate that $O_2^{-}\cdot$ is fairly innocuous to aerobic organisms.[13-15]

The ability to form electrochemically stable solutions of $O_2^{-}\cdot$[16] and $MV^{+}\cdot$[17,18] in aprotic media prompted us to investigate the reactivity of $O_2^{-}\cdot$ with $MV^{+}\cdot$. On the basis of electrochemical, spectroscopic (UV-vis, ESR, NMR, MS), and chromatographic measurements, we now report that when 1 equiv of $O_2^{-}\cdot$ is combined with 1 equiv of $MV^{+}\cdot$, a diamagnetic adduct is the initial product, which is consistent with a primary radical-radical coupling mechanism.

(1) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1979**, *254*, 10846.
(2) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1978**, *253*, 8143.
(3) Farrington, J. A.; Ebert, M.; Land, E. J.; Fletcher, K. *Biochim. Biophys. Acta* **1973**, *314*, 372.
(4) Miller, R. W.; MacDowell, F. D. H. *Biochim. Biophys. Acta* **1975**, *387*, 176.
(5) Harbour, J. J.; Bolton, J. R. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 803.
(6) Montgomery, M. R. *Res. Commun. Chem. Pathol. Pharmacol.* **1977**, *16*, 155.
(7) Baldwin, R. C.; Pasi, A.; MacGregor, J. T.; Hine, C. H. *Toxicol. Appl. Pharmacol.* **1975**, *32*, 298.
(8) Mees, G. C. *Ann. Appl. Biol.* **1960**, *48*, 601.
(9) Calderbrook, A. *Adv. Pest Control Res.* **1968**, *8*, 127.
(10) Conning, D. M.; Fletcher, K.; Swan, A. A. B. *Br. Med. Bull.* **1969**, *25*, 245.
(11) Fisher, H. K. "Biochemical Mechanisms of Paraquat Toxicity"; Autor, A. P., Ed.; Academic Press: New York, 1977; pp 57-65.
(12) Ross, W. E.; Block, E. R.; Chang, R.-W. *Biochem. Biophys. Res. Comun.* **1979**, *91*, 1302.
(13) Nilsson, R.; Pick, F. M. Bray, R. C. *Biochim. Biophys. Acta* **1969**, *192*, 145.
(14) Schmidt, M.; Bipp, H. *Z. Anorg. Allg. Chem.* **1960**, *303*, 190, 201.
(15) LeBeine, A.; Berguer, Y. *Bull. Soc. Chim. Fr.* **1966**, 2363.
(16) Sawyer, D. T.; Roberts, J. L., Jr. *J. Electroanal. Chem.* **1966**, *12*, 90.
(17) Bard, A. J.; Ledwith, A.; Shine, H. J. *Adv. Phys. Org. Chem.* **1976**, *13*, 155.
(18) Electrolysis of MV^{2+} in DMF at -0.55 V vs. SCE requires 1.05 e^- and yields a deep blue solution that is attributable to the methyl viologen radical cation, $MV^{+}\cdot$, with absorption bands at 311 nm (ϵ 4560 $M^{-1}\ cm^{-1}$) 370 (13 100), 387 (22 000), 398 (40 200), 580 (8440), 608 (10 760), 665 (4980), and 740 (1940). The ESR spectrum for this solution is similar to published spectra for $MV^{+}\cdot$.[19,20]
(19) Johnson, C. S., Jr.; Gutowsky, H. S. *J. Chem. Phys.* **1963**, *39*, 58.
(20) Kosower, E. M.; Cotter, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 5524.

0002-7863/81/1503-4268$01.25/0

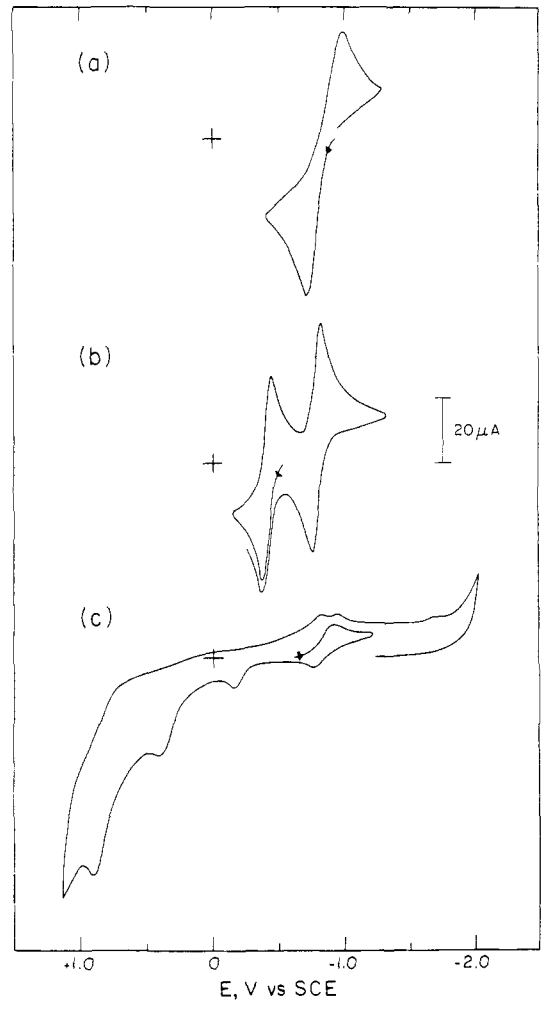
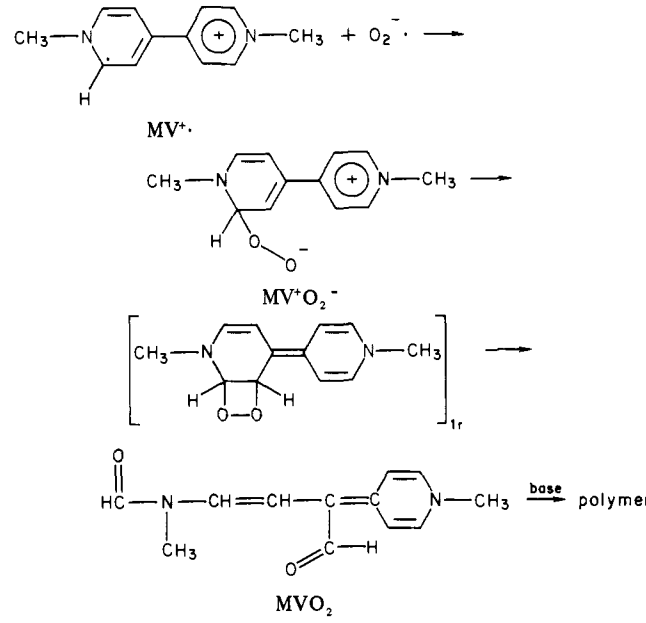


Figure 1. Cyclic voltammograms in dimethylformamide (DMF) (0.1 M tetraethylammonium perchlorate (TEAP)) of (a) 1 mM $O_2^{-}\cdot$, (b) 1 mM methyl viologen cation radical ($MV^{+}\cdot$), and (c) 0.5 mM $O_2^{-}\cdot$ plus 0.5 mM $MV^{+}\cdot$. Measurements were made with a platinum electrode (area, 0.23 cm^2) at a scan rate of 0.1 V s^{-1}.

Figure 1 illustrates the cyclic voltammograms for (a) $O_2^{-}\cdot$, (b) $MV^{+}\cdot$, and (c) the combination of one $O_2^{-}\cdot$ per $MV^{+}\cdot$, all in dimethylformamide (DMF). The cyclic voltammogram that is observed immediately after the combination of $O_2^{-}\cdot$ and $MV^{+}\cdot$ in a sealed cell indicates that a small amount of O_2 is present (E_{pc} = −0.97 V, E_{pa} = −0.80 V vs. SCE), but, overall, the voltammetry is markedly different from that for either of the reactants.[21] When equimolar solutions of blue $MV^{+}\cdot$ and $O_2^{-}\cdot$ are combined, a bronze solution results with absorption bands at 303 nm (ϵ 7080 M^{-1} cm^{-1}), 407 (10 400), and 490 (4440). While both reactants are ESR active, the bronze product solution is ESR silent at room temperature and 77 K.

Combination of equal volumes of 0.10 M $MV^{+}\cdot$ [from reduction of $MVCl_2$ by Li(Hg) in DMF] and 0.11 M $O_2^{-}\cdot$ [from dissolution of $(CH_3)_4N^{+}O_2^{-}\cdot$[22] in DMF] results in a product solution with electrochemical and spectroscopic characteristics that are identical with those for the solution of Figure 1c (there is a total absence of any oxidation state of MV). The reaction products have been characterized by C-2 reverse-phase TLC and chemical ionization LC–MS.[23]

Scheme I



On the basis of these results, we believe that the primary reaction between $MV^{+}\cdot$ and $O_2^{-}\cdot$ is a radical–radical coupling process to give an alkyl peroxide anion.[24] Two mechanistic schemes are proposed that are consistent with the product characterization. Both are based on the initial formation of a peroxide zwitterion ($MV^{+}O_2^{-}$) at the 2 position of $MV^{+}\cdot$.

In Scheme I $MV^{+}O_2^{-}$ rearranges to an unstable dioxetane intermediate[27] which cleaves to form MVO_2.[28,29] Scheme II involves oxygen-atom transfer by $MV^{+}O_2^{-}$ to the solvent or an electrophilic carbon to form $MV^{+}O^{-}$, which rearranges via a 2,3-hydride shift to give MVO. Air oxidation of MVO yields the *N*-methyl-2-pyridone derivative of MV^{2+} (MVO^{+}).[30] The significant yield of *N*-methyl-2-pyridone must result from a photochemical cleavage of $MV^{+}O^{-}$, MVO^{+}, or $MV(O)_2$ under basic conditions.[31]

(21) The oxidation wave at −0.14 V vs. SCE is due to an electroactive intermediate, which disappears within 10 min after the reactants are combined. Although the redox potentials for $O_2^{-}\cdot$ and $MV^{+}\cdot$ (Figure 1) indicate that $O_2^{-}\cdot$ should reduce some $MV^{+}\cdot$ to MV^{0}, the absence of any MV species from their combination (Figure 1c) confirms that radical–radical coupling is the dominate primary process. Addition of O_2 to MV^{0} appears to yield $O_2^{-}\cdot$ and $MV^{+}\cdot$, which then couple.

(22) McElroy, A. D.; Hashmann, J. S. *Inorg. Chem.* **1964**, *3*, 1798.

(23) Nine significant TLC spots are observed; a parallel experiment with $^{14}CH_3$-labeled $*MVCl_2$ yields the same nine spots (each represents 5–13% of the initial $*MVCl_2$ activity and their total represents about 80%) and no residual $*MVCl_2$. Use of reference compounds in conjunction with the TLC and LC–MS data permits the identification of two products, the *N*-methyl-2-pyridone derivative of MV^{2+} (MVO^{+}) (5% yield) and *N*-methyl-2-pyridone (8%). The largest m/e^{-} peak occurs at 218 amu; the ^1H NMR spectrum for this species only exhibits a broad singlet at 1.5 ppm, a sharp singlet at 3.3 ppm, and a pair of resonances at 7.2 and 7.4 ppm. One of the nine TLC spots occurs at the origin and represents about 13% of the original $*MVCl_2$; its lack of mobility is characteristic of an in situ polymerization. The appearance of an insoluble brown flocculent powder in DMF solutions of the $MV^{+}\cdot$–$O_2^{+}\cdot$ reaction mixtures supports the conclusion that one of the products polymerizes.

(24) The transiently observed anodic peak at −0.14 V vs. SCE is characteristic of a peroxide anion.[25] To invoke such a process, mechanistic pathways need to be considered which are dependent upon the relative unpaired electron densities; i.e., the proton hyperfine splitting constants for the carbon and nitrogen nuclei.[26] For $MV^{+}\cdot$ these are A_N = 4.23, $A_H(CH_3)$ = 3.99, $A_H(2)$ = 1.33, and $A_H(3)$ = 1.57 G,[19] which indicates that the maximum unpaired electron density is at carbon atom 2.

(25) Morrison, M. M.; Roberts, J. L., Jr.; Sawyer, D. T. *Inorg. Chem.* **1979**, *18*, 1971.

(26) Wertz, J. E.; Bolton, J. R. "Electron Spin Resonance: Elementary Theory and Practical Applications"; McGraw-Hall: New York, 1972; pp 96–99.

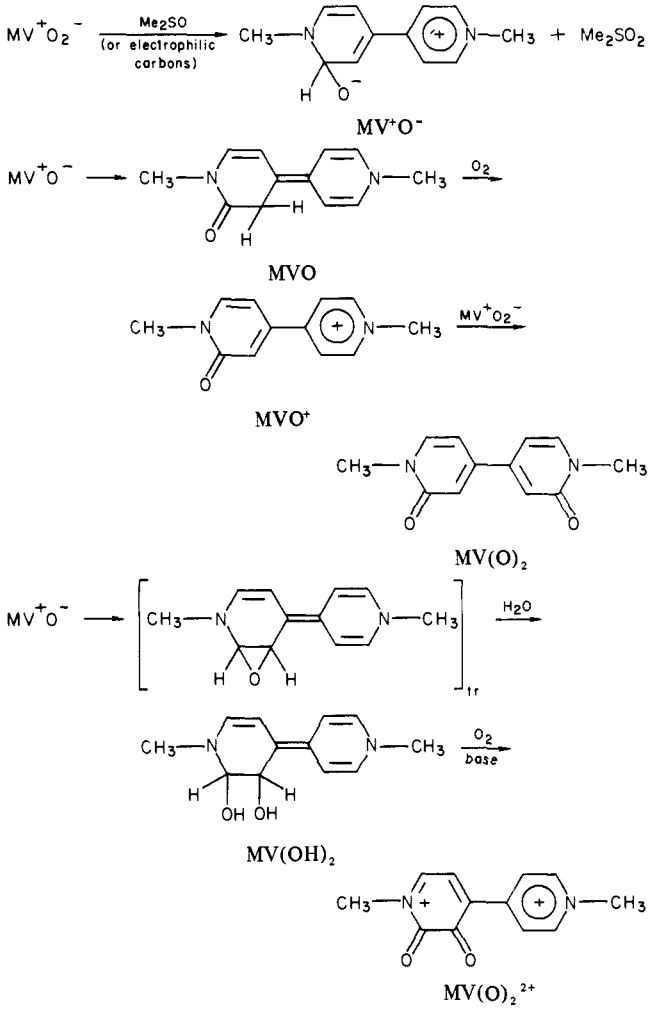
(27) Schuster, G. G. *Acc. Chem. Res.* **1979**, *12*, 366.

(28) Kopecky, K. R.; Mumford, C. *Can J. Chem.* **1969**, *47*, 709.

(29) MVO_2, which has a mass of 218 amu, should be prone to polymerize under basic conditions and at the surface of a TLC plate.

(30) The latter probably is monooxygenated by $MV^{+}O_2^{-}$ to give $MV(O)_2$. The $MV^{+}O^{-}$ zwitterion also appears to form a transient epoxide, which hydrolyzes to a glycol [$MV(OH)_2$] under the basic conditions of the reaction. It, in turn, is air oxidized to yield a dicarbonyl [$MV(O)_2^{2+}$]. Both paths appear to be involved, because species $MV(OH)_2$ and $MV(O)_2$ have been identified in the reaction mixture.

Scheme II



While the direct coupling of $O_2^{-}\cdot$ to cation radicals has been previously proposed,[33,34] we believe that this is one of the first observations of a stoichiometric process.[35] Similar radical-radical coupling between $O_2^{-}\cdot$ and N^5-ethyl-3-methyllumiflavin radical to yield a 4a-peroxide anion (an effective oxygenase) has been observed in our laboratories.[36] Hence, the $MV^+O_2^-$ peroxide from the primary coupling reaction and its degradation products (Scheme II) may be highly reactive with biological substrates.

Acknowledgment. This work was supported by the National Science Foundation under Grant CHE79-22040. We are grateful to Thomas Cairns and Emil Sigmund of the U.S. Food and Drug Administration, Los Angeles, CA, for the LC-MS analyses, Chevron Chemical Co., Richmond, CA, for samples of paraquat derivatives, and Professors Paul Haake (Wesleyan University), Christopher Foote (University of California, Los Angeles), and Robert L. Heath (University of California, Riverside) for helpful discussions.

(31) That the system is basic is confirmed by the anodic peak at +0.88 V vs. SCE (Figure 1) in DMF, which is characteristic of OH^-.[32] The anodic wave does not appear in the experiments carried out in Me_2SO, which indicates that the peroxide anion ($MV^+O_2^-$) rapidly reacts with the solvent to give the monopyridone anion (MV^+O^-) and dimethyl sulfone (the reaction of Me_2SO with peroxide anion, HO_2^-, produces Me_2SO_2).[32]

(32) Goolsby, A. D.; Sawyer, D. T. *Anal. Chem.* **1968**, *40*, 83.

(33) Eriksen, J.; Foote, C. S.; Parker, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 6455.

(34) Schapp, A. P.; Zaklika, K. A.; Kaskar, B.; Fung, L. W.-M. *J. Am. Chem. Soc.* **1980**, *102*, 389.

(35) Resonance stabilization apparently precludes significant radical coupling at the C-4 position of $MV^+\cdot$. Such a process would lead to a symmetrical dioxetane intermediate and dissociation to two *N*-methyl-4-pyridone molecules; only trace levels are detected in the product solution.

(36) Nanni, E. J., Jr.; Sawyer, D. T.; Ball, S. S., Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 2797.

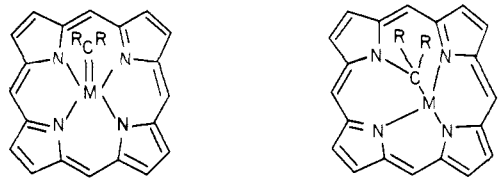
Reversible Migration of an Axial Carbene Ligand into an Iron-Nitrogen Bond of a Porphyrin. Implications for High Oxidation States of Heme Enzymes and Heme Catabolism

L. Latos-Grazynski, Ru-Jen Cheng, Gerd N. La Mar,* and Alan L. Balch*

Department of Chemistry, University of California Davis, California 95616

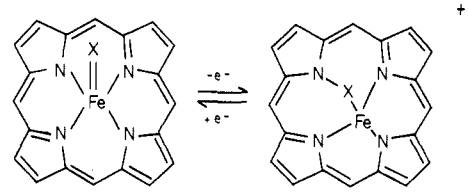
Received February 25, 1981
Revised Manuscript Received May 18, 1981

Two types of carbene adducts of metalloporphyrins are known in which the carbene is bound to the metal. One, A, involves a carbene axially coordinated to the metal[1] while the other, B, involves a carbene which has been inserted into the metal-nitrogen bond.[2-5] Carbenes are also known to add to the porphyrin ring



A B

itself to form homoporphyrins, N-alkylated porphyrins, meso-substituted porphyrins, and cyclopropanic chlorins.[3-9] Related complexes of type B are known in which a nitrene has been inserted into a metal-nitrogen bond.[10] Mansuy and co-workers have recently reported the synthesis of the vinylidene carbene complexes $[(p\text{-}ClC_6H_4)_2C{=}C{:}]FeTPP$ (**1**) (where TPP is the dianion of *meso*-tetraphenylporphyrin)[11] and have shown that these are oxidized to the species of composition $[(p\text{-}ClC_6H_4)_2C{=}C{:}]$-FeTPPY (**2**).[10] The oxidized form **2** may be readily reduced to re-form **1**. Here we demonstrate that this involves reversible carbene migration coupled to the redox reaction as shown in eq 1.



(1)

$X = (p\text{-}ClC_6H_4)_2C{=}C{:}$

The ^1H NMR spectrum of **1**, both alone and in the presence of excess 1-methylimidazole, is characteristic of a diamagnetic metalloporphyrin with full fourfold symmetry. Consequently **1** has been assigned the axial carbene structure A[11] and is similar

(1) Mansuy, D.; Lange, M.; Chottard, J. C.; Bartoli, J. F.; Chevrier, B.; Weiss, R. *Angew. Chem., Inte. Ed. Engl.* **1978**, *17*, 781-782.

(2) Callot, H. J.; Tschamber, T.; Chevrier, B.; Weiss, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 567-568.

(3) Johnson, A. W.; Ward, D.; Batten, P.; Hamilton, A. L.; Shelton, G.; Elson, C. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2076-2085.

(4) Johnson, A. W.; Ward, D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 720-723.

(5) Batten, P.; Hamilton, A. L.; Johnson, A. W.; Mahendran, M.; Ward, D.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1623-1628.

(6) Callot, H. J.; Johnson, A. W.; Sweeney, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1424-1427.

(7) Callot, H. J., Tschamber, T. *Bull. Soc. Chim. Fr.* **1973**, 3192-3198.

(8) Callot, H. J.; Tschamber, T. *J. Am. Chem. Soc.* **1975**, *97*, 6175-6178.

(9) Callot, H. J.; Tschamber, T.; Schaeffer, E. *J. Am. Chem. Soc.* **1975**, *97*, 6178-6180.

(10) Callot, H. J.; Chevrier, B.; Weiss, R. *J. Am. Chem. Soc.* **1978**, *100*, 3214-3215.

(11) Mansuy, D.; Lange, M.; Chottard, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 3214-3215.

(12) Mansuy, D.; Lange, M.; Chottard, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 6437-6439.

0002-7863/81/1503-4270$01.25/0