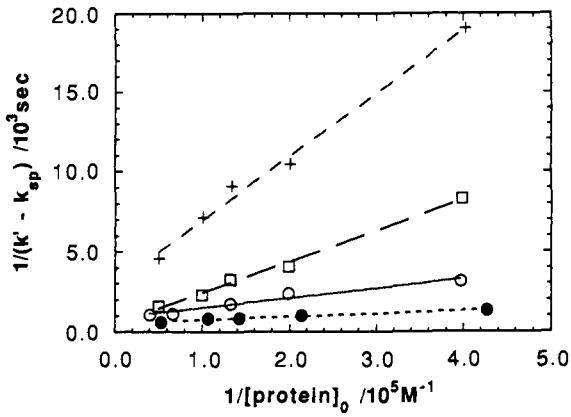

Figure 2. Plot of $1/(k - k_{sp})$ vs $1/[\text{protein}]_0$: ○, BSA; ●, BSA–palmitic acid; □, HSA; +, RSA.

To explain the acceleration of merocyanine formation by albumin the reaction was assumed to proceed through the following pathways:

$$\text{Sp} \underset{k'_{Sp}}{\overset{k_{Sp}}{\rightleftharpoons}} \text{Me} \quad (1)$$

$$\text{Sp} + \text{Alb} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} (\text{Sp–Alb}) \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} (\text{Me–Alb}) \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} \text{Me} + \text{Alb} \quad (2)$$

where k_{sp} = rate constant of the spontaneous thermal back reaction of the spiro form to the mero form, k'_{sp} = rate constant of the spontaneous thermal back reaction of the mero form to the spiro form (negligibly small), k_i = rate constant of each reaction step shown in eq 2, Sp = spiro form of 6,8-dinitro-BIPS, Me = mero form of 6,8-dinitro-BIPS, and Alb = albumin.

Equation 1 shows the reaction pathway in the absence of the albumin, while eq 2 represents those in its presence, provided that enzyme-like behavior is considered. In our model we assume as the first approximation that the spiro form is combined only at one binding site with high affinity. It may be called the "catalytic" binding site. To avoid the binding of 6,8-dinitro-BIPS to other sites with low affinities, the albumin was used in excess.

According to the above model, formation of the "spiro-form-albumin" complex is described by the Michaelis constant K_M; k_{+2} is just the catalytic constant k_{cat}. An apparent first-order rate constant k', describing the experimentally observed initial rate constant in the presence of albumin, can be expressed as

$$\frac{1}{k' - k_{sp}} = \frac{K_m}{(k_{cat} - k_{sp})} \frac{1}{[\text{albumin}]_0} + \frac{1}{(k_{cat} - k_{sp})} \quad (3)$$

assuming that [albumin] = $[\text{albumin}]_0$ (=initial concentration), which is justified for albumin in excess. k_{sp} was obtained from the thermal back reaction in the absence of protein to be k_{sp} = $(1.59 \pm 0.05) \times 10^{-5}$ s^{-1} (mean value of 21 experiments) at T = (23 ± 0.5) °C. The plots according to eq 3 are shown for BSA, BSA–palmitic acid, RSA, and HSA in Figure 2.[8] The linearity of the plots indicates that the enzymatic reaction mechanism is applicable to the present systems and that eq 3 is effective. The values of K_M and k_{cat} were calculated from the slope and intercept, respectively. K_M was on the order of 10^{-5} M (BSA, HSA, RSA) and 10^{-6} M (BSA–palmitic acid). The ratio of k_{cat}/k_{sp} was 190 (BSA), 130 (HSA), 22 (RSA), or 125 (BSA–palmitic acid). The decrease of K_M while k_{cat} is nearly unchanged indicates positive cooperation of the palmitic acid. Competitive inhibition is quite unlikely because of the large structural differences between 6,8-dinitro-BIPS and fatty acids. It is worth noting that the thermal back reaction to the merocyanine is enhanced by 2 orders of magnitude for the BSA and HSA systems.

In a few cases enzyme-like activity of albumin has been reported, mainly for hydrolysis of esters and amides.[5b,9] These interactions with different substances seem to originate in the conformational fluctuations of albumin, giving it the possibility of accepting various ligands.[5a] Therefore it is likely that albumin also interacts with spiro benzopyrans.[10]

To verify the enzyme-like activity of the albumins, temperature dependences of k_{sp} and k_{cat} were measured between 10 and 35 °C. The activation energy E_a for 6,8-dintiro-BIPS itself is about 60–80 kJ/mol, which is in good agreement with the data for substituted spiro benzopyrans.[11] In the presence of BSA, E_a decreases significantly by a factor of 1.5–2.[12]

Whether the interaction is "active", involving special amino acids of the protein, or "passive", providing a suitable microenvironment for the reaction, is being examined in our group.[13]

This paper shows enzyme-like behavior of albumins toward a photochromic molecule, making this biomolecule an interesting candidate for controlling molecular systems and devices. Furthermore, the present combination of albumins and 6,8-dinitro-BIPS supports our assumption that each protein being able to bind substances can in principle act as an enzyme if a suitable substrate is chosen.[14] Further studies on the influence of albumin on the thermal back reaction and the photochromic reactions themselves are being conducted for various photochromic molecules in our laboratory.

(8) The observed initial rate constants k' were obtained as mean values from three experiments. The standard deviations of k' were less than 10%, typically 5%.

(9) Kurono, Y.; Sugiura, H.; Ikeda, K. *Chem. Pharm. Bull.* **1985**, *33*, 3966–3971 and references cited therein.

(10) An indication that spiro pyrans can be bound to BSA is given for 1′-(β-carboxyethyl)-3′,3′-dimethyl-6-nitrospiro[2*H*-1-benzopyran-2,2′-indoline], but no enzyme-like behavior is mentioned: Rhee, K. W.; Gabriel, D. A.; Johnson, C. S., Jr. *J. Phys. Chem.* **1985**, *89*, 3193–3195.

(11) Bertelson, R. C. In *Photochromism*; Brown, G. H., Ed.; Wiley-Interscience: New York, 1971; p 176–189.

(12) The Arrhenius plot and detailed discussion will be published elsewhere.

(13) Preliminary results show that in solvents like dioxane, ethanol, or acetonitrile that are less polar than PBS buffer (2.9% (v/v) ethanol) the thermal reaction of the spiro form to the mero form is not accelerated. Therefore it is unlikely that acceleration caused by albumins is due to a "passive" interaction.

(14) The most famous examples are the catalytic antibodies; see, for example, recent reviews: (a) Schultz, P. G.; Lerner, A. R.; Bencovic, S. J. *Chem. Eng. News* **1990**, *68*, 26–40. (b) Schultz, P. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *10*, 1283.

Basic Character of Rare Earth Metal Alkoxides. Utilization in Catalytic C–C Bond-Forming Reactions and Catalytic Asymmetric Nitroaldol Reactions

Hiroaki Sasai,† Takeyuki Suzuki,† Shigeru Arai,† Takayoshi Arai,† and Masakatsu Shibasaki*,‡

Faculty of Pharmaceutical Sciences
Hokkaido University, Sapporo 060, Japan
Faculty of Pharmaceutical Sciences
University of Tokyo, Hongo
Bunkyo-ku, Tokyo 113, Japan

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In a recent paper, we reported that $Zr(O\text{-}t\text{-}Bu)_4$ was an efficient and convenient basic reagent in organic synthesis.[1] However, all reactions examined were performed with stoichiometric quantities of the reagent. We envisioned that rare earth metal alkoxides would be stronger bases than group 4 metal alkoxides due to the lower ionization potential (ca. 5.4–6.4 eV) and the lower electronegativity (1.1–1.3) of rare earth elements;[2] thus, the catalytic use of rare earth metal alkoxides in organic synthesis was expected.[3] Although a variety of rare earth metal alkoxides

† Hokkaido University.
‡ University of Tokyo.

(1) Sasai, H.; Kirio, Y.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 5306.
(2) Dean, J. A., Ed. *Lange's Handbook of Chemistry*; McGraw-Hill, 1972.

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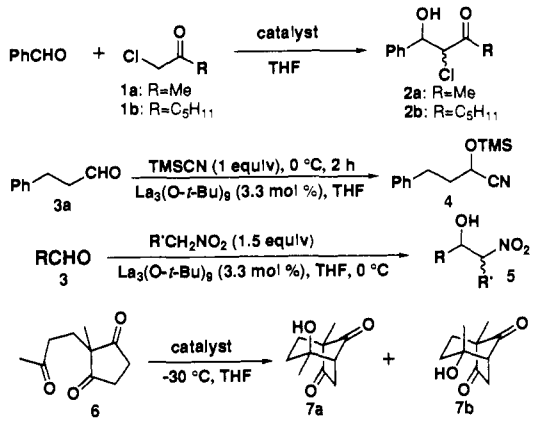
Scheme I



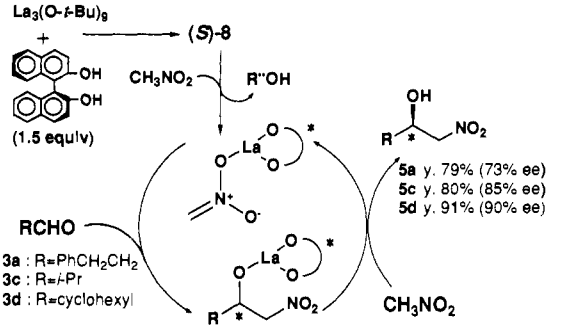
have been prepared for the last three decades,[4] to our knowledge, there have been few reports concerning the basicity of rare earth metal alkoxides.[5] Herein, we report several carbon–carbon bond-forming reactions catalyzed by rare earth metal alkoxides and their application to a catalytic asymmetric nitroaldol reaction.

We began examination of the basicity of rare earth alkoxides by comparison with the basicity of $Zr(O\text{-}t\text{-}Bu)_4$. The intermolecular aldol reaction of the α-chloro ketones **1a** and **1b** with benzaldehyde was found to proceed smoothly in spite of the use of a catalytic amount of $La_3(O\text{-}t\text{-}Bu)_9$[4d] or $Y_3(O\text{-}t\text{-}Bu)_8Cl$,[4d] giving the α-chloro-β-hydroxy ketones **2a**: $La_3(O\text{-}t\text{-}Bu)_9$ (3.3 mol %), −72 °C, 30 h, 74%; $Y_3(O\text{-}t\text{-}Bu)_8Cl$ (3.3 mol %), −43 °C, 3.5 h, 50%; and **2b**, $La_3(O\text{-}t\text{-}Bu)_9$ (3.3 mol %), −50 °C, 4 h, 83%.[6,7] On the other hand, $Zr(O\text{-}t\text{-}Bu)_4$ exhibited much lower catalytic activity to give **2a**: 140 mol %, −50 °C, 2.5 h, 86%; 10 mol %, −50 °C, 20 h, 8%. Thus, the basicity of the rare earth alkoxides appears to be stronger than that of $Zr(O\text{-}t\text{-}Bu)_4$. Use of $Ti(O\text{-}t\text{-}Bu)_4$ afforded none of the coupling product (Scheme I).

Likewise, the aldehyde **3a** was converted to the α-(trimethylsilyl)oxy nitrile **4** in 96% yield using a catalytic amount of $La_3(O\text{-}t\text{-}Bu)_9$.[8] Furthermore, the various nitroaldol reactions proceeded smoothy by the use of a catalytic amount of $La_3(O\text{-}t\text{-}Bu)_9$, giving the following coupling products: **5a**, R = $PhCH_2CH_2$, R′ = H, 85%; **5b**, R = Ph, R′ = H, 68%; **5c**, R = *i*-Pr, R′ = H, 76%; **5d**, R = cyclohexyl, R′ = H, 78%; **5e**, R = $PhCH_2CH_2$, R′ = Me, 72% (syn:anti = ca. 1:1); **5f**, R = $PhCH_2CH_2$, R′ = $PhCH_2$, 76% (syn:anti = ca. 1:1)[9] (Scheme I).

The intramolecular aldol reaction of the *meso*-triketone **6** catalyzed by rare earth metal alkoxides was also investigated. The reaction was performed with a catalytic amount of the rare earth alkoxides to afford the bicyclic products **7a** and **7b**:[10] $La_3(O\text{-}t\text{-}Bu)_9$ (3.3 mol %), 1 h, **7a** (40%) and **7b** (30%); $Y_3(O\text{-}t\text{-}Bu)_8Cl$ (3.3 mol %), 5 h, **7a** (~100%); $Y_5(O\text{-}i\text{-}Pr)_{13}O$[4g] (2 mol %), 4 h, **7a** (94%); $Zr(O\text{-}t\text{-}Bu)_4$ (10 mol %), 24 h, **7a** (30%).[11] Use of $Al(O\text{-}t\text{-}Bu)_3$ gave none of the cyclized product. It is interesting to note that, in this case, the yttrium alkoxide was more effective than $La_3(O\text{-}t\text{-}Bu)_9$.

Scheme II



Having established the several carbon–carbon bond-forming reactions catalyzed by the rare earth alkoxides, we turned our attention to a catalytic asymmetric synthesis using an optically active rare earth alkoxide. In this communication, we record our preliminary successes in a catalytic asymmetric nitroaldol reaction. The optically active lanthanum alkoxide **8** was prepared as follows. To a stirred solution of $La(O\text{-}t\text{-}Bu)_3$[4d,12] in THF ($4.9 \times 10^{-2}$ mol/L as a monomer, 7.56 mL) was added (*S*)-(−)-binaphthol (159 mg, 0.56 mmol) at room temperature, and after being stirred for 2 h at the same temperature, the solution was directly used as an asymmetric catalyst. The ^1H and ^{13}C NMR spectra of **8** showed the absence of a *tert*-butoxy group in the catalyst.[13] Reaction of nitromethane (10 equiv) with cyclohexanecarboxaldehyde in the presence of **8** (10 mol % based on La), LiCl (2 mol equiv to La),[14] and H_2O (10 mol equiv to La)[15] was found to provide the (*R*) adduct **5d**[16] with 90% ee[17] in 91% yield (THF, −42 °C, 18 h).[18] Furthermore, use of 2-methylpropanal afforded the (*R*) adduct **5c**[16] with 85% ee[17] in 80% yield, and use of hydrocinnamaldehyde gave the (*R*) adduct **5a**[16] with 73% ee[17] in 79% yield. To our best knowledge, this is the first example of a catalytic asymmetric nitroaldol reaction. The possible reaction mechanism is shown in Scheme II, suggesting that the first step of the reaction would be ligand exchange between binaphthol and nitromethane. We believe that this type of reaction will become a powerful synthetic methodology in organic synthesis as well as a novel lead

(3) For rare earth elements in organic synthesis, see the following reviews: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron*, **1986**, *42*, 6573. (b) Imamoto, T. *J. Synth. Org. Chem., Jpn.* **1988**, *46*, 540. (c) Long, J. R. *Aldrichimica Acta* **1985**, *18*, 87.

(4) (a) Mehrotra, R. C.; Singh, A.; Tripathi, U. M. *Chem. Rev.* **1991**, *91*, 1287. (b) Lebrun, A.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1991**, *32*, 2355. (c) Evans, W. J.; Olofson, J. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 2308. (d) Evans, W. J.; Sollberger, M. S.; Hanusa, T. P. *J. Am. Chem. Soc.* **1988**, *110*, 1841. (e) Evans, W. J.; Sollberger, M. S. *Inorg. Chem.* **1988**, *27*, 4417. (f) Poncelet, O.; Hubert-Pfalzgraf, L. G.; Daran, J.-C.; Astier, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1846. (g) Poncelet, O.; Sartain, W. J.; Hubert-Pfalzgraf, L. G.; Folting, K.; Caulton, K. G. *Inorg. Chem.* **1989**, *28*, 263. (h) Evans, W. J.; Sollberger, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 6095. (i) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045. (j) Hitchcock, P. B.; Lappert, M. F.; Singh, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1499. (k) Andersen, R. A.; Templeton, D. H.; Zalkin, A. *Inorg. Chem.* **1978**, *17*, 1962.

(5) Aldolization catalyzed by $t\text{-}BuOSmI_2$ has been reported for enolizable aldehydes. See ref 4i.

(6) A mixture of the diastereomers (syn/anti or anti/syn, 1:1.4).

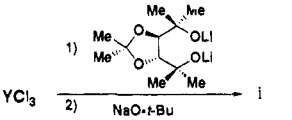
(7) $La_3(O\text{-}t\text{-}Bu)_9$ (3.3 mol %) means that there is 10 mol % of $La(O\text{-}t\text{-}Bu)_3$.

(8) For cyanosilylation under basic conditions, see: (a) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537. (b) Higuchi, K.; Onaka, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1035.

(9) For a nitroaldol reaction, see: (a) Seebach, D.; Colvin, E. R.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (b) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.

(10) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612.

(11) The intramolecular aldol reaction of **6** with the optically active yttrium alkoxide i (10 mol %), prepared as shown below, afforded **7a** with 52% ee in 60% yield (THF, −52 °C, 6 days).



(12) $La_3(O\text{-}t\text{-}Bu)_9$, prepared in situ in THF, was used directly. See ref 4d.

(13) Treatment of (*S*)-(−)-binaphthol with $La_3(O\text{-}t\text{-}Bu)_9$ (1 equiv) (gradual addition) gave the catalyst ii. Reaction of nitromethane with hydrocinnamaldehyde in the presence of ii and LiCl gave the (*R*) adduct **5a** with 44% ee.

(14) Reaction of nitromethane with aldehydes in the absence of LiCl gave adducts with lower ee's. It appears that LiCl plays a key role in the formation of some oligomeric structure and also accelerates the reaction. See ref 4d and Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, *1657*.

(15) Addition of H_2O enhances not only the rate of reaction but the enantiomeric selectivity (without H_2O: **5c**, 67% ee, **5d**, 83% ee, respectively).

(16) The absolute configuration was determined by the CD exciton chirality method using the dibenzoate derived from the corresponding amino alcohol.

(17) The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AD or CHIRALCEL OJ.

(18) Alternatively, the chiral catalyst **8** can be prepared as follows. Treatment of $LaCl_3$ (1 mmol) with dilithium binaphthoxide (1 mmol), NaO-*t*-Bu (2 mol equiv to $LaCl_3$), and H_2O (10 mol equiv to $LaCl_3$) in THF (10 mL) at room temperature for 3 days gives **8**.

for the catalytic asymmetric construction of C-C bonds.

In conclusion, we have found that rare earth alkoxides exhibit basic character, which can be utilized in aldol, cyanosilylation, and nitroaldol reactions. Furthermore, we have succeeded in preparing the optically active lanthanum alkoxide for the first time and demonstrating that it is a useful catalyst for a catalytic asymmetric nitroaldol reaction. Many applications of this new catalytic methodology in synthesis are under investigation.

Acknowledgment. This study was financially supported by a Grant-in-Aid for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: Experimental procedures and spectral data for **2b**, **5a**, (*R*)-**5d**, and **7a**, and the ^1H and ^{13}C NMR spectra of **8** and **ii** (7 pages). Ordering information is given on any current masthead page.

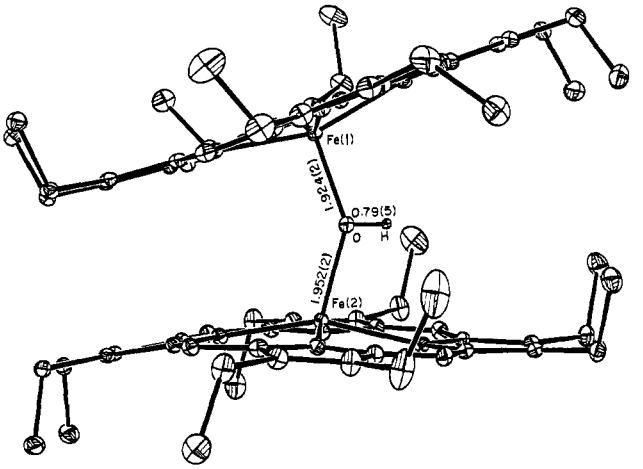


Figure 1. ORTEP diagram of the structure of the cation of $\{[Fe(OEP)]_2(OH)\}ClO_4$. Thermal ellipsoids are drawn at the 25% probability level. Porphyrin hydrogen atoms are omitted for clarity, while the refined H atom position of the bridging hydroxide ligand is shown. The Fe-O-(H)-Fe bridge is in the plane of the paper.

New Class of Bridged Diiron(III) Complexes with a Single Hydroxo Bridge. The Preparation and Structure of (μ-Hydroxo)bis((octaethylporphinato)iron(III)) Perchlorate

W. Robert Scheidt,*[1a] Beisong Cheng,[1a] Martin K. Safo,[1a] Fabio Cukiernik,[1b] Jean-Claude Marchon,*[1b] and Peter G. Debrunner*[1c]

Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, Indiana 46556
Laboratoire de Chimie de Coordination
Unité de Recherche Associée au CNRS No. 1194
Département de Recherche Fondamentale
Centre d'Études Nucléaires de Grenoble
38041 Grenoble Cedex, France
Department of Physics, University of Illinois
Urbana, Illinois 61801

Received December 20, 1991

We report that the μ-oxo-bridged iron(III) octaethylporphyrinate, $[Fe(OEP)]_2O$, can be protonated to yield the μ-hydroxo species, $\{[Fe(OEP)]_2(OH)\}^+$, via a mixed-phase reaction.[2] The formulation of this complex has been confirmed by an X-ray diffraction study[3] which reveals a single bridging group and a single counterion per two iron(III) porphyrinate units as shown in Figure 1. The lack of any other "supporting" bridging ligands for a (μ-hydroxo)diiron(III) complex is unprecedented[4] as all such previously characterized complexes have either one or two additional bridging ligands, typically either carboxylate or hydroxide groups. Thus this compound represents the first example of a new class of bridged diiron(III) complexes with a single hydroxo bridge. Moreover, model hydroxoiron porphyrinate species are of biological interest, as they have been suggested as possible intermediates[5] in the reduction of dioxygen to water by the hemoprotein cytochrome *c* oxidase, and the biophysical properties of well-defined model species are required in defining these intermediates.

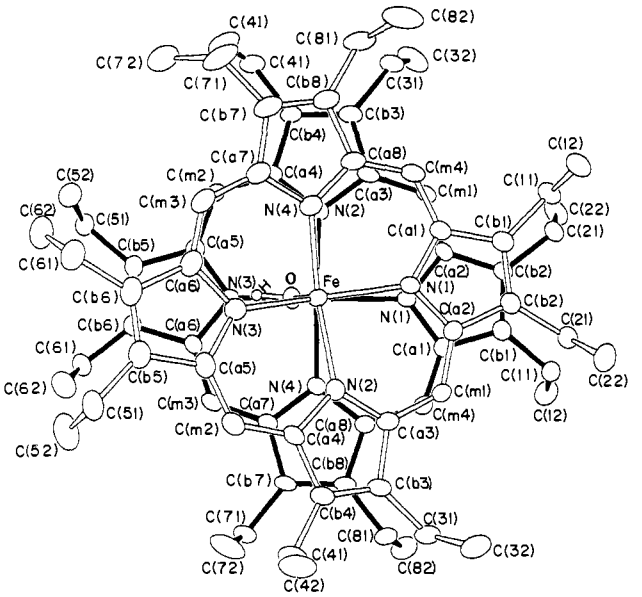


Figure 2. "Top view" of the cation of $\{[Fe(OEP)]_2(OH)\}ClO_4$ with the Fe(1)···Fe(2) axis perpendicular to the plane of the paper. Thermal ellipsoids are drawn at the 48% probability level. Porphyrin ring 2 is drawn with solid bonds while ring 1 is drawn with open bonds.

The structure of this new molecule exhibits several interesting features, many that are distinct from previously characterized (μ-hydroxo)diiron(III) complexes. The two Fe–O(OH) distances of 1.924 (3) and 1.952 (3) Å are similar to or slightly shorter than those observed in previously characterized multibridged (μ-hydroxo)diiron(III) complexes, whose values range from 1.96 to 2.06 Å,[4,6,7] but are significantly longer than those of any μ-oxo

(1) (a) University of Notre Dame. (b) Centre d'Études Nucléaires de Grenoble. (c) University of Illinois at Urbana—Champaign.

(2) To $[Fe(OEP)]_2O$ (350 mg, 0.293 mmol) in CH_2Cl_2 (15 mL) was slowly added 20 mL of dilute aqueous $HClO_4$ (0.220 mmol) with magnetic stirring. After stirring for an additional 3 min, the two phases were separated and the CH_2Cl_2 phase was dried with $MgSO_4$, filtered, and washed with CH_2Cl_2. The filtrate was taken to dryness, redissolved in 15 mL of CH_2Cl_2, and crystallized by allowing hexane to diffuse into the solution. After 10 days, crystalline $\{[Fe(OEP)]_2(OH)\}ClO_4$ was isolated.

(3) The complex crystallizes in the triclinic space group $P\bar{1}$, with a = 14.813 (3) Å, b = 14.838 (5) Å, c = 18.389 (5) Å, α = 80.75 (3)°, β = 70.40 (2)°, and γ = 89.65 (2)°, V = 3753.0 Å^3, Z = 2($\{[Fe(OEP)]_2(OH)\}ClO_4 \cdot 3CH_2Cl_2$), 14 983 observed data, all observations at 124 K. Low-temperature data collection is necessary to avoid loss of CH_2Cl_2 solvate molecules. The structure was solved by direct methods (MULTAN) and difference Fourier techniques. Most porphyrin hydrogen atoms, including the hydroxo hydrogen atom, were located from difference Fourier syntheses. All hydrogen atoms were idealized except the hydroxo hydrogen atom, whose coordinates and temperature factor were refined by full-matrix least-squares methods. Final refinements with anisotropic thermal parameters for all non-hydrogen atoms and an isotropic thermal parameter for the μ-hydroxo H atom led to R_1 = 0.076, R_2 = 0.084.

(4) Kurtz, D. M., Jr. *Chem. Rev.* **1990**, *90*, 585.

(5) Han, S.; Ching, Y.-C.; Rousseau, D. L. *Nature* **1990**, *348*, 89 and references therein.

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