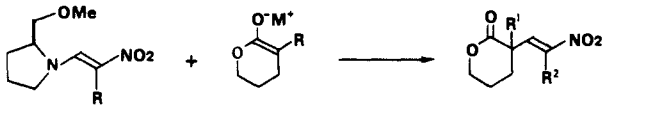
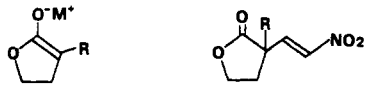
We have chosen nitro enamines **1a–c**[5,6] as a chiral starting material because nitro enamines[8] have been known to react with a variety of nucleophiles affording addition–elimination products.[9] Moreover, α,β-unsaturated nitro groups are a versatile moiety for further transformations.[10] The reaction of nitro enamine **1a** with enolate **2** (M = Li, 3 equiv) in dimethoxyethane–ether (4:3) at −78 °C yielded **5a** rich in (−)-isomer (run 1 in Table I). Counter



1a R=H; **1b** R=CH_3; **1c** R=C_2H_5

2 R=CH_3; **3** R=C_2H_5; **4** R=$CH_2CH{=}CH_2$

5a R^1=CH_3, R^2=H; **5b** R^1=CH_3, R^2=CH_3; **5c** R^1=CH_3, R^2=C_2H_5; **6a** R^1=C_2H_5, R^2=H; **6b** R^1=C_2H_5, R^2=CH_3; **6c** R^1=C_2H_5, R^2=C_2H_5; **7a** R^1=$CH_2CH{=}CH_2$, R^2=H; **7b** R^1=$CH_2CH{=}CH_2$, R^2=CH_3; **7c** R^1=$CH_2CH{=}CH_2$, R^2=C_2H_5

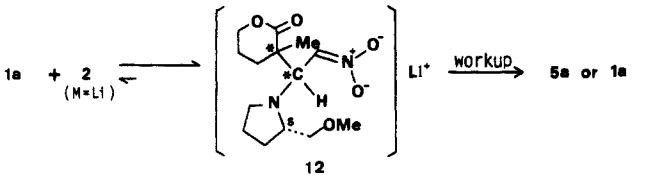


8 R=CH_3; **9** R=C_2H_5

10 R=CH_3; **11** R=C_2H_5

cations have a remarkable effect on the reaction. Both the chemical yield and the enantiomeric excess (ee) were increased when Zn^{2+} was used as a countercation (runs 1–3 in Table I). The similar tendency was observed in the reaction of the enolate **3** with **1a**. Thus, Zn^{2+} was chosen as a countercation and reactions of δ-lactone enolates **2–4** with nitro enamines **1a–1c** were performed. The results are compiled in Table I. Substituted nitro enamines **1b,c** gave better results than the parent nitro enamine **1a** in terms of the % ee.

To gain an insight into the origin of the asymmetric induction, the reaction of lithium enolate **2** (M = Li) with nitro enamine **1a** was studied in more detail. The crossover experiment[11] proved that addition of lithium enolate **2** onto nitro enamine **1a** was readily reversible. Quenching conditions are important to obtain a good yield of the product. Thus, starting nitro enamine **1a** was recovered without any trace of the desired product **5a** when the reaction was quenched by pouring into ice–water. However, quenching the reaction by addition to a solution of *p*-toluenesulfonic acid in dichloromethane–THF (4:1) at room temperature yielded **5a** without any detectable amount of the starting nitro enamine **1a**.



12

Table I. Asymmetric Nitroolefination of Lactone Enolates via Addition–Elimination Sequence

run	nitro enamine	counter-cation	enolate[a]	product[b]	yield, %	$[\alpha]^{20}_D$ $CHCl_3$	% ee[c]
1	**1a**	Li^+	**2**	**5a**	50	−5.4	41
2	**1a**	Cu^+	**2**	**5a**	76	−9.7	70
3	**1a**	Zn^{2+}	**2**	**5a**	99	−12.3	86
4	**1a**	Li^+	**3**	**6a**	56	+8.3[d]	35
5	**1a**	Cu^+	**3**	**6a**	42	+0.71	82
6	**1a**	Zn^{2+}	**3**	**6a**	99	+0.69[e]	82
7	**1a**	Zn^{2+}	**4**	**7a**	63	−24.8	88
8	**1b**	Zn^{2+}	**2**	**5b**	69	−50.8	93
9	**1b**	Zn^{2+}	**3**	**6b**	65	−25.7	90
10	**1b**	Zn^{2+}	**4**	**7b**	54	−54.3	92
11	**1c**	Zn^{2+}	**2**	**5c**	87	−46.1	85
12	**1c**	Zn^{2+}	**3**[f]	**6c**	89	−37.2	96
13	**1c**	Zn^{2+}	**4**	**7c**	69	−67.8	96
14	**1a**	Cu^+	**8**	**10**	82	−21.3	56
15	**1a**	Zn^{2+}	**9**	**11**	72	−22.6	63

[a] Three equivalents of enolate were used unless otherwise stated. [b] Absolute stereochemistry of the major enantiomer was not determined. [c] Determined by 400-MHz ^1H NMR with $Eu(hfc)_3$. [d] Determined at 435 nm. [e] +20.2° at 435 nm. [f] Six equivalents of enolate were used.

These facts indicate that an equilibrium mixture of the adducts **12** exists in the reaction medium and elimination of either the prolinol or lactone moiety takes place depending upon the workup procedure. The observed asymmetric induction, therefore, depends upon the thermodynamic stabilities of the four possible isomers of adduct **12** arising from the addition of enolate **2** (M = Li) to nitro enamine **1a**. The similar crossover experiment using zinc enolates **2** and **3** showed that the addition of zinc enolate **2** to nitro enamine **1a** was no more reversible. Thus, the asymmetric induction is controlled kinetically, where the addition of the enolate decides the absolute stereochemistry of the product when zinc enolate **2** is used.

In conclusion, we have developed the new method for the construction of a chiral quaternary carbon center. The remarkable feature of this asymmetric synthesis consists in the direct formation of the enantiomer in one pot with high ee. Attempted application of this method to other substrates such as α-substituted ketones, esters, and amides proceeded but failed to yield high ee.

(5) These compounds are easily prepared from the corresponding 1-morpholino-2-nitro olefins[7] and (*S*)-2-(methoxymethyl)pyrrolidine in methanol in more than 90% yield.

(6) Satisfactory spectral data and elemental analyses were obtained for all new compounds.

(7) Faulgues, M.; Rene, L.; Royer, R. *Synthesis* **1982**, 260.

(8) For an extensive review, see: Rajappa, S. *Tetrahedron* **1981**, *37*, 1453.

(9) Severin, T.; Pehr, H. *Chem. Ber.* **1979**, *112*, 3559 and previous papers in this series.

(10) (a) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294. (b) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149.

(11) Lactones **5a** (30%) and **6a** (49%) were obtained when **3** (M = Li, 1.5 mmol) was added to a reaction mixture of **2** (M = Li, 1.5 mmol) and **1a** (0.5 mmol). On the other hand, **5a** (76%) was obtained as a sole product when the same reaction mixture was quenched before the addition of **3** (M = Li). Yields were determined by HPLC with phenanthrene as an internal standard. The formation of **6a** through addition of **3** (M = Li) to **5a** followed by elimination of **2** (M = Li) was not recognized in a separate experiment.

Evidence of Tautomerism in a Triply ^{15}N Labeled Monoacetylporphyrin in NMR: Kinetic HH/HD Isotope Effects and Thermodynamics in CD_2Cl_2

Martin Schlabach,[1a] Bernd Wehrle,[1a]
Hans-Heinrich Limbach,*[1a] Edward Bunnenberg,[1b]
Andreas Knierzinger,[1c] Arthur Y. L. Shu,[1d]
Bo-Ragnar Tolf,[1e] and Carl Djerassi*[1d]

Institut für Physikalische Chemie der Universität Freiburg i. Br., D-7800 Freiburg, West Germany
Department of Chemistry, Stanford University
Stanford California 94305

Received January 24, 1986

Little is known about the influence of the shape of the double-minimum potential on rate constants of hydrogen migration in porphyrins.[2-9] Although qualitative information on tautom-

(1) (a) Institut für Physikalische Chemie der Universität Freiburg i.Br. (b) Decreased. (c) Same as ref 1d; present address: F. Hoffman-La Roche, Bau 86/425, CH-Basel, Switzerland. (d) Department of Chemistry, Stanford University. (e) Same as ref 1d; present address: Pharmacia AB, S-75104 Uppsala 1, Sweden.

(2) (a) Storm, C. B.; Teklu, Y. *J. Am. Chem. Soc.* **1974**, *94*, 53. (b) Storm, C. B.; Teklu, Y. *Ann. N. Y. Acad. Sci.* **1973**, *206*, 631. (c) Abraham, R. J.; Hawkes, G. E.; Smith, K. M. *Tetrahedron Lett.* **1974**, 1483. (d) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 1603. (e) Gust, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 3637. (f) Yeh, H. J. C.; Sato, M.; Morishima, I. *J. Magn. Reson.* **1977**, *26*, 365. (g) Irving, C. S.; Lapidot, A. *J. Chem. Soc., Chem. Comm.* **1977**, 184. (h) Boxer, S. C.; Closs, G. L.; Katz, J. J. *J. Am. Chem Soc.* **1974**, *96*, 7058.

0002-7863/86/1508-3856$01.50/0

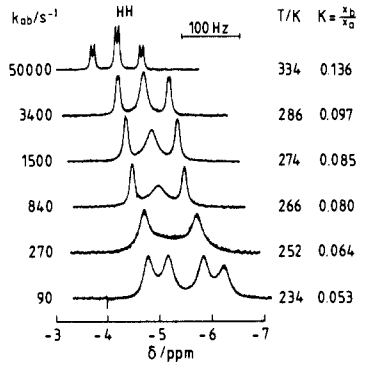
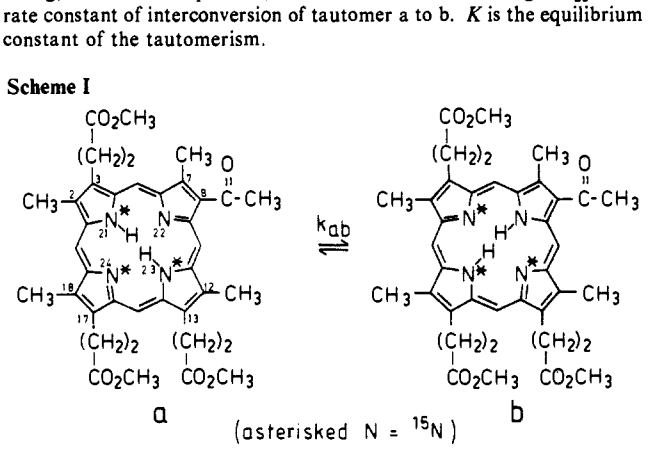


Figure 1. Superposed experimental and calculated 90-MHZ ^1H NMR signals of the inner hydrogen atom of I in highly purified CD_2Cl_2 (12.8 mg in 0.5 mL = 0.038 M), as a function of temperature. The spectra were measured on a Bruker CXP-100 spectrometer: 25-deg pulses, 2.2-s repetition time, quadrature detection, 1-Hz line broadening, 4–8K zero filling, 2000-Hz sweep width, 200–400 scans on the average. k_{ab} is the rate constant of interconversion of tautomer a to b. K is the equilibrium constant of the tautomerism.

Scheme I



erism in asymmetric porphyrins has been obtained,[2a,b,g,h] rate constants as a function of equlibrium constants have been reported so far only for *meso*-tetraphenylporphine (TPP) whose symmetrical double well is perturbed in the solid state.[5] We report here for the first time rate and equilibrium constants of tautomerism, including kinetic HH/HD isotope effects, in a chemically perturbated porphyrin, 8-acetyl-3,13,17-tris(2-(methoxycarbonyl)-ethyl)-2,7,12,18-tetramethyl-(21*H*,23*H*)-(21-^{15}N,23-^{15}N,24-^{15}N)porphyrin (I), dissolved in CD_2Cl_2. The synthesis of the triply ^{15}N labeled compound I by variation of literature procedures[10] allowed us to establish the tautomerism depicted in Scheme I, which was postulated previously on the basis of MCD measurements.[9]

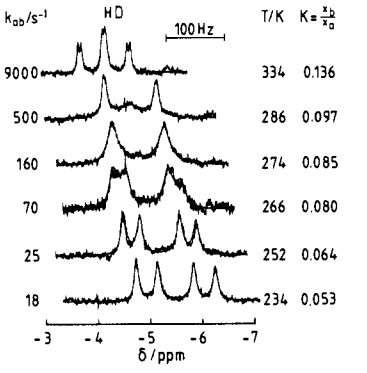


Figure 2. Superposed experimental and calculated 90-MHz ^1H NMR signals of the residual inner hydrogen atoms of I after 95% deuteration of the inner proton sites. The concentration and the spectral parameters are the same as in Figure 1, with the exception of the number of scans, which were between 800 and 1400 on the average.

As shown in Figures 1 and 2 we observe for the inner H atoms of I in CD_2Cl_2[11] at low temperature two ^1H–^{15}N doublets with equal coupling constants $^1J_{^{15}N-^1H}$ indicating the presence of only one tautomer a in which the inner protons are both bound to ^{15}N atoms. At high temperatures a coalesced triplet with a doublet substructure appears. The effective splittings are given by $J_i = x_i {}^1J_{^{15}N-^1H}$, where x_i is the probability of finding an inner proton on N atom i. The triplet indicates a fast tautomer b, in which one H atom is bound to a ^{15}N atom and the other to the unlabeled N-22 atom. The ratio of the doublet vs. the triplet splitting increases with temperature and is equal to the equilibrium constant of the tautomerism. We find that $K = 10^{0.3\pm0.5} \exp(-7.2\text{-}(\text{kJmol}^{-1})/RT)$. If we assume, as usual that the inner H atoms are localized on opposite N atoms, our results can only be explained by the tautomerism of Scheme I. In this case the permutation and the tautomer formation processes are correlated and depend only on one rate constant, k_{ab}. If one or both of the observed tautomers had the inner protons on adjacent N atoms, the two processes would be uncorrelated and would have to be described by two different rate constants. As shown in Figures 1 and 2, we find excellent agreement between the experimental and calculated spectra[12] for the model of Scheme I involving only the rate constant k_{ab}, which supports the assumption that the inner protons are located on opposite N atoms. In addition, the signals of the inner hydrogen atoms do not seem to be affected at 90 MHz by a possible rotation of the acetyl group discussed in connection with our earlier MCD studies.[9] Particularly noteworthy is the asymmetric line shape at 252 K (Figure 1) which arises from the chemical shift decrease when a H atom jumps into the N-22 site. Similar effects have been observed for the imino proton signals

(3) Hennig, J.; Limbach, H. H. *J. Chem. Soc., Faraday Trans. 2* **1979**, *75*, 752. Limbach, H. H.; Hennig, J.; Gerritzen, D.; Rumpel, H. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 822. Hennig, J.; Limbach, H. H. *J. Am. Lchem. Soc.* **1984**, *106*, 292. Hennig, J.; Limbach, H. H. *J. Magn. Reson.* **1982**, *49*, 322.

(4) Limbach, H. H.; Hennig, J. *J. Chem. Phys.* **1979**, *71*, 3120. Limbach, H. H.; Hennig, J.; Stulz, J. *J. Chem. Phys.* **1983**, *78*, 5432. Limbach, H. H. *J. Chem. Phys.* **1984**, *80*, 5322.

(5) Limbach, H. H.; Hennig, J.; Kendrick, R.; Yannoni, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 4059. Limbach, H. H.; Gerritzen, D.; Rumpel, H.; Wehrle, B.; Otting, G.; Zimmermann, H.; Kendrick, R. D.; Yannoni, C. S. In *Photoreaktive Festköper*; Sixl, H., Friedrich, J., Bräuchle, C.; Karlsruhe **1985**; pp 19–43.

(6) Butcher, R. J.; Jameson, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 2978.

(7) Stilbs, P.; Moseley, M. E. *J. Chem. Soc., Faraday Trans. 2* **1980**, *76*, 729. Stilbs, P. *J. Magn. Reson.* **1984**, *58*, 152.

(8) Sarai, A. *J. Chem. Phys.* **1982**, *76*, 5554; **1984**, *80*, 5341. Bersuker, G. I.; Zolinger, V. Z. *Chem. Phys.* **1984**, *86*, 57. Siebrand, W.; Wildman, T. A.; Zgierski, M. Z. *J. Am. Chem. Soc.* **1984**, *106*, 4089.

(9) Lu, Y.; Shu, A. Y.; Knierzinger, A.; Clezy, p. S.; Bunnenberg, E.; Djerassi, C. *Tetrahedron Lett.* **1983**, *24*, 2433. Djerassi, C.; Lu, Y.; Waleh, A.; Shu, A. Y. L.; Goldbeck, L. A. K.; Crandell, C. W.; Weee, A. G H.; Knierzinger, A.; Gaete-Holmes, R.; Loew, G. H.; Clezy, P.; Bunnenberg, E. *J. Am. Chem. Soc.* **1984**, *106*, 4241.

(10) Chandry, J. A.; Clezy, P. S.; Diakiw, V. *Aust. J. Chem.* **1977**, *30*, 879. Smith, K.; Langry, K. C. *J. Org. Chem.* **1983**, *48*, 500.

(11) Sealed pure samples were prepared on a vacuum line as described in ref 3 and by Gerritzen et al. (Gerritzen, D.; Limbach, H. H. *J. Am. Chem. Soc.* **1984**, 106, 869) using basic alumina as drying agent. However, impurities were produced by thermal decomposition of residual CD_2Cl_2 in the gas phase or on the glass walls during the sealing of the NMR tubes, even though the frozen solutions were kept at 77 K. These impurities catalyzed intermolecular proton exchange leading to a singlet for the inner hydrogen atoms of I. Therefore, we employed here NMR tubes with a needle valve (see: Mohanty, S.; Bernstein, H. J. *J. Chem. Phys.* **1971**, *54*, 2254). In order to reduce rotational sidebands and the gas volume above the solutions, a version was developed (available from Normag, D-6238 Hofheim) where the valve (10-mm o.d.) is placed in the usual 10-mm rotor. Thus, spectra of very pure acid-free CD_2Cl_2 solutions could be obtained at elevated temperatures without refluxing of the solvent.

(12) For this model the line shapes have to be described in terms of eight superposed four-site systems as shown previously for the symmetrical case.[3] As automated version of the program was written involving routines of: Marquardt, D. W. Share Distribution Center, 1964, revised Program 1428. Ehrig, R. Ph.D. Thesis, Freiburg, 1980 At low temperature, k_{ab}, the chemical shifts υ_i, and the residual line broadening W_0 could be obtained. W_0 increased below 220 K due to T_2 effects (see ref 3,7). K was extrapolated to low temperatures. At higher temperatures fixed extrapolated values for υ_i were employed. This introduced no uncertainty in k_{ab} which is determined at higher temperature by the differential line broadening of the inner and outer triplet lines. The spectra in Figure 2 were calculated by taking into account the presence of ca. 5% of I-H_2.

of ^{15}N labeled t-RNA, where, however, an interference between different relaxation mechanisms is discussed.[13]

From the measurements shown partly in Figures 1 and 2, we calculate $k_{ab}^{HH} = 10^{11} \exp(-41(\text{kJmol}^{-1})/RT)$ and $(k^{HH}/k^{HH})_{298K} = 9$. These data are not affected by intermolecular proton exchange.[11] Although the chemical shifts depend strongly on concentration and temperature, indicating aggregation of I, preliminary measurements show that the rate constants are not influenced by this phenomenon, which is consistent with the observation of the absence of kinetic solution–solid state effects for *meso*-tetratolylporphine.[5]

We find a surprising coincidence of the rate constants k_{ab}^{HH} derived here for I with the symmetrical rate constants of TPP in solution,[3] where $k^{HH} = 10^{10.9} \exp(-40(\text{kJmol}^{-1})/RT)$ and $(k^{HH}/k^{HD})_{298}K = 10$. The acetyl group in I, therefore only decreases the basicity of the adjacent N atom (i.e., increases the energy of the corresponding tautomer) but does affect significantly the barrier of the migration. A similar coincidence was found previously[5] for the solid-state tautomerism of TPP, where only the energy of the dominant tautomer was lowered. As far as the theory is concerned, it seems that the idea of thermally activated hydrogen tunneling in porphyrins[3-5] has been accepted,[6,8] in spite of the absence of a definite tunneling model. However, a coherent tunneling process,[4] where the tunneling rates would be very sensitive to perturbations, can be excluded. The possibility of a nonconcerted hydrogen motion warrants reconsideration. In order to contribute to a better understanding of these processes, we are currently studying the complex kinetic HH/HD/DD isotope effects of the tautomerism in I and of related compounds in solution and in the solid state.

Acknowledgment. The line-shape simulations were done on the Univac 1108 computer of the Rechenzentrum der Universität Freiburg. We thank the Deutsche Forschungsgemeinschaft, Bonn Bad Godesberg, the Fonds der Chemischen Industrie, Frankfurt, and the National Institutes of Health (Grant GM-20276) for financial support.

(13) Rüterjans, H.; Kaun, E.; Hull, W.; Limbach, H. H. *Nucleic Acid Res.* **1982**, *10*, 7027. Gueron, M.; Leroy, J. L.; Griffey, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 7262. Goldmann, M. *J. Magn. Reson.* **1984**, *60*, 437.

NMR Studies of Metalloporphyrin Radicals. Iron(II) Oxophlorin Radical Formed from Iron(III) *meso*-Hydroxyoctaethylporphyrin

Isao Morishima,* Hiroshi Fujii, and Yoshitsugu Shiro

Division of Molecular Engineering
Graduate School of Engineering
Kyoto University, Kyoto 606, Japan

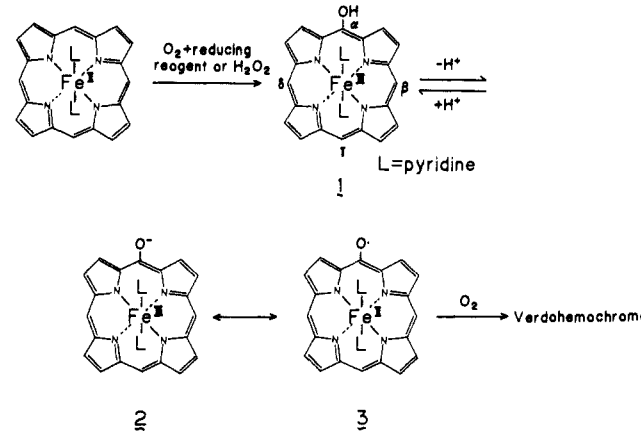
Seiyo Sano

Department of Public Health
Faculty of Medicine
Kyoto University, Kyoto 606, Japan

Received December 10, 1985

The Fe(II) oxophlorin radical **3**, a redox valence isomer of Fe(III) *meso*-oxophlorin anion **2** formed from Fe(III) *meso*-hydroxyporphyrin **1**, has been a putative key intermediate in the heme catabolism, in which the heme ring is cleaved by the coupled oxidations (Scheme I).[1,2] However, evidence for iron oxophlorin radical **3** has not been obtained[3] until we observed the unusual

Scheme I



hyperfine-shifted proton NMR spectrum of Fe(III) *meso*-hydroxyhemin in aqueous pyridine solution which was attributed to Fe(II) oxophlorin radical rather than the Fe(III) state on the basis of unusually large hyperfine shifts for the meso protons.[4] To further confirm Scheme I and to better characterize the electronic state of the iron oxophlorin radical, we examined here the NMR and UV spectra of the iron oxophlorin radical derived either from Fe(III) *meso*-hydroxyoctaethylporphyrin (OEP) under various solution conditions or directly from Fe(II) porphyrin bis(pyridine) complex plus H_2O_2.

Fe(III) *meso*-hydroxyOEP was obtained by hydrolysis of the corresponding *meso*-benzoyloxyOEP.[1] When we dissolved it in pure pyridine under anaerobic condition, we obtained the sharp hyperfine-shifted ^1H NMR spectrum in the upfield and downfield regions (Figure 1a). The two proton peaks in the far upfield region at −154 and −111 ppm were readily assigned to the meso protons by utilizing the deuterium-labeled compound. The four methylene proton resonances, one at 32 ppm and others in the 6 to −5 ppm region, are also quite unique in their shift positions compared with those established for Fe(II) or Fe(III) paramagnetic porphyrin complexes.[5] The ESR was silent at the temperatures employed for the NMR measurements,[6] but the magnetic susceptibility measurement by the NMR Evans method showed a single electron spin ($\mu_{eff} = 2.4\ \mu_B$ at 23 °C). All of the NMR peaks exhibited an unusual temperature-dependent shift without obeying the Cuire law (Figure 2A). Its electronic spectrum with absorption maxima at 606 and 649 nm (Figure 1c) which is quite different from those for Fe(II) or Fe(III) porphyrin complexes did not experience any significant changes with temperature variation from 20 to −30 °C except for slight intensity changes having isosbestic points at 662 and 710 nm. Upon addition of acid, the meso proton resonances drastically shifted downfield (Figure 1b), depending on the acid concentration. This is most likely due to an equilibrium shift toward the protonated ferric low spin form (**1**) (Scheme I), which was further confirmed

(1) Bonnett, R.; Dimsdale, M. J. *J. Chem. Soc., Perkin Trans 1* **1972**, 2540–2548.

(2) Schmid, R.; McDonagh, A. F. *Ann. N. Y. Acad. Sci.* **1975**, *244*, 533–552. Schmid, R.; McDonagh, A. F. *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 7, pp 257–292.

(3) It has been reported that oxophlorine radical is formed on oxidation of oxophlorin (the predominant keto form of *meso*-hydroxyporphyrin) either in its metal-free or zinc-complex form; Bonnett, R.; Dimsdale, M. J.; Sales, K. D. *J. Chem. Soc.* **1970**, 962–963. Fuhrhop, J.-H.; Besecke, S.; Subramanian, J. *J. Chem. Soc., Chem. Commun.* **1973**, 1–2. Fuhrhop, J.-H.; Besecke, S.; Subramanian, J.; Mengersen, Chr.; Riesner, D. *J. Am. Chem. Soc.* **1975**, *97*, 7141–7152.

(4) (a) Sano, S.; Sugiura, Y.; Maeda, Y.; Ogawa, S.; Morishima, I. *J. Am. Chem. Soc.* **1981**, *103*, 2888–2889. (b) Sano, S.; Sano, T.; Morishima, I.; Shiro, Y.; Maeda, Y. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 531–535.

(5) We examined paramagnetic NMR spectral characterization of a variety of Fe(III) *meso*-benzoyloxyOEP complexes in high- and low-spin states. No unusual hyperfine shifts as compared with Fe(III) OEP analogues were noticed.

(6) In our previous report,[4b] we described the ESR spectrum ($g = 2.31$, 2.002, 1.78) obtained at 77 K for **3** derived from Fe(III) *meso*-hydroxyhemin in aqueous pyridine, which was attributed to the low-spin Fe(I) state formed from **3** via an intramolecular reduction at low temperature. The similar ESR spectrum was obtained for the present OEP analogue at 77 K, but no ESR signal was detected at temperatures above 180 K. Thus, we tentatively interpret these findings in a way that oxophlorin radical **3** with an enhanced electron spin relaxation predominates at room temperature.

0002-7863/86/1508-3858$01.50/0