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HINDERED ROTATION OF AXIALLY COORDINATED 2-METHYLIMIDAZOLES IN TETRAMESITYLPORPHYRINATO-IRON(III) COMPLEXES

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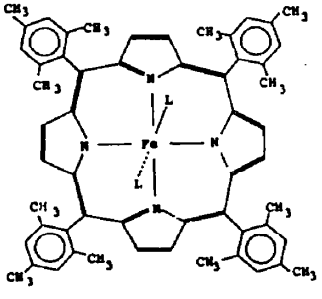
Abstract. Hindered rotation of coordinated imidazoles in the title complex has been observed by the dynamic NMR method. At low temperature, where the rotation of the imidazoles was slow on the NMR time scale, only the conformer with C_2 symmetry was observed. The dispersion of the pyrrole signals, 7.3 ppm at -48°C, has been ascribed to the deviations from planarity of the porphyrin ring rather than an orientation effect of the axial ligands, since they must be perpendicular to each other. The activation enthalpy and entropy for ligand rotation were determined to be 12.9 ± 0.4 Kcal/mol and 3.7± 1.6 e. u., respectively.

INTRODUCTION

One of the characteristic features in the proton NMR spectra of low spin ferric porphyrins in synthetic compounds, simple natural hemins, and heme proteins is that the four methyl groups at the pyrrole β positions of the porphyrin core show resonance lines over a very wide range of magnetic field. For example, the difference in chemical shifts of these methyl signals is as much as 20 ppm in cytochrome b[1] and about 12 ppm in cytochrome c cyanide.[2] By contrast, all of the four methyl signals of bis(imidazole) (porphyrinato) iron(III) appear within 4 ppm.[3] Since the large downfield shifts of these methyl groups are caused by the contact interaction with the unpaired electron on the central iron, [4] the above results indicate that the electron spin is transferred unequally to the pyrrole rings of the porphyrin.

Two hypotheses have been proposed to explain the difference in methyl contact shifts in the hemoproteins: (1) steric interactions between the protein and certain parts of the porphyrin core may affect the spin density of the four pyrrole rings,[5] and (2) the proximal histidyl imidazole may be fixed in such a way as to interact with only one of the dπ orbitals of iron, making it possible for the dπ orbital to interact with one of the porphyrin 3e (π) orbitals.[6] Either (1) or (2) could cause an asymmetric distribution of electron spin. Suitable model compounds in which the coordinating imidazole is fixed may elucidate these possibilities. The fixation of an axial imidazole has been achieved in several cases [7] for imidazole-appended iron porphyrins. Although the proton NMR spectra of these complexes exhibited a dispersion of the pyrrole signals, it has been difficult to extract the orientation effect of the axial imidazole because of the unsymmetrical substitution of these complexes. More recently, Walker et al.[8] used symmetrically substituted porphyrin atropisomers of tetrakis(*o*-pivalamidophenyl)porphyrin, to restrict the rotation of planar axial ligands and hold them either parallel or perpendicular to each other. In the bis(1-methylimidazole) complex of the αααββ isomer, 1, where the planes of the two imidazoles are parallel, the pyrrole protons appeared as two signals at δ -17.1 and -20.0 at 21°C. Since the difference in chemical shift was rather small and since these protons are in principle diastereotopic regardless of the rotation of imidazoles, some effects other than the orientation may contribute.

In this paper we describe the fixation of axially coordinated imidazoles in a highly symmetrical low spin ferric porphyrin, bis(2-methylimidazole) (tetramesitylporphyrinato) iron(III) chloride, (2-MeIm)$_2$ (TMPFe)Cl, 2, in which the pyrrole protons become non-equivalent only when the rotation of imidazoles is restricted on the NMR time scale.



2 : L = 2-methylimidazole

3 : L = 1,2-dimethylimidazole

RESULTS AND DISCUSSION

The visible spectrum of 2 is quite similar to that of (2-MeIm)$_2$(TPPFe)Cl,[9] showing absorption maxima at 410, 477, 564, and 596 nm in dichloromethane solution. The proton NMR spectrum of 2 in a solution obtained by the addition of 2.5 mol equiv of 2-methylimidazole into a 0.029M of $CDCl_3$ solution of TMPFeCl [10] in an NMR sample tube, showed very broad *o*-methyl and pyrrole signals at δ 1.5 and -10.5, respectively, at 26°C. When the temperature was lowered, proton signals due to the porphyrin further broadened and finally split into two to four peaks as shown in Fig. 1. These signals were assigned unambiguously on the basis of their integral intensities and by comparison of the proton NMR spectra with those of the corresponding *m*-deuterated and pyrrole-deuterated complexes.[11] The signals ascribable to the coordinated 2-methylimidazole were assigned by the comparison with those of analogous complexes.[12] The chemical shifts of the signals observed at -48°C are listed in Table 1. The chemical shift of each signal varied linearly with T^{-1} (Fig. 2). Extrapolation of the chemical shifts of the four pyrrole signals gave values of δ -13.1, -11.6, -10.4, and -8.5 at 21°C.

Table 1 Chemical Shifts of 2 in $CDCl_3$ -48° C (δ from internal TMS)

				2-methylimidazole ligand			
o-CH_3	*m*-H	*p* -CH_3	pyrrole-H	1-H	2-CH_3	4-H	5-H
-5.5	5.9 (4H)	1.19	-20.2	13.1	5.3	30.5	7.8
-1.5	6.8 (2H)	2.2	-18.6				
4.5	9.3 (2H)		-16.5				
8.6			-12.9				

The temperature dependence of the proton NMR line shape was interpreted to result from slow rotation of the 2-methylimidazole ring about Fe - N bond on the NMR time scale. At the low temperature limit the two axial ligand planes would lie over the N(1)-N(3) and/or N(2)-N(4) axes, since severe steric repulsions are expected between the mesityl *o*-methyls and the imidazole methyl groups. Thus, three forms, with C_{2v}, C_{2h}, and C_2 symmetries, can be considered as possible conformations. The fact that both the pyrrole and *o*-methyl protons gave four signals of equal intensity rules out the former two conformations and supports the conformation with C_2 symmetry, in which the dihedral angle between the two imidazole planes is expected to be nearly 90°, as the sole stable species. Although the *p*-methyl protons should give three signals with relative intensities of 2:1:1 in this conformation, only two signals with equal intensities were observed. This can be ascribed to the accidental coincidence in chemical shifts of two of the three methyl resonances. Since the peaks due to any minor conformers were not observed at -48°C, the population of these conformers must be less than 5%. The free energies of the C_{2v} and C_{2h} conformers can be calculated to be higher than that of the conformer C_2 by at least 1.0 Kcal/mol at -48°C. The preference for the C_2 conformation can be ascribed to steric effects rather than electronic effects, since the steric repulsion between the porphyrin and the 2-methylimidazole ligands can be minimized by a quasi-S_4 ruffling[13] of the porphyrinato core and this is only possible in the C_2 conformation. This result is consistent with the crystal structure of (2-MeIm)$_2$(TPPFe)Cl, in which the dihedral angle between the two axial planes is 88.2°.[13]

Hindered rotation is not the only process that could explain the conversation from one C_2 conformation to another. An intermolecular process involving the dissociation of the coordinating imidazole[14] is also possible. This process is ruled out, however, since the methyl groups of free and coordinated imidazole gave separate signals at δ2.4 and 5.6, respectively, even at 26°C where the other signals have collapsed to singlets.[15]

Since the two ligands in 2 are perpendicular to each other and lie over two opposite nitrogens of the porphyrin, they can raise the energy levels of both d_{xz} and d_{yz} orbitals of the iron to a similar extent.[7,8] This indicates that the single unpaired electron of the low spin iron(III) can be transferred equally to each of the four pyrrole rings. For this reason, the dispersion in chemical shifts of the pyrrole protons, 4.6 ppm at 21°C, has been attributed to steric perturbations rather than

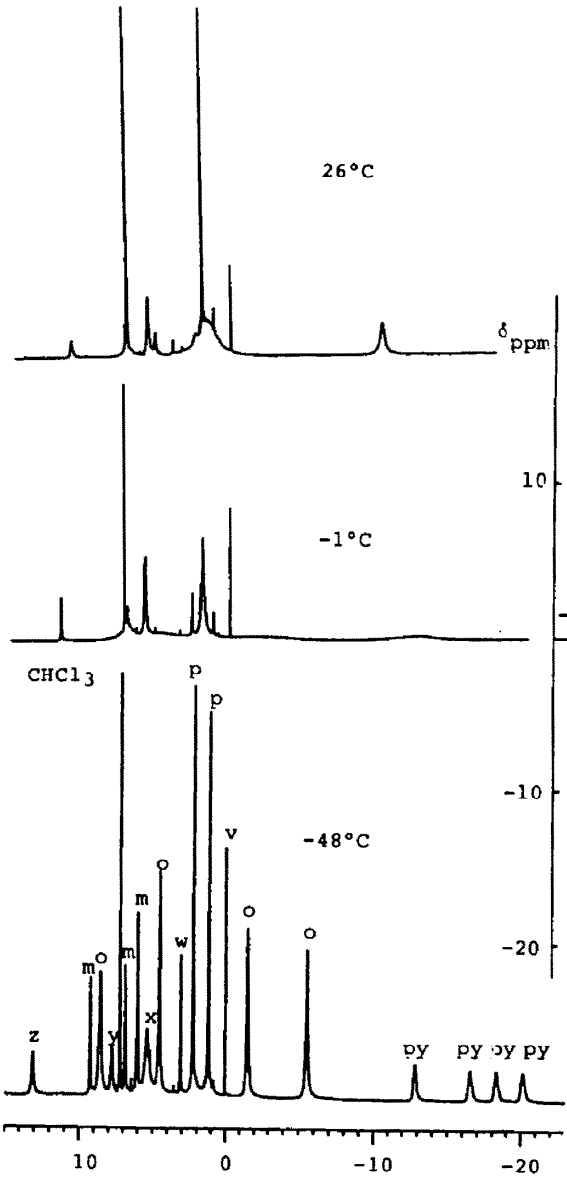


Fig. 1 Temperatue dependent proton NMR spectra of 2. (360 MHz, $DCDl_3$)

Signal assignment at -48°C.

w: free 2-MeIm

x: coordinating 2-MeIm

y: 5-H of coordinating 2-MeIm

z: 1-H of coordinating 2-MeIm

py:pyrrole-H

o :ortho-methyl

m::meta-H

p :para-methyl

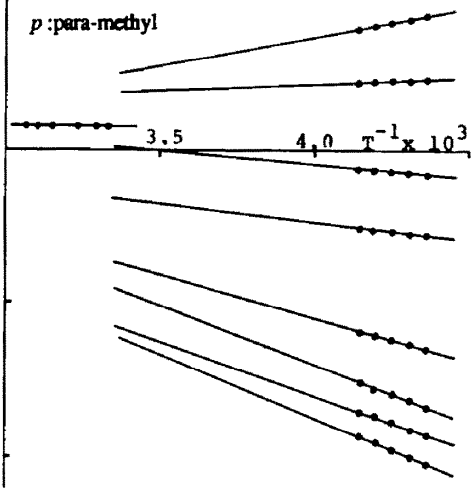
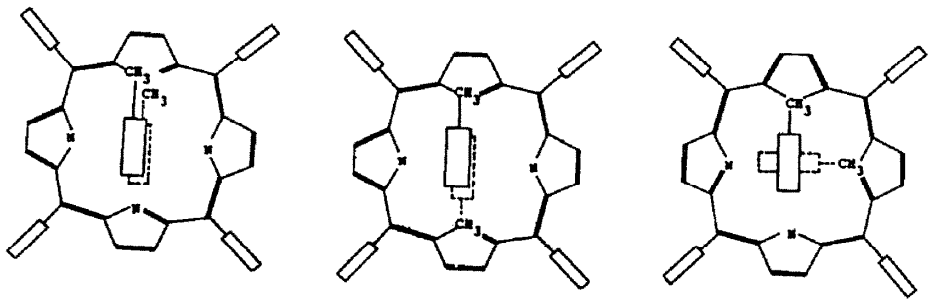


Fig. 2 Temperature dependence of the proton chemical shifts (δ) of 2 in $CDCl_3$: (●)*o*-methyl; (○) pyrrole-H.



C_{2v} C_{2h} C_2

any orientation effect of the axial ligand, although this dispersion is larger than that of 1 where two axial ligands must be parallel. Probably the deviation of the porphyrinato core from planarity due to the hindered rotation of 2-methylimidazoles causes the asymmetric spin distribution observed in this system. The result suggests that the large dispersion of the chemical shifts of the peripheral methyl groups in various hemoproteins may also be ascribed to deformations of the porphyrin ring due to the hindered rotation of hystidinyl imidazole ligand.

The temperature dependence of the chemical shifts of the *o*-methyl signals gave further subtle information on the conformation of this complex. At higher temperatures where the rotation of the 2-methylimidazoles was fast on the NMR time scale, the chemical shift of the *o*-methyl signal was almost temperature independent (Fig. 2). Since the hyperfine shifts of the meso-aromatic protons in low spin (tetraarylporphyrinato)iron(III) complexes derive largely from the dipolar term,[3] the above results indicate that the average position of *o*-methyl protons is near the magic angle. Upon lowering the temperature, two of the signals move upfield, one shows a large downfield shift and one stays nearly at the same position. These changes are best interpreted to result from differences in the dihedral angles between each mesityl ring and porphyrin plane at low temperature.

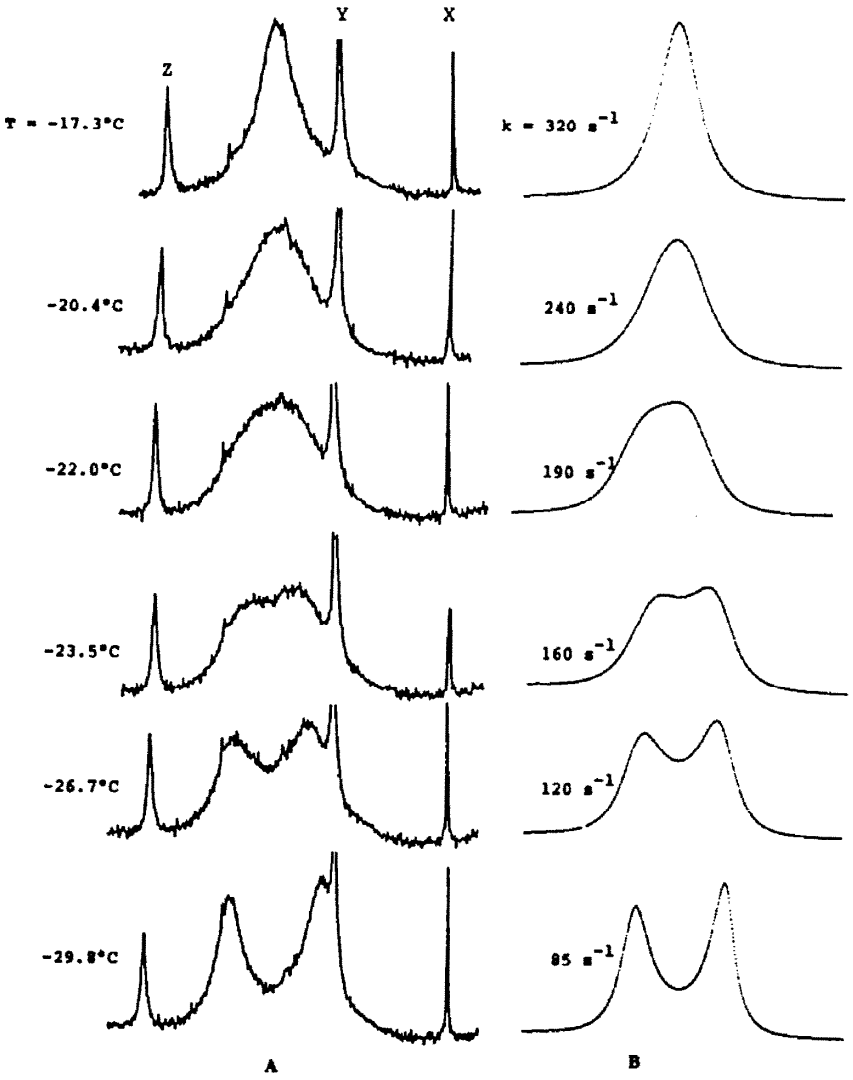


Fig. 3 (A) Temperature dependent NMR spectra (90 MHz) of *p*-methyl signals of complex 2 in 0.029 M of $CDCl_3$ solution. X is TMS, Y is impurity and Z is the methyl signal of free 2-methylimidazole. (B) Calculated spectra for various rate constants.

The activation parameters for rotation about the Fe - N bond of complex 2 were obtained by the total line shape analysis[16] of the *p*-methyl signals in the temperature range between -31.3°C and -12.6°C, a range over which the line shapes changed drastically (Fig. 3). The chemical shifts of these protons in this temperature range were determined by the extrapolation of the linear lines obtained at temperatures lower than -35°C. The results are given in Table 2. The hindered rotation observed here is caused by the large repulsive interaction between the mesityl methyl and the imidazol methyl groups at the transition state for rotation where these two methyl groups abut one another. Thus, when one of the methyl groups was absent, the barrier to rotation decreased greatly; the pyrrole signals showed no dispersion either in (1-MeIm)$_2$(TMPFe)Cl or in (2-MeIm)$_2$(TPPFe)Cl even at -60°C. By contrast, splitting of the signals was observed in the bis(1,2-dimethylimidazole) complex of TMPFeCl 3. The activation parameters for rotation of the axial ligand in 3 are also given in Table 2. The ratio of the rate constants of these two complexes, k(3)/k(2), was calculated to be 3.4 at 25°C based on the data in Table 2. The difference is probably ascribed to the longer Fe - N(axial) bond in 3 due to the buttressing effect of the 1-methyl group.

Table 2. Activation Parameters for Axial Ligand Rotation

Complexes	$\Delta H^{\neq}$ (Kcal/mol)	$\Delta S^{\neq}$ (e.u.)	$\Delta G^{\neq}$ (at 25°C) (Kcal/mol)
2	12.9±0.4	3.7±1.6	11.8
3	12.6±0.8	5.2±3.6	11.0

To our knowledge, these are the first examples in which the hindered rotation of axially coordinating imidazoles has been observed in solution by proton NMR spectroscopy.[17] Complexes exhibiting this property would be useful to elucidate the relationships between properties of metalloporphyrins and axial ligand orientations.[18]

EXPERIMENTAL SECTION

Sample Preparation. 5,10,15,20-Tetramesitylporphyrin, [(TMP)H$_2$], and 5,10,15,20-Tetraphenylporphyrin, [(TPP)H$_2$], were synthesized by published procedures.[10] The ferric complexes of these porphyrins were prepared by the method of Kobayashi et al.[18] 2-Methylimidazole was purchased from Tokyo Kasei Kogyo, purified by recrystallization from benzene, and dried at 2 torr for 5 h at room temperature. 1-Methylimidazole and 2,3-dimethylimidazole were also purchased from Tokyo Kasei Kogyo and distilled before use. The proton NMR spectra of these imidazoles reflected a very high (<99%) degree of purity. The appropriate chloroiron(III) porphyrin complex was weighed out accurately and placed in an NMR sample tube. Chloroform-*d* was then added to make a 0.02 - 0.03 M solution. To this solution 2.5 mol equiv of imidazole derivative was added either as solid or as $CDCl_3$ solution. In every case, a molar ratio of 2.5:1 for base : complex yielded exclusively the low spin bis(imidazole) complex at low temperature.

Total Line Shape Analysis. Proton NMR spectra for the line shape analysis were recorded with a JEOL FX90Q or Bruker WM-360 spectrometer at various temperatures. The spectrometer temperature was calibrated by the shift difference between the proton resonances in methanol.[19] In the case of complex 2 the line shape of the *p*-methyl signals changed from a broad doublet to a broad singlet over the temperature range between -30 and -17°C as shown in Figure 3 (A). These signals were analyzed by the modified Binsch program.[16a] Since the chemical shifts of the *p*-methyl signals correlated linearly with the reciprocal of the temperature below -35°C, intrinsic chemical shifts between -30 and -17°C were determined by the extrapolation of the linear line. Apparent transverse relaxation times, $T_{1/2}$, of the *p*-methyl signals at high and low magnetic field were determined on the basis of the half height width, $W_{1/2}$, at -50.9°C to be 0.04s ($W_{1/2}$ = 8.0Hz) and 0.06s ($W_{1/2}$ = 5.3 Hz), respectively. Relaxation times were not corrected for temperature since they did not affect the line shapes in the analyzed temperature range where the signals were very broad ($W_{1/2}$ = 30 Hz at -31.3°C). Theoretical spectra were obtained by using the chemical shifts, apparent relaxation times, and appropriate rate constants of the modified Binsch program. Representative calculated spectra are also shown in Figure 3 (B). The rate constant at each particular temperature was obtained by a visual fitting of the observed and calculated spectra. Activation parameters were then calculated by putting the rate constants into Eyring's equation. Spectral changes in the *p*-methyl signals of complex 3 were similarly analyzed.

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REFERENCES

1. (a) Keller, R.M.; Wüthrich, K., *Biochim. Biophys. Acta* **1980**, *621*, 204; (b) La Mar, G.N.; Burns, P.D.; Jackson, J.T.; Smith, K.M.; Langry, K.C.; Strittmatter, P.J.; *J. Biol. Chem.* **1981**, *256*, 6075.

2. (a) Wüthrich, K., *Proc. Natl. Acad. Sci., USA* , **1969**, 1071; (b) Smith, M.; McLendon, G., *J. Am. Chem. Soc.*, **1981**, *103*, 4912.

3. La Mar, G.N.; Walker, F.A. in "The Porphyrins", Dolphin, D., Ed.; Academic Press: New York, **1979**, Vol. IV, pp. 61-157

4. La Mar, G.N.; Walker, F.A., *J. Am. Chem. Soc.*, **1973**, *93*, 1782.

5. (a) La Mar, G.A.; Budd, D.L.; Vicio, D.B.,; Smith, K.M.; Langry, K.C., *Proc. Natl. Acad. Scie., USA* , **1978**, 5755. (b) La Mar, G.N.; Viscico, D.B.; Smith, K.M.; Caughey, W.S.; Smith, M.L.; *J. Am. Chem. Soc.*, **1978**, *100*, 8085.

6. (a) Shulman, R.G.; Glarum, S.H.; Karplus, M., *J. Mol. Biol.*, **1971**, *57*, 93. (b) Morishima, I; Neya, S.; Inubushi, T.; Yonexawa, T.; Iizuka, T. *Biochim. Biophys. Acta*, **1978**, *534*, 307. (c) Satterlee, J.D.; Erman, J.E.; La Mar, G.N.; Smith, K.M.; Langry, K.C., *J. Am. Chem . Soc.*, **1983**, *105*, 2099.

7. (a) Traylor, T.G.; Berzinis, A.P., *J. Am. Chem. Soc.*, **1980**, *102*, 2844; (b) Goff, H., *J. Am. Chem. Soc.*, **1980**, *102*, 3252; (c) Walker, F.A., *J. Am. Chem. Soc.*, **1980**, *102*, 3254.

8. Walker, F.A.; Buehler, J.; West. J.T.; Hinds, J.L., *J. Am. Chem. Soc.*, **1983**, *105*, 6923.

9. Walker, F.A.; Lo, M.W.; Ree, M.T., *J. Am. Chem. Soc.*, **1976**, *98*, 5552.

10. Groves, J.T.; Nemo, T.E., *J. Am. Chem. Soc.*, **1983**, *105*, 6243.

11. Groves, J.T.; Quinn, R.; McMurry, T.J.; Nakamura, M.; Lang, G.; Boso, B., *J. Am. Chem. Soc.*, **1985**, 107, 354.

12. (a) Satterlee, J.D.; La Mar, G.N., *J. Am. Chem. Soc.*, **1976**, *98*, 2804; (b) Satterlee, J.D.; La Mar, G.N.; Frye, J.S., *J. Am. Chem. Soc.*, **1976**, *98*, 7279.

13. (a) Collins, D.M.; Countryman, R.; Hoard, J.L., *J. Am. Chem . Soc.*, **1972**, *94*, 2066. (b) Kirner, J.F.; Hoard, J.L.; Reed, C. A., Abstracts of Papers, 175th National Meeting of the American Chemical Society, Anaheim, CA., March 1978.

14. Satterlee, J.D.; La Mar, G.N.; Bold, T.J., *J. Am. Chem. Soc.*, **1977**, *99*, 1088.

15. At higher temperature broadening of these signals was observed together with the appearance of some signals due to high spin TMPFeCl. The activation free energy corresponding to this process was roughly estimated from the coalescence temperature (54°C) to be 14.2 Kcal/mol. which is higher than that of the hindered rotation of imidazole ring in 2 by ca. 2.5 Kcal/mol.

16. (a) Binsch, G. in "Topics in Stereochemistry", Eliel, E.L., and Allinger, N.L., Ed.; John Wiley & Sons: New York, 1968, Vol. 3, pp. 97-192; (b) Sandstrom, J. in "Dynamic NMR Spectroscopy"; Academic Press: London, 1982; (c) Oki, M. in "Application of Dynamic NMR Spectroscopy of Organic Chemistry", Marchand, A. P., Ed.; VCH Publishers: 1985.

17. Recently, iron-porphyrin rotation has been observed for reconstituted myoglobin by H-NMR; Neya, S.; Funasaki, N., *J. Biol. Chem.*, **1987**, *262*, 6725.

18. (a) Byrn, M.P.; Katz, B.A.; Keder, N.L.; Levan, K.R.; Magurany, C. J.; Miller, K.M.; Pritt, J.W.; Strouse, C.E., *J. Am. Chem. Soc.*, **1983**, *105*, 4916; (b) Walker, F.A.; Reis, D.; Balke, V.L. *J. Am. Chem. Soc.*, **1984**, *106*, 6888; (c) Walker, F.A.; Huynh, B.H.; Scheidt, W.R.; Osvath, S.R., *J. Am. Chem. Soc.*, **1986**, *108*, 5288.

19. Kobayashi, H.; Higuchi, T.; Kaizu, Y.; Osada, H.; Aoki, M. *Bull. Chem. Soc. Jpn.*, **1975**, *48*, 3137.

20. Van Geet, A. L., *Anal. Chem.*, **1970**, *42*, 679.