Equilibria of Imidazole Derivatives with (Protoporphyrin IX dimethyl ester)iron(III) Chloride

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The equilibria of sterically hindered and unhindered imidazoles (B) with (protoporphyrin IX dimethyl ester)-iron(III) chloride (Fe(PPDME)Cl) have been spectrophotometrically investigated in chloroform and 1,2-dichloroethane. The addition reaction of hindered imidazole with Fe(PPDME)Cl proceeds in two steps to give $Fe(PPDME)B_2Cl$, with a formation constant, K_1, greater than K_2. The mono-adduct of hindered imidazoles exhibits an absorption band at around 590 nm, which shifts to longer wavelengths as the formation constant K_1 decreases in this order; 2,4-dimethyl->2-methyl->2-ethyl->2-phenyl->1,2-dimethylimidazole. The addition reaction of an unhindered imidazole with Fe(PPDME)Cl proceeds in an apparent one step to give $Fe(PPDME)B_2Cl$, with an overall formation constant of β_2. The log β_2 linearly increases with the basicity, $pK_a(BH^+)$, of unhindered imidazoles. The log β_2 for the system with NH-containing imidazoles is greater than that for the system with *N*-substituted imidazoles by about 3.1 log units, on the average, based on the stabilization of the positive charge on iron(III) through NH···Cl hydrogen bonding. The solvent effect on the formation constants is also discussed.

Imidazole is known to coordinate axially to heme iron in such hemoproteins as hemoglobin, myoglobin, cytochromes, peroxidases, and catalases.[1] The proximal and the distal histidine imidazoles play an important role in the heme-heme interaction and the Bohr effect in hemoglobin.[2] The state and the nature of the heme iron–imidazole bonds in the other hemoproteins are also closely related to the function of hemoproteins; thus, many investigations have been directed toward elucidating the thermodynamic properties of porphyrin iron model complexes with the imidazole derivatives.[3–21,23,25,26] La Mar and his coworkers have systematically investigated the kinetics and the thermodynamics of axial ligation in iron(III) complexes with synthetic porphyrins on the basis of proton NMR results.[21–26] Walker *et al.* followed the reaction of iron(III) para-substituted tetraphenylporphyrins with various imidazole derivatives by measuring the visible absorption spectrum in such noncoordinating solvents as chloroform, dichloromethane, and benzene; the effects of the solvent and the base on the equilibrium constant were also discussed.[14] The reaction of porphyrin iron(III) with imidazole in such coordinating solvents as dimethyl sulfoxide[18,19] and aqueous ethanol has also been studied.[5,6,12] The formation of a hemin complex with a mixed ligand of cyanide and imidazole in dimethyl sulfoxide has recently been studied by means of proton NMR.[20] Generally, the thermodynamics in coordinating solvents as compared with that in noncoordinating solvents is complicated by the solvation or the coordination of the solvent which remains unidentified.[19]

The imidazole derivatives are classified into two groups for steric reasons. They are sterically hindered imidazoles (2-methyl-, 1,2-dimethylimidazole, *etc.*), with significant steric interaction between the porphyrin core and the substituent adjacent to the bonding nitrogen, and unhindered imidazoles (imidazole, 4-methyl-, 1-methylimidazole, *etc.*). The majority of studies of porphyrin iron complexes with the imidazole derivatives as axial ligand(s) have been of unhindered imidazoles; there have been only a few of hindered imidazoles. The porphyrin iron complexes with unhindered imidazoles have been isolated as bis-adducts,[27–29] whereas those with hindered imidazoles have been isolated as mono-adducts.[30,31]

The reaction of porphyrin iron(III) chloride (FePCl) with nitrogenous bases (B) in solution is considered to proceed in two steps:

$$FePCl + B \overset{K_1}{\rightleftarrows} FePBCl \quad (1)$$

$$K_1 = [FePBCl]/[FePCl][B] \quad (2)$$

$$FePBCl + B \overset{K_2}{\rightleftarrows} FePB_2Cl \quad (3)$$

$$K_2 = [FePB_2Cl]/[FePBCl][B] \quad (4)$$

The overall reaction is:

$$FePCl + 2B \overset{\beta_2}{\rightleftarrows} FePB_2Cl \quad (5)$$

$$\beta_2 = [FePB_2Cl]/[FePCl][B]^2 \quad (6)$$

$$(\beta_2 = K_1K_2)$$

Whether the chloride in the mono-adduct FePBCl is in the inner (six-coordinated) or outer coordination sphere (five-coordinated, ion-pair) is unknown, but in the former case the chloride ligand is considered to coordinate weakly to iron(III) because no change in the spin state ever occurs upon the addition of the first axial base.[11]

When unhindered imidazole is added to a porphyrin iron(III) chloride solution, the change in the visible absorption spectrum apparently exhibits the bis-adduct formation in general, though the isosbestic points indicating the mono-adduct formation are rarely found in the lower concentration of the imidazole.[14] Thus, the stepwise formation constant, K_2, is found to be much greater than K_1, so that only the overall formation constant, β_2, can be estimated from the finding regarding the spectral change. In the NMR spectrum of the porphyrin iron(III)–unhindered imidazole system, only the signals arising from the porphyrin iron(III) and the bis-adduct are detectable in solution.[21]

Upon the addition of hindered imidazole to a porphyrin iron(III) chloride solution, the NMR spectra exhibit only the bis-adduct formation for synthetic porphyrins,[25] whereas the visible absorption spectra exhibit the mono-adduct formation intermediately.[14]

It is known that the thermodynamics of metallopor-

phyrin complexes is highly sensitive to the porphyrin basicity[32] and that the basicity of the protoporphyrin IX, which occurs naturally, is different from that of such synthetic porphyrins as tetraphenyl- and octaethylporphyrin.[33] For understanding the nature of the iron–imidazole bond in the hemoproteins it is, therefore, considered useful to investigate the thermodynamics of the protoporphyrin iron complex with imidazole. In this paper we wish to report on our spectroscopic studies of the equilibria of sterically hindered and unhindered imidazoles with (protoporphyrin IX dimethyl ester) iron(III) chloride in chloroform and 1,2-dichloroethane, and to discuss the effect of the solvent and the base on the formation constant and the visible absorption spectra. Furthermore, the steric interaction of the porphyrin core with the base will be discussed.

The abbreviations used are as follows: (protoporphyrin IX dimethyl ester)iron(III) chloride, Fe(PPDME)Cl. Unhindered imidazoles: imidazole, Im; 4-methylimidazole, 4MeIm; 4-phenylimidazole, 4PhIm; histamine, Him; 1-methylimidazole, NMeIm; 1-ethylimidazole, NEtIm; 1-acetylimidazole, NAcIm; 5-chloro-1-methylimidazole, 5ClNMeIm. Hindered imidazoles: 2-methylimidazole, 2MeIm; 2-ethylimidazole, 2EtIm; 2-phenylimidazole, 2PhIm; 2,4-dimethylimidazole, 2,4DMeIm; 1,2-dimethylimidazole, 1,2DMeIm.

Experimental

The Fe(PPDME)Cl was prepared as described before.[34] The Im, 4PhIm, NAcIm, 2MeIm, 2PhIm, and Him were recrystallized three times from chloroform–petroleum ether or acetone–petroleum ether and dried *in vacuo*. The 4MeIm, 2EtIm, and 2,4DMeIm were purified three times by vacuum sublimation and dried *in vacuo*. The NMeIm, NEtIm, 5ClNMeIm, and 1,2DMeIm were distilled four times at reduced pressure under N_2. Chloroform and 1,2-dichloroethane of an analytical grade were purified by the usual method. The ethanol was of a spectro-grade. The other reagents were of an analytical grade and were used without further purification.

The visible absorption spectrum was recorded on a Shimadzu MPS-5000 spectrophotometer at 25.0±0.2 °C. The plot of the absorbance at several wavelengths against the concentration of Fe(PPDME)Cl in chloroform was found to be linear in the concentrations below 0.3 mM; thus, the concentration of Fe(PPDME)Cl in measurements of the formation constants was maintained at 0.15 mM unless otherwise stated. The measurements of the spectral change upon the addition of bases to the Fe(PPDME)Cl solution were repeated several times in order to confirm the reproducibility.

Results

Absorption Spectra and Equilibria of the Fe(PPDME)Cl–Unhindered Imidazole System. The addition of imidazole to Fe(PPDME)Cl in chloroform resulted in the spectral changes shown in Fig. 1, which illustrates six concentrations of imidazole out of the 18 measured. The absorption maxima for the (protoporphyrin IX dimethyl ester)iron(III) complex with imidazole were 356.2 (26.1×10^3), 414.3 (124×10^3), 480.1 sh(7.65×10^3), 538.5 (10.8×10^3), and 563.4 sh(8.75×10^3), nm where sh is an absorption as a shoulder and where the

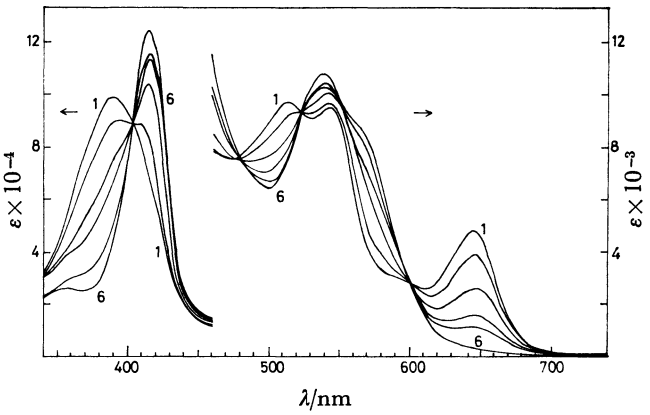


Fig. 1. Spectral changes observed upon addition of imidazole (0—12 mM) to an 0.15 mM solution of Fe(PPDME)Cl in chloroform (illustrated for 6 concentrations out of 18 ones measured). Imidazole concentrations: 1, 0 mM; 2, 0.3 mM; 3, 0.6 mM; 4, 0.9 mM; 5, 1.2 mM; 6, 12 mM.

values in parentheses are the molar extinction coefficients. The wavelengths of the absorption maxima in the case of the addition of the other seven unhindered imidazoles agreed with those of imidazole within ±2 nm. As is shown in Fig. 1, the isosbestic points were observed at 402, 480, 524, and 596 nm. For the molar ratios lower than [Im]/[Fe(PPDME)Cl]=2, the isosbestic point at 480 nm shifted slightly to the shorter wavelength side and the absorbance of the band at 540 nm was slightly lowered relative to that for Fe(PPDME)Cl; this behavior was found also in the case of the addition of the other seven unhindered imidazoles and was, indeed, even more distinct in the system with a smaller formation constant.

The spectral changes in Fig. 1, where the spectra of free Fe(PPDME)Cl changed to low-spin spectra,[35] indicate that the reaction of imidazole with Fe(PPDME)Cl proceeds in an apparent one step, based on the overall process of Eq. 5. Plots of A_0-A at 645 nm against log [B] are shown in Fig. 2, where A is the observed absorbance at a given wavelength, A_0 is the absorbance of Fe(PPDME)Cl in the absence of a base, and [B] is the

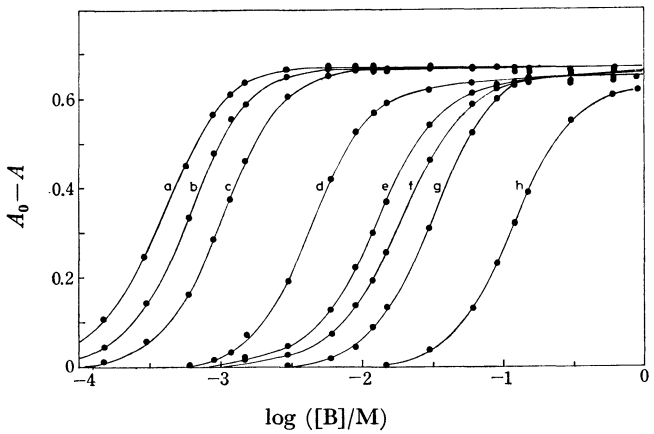


Fig. 2. Plots of A_0-A at 645 nm against log [B] for the addition of various unhindered imidazoles: a, Him; b, Im; c, 4MeIm; d, 4PhIm; e, NMeIm; f, NEtIm; g, NAcIm; h, 5ClNMeIm.

Table 1. Formation constants of (protoporphyrin IX dimethyl ester)iron(III) complexes with unhindered imidazoles at 25 °C

Solvent	Base	$pK_a(BH^+)$[a]	[Fe(PPDME)Cl]/mM	log K_1[b]	log β_2[b]
$CHCl_3$	4MeIm	7.22	0.15	2.7	6.68±0.03
	Im	6.65	0.15	2.8	6.72±0.04
	Him	5.73	0.15	3.3	7.17±0.06
	4PhIm	5.70	0.15	2.2	5.40±0.05
	NMeIm	7.33	0.15	1.6	3.77±0.05
			0.015	1.5	3.80±0.13
			0.0075	1.6	3.88±0.37
	NEtIm	7.30	0.15	1.5	3.65±0.07
	5ClNMeIm	4.75	0.15	0.6	1.86±0.05
	NAcIm	3.6	0.15	1.2	2.90±0.05
$ClCH_2CH_2Cl$	Im	6.65	0.15	2.1	5.20±0.04
	NMeIm	7.33	0.15	2.0	4.19±0.04
	NAcIm	3.6	0.15	0.9	2.13±0.02

a) A. Albert, *Phys. Methods Heterocycl. Chem.*, **1**, 1 (1963). A. R. Katritzky and A. J. Boulton, *Adv. Heterocycl. Chem.*, **12**, 103 (1970). Corrected for the presence of two protons in the conjugate acid (log 2) for NH imidazoles.[14] b) β_2, in units of M^{-2}; K_1, in units of M^{-1}.

Table 2. Formation constants of various porphyrin iron(III) complexes with unhindered imidazoles in chloroform

Porphyrin complex[a]	Base	T/°C	log β_2	References
Fe(PPDME)Cl	Im	25	6.72	This work
	NMeIm	25	3.77	This work
Fe(TPP)Cl	Im	25	6.20	14
	NMeIm	25	3.18	14
Fe(OEP)Cl	Im	25	6.03	14
	NMeIm	25	3.83	14
Fe(DPDME)Cl	Im	30	6.45	8

a) PPDME, protoporphyrin IX dimethyl ester; TPP, tetraphenylporphyrin; OEP, octaethylporphyrin; DPDME, deuteroporphyrin IX dimethyl ester.

concentration of the base. A_0-A for all the unhindered imidazoles varies with log [B] with a similar tendency, showing that the reaction of the unhindered imidazole with Fe(PPDME)Cl proceeds in an apparent one step. Then, the overall formation constant (β_2) is given by

$$\beta_2 = \frac{[FePB_2Cl]}{([FePCl]_T-[FePB_2Cl])([B]_T-2[FePB_2Cl])^2} \quad (7)$$

where $[FePCl]_T$ and $[B]_T$ are the total concentrations of Fe(PPDME)Cl and a base respectively. Since $[FePB_2Cl]=(A-A_0)/(\varepsilon_2-\varepsilon_0)$[36] where ε_0 is the molar extinction coefficient of Fe(PPDME)Cl in the absence of a base and where ε_2 is that of $Fe(PPDME)B_2Cl$ in the presence of a large excess of a base, Eq. 7 becomes:

$$\beta_2 = \frac{(A-A_0)/(\varepsilon_2-\varepsilon_0)}{\{[FePCl]_T-(A-A_0)/(\varepsilon_2-\varepsilon_0)\}\{[B]_T-2(A-A_0)/(\varepsilon_2-\varepsilon_0)\}^2} \quad (8)$$

By the method of Momenteau,[8] $1/(A_0-A)$ was plotted against $1/[B]_T^2$ at the wavelengths at 500, 540, 560 (or 570), and 645 nm. From the data in the linear part of the plots, β_2 was calculated by means of Eq. 8, and then the mean values and the standard deviations were evaluated (Table 1). From the data in the nonlinear part of the plot at 500 nm in the lower base concentrations, in which the isosbestic point at 480 nm shifts as described above, the formation constant, K_1, could be estimated. From Eq. 2 and the relation $[FePBCl]=(A-A_0)/(\varepsilon_1-\varepsilon_0)$,[36] K_1 is given by

$$K_1 = \frac{(A-A_0)/(\varepsilon_1-\varepsilon_0)}{\{[FePCl]_T-(A-A_0)/(\varepsilon_1-\varepsilon_0)\}\{[B]_T-(A-A_0)/(\varepsilon_1-\varepsilon_0)\}} \quad (9)$$

where ε_1 is the molar extinction coefficient of Fe(PPDME)BCl. Assuming that the spectra of mono- and bis-adducts are similar at 500 nm, the value of ε_2 in the calculation of β_2 was used as that of ε_1 in Eq. 9.[14] Thus, the values of K_1 in Table 1 are only approximate, but they are, nevertheless, of the correct order of magnitude.

Absorption Spectra and Equilibria of the Fe(PPDME)Cl–Hindered Imidazole System. The addition of hindered imidazoles to Fe(PPDME)Cl in chloroform resulted in the spectral changes summarized in Figs. 3 (base: 2-methylimidazole) and 4 (base: 2-ethylimidazole). The absorption maxima of the product obtained were 360.0

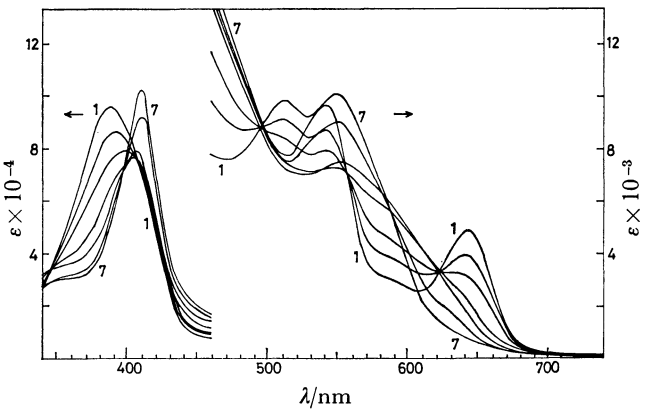


Fig. 3. Spectral changes observed upon addition of 2-methylimidazole (0—1.2 M) to an 0.15 mM solution of Fe(PPDME)Cl in chloroform (illustrated for 7 concentrations out of 18 ones measured). 2-Methylimidazole concentrations: 1, 0 mM; 2, 9 mM; 3, 15 mM; 4, 30 mM; 5, 90 mM; 6, 0.3 M; 7, 1.2 M.

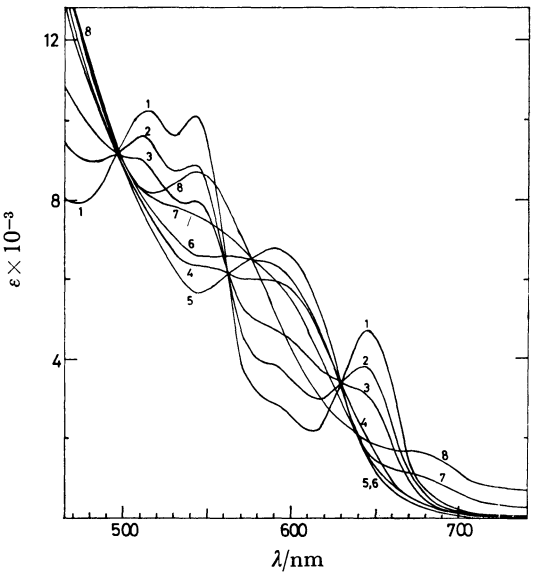


Fig. 4. Spectral changes observed upon addition of 2-ethylimidazole (0—3 M) to an 0.015 mM solution of Fe(PPDME)Cl in chloroform (illustrated for 8 concentrations out of 17 ones measured). 2-Ethylimidazole concentrations: 1, 0 mM; 2, 9 mM; 3, 15 mM; 4, 30 mM; 5, 0.12 M; 6, 0.6 M; 7, 1.2 M; 8, 3 M.

sh, 410.6, 451.0 sh, and 550.0 nm for 2-methylimidazole, and 410.8, 450.0 sh, and 544 nm for 2-ethylimidazole. In the case of the addition of 2,4-dimethylimidazole, the spectral changes were similar to those in Fig. 3. In the case of the addition of 1,2-dimethyl- and 2-phenylimidazole, however, even when the base was added up to the solubility limit, the spectrum was not further changed from that similar to the intermediate spectrum in Fig. 3 and in Fig. 4 respectively. The isosbestic points for 2-methylimidazole (Fig. 3) were observed at 496, 558, and 625 nm for the lower molar ratios of [2MeIm]/[Fe(PPDME)Cl] and at 586 nm for the higher ratios, while those for 2-ethylimidazole (Fig. 4) were observed at 494, 563, and 628 nm for the lower molar ratios of [2EtIm]/[Fe(PPDME)Cl] and at 582 and 643 nm for the higher ratios. No distinct isosbestic points were present in the range of the Soret band, as is shown in Fig. 3. These spectral changes appear to be markedly different from those for unhindered imidazoles. The two sets of isosbestic points indicate that the equilibria involve mono- and bis-adducts.

This spectral behavior shows that the addition of hindered imidazoles to Fe(PPDME)Cl occurs in two steps. Since the equilibrium involve mono- and bis-adducts, the following relation can be derived:

$$[\mathrm{FePCl}]_T = [\mathrm{FePCl}] + [\mathrm{FePBCl}] + [\mathrm{FePB_2Cl}] \quad (10)$$

$$[\mathrm{B}]_T = [\mathrm{B}] + [\mathrm{FePBCl}] + 2[\mathrm{FePB_2Cl}] \quad (11)$$

$$A = \varepsilon_0[\mathrm{FePCl}] + \varepsilon_1[\mathrm{FePBCl}] + \varepsilon_2[\mathrm{FePB_2Cl}] \quad (12)$$

where the absorbances are for a 1-cm light path. In the second step of the reaction, $[\mathrm{FePCl}]_T$ can be approximately equal to $[\mathrm{FePBCl}]+[\mathrm{FePB_2Cl}]$, A, to $\varepsilon_1[\mathrm{FePBCl}]+\varepsilon_2[\mathrm{FePB_2Cl}]$, and $[\mathrm{B}]_T$, to $[\mathrm{B}]$, because a base was present in a large excess relative to $[\mathrm{FePCl}]_T$. Thus, K_2 is given by

$$K_2 = \frac{[\mathrm{FePB_2Cl}]}{([\mathrm{FePCl}]_T - [\mathrm{FePB_2Cl}])[\mathrm{B}]_T} \quad (13)$$

Then,

$$A = \varepsilon_1([\mathrm{FePCl}]_T - [\mathrm{FePB_2Cl}]) + \varepsilon_2[\mathrm{FePB_2Cl}],$$

and letting

$$A_1 = \varepsilon_1[\mathrm{FePCl}]_T, \quad (14)$$

we obtain:

$$[\mathrm{FePB_2Cl}] = (A - A_1)/(\varepsilon_2 - \varepsilon_1) \quad (15)$$

From Eqs. 13 and 15, the following equation is derived:

$$\frac{[\mathrm{FePCl}]_T}{A - A_1} = \frac{1}{K_2(\varepsilon_2 - \varepsilon_1)} \frac{1}{[\mathrm{B}]_T} + \frac{1}{\varepsilon_2 - \varepsilon_1} \quad (16)$$

Such a value of A_1 that a plot of $[\mathrm{FePCl}]_T/(A-A_1)$ against $1/[\mathrm{B}]_T$ gives a straight line at a given wavelength was convergently computed by the use of the least-squares method. From this straight line (its slope and intersection with the ordinate), the A_1 value, and Eq. 14, the values of ε_1, ε_2, and K_2 were obtained. Such a calculation was made on three or four wavelengths; the mean of the K_2 values thus obtained given in Table 2. The ε_1 value evaluated from the above calculation agreed reasonably well with that estimated directly from the results of spectral changes at some wavelengths (*e.g.*, at 586 nm in Fig. 3).

Further, by the use of the ε_1 value thus obtained, K_1 in the first step of the reaction was calculated by means of Eq. 9; then, the mean values and the standard deviations were evaluated (Table 3). In the case of 1,2-dimethyl- and 2-phenylimidazole, K_1 was calculated by the use of the ε_1 value estimated from the spectral changes.

Dissociation of Fe(PPDME)B$_2$Cl and Equilibria in a Chloroform–Ethanol Mixed Solvent. When the

Table 3. Formation constants of porphyrin iron(III) complexes with hindered imidazoles at 25 °C

Porphyrin complex	Solvent	Base	pK_a(BH$^+$)[a]	log K_1[b]	log K_2[b]	log β_2[b]	References
Fe(PPDME)Cl	$CHCl_3$	2,4DMeIm	8.06	1.78±0.07	0.77		This work
		1,2DMeIm	7.85	0.71±0.04	<-0.6		
		2EtIm	7.70	1.31±0.04	0.02		
		2MeIm	7.56	1.75±0.07	0.78		
		2PhIm	6.09	1.04±0.05			
	$ClCH_2CH_2Cl$	2MeIm	7.56	1.24±0.07	0.66		
Fe(TPP)Cl	$CHCl_3$	1,2DMeIm	7.85	0.53		0.97	14
		2MeIm	7.56	1.20		3.52	14

a) See Footnote a of Table 1. b) β_2, in units of M^{-2}; K_1 and K_2, in units of M^{-1}.

reaction of (tetraphenylporphyrinato)iron(III) chloride (Fe(TPP)Cl) with 1-methylimidazole in chloroform was examined under a low concentration of Fe(TPP)Cl (7.6×10^{-7} M), the following equilibrium was observed in the system[14]

$$Fe(TPP)Cl + 2NMeIm \rightleftarrows Fe(TPP)(NMeIm)_2^+ + Cl^- \quad (17)$$

In this study, a similar examination was made in [Fe(PPDME)Cl]$=7.5\times10^{-6}$ M. As is shown in Table 1, the value of β_2 was essentially independent of [Fe(PPDME)Cl], though the value and the deviation increased only slightly with lowering of [Fe(PPDME)Cl]. Thus, for Fe(PPDME)Cl in chloroform the influence of the equilibrium of Eq. 17 is considered to be negligible in concentrations higher than [Fe(PPDME)Cl]$=7.5\times10^{-6}$ M.

The effects of the polar and hydrogen-bonding solvent on the formation constant were investigated in chloroform containing 1, 5, and 10 vol % ethanol for the three bases of imidazole, 1-methyl-, and 2-methylimidazole. For the addition of imidazole and 1-methylimidazole, the overall spectral changes in the mixed solvents were similar to those for imidazole in chloroform (in Fig. 1), whereas for the addition of 2-methylimidazole they were similar not to those for 2-methylimidazole in chloroform (in Fig. 3), but to those for 2-ethylimidazole in chloroform (in Fig. 4). As is shown in Table 4, β_2 decreased for imidazole, but increased for 1-methylimidazole, with an increase in the ethanol content. For 2-methylimidazole, as the ethanol content increased, K_1 markedly increased, whereas K_2 slightly decreased.

The spectra of Fe(PPDME)Cl in these mixed solvent was unchanged at the content of ethanol lower than 20 vol %, whereas above that point spectral changes which seemed to originate from ethoxo coordination were observed.

Table 4. Formation constants of (protoporphyrin IX dimethyl ester)iron(III) complexes in chloroform–ethanol mixed solvents at 25 °C

Solvent	Base	log K_1[a]	log K_2[a]	log β_2[a]
$CHCl_3$	Im	2.8		6.72±0.04
	NMeIm	1.6		3.77±0.05
	2MeIm	1.75±0.07	0.78	
$CHCl_3$–1%EtOH	Im	3.0		6.79±0.07
	NMeIm	1.7		3.94±0.04
	2MeIm	2.05±0.07	0.3	
$CHCl_3$–5%EtOH	Im	2.7		6.50±0.11
	NMeIm	1.6		3.99±0.21
	2MeIm	3.11±0.06	<0.03	
$CHCl_3$–10%EtOH	Im	2.6		6.35±0.14
	NMeIm	1.8		4.48±0.26

a) See Footnote b of Table 3.

Discussion

Absorption Spectra of the Fe(PPDME)Cl–Imidazoles System. Upon the addition of unhindered imidazole to a Fe(PPDME)Cl solution, the spectra changed from those of free Fe(PPDME)Cl (high-spin) to those of the bis-adduct, Fe(PPDME)B_2Cl (low-spin). These overall spectral changes are very similar to those for the (deuteroporphyrin IX dimethyl ester)iron(III)–imidazole system.[8] The fact that the low-spin bis-adducts formed have essentially identical spectra for the eight unhindered imidazoles indicates that the stereochemistry of the bis-adducts is not appreciably dependent on the nature of these axial bases.

Upon the addition of hindered imidazole to a Fe(PPDME)Cl solution, the spectra of mono-adduct Fe(PPDME)BCl was intermediately obtained in the course of spectral changes from Fe(PPDME)Cl to Fe(PPDME)-B_2Cl, as is shown in Figs. 3 and 4.[37] The spectra of a bis-adduct with hindered imidazoles are similar to those with unhindered imidazoles, but the wavelengths of the absorption maxima at around 545 and 570 nm for the former were found to change with the degree of steric hindrance. It has been pointed out by Smith and Williams that these absorption bands in the low-spin spectra of the porphyrin iron(III) complex are sensitive to the nature of the axial ligands.[35] The wavelengths of the Soret and the characteristic bands (around 590 nm) in the mono-adduct spectra are given in Table 5. The wavelength of this Soret band is intermediate between that for Fe(PPDME)Cl and Fe(PPDME)B_2Cl. The band at around 590 nm is considered to be a charge-transfer band characteristic of high-spin five-coordinated porphyrin iron(III) complexes.[35,38] These mono-adducts may be either five-coordinated ion-pairs, in which chloride is in the outer coordination sphere, or

Table 5. Absorption maxima for high-spin five-coordinated porphyrin iron(III) complexes

Porphyrin[a] complex	Solvent	Base or ligand	λ max/nm		References
Fe(PPDME)	$CHCl_3$	Cl^-	389	644	This work
		1,2DMeIm	405	595 sh	
		2PhIm	401	593	
		2EtIm	400	586	
		2MeIm	406	580 sh	
		2,4DMeIm	405	577	
	CH_2Cl_2–10%EtOH	Ethoxo	400	580, 598 sh	39
Fe(DPDME)	benzene	F^-	393	587	38
		Cl^-	373	628	38
		I^-	368	641	38
μ-oxo[Fe(PPDME)]$_2$			397	573, 599	40

a) See Footnote a of Table 2.

six-coordinated complexes in which the interaction of chloride with iron(III) is considerably weak. The wavelength of this characteristic band is comparable to those of the following complexes: (deuteroporphyrin IX dimethyl ester)iron(III) with fluoride,[38] ethoxo(protoporphyrin IX dimethyl ester)iron(III),[39] and μ-oxo-bis-(protoporphyrin IX dimethyl ester iron(III))[40] (Table 5). In these complexes, it is known that the interaction of iron with the axial ligand is relatively strong and that the iron atom is displaced from porphyrin plane toward the axial ligand[38]; thus, it seems that the second axial ligand can not readily coordinate to iron(III).

Effect of the Base on Formation Constant. In the case of hindered imidazoles, no correlation between the basicity of these bases and the formation constants is found, as is shown in Table 3. On the contrary, in the case of unhindered imidazoles such a correlation is clearly found, as is shown in Fig. 5; that for NH imidazoles (Im, 4MeIm, 4PhIm) is different from that for NR imidazoles (NMeIm, NEtIm, 5ClNMeIm), though the plots for histamine and 1-acetylimidazole in Fig. 5 deviate from straight lines.

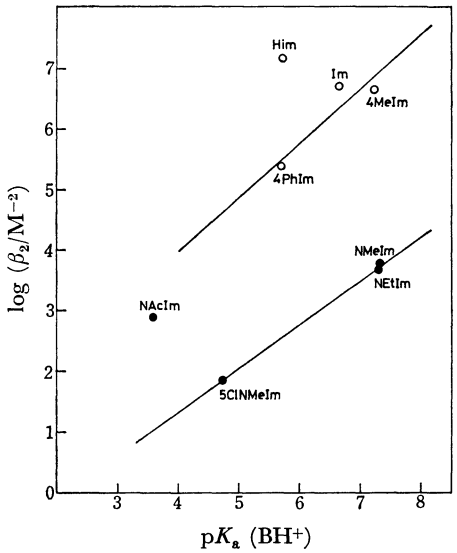
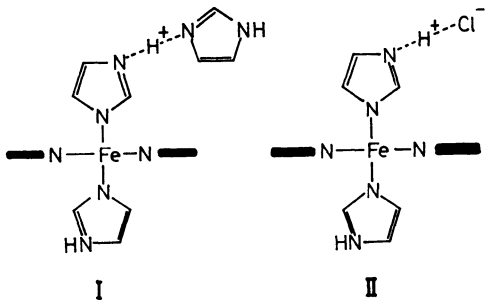


Fig. 5. Relationships between log β_2 and the basicity of unhindered imidazoles: ○, β_2 for NH imidazoles; ●, β_2 for NR imidazoles.

For the (protoporphyrin IX dimethyl ester)iron(III) and the (tetraphenylporphyrinato)iron(III) complexes, the log β_2 values for NH imidazole are larger than that for NR imidazole by about 3.1 and 3.3 log units on the average respectively. The larger value of β_2 for NH imidazole is considered to be based on the stabilization by the delocalization of the positive charge on iron(III) through Interaction I[14] or II.[25,26] In the case of the Interaction I, the delocalization of the positive charge on iron(III) leads to an increase in β_2, whereas the association between coordinated and free NH imidazole may lead to a decrease in β_2. Thus, it seems unlikely that the Interaction I contributes to the increase of about 3 log unit in β_2. The interaction of chloride with the NH group of imidazole has been suggested in a study of the crystal structure of bis(imidazole)tetraphenylporphyrinatoiron(III) chloride.[27] Furthermore, the appreciable



interaction of halide with the NH group of coordinated NH imidazoles has been confirmed by EPR and NMR measurements of the deuteroporphyrin IX dimethyl ester[9] and teraphenylporphyrin iron(III) complexes with NH imidazoles in solution.[26] Accordingly, the stabilization of the complex with NH imidazoles may be mainly due to Interaction II. Thus, it seems unreasonable that the complexes with NH imidazoles are represented by the formula of the ion-pair, Fe(PPDME)-$B_2^+Cl^-$.

The log β_2 for histamine is larger than that which would be predicted from the straight line of NH imidazole in Fig. 5, which is probably based on the additional stabilization of the complex by intramolecular hydrogen bonding between the amino group and the carbonyl group at the porphyrin periphery.[31] The log β_2 for 1-acetylimidazole is also larger than that which would be predicted from the straight line of NR imidazole in Fig. 5. In 1-acetylimidazole, which is known to be a good acetylating reagent, the nitrogen atom at the 1-position of the imidazole ring is susceptible to nucleophilic attack because the acetyl group with an electron-withdrawing ability attracts the electron on the nitrogen atom.[41] In this case, the chloride of the nucleophilic reagent in Fe(PPDME)Cl can interact with the nitrogen atom. Thus, through such interaction the positive charge on iron(III) is delocalized and stabilized; consequently, the formation constant may increase relatively.

In these cases, the two axial imidazoles of the bis-adduct are nonequivalent, because only one chloride is present in a bis-adduct molecule.[25] For both NH and NR imidazoles, the ratios of log K_1/log β_2 are in the narrow range of 0.3—0.4. Thus, it is not possible to specify whether the stabilization of the complex based on the interaction with chloride is accompanied by the axial coordination of NH imidazole in the first step, in the second step, or in the intermediate state.

The coordination of 4-substituted imidazoles to iron(III) may be equivalent to that of 5-substituted ones caused by rapid tautomerism, for no lowering of the formation constants based on the steric effect was observed.

The basicity of the protoporphyrin IX dimethyl ester is higher than that of tetraphenylporphyrin and lower than that of octaethylporphyrin;[33] therefore the decreasing order of the formation constant for these porphyrin iron(III) complexes can be expected to be: TPP> PPDME>OEP.[21,22,32,42] Such a trend, however, is not clearly found in Table 2. The formation constants for (protoporphyrin IX dimethyl ester)iron(III) complexes should be compared with those for substituted deutero-

porphyrin iron(III) complexes, for which few data have been reported.

Solvent Effect on Formation Constants. The solvent effect on formation constants may be described in terms of the polarity and the hydrogen-bonding ability of the solvents. When the forms of mono- and bis-adducts are the ion-pairs of Fe(PPDME)B$^+$Cl$^-$ and Fe(PPDME)-B$_2^+$Cl$^-$ respectively, these formation constants can be expected to increase with the polarity of the solvents.[10,11,15] The hydrogen bonding between base and solvent complicates the situation. As for the thermodynamics of the (tetraphenylporphyrinato)iron(III) complex with imidazole in various solvents (acetone, ethyl acetate, DMF, $CHCl_3$, and CH_2Cl_2), it has been reported by Ciaccio *et al.* that the hydrogen-bonding solvents combine with free imidazole to decrease the formation constants,[15] while Walker *et al.* have reported that chloroform, with a weak hydrogen-bonding ability, reduces the self-association of NH imidazole and thus allows the formation constants to be larger than in other solvents.[14]

NR imidazoles are not capable of self-association, but the nitrogen at the 3-position of free NR imidazole can hydrogen-bond to the hydrogen-bonding active group such as NH, OH, and CH in solvent molecules. Such a hydrogen bonding can decrease the formation constants, as has been pointed out by Ciaccio *et al.*[15] Since chloroform is stronger in hydrogen-bonding ability[43] and lower in polarity than 1,2-dichloroethane, β_2 ($CHCl_3$) $<\beta_2$ ($C_2H_4Cl_2$) for 1-methylimidazole in Table 1 seems to be reasonable.

On the contrary, for imidazole, 2-methyl-, and 1-acetylimidazole the formation constants in chloroform are larger than in 1,2-dichloroethane (Tables 1 and 2). The explanation for NH imidazole that the self-association is reduced with the hydrogen-bonding ability of solvents and that, thus, the formation constants are: in $CHCl_3$ <in $C_2H_4Cl_2$ is inapplicable to that for the 1-acetylimidazole of the NR imidazole.[44] A feature common to the complexes with these three imidazole bases is that the chloride strongly interacts with the coordinated base; thus, the complex is markedly stabilized, as described above. This interaction between the chloride and the coordinated base may be weakened with the solvent polarity because of a concomitant slight dissociation of the chloride ion; consequently, the formation constants of the complexes may decrease with the solvent polarity. To the solvent effect on the complex formation with these imidazole bases, the contribution of the polarity is considered to surpass that of the hydrogen-bonding ability.

Ethanol is the polar and the hydrogen-bonding solvent. The polarity of a chloroform–ethanol mixed solvent can increase with the ethanol content. The fact that β_2 for imidazole decreases with the ethanol content suggests that the interaction between the chloride and the imidazole NH group is weakened with the polarity of the solvent, thus lowering the stability of the complex (Table 4). Since the complex with 1-methylimidazole is an ion-pair in contrast to that with imidazole, the β_2 increases with the polarity of the solvent. Thus, for the system of imidazole and 1-methylimidazole, the effect of the addition of ethanol to the chloroform solution may be explained on the basis of the increase in polarity. The fact that K_1 for 2-methylimidazole markedly increases with the ethanol content, whereas K_2 slightly decreases, indicates that the stability of the mono-adduct is remarkably enhanced with the ethanol content; the reason for this remains to be clarified.

In the (protoporphyrin IX dimethyl ester)iron(III) complexes, the solvent effect is further complicated by the possibility of the hydrogen bonding of the solvent molecule with the ester carbonyl group at the porphyrin periphery relative to the cases of the tetraphenylporphyrin and octaethylporphyrin iron(III) complexes.

Steric Effect on Formation Constants. As is shown in Table 3, the formation constants of the complexes with hindered imidazoles are found to decrease with the degree of steric hindrance provided by the 2-substituent. The formation constant, K_1, for 1,2-dimethylimidazole is the smallest in the systems studied here, for the 1-methyl group hinders the bending of the 2-methyl group to avoid the steric interaction with the porphyrin plane.[25] The plot of log K_1 against the wavelength of the absorption maximum at around 590 nm characteristic of the mono-adduct is found to be linear, as is shown in Fig. 6. In the mono-adduct which exhibits this band on the longer-wavelength side, the displacements of the iron atom from the porphyrin plane are considered to be larger.

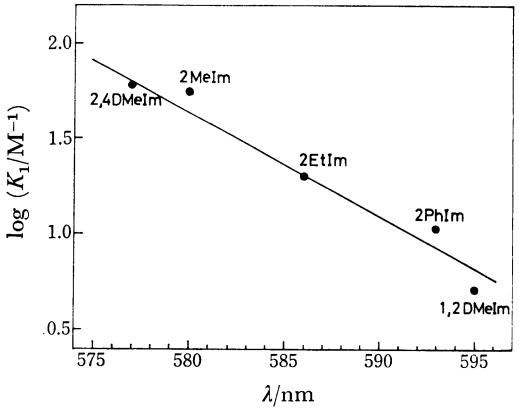


Fig. 6. Relationships between log K_1 and the wavelength of absorption maxima for the mono-adduct with hindered imidazole.

In the porphyrin iron(III) complex, in which a change in the spin state from high- to low-spin occurs upon the addition of the second axial base, the formation constant, K_1, can be smaller than K_2. Accordingly, the relation of $K_1>K_2$ for the complexes with hindered imidazoles is probably based on the steric reason. On the contrary, for the tetraphenylporphyrin iron(III) complex with 2-methylimidazole it is reported to be $K_1 <\beta_2/K_1$ ($=K_2$).[14] It seems that the bis-adduct of (protoporphyrin IX dimethyl ester)iron(III) with hindered imidazoles is not readily isolated because $K_1<K_2$.

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