# Dissociation Rates of Axially Coordinated Imidazoles and Formation Constants of Low Spin Ferric Complexes Derived from Tetraphenylporphyrin and Tetramesitylporphyrin

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## Abstract

The dissociation rates of axially coordinated imidazole in bis-ligated low spin ferric complexes of synthetic porphyrins such as tetraphenylporphyrin (TPP) and tetramesitylporphyrin (TMP) were measured by NMR method. In both TPP and TMP complexes, the axial lability of imidazoles increased in the order 1-methylimidazole < 2-methylimidazole < 2-ethylimidazole ~ 1,2-dimethylimidazole. The results were explained in terms of the steric repulsion between the 2-alkyl group of imidazole and the porphyrin ring. The dissociation rates of TPP complexes were then compared with those of TMP complexes carrying the same axial ligands. In every case examined, imidazole dissociated faster from the TPP complex than from the TMP complex. The results were ascribed to the stability of the bis-ligated TMP complex relative to the corresponding TPP complex; the formation constant of the TMP complex having 2-MeIm as axial ligand was larger than that of the corresponding TPP complex by a factor of *c.* 600. A hypothesis has been proposed to explain the stability of the sterically hindered porphyrin complex relative to the less hindered complex.

## Introduction

The low spin ferric complexes of some synthetic porphyrins are of considerable interest since they can be the model compounds of naturally occurring heme proteins such as cytochrome *b* [1] and cytochrome *c* [2]. Among them, the complexes with axially coordinated imidazoles have attracted much attention because most of the heme proteins carry at least one iron–imidazole linkage. Through extensive studies using model compounds, several lines of evidence have been accumulated showing that the orientation of axially coordinated imidazoles [3] plays an important role to determine various physicochemical properties such as redox potential [4], spin state [5], NMR [6–10], EPR [11–14], and Mössbauer [14]. The coordination of imidazole toward iron(III), however, includes dynamic process; the dissociation of imidazole ligand certainly takes place [15, 16] as well as the internal rotation of imidazole ring about the iron–nitrogen bond [17, 18]. Thus, some of the spectral properties including those of NMR must be time averaged. This indicates that the study on stability and lability of axially coordinated imidazole is necessary to understand the properties of ferric complexes.

The formation of a low spin ferric porphyrin complex, $PFeL_2^+$, from the corresponding high spin complex, $PFe^+$, consists of two steps (1) and (2) as studied by UV [19, 20] and $^1H$ NMR [21] spectral techniques, where P is a porphyrin and L is an unspecified axial ligand, and $K_1$ and $K_2$ are the equilibrium constants corresponding to (1) and (2), respectively. However, the only observable process is the overall reaction given by (3) since $K_2$ is larger than $K_1$ to a great extent. Thus, the stability of low spin ferric complexes has been discussed by the magnitude of formation constant $\beta_2$ defined as $\beta_2 = K_1K_2$.

$$PFe^+ + L \overset{K_1}{\rightleftharpoons} PFeL^+ \quad (1)$$

$$PFeL^+ + L \overset{K_2}{\rightleftharpoons} PFeL_2^+ \quad (2)$$

$$PFe^+ + 2L \overset{\beta_2}{\rightleftharpoons} PFeL_2^+ \quad (3)$$

The lability of axial ligands was first reported by La Mar *et al.* [15] by $^1H$ NMR linewidth analysis. According to their work, ligand exchange proceeds by a dissociative mechanism (4) in the presence of excess ligand and the mono-ligated species, $PFeL^+$, is assumed to be the activated complex.

$$PFeLL^+ + L^* \rightleftharpoons [PFeL^+ + L] + L^* \rightleftharpoons PFeL^*L^+ + L \quad (4)$$

In the low spin ferric complexes derived from *meso*-tetraphenylporphyrin (TPP), the lability increases in the order, 5-methylimidazole < 1-methylimidazole ≪ 5-chloro-1-methylimidazole, which is the reverse order for the trend in $\beta_2$ values [19]. The result suggests that, in the case of TPP complexes, the

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dissociation rates of the axial ligands correlate with the magnitude of formation constants. Since heme groups in naturally occurring heme proteins are located in sterically hindered environments of the binding pockets, the dissociation rates must be affected by the steric interaction between ligand and environment. Thus, it is important to pursue how the steric environment of porphyrin affects the axial lability of imidazoles. Although a considerable amount of work has been done on ferrous complexes [22, 23] in connection with $O_2$ and CO binding behavior, little is known about low spin ferric complexes. In this paper we would like to present the results on stability and lability of the coordinated imidazoles in some low spin ferric complexes derived from sterically hindered tetramesitylporphyrin (TMP), and discuss the steric effects on the rates of dissociation as well as the formation constants.

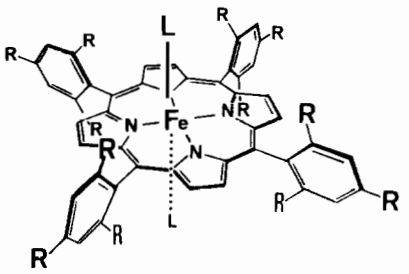
## Experimental

*Sample Preparation*

Porphyrins and their ferric complexes were prepared by the reported procedure [24]. Imidazole bases such as 1-methylimidazole (1-MeIm), 2-methylimidazole (2-MeIm), 2-ethylimidazole (2-EtIm) and 1,2-dimethylimidazole (1,2-$Me_2$Im) were recrystallized and/or distilled shortly before use. In each case, the bis-imidazole complex was prepared *in situ* by the addition of 6.0 eq. of base into high spin *meso*-tetraphenylporphyrinatoiron(III) chloride, (TPP)FeCl, or *meso*-tetramesitylporphyrinatoiron(III) chloride, (TMP)FeCl. The formation of the low spin complexes was confirmed by the disappearance of m-signals of the high spin complex and the concomitant appearance of the pyrrole signals at high magnetic field. The concentration of the ferric porphyrins for kinetic measurements was in the range of 0.013 to 0.015 M. The low spin complexes examined in this study are given in Fig. 1 together with their abbreviations.

*NMR Spectra*

Samples for NMR measurements were prepared under nitrogen using $CDCl_3$ as solvent. $^1H$ NMR spectra were recorded on a Jeol FX90Q spectrometer operating at 89.55 MHz. Between 64 and 256 transients were accumulated using 16 K data points over a bandwidth of 5000 to 10 000 Hz with a 15 microsecond 45 pulse. Chemical shifts were read based on the internal TMS. The spectrometer temperature was calibrated by the difference in chemical shifts between methyl and hydroxyl signals of methanol. Spin-lattice relaxation times, $T_1$, of some protons were measured by conventional inversion-recovery method. Activation parameters for ligand dissociation were determined by NMR method and will be described in detail in the next section.




| Complexes | R | L | Abbreviation |
|---|---|---|---|
| 1 | H | 1-MeIm | (TPP)Fe(1-MeIm)$_2^+$ |
| 2 | H | 2-MeIm | (TPP)Fe(2-MeIm)$_2^+$ |
| 3 | H | 2-EtIm | (TPP)Fe(2-EtIm)$_2^+$ |
| 4 | H | 1,2-$Me_2$Im | (TPP)Fe(1,2-$Me_2$Im)$_2^+$ |
| 5 | $CH_3$ | 1-MeIm | (TMP)Fe(1-MeIm)$_2^+$ |
| 6 | $CH_3$ | 2-MeIm | (TMP)Fe(2-MeIm)$_2^+$ |
| 7 | $CH_3$ | 2-EtIm | (TMP)Fe(2-EtIm)$_2^+$ |
| 8 | $CH_3$ | 1,2-$Me_2$Im | (TMP)Fe(1,2-$Me_2$Im)$_2^+$ |

Fig. 1. Low spin ferric porphyrin complexes, PFe$L_2^+$.

## Results and Discussion

*Assignment of Spectra*

The methyl signals of the coordinated imidazoles in (TPP)Fe(1-MeIm)$_2^+$ and (TPP)Fe(2-MeIm)$_2^+$ were assigned by Satterlee and La Mar [25] based on the integral intensities. The methyl signals of the other complexes were assigned by the saturation transfer method [26]. The assignment of the methyl signal of (TMP)Fe(2-EtIm)$_2^+$ is described below as a typical example. Irradiation of a broad signal at −2.6 ppm at 17 °C decreased the intensity of the signal at 1.3 ppm. This indicates that the signals at −2.6 and 1.3 ppm exchange their magnetic sites. Since the signal at 1.3 ppm is due to the methyl of free 2-EtIm, the broad signal at −2.6 ppm is unambiguously assigned to the methyl of the coordinated 2-EtIm. The chemical shifts of some typical protons of these complexes are listed in Table 1.

*Determination of Dissociation Rates*

*(1) Dynamic NMR method*

Since the line shape of the methyl signals of imidazoles showed temperature dependence, the rates of ligand dissociation were determined by the dynamic NMR (DNMR) method [27–29]. At low temperature where the rate of dissociation is slow on the NMR time scale, the methyl protons of the coordinated and free bases gave separate signals. On raising the temperature these signals broadened and in some cases began to coalesce. The intrinsic chemical shifts and effective spin–spin relaxation time ($T_2'$) of the methyl protons in the exchange region were extrapolated from low temperature where the rate

TABLE 1. Chemical shifts of some protons of $PFeL_2^+$ ($CDCl_3$, δ from TMS at −5 °C)

| Complexes | | Imidazole methyl | | Aryl protons | | | Pyrrole-H |
|---|---|---|---|---|---|---|---|
| | | 1-Me | 2-Me | *o*-H | *m*-H | *p*-H | |
| (TPP)Fe(1-MeIm)$_2^+$ | (1) | 21.1 | | 4.4 | 5.9 | 5.9 | −20.5 |
| (TPP)Fe(2-MeIm)$_2^+$ | (2) | | 11.1 | 4.5 | 6.6 | 6.1 | −15.8[a] |
| (TPP)Fe(2-EtIm)$_2^+$ | (3) | | −1.5 | 4.6 | 6.9 | 6.2 | −14.7[a] |
| (TPP)Fe(1,2-Me$_2$Im)$_2^+$ | (4) | 11.1 | 7.4 | 4.9 | 7.2 | 6.4 | −13.9[a] |
| (TMP)Fe(1-MeIm)$_2^+$ | (5) | 18.7 | | 0.6(Me) | 5.7 | 1.5(Me) | −20.4 |
| (TMP)Fe(2-MeIm)$_2^+$ | (6) | | 5.7 | 1.5(Me) | 7.2 | 1.9(Me) | −13.1[a, b] |
| (TMP)Fe(2-EtIm)$_2^+$ | (7) | | −2.7 | 1.6(Me) | 7.8 | 2.1(Me) | −12.3[a, b] |
| (TMP)Fe(1,2-Me$_2$Im)$_2^+$ | (8) | 7.0 | 0.8 | 1.6(Me) | 8.0 | 2.2(Me) | −9.6[a, b] |

[a]Chemical shifts were extrapolated from low temperature since some of the peaks were very broad due to the ligand exchange. [b]Below −30 °C, each signal of the porphyrin split into 2, 3, or 4 peaks due to the hindered rotation of the coordinated imidazoles [18]. The chemical shifts of the porphyrin protons are the average values.

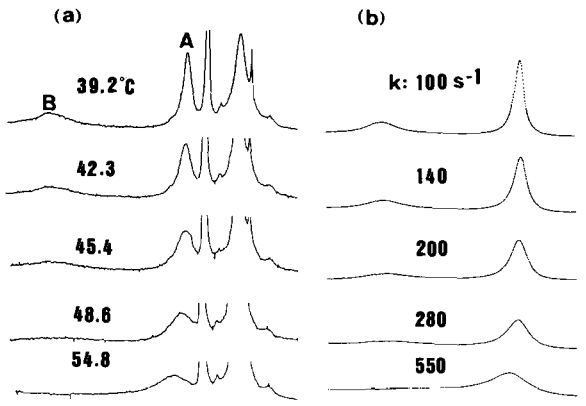



Fig. 2. DNMR spectra of (TMP)Fe(2-MeIm)$_2^+$ (6). (a) Observed spectra in $CDCl_3$ solution. A and B are the methyl signals of free and coordinated 2-MeIm, respectively. (b) Calculated spectra for various rate constants.

of exchange is negligibly small [15]. The population ratio of the free and coordinated bases, $K$ = [free base]/[coord. base], was taken as 2.0 in each case, since 6.0 eq. of base was added relative to the high spin ferric complex. Integral intensities of these signals also supported the value. Calculated spectra were generated by using the chemical shifts, effective spin–spin relaxation time, population ratio, and appropriate rate constants into a modified Binch program [30]. The rate constant at a particular temperature was obtained by visual fitting of the observed and calculated spectra. As a typical example, the DNMR spectra of (TMP)Fe(2-MeIm)$_2^+$ are given in Fig. 2.

*(2) Saturation transfer method*

The DNMR method is useful when the line shape changes drastically. However, as Satterlee *et al.* [15b] pointed out, low spin complexes decompose to form presumably mono-ligated species at higher temperatures. In fact, some complexes such as (TPP)Fe(1-MeIm)$_2^+$ and (TMP)Fe(1-MeIm)$_2^+$ showed broadening of the pyrrole signal at the temperature range where imidazole signals broadened. In such a case, eqn. (4) is no longer valid. Thus, the rate constants have to be determined at a lower temperature. The saturation transfer method [28, 31, 32] is ideal for this purpose; this method is applicable to the exchange process with the rate constant comparable to $1/T_1$, where $T_1$ is the spin-lattice relaxation time of the nuclei involved in the exchange process. Since $1/T_1$ is generally smaller than the rate constants obtained by the DNMR analysis, the method gives us the information on exchange rate at lower temperatures.

In the exchange system between sites A and B, the observed spin-lattice relaxation time of the protons at site A, $T'_{1A}$, is given by a rather complicated equation including rate constants and population ratios [33]. However, if the $z$ magnetization at site B is selectively saturated by irradiation with a sufficiently strong rf field, the $T'_{1A}$ is expressed by a simple eqn. (5) [32]. Here, $T_{1A}$ is an intrinsic spin-lattice relaxation time and $k_A$ is a rate constant from site A to site B. Under this condition, the $z$ magnetization at site A, originally given as $M_{zA}(0)$, decreases to a new steady state value, $M_{zA}(\infty)$, as eqn. (6) shows. Since $T'_{1A}$ and $M_{zA}(0)/M_{zA}(\infty)$ are easily obtained by the conventional inversion-recovery method and integration of the signals, respectively, we can determine both $T_{1A}$ and $k_A$ by solving the simultaneous eqns. (5) and (6). The rate constant for the reverse process, $k_B$, is calculated from (7) where $P_A$ and $P_B$ are the population at sites A and B, respectively.

$$1/T'_{1A} = 1/T_{1A} + k_A \tag{5}$$

$$M_{zA}(0)/M_{zA}(\infty) = 1 + k_A T_{1A} \tag{6}$$

$$k_B = (P_A/P_B)k_A \quad (7)$$

In order to check the reliability of the rate constants determined by this method, the dissociation rates of (TMP)Fe(2-MeIm)$_2^+$ were analyzed by both DNMR and saturation transfer methods. Eyring's plot of the rate constants obtained by these methods yielded a moderately good linear line as shown in Fig. 3.

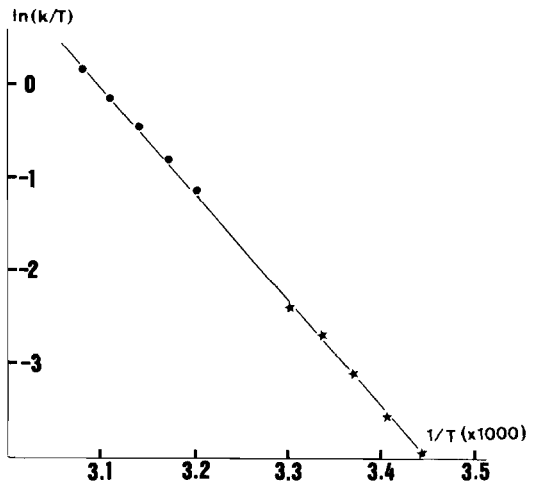



Fig. 3. Eyring's plot of (TMP)Fe(2-MeIm)$_2^+$ (6) obtained by DNMR (●) and saturation transfer (★) methods.

*Activation Parameters for Dissociation*

Activation parameters for dissociation were determined by putting the rate constants into Eyring's equation and they have been listed in Table 2 together with the rate constants at 25 °C and the temperature range in which the spectra were analyzed. One of the characteristic features of the data of Table 2 is that all the complexes examined gave large positive values (14 to 23 e.u.) for activation entropy. The results indicate that the ligand exchange of the TMP complexes is dissociative as in the case of the TPP complexes [15]. In fact, the rates of ligand exchange of (TMP)Fe(2-EtIm)$_2^+$, for example, were independent of the concentration of 2-EtIm within error limit; DNMR analysis gave activation free energies of 14.8 and 14.7 kcal/mol at 25 °C when 8.0 and 4.0 eq. of 2-EtIm were added, respectively. Both activation enthalpies and entropies changed depending upon complexes; the complex with a larger activation enthalpy tends to have a larger activation entropy. As a result, the activation free energies paralleled the activation enthalpies, although the former were less sensitive to the change in axial ligands. Since the activation enthalpies and entropies contain large errors due to the inherent problems of the DNMR method especially when the change in line shape is simple as in the present case [29], we will discuss the axial lability of imidazoles in terms of the activation free energies or the rate constants in the following section.

*Comparison of Ligands*

The data in Table 2 indicate that the rates of dissociation increase in the order 1-MeIm < 2-MeIm < 2-EtIm ~ 1,2-Me$_2$Im in both series. Since the steric repulsion between the substituent at position 2 of imidazole and the porphyrin ring increases in the the same order [34], the results suggest that the complex with a sterically hindered base becomes unstable. If this is the reason for the difference in lability, it may be reflected in the formation constants of these complexes; the formation constant of the 1-MeIm complex is expected to be much larger

TABLE 2. Activation and kinetic parameters for dissociation of axial ligands in PFeL$_2^+$ (CDCl$_3$, 25 °C)

| Complexes | | $\Delta H^{\neq}$ (kcal/mol) | $\Delta S^{\neq}$ (e.u.) | $\Delta G^{\neq}$ (kcal/mol) | $k^a$ ($s^{-1}$) | Method[b] | Temperature[c] (°C) |
|---|---|---|---|---|---|---|---|
| (TPP)Fe(1-MeIm)$_2^+$ | (1) | 20.4 | 19.4 | 14.6 | 120 | S | 8 ~ 24 |
| | | 20.1 | 17.3 | 14.9 | 66 | W[d] | 15 ~ 40[e] |
| (TPP)Fe(2-MeIm)$_2^+$ | (2) | 16.9 | 16.1 | 12.1 | 8900 | D | −15 ~ 2 |
| (TPP)Fe(2-EtIm)$_2^+$ | (3) | 15.4 | 16.5 | 10.5 | 120000 | D | −36 ~ −23 |
| (TPP)Fe(1,2-Me$_2$Im)$_2^+$ | (4) | 14.7 | 13.9 | 10.6 | 110000 | D | −53 ~ −30 |
| (TMP)Fe(1-MeIm)$_2^+$ | (5) | 22.4 | 20.4 | 16.3 | 7.0 | S[f] | 24 ~ 36 |
| (TMP)Fe(2-MeIm)$_2^+$ | (6) | 22.3 | 21.5 | 15.9 | 14 | S[f] | 17 ~ 30 |
| | | 21.4 | 19.1 | 15.7 | 18 | D | 39 ~ 55 |
| | | 22.8 | 23.2 | 15.9 | 14 | S + D | 17 ~ 55 |
| (TMP)Fe(2-EtIm)$_2^+$ | (7) | 20.2 | 18.0 | 14.8 | 87 | D | 11 ~ 33 |
| (TMP)Fe(1,2-Me$_2$Im)$_2^+$ | (8) | 19.9 | 17.5 | 15.1 | 100 | S | −5 ~ 3 |

[a]Rate constants extrapolated to 25 °C. [b]S, D, and W stand for saturation transfer, dynamic NMR, and linewidth analysis, respectively. [c]Temperature range in which spectra were analyzed. [d]Ref. 15. [e]Calculated from Fig. 3 of ref. 15. [f]Values are slightly different from those reported originally [16].

than those of 2-MeIm, 2-EtIm and 1,2-$Me_2$Im complexes. In fact, Walker *et al.* [19] reported, based on UV results, that the $\beta_2$ of (TPP)Fe(1-MeIm)$_2^+$ is 160 times larger than that of the corresponding 1,2-$Me_2$-Im complex. On the contrary, the $\beta_2$ of the 2-MeIm complex is reported to be twice as much as that of the 1-MeIm complex. Since the concentrations of the complexes in the present study are quite different from those examined by Walker, we measured the relative values of formation constants of both TMP and TPP complexes in a different way; competitive ligation of mixed imidazole bases toward a high spin ferric porphyrin.

Figure 4a shows the $^1$H NMR spectrum obtained with [(TPP)FeCl] = 0.014 M, [1-MeIm] = 0.056 M (4.0 eq.) and [2-MeIm] = 0.056 M (4.0 eq.) at −35 °C. Three peaks appeared at −25.2, −23.3 and −20.3 ppm with the population ratios of 0.38:0.40:0.22. These signals were assigned to the pyrrole protons of (TPP)Fe(1-MeIm)$_2^+$ (**1**), (TPP)Fe(1-MeIm)(2-MeIm)$^+$ and (TPP)Fe(2-MeIm)$_2^+$ (**2**), respectively. By putting the populations of the complexes and the concentrations of the free bases into (9), we obtained the ratio of formation constants between **1** and **2**, $\beta_2(\mathbf{1})/\beta_2(\mathbf{2})$, to be 2.1 ± 0.2. The ratio showed no appreciable dependence on temperature between −50 and −20 °C where the pyrrole protons of the three species gave separate signals.

$$2(\text{1-MeIm}) + 2 \overset{K}{\rightleftharpoons} 2(\text{2-MeIm}) + \mathbf{1} \quad (8)$$

$$K = [\mathbf{1}][\text{2-MeIm}]^2/[\mathbf{2}][\text{1-MeIm}]^2 = \beta_2(\mathbf{1})/\beta_2(\mathbf{2}) \quad (9)$$

Competitive ligation of 1-MeIm (4.0 eq.) and 2-EtIm (4.0 eq.) toward (TPP)FeCl was similarly studied at −35 °C. In this case, (TPP)Fe(1-MeIm)$_2^+$ (**1**) was the major product (89%), while (TPP)Fe(2-EtIm)$_2^+$ (**3**) was obtained only in 2.3%. By the similar analysis described above, the $\beta_2(\mathbf{1})/\beta_2(\mathbf{3})$ was determined to be 130 ± 30. Competitive ligation of 1-MeIm (3.0 eq.) and 1,2-$Me_2$Im (36 eq.) toward (TPP)FeCl was carried out at a lower temperature (−55 °C) since the exchange of the 1,2-$Me_2$Im ligand between the mixed imidazole complex, (TPP)-Fe(1-MeIm)(1,2-$Me_2$Im)$^+$, and (TPP)Fe(1,2-$Me_2$Im)$_2^+$ (**4**) is expected to be fast on the NMR time scale at −35 °C to give an averaged pyrrole signal. In spite of the large excess of 1,2-$Me_2$Im, only two pyrrole signals corresponding to (TPP)Fe(1-MeIm)$_2^+$ (**1**) and the mixed imidazole complex were observed with a 10:1 ratio. No pyrrole signal ascribable to (TPP)Fe(1,2-$Me_2$Im)$_2^+$ (**4**) was detected. If we assume that the population of **4** is 5%, then $\beta_2(\mathbf{1})/\beta_2(\mathbf{4})$ is calculated to be 16000. Since the content of **4** is supposed to be less than 5%, the $\beta_2(\mathbf{1})/\beta_2(\mathbf{4})$ must be larger than 16000. In order to ascertain this value, competitive ligation was carried out at −55 °C using 2-EtIm (2.0 eq.) and 1,2-$Me_2$Im (6.0 eq.). In this case, three pyrrole signals due to (TPP)Fe(2-EtIm)$_2^+$ (**3**), mixed imidazole complex, and (TPP)-Fe(1,2-$Me_2$Im)$_2^+$ (**4**) appeared in the small range of magnetic field with the population ratios of 0.4:0.5:0.1. Thus, $\beta_2(\mathbf{3})/\beta_2(\mathbf{4})$ is calculated to be 230 ± 50. $\beta_2(\mathbf{1})/\beta_2(\mathbf{4})$ is then estimated to be 130 × 230 ≒ 30000, which is consistent with the value described above.

The relative values of formation constants are given in the first column of Table 3. The formation constant of (TPP)Fe(1-MeIm)$_2^+$ is only twice as much as that of (TPP)Fe(2-MeIm)$_2^+$ in spite of the steric repulsion between the ligand and the porphyrin in the latter complex. The result is explained in terms of stability of the latter complex due to the intermolecular hydrogen bond of the coordinated 2-MeIm

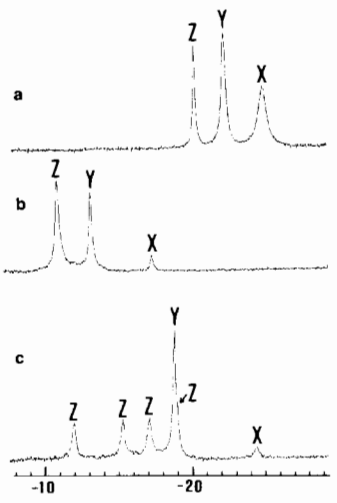



Fig. 4. Partial $^1$H NMR spectra obtained by the addition of 4.0 eq. of 1-MeIm and 4.0 eq. of 2-MeIm to 1.0 eq. of (a) (TPP)FeCl at −35 °C, (b) (TMP)FeCl at 24 °C, and (c) (TMP)FeCl at −35 °C. X, Y and Z are the pyrrole signals of the bis(1-MeIm) complex, mixed imidazole complex and bis(2-MeIm) complex, respectively.

TABLE 3. Relative values of formation constants ($CDCl_3$, −35 °C)

| Complexes | | $\beta_2$[a] | $\beta_2$[b] | $\beta_2$[c] |
|---|---|---|---|---|
| (TPP)Fe(1-MeIm)$_2^+$ | (1) | 1.0 | 1.0 | 1.0 |
| (TPP)Fe(2-MeIm)$_2^+$ | (2) | 0.48 | 2.2 | 0.48 |
| (TPP)Fe(2-EtIm)$_2^+$ | (3) | 0.008 | | 0.008 |
| (TPP)Fe(1,2-$Me_2$Im)$_2^+$ | (4) | <0.00006[d] | 0.0062 | <0.00006 |
| (TMP)Fe(1-MeIm)$_2^+$ | (5) | 1.0 | | 16 |
| (TMP)Fe(2-MeIm)$_2^+$ | (6) | 17 | | 270 |
| (TMP)Fe(2-EtIm)$_2^+$ | (7) | 1.0 | | 16 |
| (TMP)Fe(1,2-$Me_2$Im)$_2^+$ | (8) | 0.008 | | 0.13 |

[a]Formation constants relative to **1** in TPP system and **5** in TMP system. [b]Calculated from Table III of ref. 15. [c]Formation constants relative to **1** in both systems. [d]Result at −55 °C.

with free 2-MeIm and/or chloride ion [19–21]. Thus, the large decrease in formation constant on going from the 2-MeIm to the 2-EtIm complex is ascribed to the increase in the steric repulsion. The extremely small formation constant of the 1,2-$Me_2$-Im complex is then ascribed to the presence of the 2-methyl group together with the lack of stabilization due to the hydrogen bond. The existence of the 1-methyl group may further strengthen the steric repulsion through buttressing effect [21, 35].

In the second column of Table 3 are given the relative values of formation constants calculated from ref. 19. Some discrepancies were observed between the reported values and ours; the reported value of (TPP)Fe(1,2$Me_2$Im)$_2^+$ is larger than ours by at least 100 times. These discrepancies may be caused by the difference in methods, concentration of the complexes and the temperature range studied.

Competitive ligation of 1-MeIm and 2-MeIm was studied in the TMP system as well. Figures 4b and 4c show the $^1$H NMR spectra obtained by the addition of 4.0 eq. of 1-MeIm and 4.0 eq. of 2-MeIm into (TMP)FeCl (1.0 eq.) at 24 and −35 °C, respectively. As in the case of the TPP system, three pyrrole signals due to (TMP)Fe(1-MeIm)$_2^+$ (**5**), (TMP)Fe(1-MeIm)(2-MeIm)$^+$ and (TMP)Fe(2-MeIm)$_2^+$ (**6**) were observed at 24 °C (Fig. 3b). The pyrrole signal of (TMP)Fe(2-MeIm)$_2^+$ (**6**) split into four signals at −35 °C (Fig. 3c), since the internal rotation of the coordinated 2-MeIm is hindered and two imidazole rings are fixed to form the $C_2$ conformation [18]. Contrary to the TPP system, the spectra clearly show that the major product is (TMP)Fe(2-MeIm)$_2^+$ (**6**) both at 24 and −35 °C. $\beta_2(\mathbf{5})/\beta_2(\mathbf{6})$ is determined to be 0.059 ± 0.006, which is independent of temperature within error limit. Similar experiments were carried out using 1-MeIm and 2-EtIm and using 1-MeIm and 1,2-$Me_2$Im. The results are also given in the first column of Table 3.

The data in Tables 2 and 3 indicate that the correlation between rate constants and formation constants is very poor; although a large increase in rate constant was observed in the TPP system when the axial ligand changed from 1-MeIm to 2-MeIm, the decrease in formation constant was very small. Furthermore, the formation constant increased (17 times) in the case of the TMP system in spite of the small increase in rate constant. These results suggest that the labile nature of (TMP)Fe(2-MeIm)$_2^+$ (**6**) relative to (TMP)Fe(1-MeIm)$_2^+$ (**5**), for example, is ascribed to the difference in stability between the activated complexes. Since mono-ligated species, (TMP)Fe(1-MeIm)$^+$ (**5′**) and (TMP)Fe(2-MeIm)$^+$ (**6′**), are assumed to be the activated complexes in the dissociation process of **5** and **6**, respectively, the results indicate that the difference in free energies between **5′** and **6′** is larger than that between **5** and **6**. One reason for the stability of **6′** relative to **5′** is the release in steric repulsion [36] which exists between the 2-methyl of imidazole and the porphyrin ring at the ground state; the repulsion would decrease on going from the bis-ligated ground state to the mono-ligated transition state where iron is located out of the porphyrin plane. The same hypothesis can be applied to explain an increase in the dissociation rate on going from the 1-MeIm to 2-MeIm complex in the TPP system. The extremely labile nature of (TPP)Fe(1,2-$Me_2$Im)$_2^+$ (**4**) and (TMP)Fe(1,2-$Me_2$Im)$_2^+$ (**8**) is thus ascribed to the instability of the ground state as mentioned before together with the stability of the mono-ligated species due to the release of steric strain.

*Comparison of Porphyrins*

The activation free energies of ligand dissociation in Table 2 clearly indicate that the TPP complexes are more labile than the corresponding TMP complexes by 2 to 4 kcal/mol at 25 °C. Since the rate of dissociation is determined by the difference in free energies between the ground and transition states, the results can be explained either in terms of the stabilization of the bis-ligated TMP complex relative to the corresponding TPP complex or in terms of the destabilization of the mono-ligated TMP complex relative to the corresponding TPP complex. In order to find out which is the case, 2.0 eq. of 1-MeIm were added at −35 °C to the $CDCl_3$ solution containing 0.011 M of (TPP)FeCl and 0.011 M of (TMP)FeCl. The $^1$H NMR spectrum showed two signals at 24.2 and 21.2 ppm ascribable to the methyl protons of the coordinated 1-MeIm of (TPP)Fe(1-MeIm)$_2^+$ (**1**) and (TMP)Fe(1-MeIm)$_2^+$ (**5**), respectively. Integration of these signals revealed the 1:4 formation of **1** and **5**. No signals due to complexes other than **1**, **5** and the starting high spin species were detected in the spectrum. Further addition of the imidazole increased the signals of **1** and **5**. When 4.0 eq. of 1-MeIm were added, all the high spin complexes were converted into the low spin complexes. Thus, the equilibrium constant of (10), which is equal to the ratio of formation constants as (11) shows, is determined to be 16.

$$\text{(TMP)Fe}^+ + \text{(TPP)Fe(1-MeIm)}_2^+ \overset{K}{\rightleftharpoons} \text{(TMP)Fe(1-MeIm)}_2^+ + \text{(TPP)Fe}^+ \qquad (10)$$

$$K = [\mathbf{5}][\text{(TPP)FeCl}]/[\mathbf{1}][\text{(TMP)FeCl}] = \beta_2(\mathbf{5})/\beta_2(\mathbf{1}) \qquad (11)$$

The result is quite unusual in the sense that the formation constant of the sterically hindered TMP complex is larger than that of the less hindered TPP complex. The relative values of the formation constants of TMP complexes were multiplied by 16 for direct comparison with those of TPP complexes and they are listed in the third column of Table 3.

A similar experiment was carried out using 2-MeIm; the equimolar mixture of (TPP)FeCl and (TMP)FeCl was titrated with 2-MeIm at −35 °C. Surprisingly, only the signals due to (TMP)Fe(2-MeIm)$_2^+$ (**6**) were observed until more than 2.0 eq. of the base were added. The result clearly demonstrates that 2-MeIm binds more strongly to high spin (TMP)FeCl than to less hindered (TPP)FeCl. If we assume that (TPP)Fe(2-MeIm)$_2^+$ (**2**) is formed in 5% yield after the addition of 2.0 eq. of 2-MeIm, the ratio of the formation constant, $\beta_2(\mathbf{6})/\beta_2(\mathbf{2})$, is calculated to be 360. Since 5% is within the range of detection, the ratio must be larger than 360. The result is consistent with $\beta_2(\mathbf{6})/\beta_2(\mathbf{2}) = 560$, calculated from the data in the third column of Table 3.

The ratios of the formation constants between TMP and TPP complexes, $\beta_2$(TMP)/$\beta_2$(TPP), are 16, 560, 2000 and >2200 for L = 1-MeIm, 2-MeIm, 2-EtIm and 1,2-Me$_2$Im, respectively. The result indicates that the difference in free energies between TPP and TMP systems is larger in low spin complexes than in high spin complexes. In other words, (TMP)-FeCl is stabilized to a greater extent than (TPP)FeCl by the formation of the bis-ligated complex. Correspondingly, the ratio of rate constants, $k$(TMP)/$k$-(TPP), decreases as the axial ligand changes from 1-MeIm (0.05) to 2-MeIm (0.002) and then to 2-EtIm or 1,2-Me$_2$Im (both 0.001). It is noteworthy that the ratios of rate constants correlate with the corresponding ratios of formation constants. Thus, the labile nature of the TPP complexes relative to the corresponding TMP complexes is ascribed to the stability of the latter relative to the former complexes.

The question arises as to why the hindered porphyrin complexes are more stable than the less hindered ones. Electronic effects of the phenyl substituent are to be considered first. According to refs. 19 and 21, substituents with electron donating ability increase the formation constant through resonance effect; the formation constant of ($p$-Me)-(TPP)Fe(1-MeIm)$_2^+$ is $c$. twice as much as that of the parent (TPP)Fe(1-MeIm)$_2^+$. Since there are three methyl groups in each benzene ring in TMP complexes, further increase in formation constant can be expected. However, because of the presence of two *ortho*-methyl groups, the mesityl rings are perpendicular to the porphyrin ring, minimizing the electron donating ability of the methyl groups. Thus, it is difficult to explain the large difference in formation constants between the two systems by the electronic effects of the phenyl substituents. Furthermore, the data in Table 3 indicate that the ratio of formation constants, $\beta_2$(TMP)/$\beta_2$(TPP), increases as the axial ligand becomes more bulky. These anomalous results on stability and lability of TMP complexes can be explained if we assume an attractive, rather than a repulsive, interaction between the mesityl groups and the coordinated imidazoles.

In many small organic compounds, the attractive interactions between hydrocarbon moieties can rarely be observed. In principle, however, van der Waals attraction exists between two non-polar groups if they are located at a suitable distance. In fact, some organic compounds have been found recently showing that the attractive interactions between two alkyl groups [37–39] or between alkyl and phenyl groups [40, 41] are playing an important role in determining conformational equilibria and complexation reaction [42, 43]. In TMP complexes, the interaction of the *o*-methyls of mesityl rings with the pi systems of imidazoles and/or the 2-alkyl groups of imidazoles could be attractive; the distance between these groups could be adjusted suitably for van der Waals attraction by rotating slightly the mesityl ring around the C(mesityl)–C(meso) bond or by tilting the iron–imidazole bond [5]. Although the stabilization energy due to van der Waals interaction is generally small, there are four to eight sites for such an interaction above and below the porphyrin ring as shown in Fig. 5. Thus, it might be possible that the total attractive energy is as much as 3 kcal/mol. Quite recently, Kyuno *et al.* [44] observed that the base affinity of the *trans*-$\alpha^2$ atropisomer of Co(II) picket fence porphyrin is several times higher than the other three isomers and ascribed it to the non-bonded attractive interaction between the ligated base and the pickets. Thus, this kind of weak attractive interaction between two nonpolar groups may be quite common in metal complexes and consequently, in many biological systems, regulating the kinetic and thermodynamic behavior of the ligated molecules. A further study to prove this hypothesis is in progress.

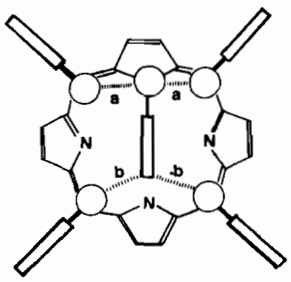



Fig. 5. Possible attractive interactions between (a) two alkyl groups and (b) alkyl and pi system of imidazole in the bis-ligated low spin TMP complex.

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