A Study of Chloride Ion Dissociation from Six-coordinate Iron(III) Porphyrin Complexes. Rate Enhancements due to Steric Strain from *trans*-Coordinated (Proximal) Imidazoles

YUN ZHANG, J. G. JONES* and D. A. SWEIGART**
Department of Chemistry, Brown University, Providence, RI 02912 (U.S.A.)
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Abstract

The reaction of iron(III) tetraphenylporphyrin chloride, Fe(TPP)Cl, with imidazoles, RIm, substituted at the C-2 or C-4 position to give Fe(TPP)-$(RIm)_2^+Cl^-$ has been studied at variable temperatures in dichloromethane. A coordinated (proximal) imidazole having a methyl substituent at C-2 or C-4 introduces a steric interaction with the porphyrin ring and this decreases by about a factor of ten the formation constant of the transient six-coordinate species Fe(TPP)(RIm)Cl. Conversely, the steric effect increases by a factor of ten or more the rate of chloride ion dissociation from Fe(TPP)(RIm)Cl; by comparison to results with cobalt(III) porphyrins, it is shown that this steric acceleration is independent of the spin state. These results model proximal steric strain in certain hemoproteins.

Introduction

Proximal and distal histidyl imidazole residues which occur in a variety of hemoproteins are believed to play an important role in substrate binding and reactivity. Polarity effects and hydrogen bonding from the distal imidazole significantly influence oxygen binding in hemoglobin and myoglobin and peroxide O–O bond cleavage in cytochrome *c* peroxidase [1]. Hydrogen bonding from the coordinated (proximal) imidazole N–H is thought to influence ligand binding, conformational changes and redox potential modulation in hemoproteins [2].

Model systems having a substituent at C-2 of the proximal imidazole show that significant steric strain occurs between the 2-substituent and the porphyrin ligand (Fig. 1). This causes the metal to be displaced from the porphyrin core in the ligated (six-coordinate) complex and/or leads to substantial deviations of the porphyrin ligand from planarity. These effects are seen in X-ray structures of Fe(TpivPP)(1,2-Me_2Im)O_2 [3] and Fe(TPP)(1,2-Me_2Im)N_3 [4] (TPivPP and TPP are the dianions of picket fence porphyrin and tetraphenylporphyrin, respectively). Proximal strain in model systems is manifested in reduced O_2 and CO affinities, due to both decreased association and increased dissociation rates [5]. In T-state hemoglobin the proximal imidazole is sterically constrained to tilt off the heme normal. This tilting as well as the iron displacement from the porphyrin core are important aspects of the mechanism of cooperative oxygen binding [6]. It is also one of the reasons for lower oxygen binding constants and increased dissociation rates relative to the relaxed R-state protein.

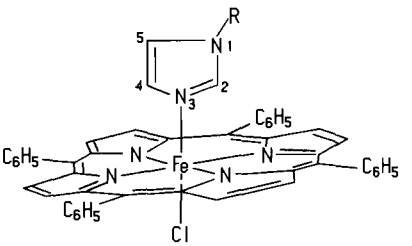

Fig. 1. The reaction intermediate which is subject to proximal steric interaction between the porphyrin ring and C-2 or C-4 substituents on the imidazole.

A number of the proximal and distal effects noted above has been illustrated through kinetic [7, 8] and electrochemical [9] studies of the reaction of iron(III) and cobalt(III) porphyrin halides with imidazoles. For example, the reaction of Fe(Por)X with 1-methylimidazole (1-MeIm) according to reaction (1) follows the mechanism outlined by eqns. (2)–(4), with the observed rate constant given in eqn. (5). The intermediate Fe(Por)(1-MeIm)X is formed rapidly in a pre-equilibrium step which is followed by rate limiting ionization of X^- (Cl^-, F^-,

*Permanent address: Department of Chemistry, University of Ulster, Coleraine, Northern Ireland BT52 1SA, U.K.
**Author to whom correspondence should be addressed. Recipient, NIH Research Career Development Award, 1983–1988.

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N_3^-). When the imidazole nucleophile is not substituted at the N-1 position, i.e. contains the N–H moiety, the rate of reaction (1) is greatly accelerated and the rate law, in contrast to eqn. (5), becomes second order in the imidazole even though the metal binds to the imine nitrogen (N-3). These changes occur because the halide ionization step is assisted by hydrogen bonding from the N–H group, and as such these reactions model distal type hydrogen bonding.

$$\text{Fe(Por)X} + 2\ \text{1-MeIm} \xrightarrow{\beta_2} \text{Fe(Por)(1-MeIm)}_2^+\text{X}^- \quad (1)$$

$$\text{Fe(Por)X} + \text{1-MeIm} \overset{K_1}{\rightleftharpoons} \text{Fe(Por)(1-MeIm)X} \quad (2)$$

$$\text{Fe(Por)(1-MeIm)X} \xrightarrow{k_1} \text{Fe(Por)(1-MeIm)}^+\text{X}^- \quad (3)$$

$$\text{Fe(Por)(1-MeIm)}^+\text{X}^- + \text{1-MeIm} \xrightarrow{\text{fast}} \text{Fe(Por)(1-MeIm)}_2^+\text{X}^- \quad (4)$$

$$k_{obs} = k_1K_1[\text{1-MeIm}]/(1 + K_1[\text{1-MeIm}] \quad (5)$$

Proximal imidazole hydrogen bonding was probed [9] by redox potential measurements of Fe(Por)-$(HIm)_2^+$ in the presence of bases that associate with the imidazole N–H. It was found that such hydrogen bonding shifts the Fe(III)/Fe(II) reduction potential negative by *c.* 60 mV and confirmed that this mechanism for redox potential modulation in hemoproteins is viable.

This paper is concerned with the role of proximal imidazole steric strain in reactions of Fe(TPP)Cl with 1-substituted imidazoles bearing additional groups on C-2 or C-4. The complex subject to the steric effect occurs as a reaction intermediate and is shown in Fig. 1. Within the context of the mechanism in eqns. (2)–(5), the steric effect was anticipated to be reflected in smaller K_1 and larger k_1 values. This was found to be the case. In a previous study [8] with Co(TPP)Cl it was not possible to measure K_1 values for the general imidazole RIm because $K_1[\text{RIm}] \gg 1$ in eqn. (5), but it was demonstrated that having a 2-methyl or 2-phenyl substituent on the imidazole increases k_1 by at least a factor of ten. With iron as the metal the situation is more complicated because the observed rate is in many cases largely determined by the composite constant k_1K_1 (eqn. (5), $1 \gg K_1[\text{RIm}]$) and it happens that changes in K_1 and k_1 with variation of the imidazole substituents often fortuitously cancel, so that the observed reaction rate changes little. However, experiments at variable temperatures allowed K_1 and k_1 to be separated and showed that both are quite sensitive to steric effects originating from the coordinated imidazole in Fe(Por)(RIm)X.

Experimental

Dichloromethane was refluxed under nitrogen over calcium hydride and distilled prior to use. Acetone was purified and dried as previously described [8]. The commercially available imidazoles were purified by vacuum distillation from calcium hydride (1-MeIm, 1-PhIm, 1,2-Me_2Im). The imidazole 4,5-Me_2Im was synthesized from acetoin and formamide [10] and methylated with methyl iodide, using sodamide (prepared *in situ*) in liquid ammonia to remove the N–H proton [11]. (Deprotonation with NaH in ether is unsatisfactory due to the sparing solubility of 4,5-Me_2Im.) The ^{1}H NMR spectrum of the product, 1,4,5-Me_3Im, agreed with the literature [12]. The isomers 1-Me-2-PhIm, 1-Me-4-PhIm and 1-Me-5-PhIm were synthesized as previously described [8]. The N-1 substituted imidazoles are very hydroscopic and all solutions were prepared in a dry box under nitrogen or argon. The porphyrin complexes Fe(TPP)Cl and Fe(OEP)Cl (OEP is the dianion of octaethylporphyrin) were purchased from Strem and Aldrich, respectively, and checked for purity by optical spectroscopy.

Kinetic measurements were made at room temperature with a Dionex stopped-flow instrument and at lower temperatures with a home-made instrument of the Canterbury design. The imidazole nucleophile was in at least a hundredfold excess over the Fe(Por)Cl concentration, which was typically *c.* 5×10^{-5} M. The reactions were followed at 510 nm and the absorbance–time data treated in the usual manner. Equilibrium constants for reaction (1) (with a variety of imidazoles) were determined from absorbance data in the manner previously described [7].

Results and Discussion

The reaction of Fe(TPP)Cl with 1-MeIm has been shown [7] to be consistent with the mechanism described by eqns. (2)–(5). The results presented herein indicate that this mechanism holds for any 1-substituted imidazole. Table 1 gives the relevant rate and equilibrium constants derived from the kinetic data. Figure 2 shows the rate profile for 1-MeIm in dichloromethane. The curvature in the plots at 25 and −30 °C is due to saturation of the pre-equilibrium (eqn. (2)) and a reciprocal plot of eqn. (5) was used to evaluate K_1 and k_1 separately. The intermediate Fe(TPP)(RIm)Cl (Fig. 1) was detected spectroscopically by mixing RIm and Fe(TPP)Cl at low temperatures (*c.* −80 °C). In previous work [7] we established that Fe(TPP)(RIm)Cl is six-coordinate and high spin.

Inspection of the data in Table 1 for 1-MeIm and 1-PhIm shows that K_1 is markedly temperature dependent ($\Delta H^\circ \approx -40$ kJ/mol). As the temperature

TABLE 1. Summary of kinetic data for the reaction of Fe(TPP)Cl with imidazoles in dichloromethane

RIm	T (°C)	K_1 (M^{-1})	k_1 (s^{-1})	k_1K_1	β_2 (M^{-2})
1-MeIm	25	1.6 ± 0.3	90 ± 10	140 ± 20	4000 ± 1000
1-MeIm	−30	70 ± 5	0.8 ± 0.1	58 ± 5	
1,2-Me_2Im	25			90 ± 7	40 ± 10
1,2-Me_2Im	−30	6 ± 1	10 ± 1	62 ± 5	
1-PhIm	25	0.7 ± 0.3	12 ± 2	9 ± 1	820 ± 200
1-PhIm	−6	4 ± 1.5	1.7 ± 0.5	6 ± 1	
1-PhIm	−30	16 ± 2	0.28 ± 0.02	4.5 ± 0.2	
1,4,5-Me_3Im	25			700 ± 70	50 ± 20
1,4,5-Me_3Im	−30	10 ± 2	25 ± 3	250 ± 50	
1-Me-5-PhIm	25			400 ± 30	
1-Me-4-PhIm	25	no reaction			
1-Me-2-PhIm	25	no reaction			

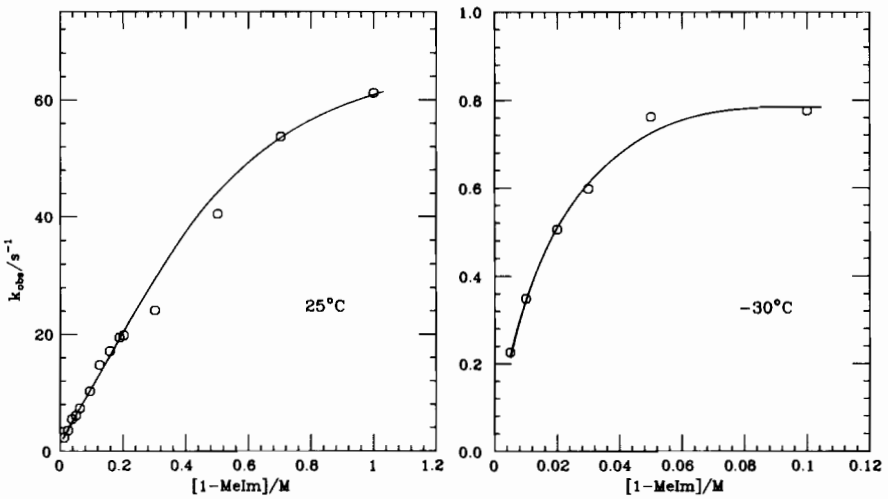

Fig. 2. Kinetic profiles for the reaction of Fe(TPP)Cl and 1-MeIm in dichloromethane.

is lowered K_1 increases and the rate constant k_1 decreases, with the result that the composite constant k_1K_1 is only weakly temperature dependent. The lower proton basicity of 1-PhIm compared to 1-MeIm probably accounts for the lower values of K_1, k_1, and β_2 for the former.

Placing a substituent on C-2 or C-4 of the imidazole is expected to produce a steric interaction with the porphyrin ligand in Fe(TPP)(RIm)Cl (Fig. 1). The steric effect with 1,2-Me_2Im compared to 1-MeIm is immediately apparent from the hundredfold decrease in β_2 at 25 °C. Figure 3 shows the kinetic plots with 1,2-Me_2Im. The steric effect in K_1 and k_1 could not be quantitatively determined at 25 °C because the kinetic plot does not show curvature, meaning that only the product k_1K_1 could be obtained from eqn. (5) ($1 \gg K_1$[1,2-Me_2Im]). (The non-zero intercept in the room temperature plot occurs because the reaction does not go to completion.) However, the expected increase in K_1 as the temperature is lowered to −30 °C allowed the separate determination of K_1 and k_1 (Fig. 3). Compared to 1-MeIm at this temperature, K_1 is smaller and k_1 larger by about a factor of ten, with the product k_1K_1 being almost the same for both imidazoles. The sharp decrease in K_1 and β_2 for 1,2-Me_2Im shows that the greater basicity of 1,2-Me_2Im compared to 1-MeIm is dominated by a larger effect due to steric interactions. This in turn indicates that the increased k_1 with 1,2-Me_2Im reflects a steric rather than an electronic effect. The hundredfold decrease in β_2 seems to be equally divided between the first imidazole addition (K_1) and the chloride substitution by the second imidazole molecule (K_2).

Placing a methyl substituent at the imidazole C-4 leads to steric effects similar to those found with 1,2-Me_2Im. Thus, 1,4,5-Me_3Im has a significantly smaller K_1 and β_2, and larger k_1 than does 1-MeIm. The steric interactions are easily shown in a qualitative way with the isomers 1-Me-2-PhIm, 1-Me-4-PhIm and 1-Me-5-PhIm: the first two do not react with Fe(TPP)Cl while the third reacts normally.

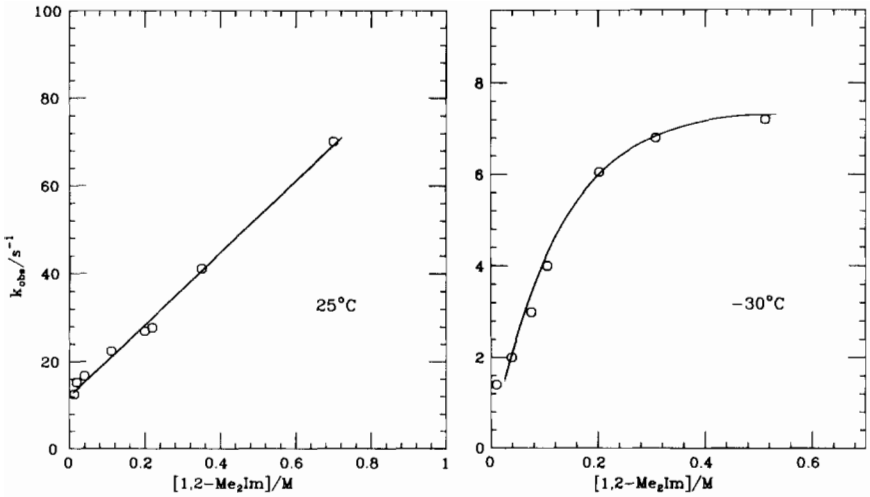

Fig. 3. Kinetic profiles for the reaction of Fe(TPP)Cl and 1,2-Me_2Im in dichloromethane.

In a previous study [8] we showed that the steric acceleration factor for chloride dissociation from Co(TPP)(RIm)Cl due to C-2 substituents on the imidazole falls in the range of ten to thirty. In other words, the steric acceleration is similar for M(TPP)(RIm)Cl (M = Co, Fe) even though the cobalt complex is low spin and the iron complex high spin.

In this paper we have shown that axial ligand dissociation from iron(III) porphyrins is significantly accelerated by steric interactions between the porphyrin ring and a *trans*-coordinated imidazole that is substituted at the C-2 or C-4 position. This steric effect is also responsible for decreased equilibrium constants for imidazole coordination to the iron.

The constants K_1 and k_1 can also be altered by changing the substituents on the periphery of the porphyrin ligand. A comparison of 1-MeIm reacting with Fe(TPP)Cl and Fe(OEP)Cl illustrates this point. In acetone at 25 °C, the product k_1K_1 was found to be identical (14 ± 1.5 M^{-1} s^{-1}) for both porphyrins. In spite of this apparent similarity, analysis of the data showed that K_1 is at least five times smaller and k_1 at least five times larger for Fe(OEP)Cl. These changes in K_1 and k_1 are in the direction expected for the more electron-releasing porphyrin (OEP).

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