Studies on Reactions of Imidazole with a Cr(III)-Porphyrin

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*Dynamics of imidazole binding to tetra-*p*-sulfo-phenylporphinatochromium(III) have been investigated as a function of hydrogen ion concentration. Labile substitution of imidazole at axial position is shown to be due to* trans *activation by the bound hydroxide ion. Rate of addition of a second imidazole, to form a bis complex, was found to be slower than the substitution of the first imidazole. Neither imidazolium nor the anion of imidazole was found to react with the Cr(III) porphyrin.*

Introduction

Since the discovery of labile substitution reactions of vitamin B_{12}, a low-spin d^6 cobalt(III) complex, numerous reports of such reactions of cobalt porphyrin have appeared in the literature [1–7]. To eliminate the possibility of involvement of a lower oxidation state a chromium porphyrin was investigated [2]. The faster ligand substitutions of the chromium porphyrin confirmed the labilizing influence of the porphyrin ligand. Yet, several questions remain unanswered. In the case of cobalt porphyrins, the substitution of a second ligand was found to be faster than that of the first ligand [1, 3–7]. A similar observation was noted for substitution of imidazole with ferric porphyrins [8, 9]. Whether the same holds true for other metalloporphyrins as well remains to be proven. This article describes the results of an investigation into the kinetics of imidazole substitution reactions of water soluble tetra-*p*-sulfophenylporphinatochromium(III), $[Cr(III)P(H_2O)_2]$.

Experimental

Synthesis of $[Cr(III)P(H_2O)_2]$ was reported earlier [2]. Though the compound analysed well, the absorption spectrum of the sample in acid solution appeared to be a composite spectrum of a mixture. Moreover, on standing for a few minutes, this acid solution gave a green colored precipitate. The aggregation behavior of metal free sulfonated porphyrin in acid solution is well known. Thus it appeared that the sample was a mixture of two isomers: one with chromium inside (in the center of porphyrin) and the other with chromium outside (attached to sulfonic acid groups). The sample was purified as follows: On passing a concentrated solution of $[Cr(III)P(H_2O)_2]$ through a cation exchange resin in H^+ form, the isomer with chromium outside precipitated as diacid, which was filtered or centrifuged. The solution contained the pure form of the complex with chromium in the center.
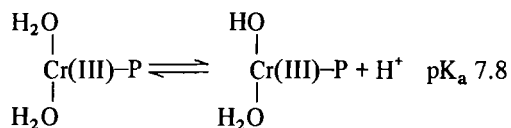
Imidazole (Aldrich) was purified by vacuum sublimation. Sodium borate (Fisher), Sodium Perchlorate (G. F. Smith Chemical Co.) and 1,4-piperazinebis-(ethanesulfonic acid) (PIPES) (Calbiochem) were used as obtained. A Beckman ACTA CIII spectrophotometer and a Radiometer PHM64 pHmeter were used for titration and kinetic studies. Faster kinetic runs (half life <10 sec) were followed in a Durrum stopped flow apparatus.

Titrations and kinetic studies were carried out in thermostated cells at 25 °C and 0.2F ionic strength (NaClO₄). All reactions were studied under pseudo first order conditions. Plots of $\log(A - A_\infty)$ *versus* time were linear for several half lives. Rate constants of duplicate runs were within ±5%.

Consecutive reactions (1 and 2, 3 and 4) were followed in the manner described below to avoid the complications of any multiphasic kinetics. Reactions 1 and 3 were monitored by following the disappearance of the reactant species at 435 nm and 440 nm respectively. Reactions 2 and 4 were followed by monitoring the appearance of the product at 453 nm as the light absorbing products in both the reactions were the same. Furthermore, reactions 1 and 3 were almost always at least tenfold faster than the corresponding reactions 2 and 4 at any given imidazole concentration. This is similar to a situation [17] where A goes to B essentially quantitatively. At a much slower rate, by a factor of at least ten, B goes to C. So these reactions could be and were followed independently. All these reactions gave good first order plots at least up to 3 or 4 half lives (maximum absorbance changes that could be plotted with any sensitivity). Porphyrin concentration for all the studies ranged in $(1-4) \times 10^{-6} M$.

Results

Earlier studies, which are reconfirmed here [10], indicated that [Cr(III)P(H₂O)₂] undergoes a protolytic dissociation in the pH range of 7 to 8. The reaction is as follows:

$$
\begin{array}{ccc}
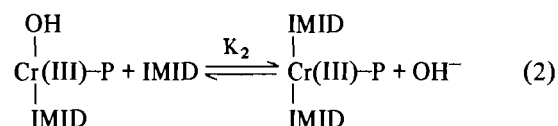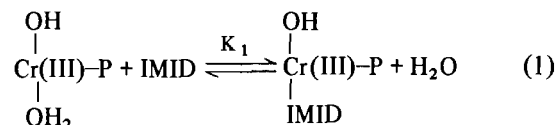H_2O & & HO \\
| & & | \\
Cr(III)\text{–}P & \rightleftharpoons & Cr(III)\text{–}P + H^+ \quad pK_a\ 7.8 \\
| & & | \\
H_2O & & H_2O
\end{array}
$$

The reaction of imidazole with [Cr(III)P(H₂O)₂] was investigated at pH 6.6 (PIPES Buffer) and at pH 10.0 (sodium borate buffer). At pH 10.0 the solution contains about 0.6% of the porphyrin in the diaquo-form.

Studies at pH 10.0

Spectral changes with increasing imidazole concentrations in the Soret region are shown in Fig. 1. The [Cr(III)P(OH)(H₂O)] species absorbs at 435 nm. In the first part of titration, the absorbance increases at 439 nm with increasing imidazole concentrations. Concomittantly the absorbance decreases at 435 nm. An isosbestic point is observed at 438 nm. On further addition of imidazole a new peak at 452 appears. Associated with this peak, an isosbestic point is noted at 446.5 nm and the isosbestic at 438 nm is no longer to be found. These changes may be attributed to the stepwise addition of imidazole (IMID) to Cr(III)–P as follows:

$$
\begin{array}{ccc}
OH & & OH \\
| & K_1 & | \\
Cr(III)\text{–}P + IMID & \rightleftharpoons & Cr(III)\text{–}P + H_2O \qquad (1) \\
| & & | \\
OH_2 & & IMID
\end{array}
$$

$$
\begin{array}{ccc}
OH & & IMID \\
| & K_2 & | \\
Cr(III)\text{–}P + IMID & \rightleftharpoons & Cr(III)\text{–}P + OH^- \qquad (2) \\
| & & | \\
IMID & & IMID
\end{array}
$$

From Fig. 1 it is clear that the region of imidazole concentration within only two porphyrin species exist in solution is very limited. In Fig. 2, a plot of
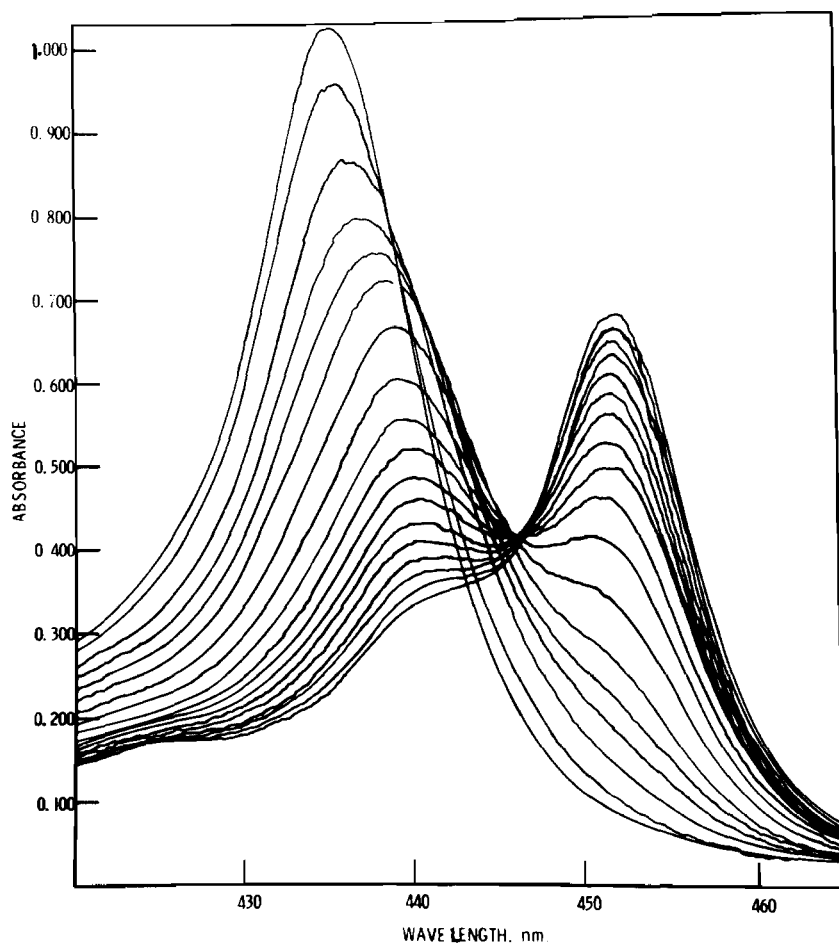

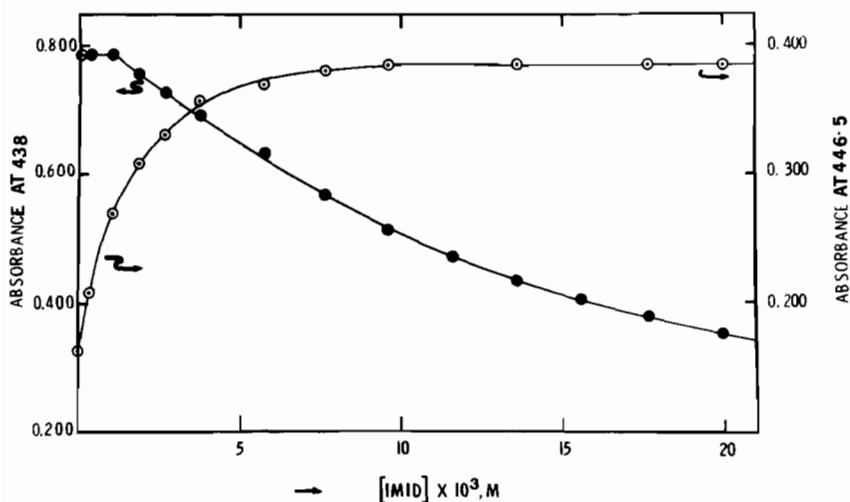Fig. 1. Spectrophotometric titration of [Cr(III)P(H₂O)₂] with imidazole.

Fig. 2. Changes in the absorbance of Chromium(III) porphyrin at 438 nm and 446.5 nm with the addition of imidazole.
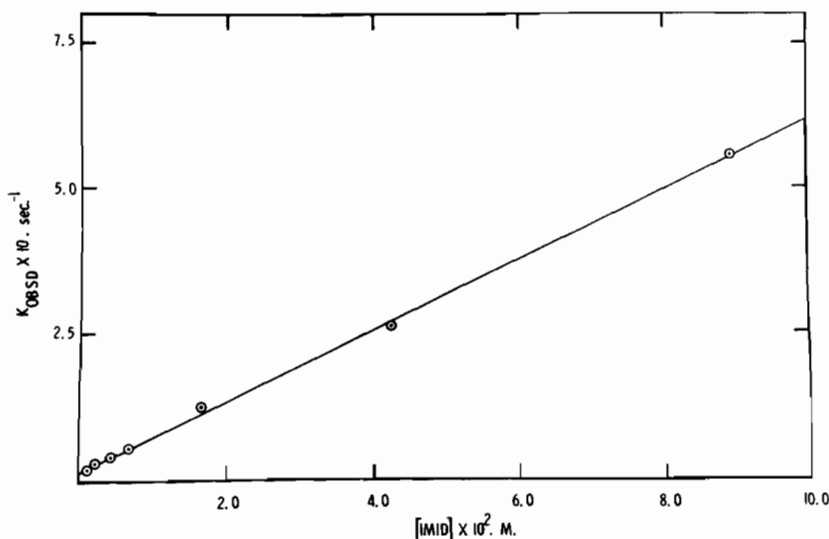

Fig. 3. Dependence of k_{obs}, pseudo first order rate constants, on imidazole concentrations at pH 10.0 for reaction (1).

absorbance at 438 nm and 446.5 nm (isosbestic points) *versus* varying imidazole concentrations is presented. The plateaus in each curve indicate the concentration region where predominantly two chromophoric species exist in solution. Using the absorbance of one curve at varying imidazole concentrations (in the region corresponding to a flat portion of the other curve) one can compute the equilibrium constants employing the equation

$$K = [A_i - A]/(A - A_f)(IMID)$$

where A_i, A_f, and A represent absorbance initially, absorbance at the end of the titration and absorbance corresponding to various imidazole concentrations (IMID). The equilibrium constants K_1 and K_2 thus computed are $589 \pm 16 \, M^{-1}$ and $74 \pm 2 \, M^{-1}$ respectively. The uncertainties reported here and through-

out this article are standard deviations from least squares computer runs.

The kinetics of reaction (1) were investigated with imidazole concentrations varying from 1.23×10^{-3} M to 8.93×10^{-2} M. According to equilibrium studies described above, in the imidazole concentration range of 1.23×10^{-3} to 1.5×10^{-2} M, reaction (1) approaches equilibrium [18] and in the range of 1.5×10^{-2} to 8.93×10^{-2} M, reaction (1) tends toward essential completion. At pH 10.0 the rate law was found to be

$$\frac{d\ln\left[[Cr(III)P(OH)H_2O] - [Cr(III)(OH)P(H_2O)]eq\right]}{dt} = k_{obs}$$

where $k_{obs} = [k_f[IMID] + k_r]$ and k_f and k_r are constants. A plot of k_{obs} *versus* imidazole concentrations (Fig. 3) is found to be a straight line with a
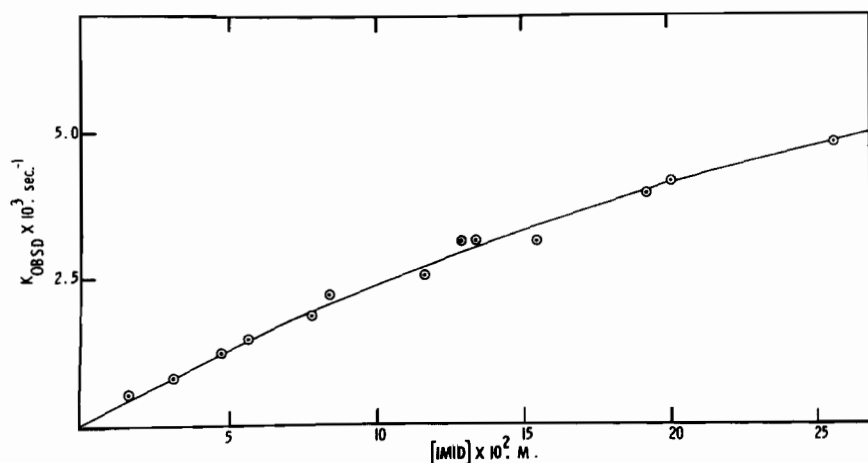
Fig. 4. Dependence of k_{obs}, pseudo first order rate constants, on imidazole concentrations at pH 10.0 for reaction (2).
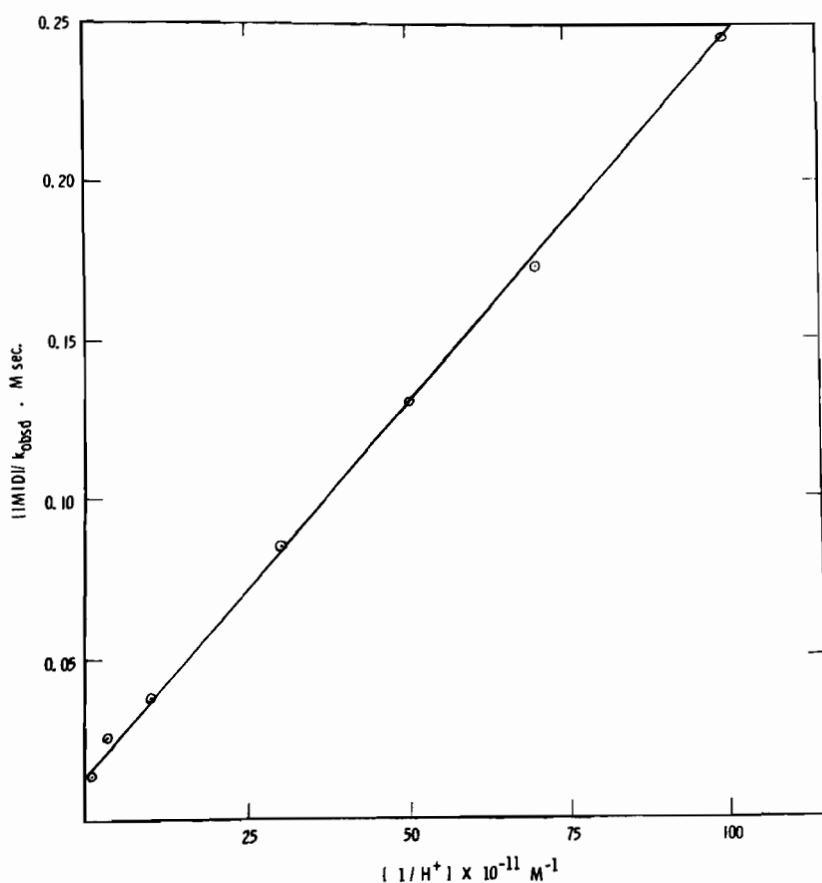

Fig. 5. Dependence of k_{obs} on (H⁺) for reaction (1).

slope of $60.30 \pm 0.80\ M^{-1}\ sec^{-1}$ and an intercept of $0.14 \pm 0.03\ sec^{-1}$.

The kinetics of reaction (2) were studied over a range ((1.6 to 27) $\times\ 10^{-2}\ M$) of imidazole concentrations. A plot of k_{obs}, pseudo first order rate constants, *versus* [IMID] is shown in Fig. 4. As the observed rate constants tend to level off with increasing imidazole concentrations, a plot of $1/k_{obs}$ against $1/$

[IMID] was attempted. This yielded a straight line with a slope of $15.7 \pm 0.5\ sec\ M$ and intercept of $50 \pm 6\ sec$.
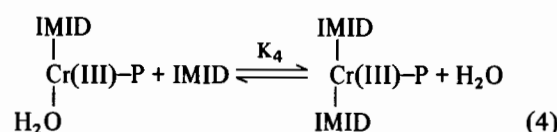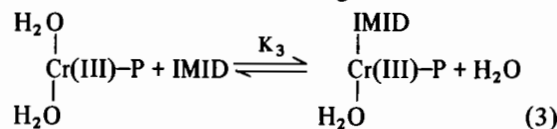
Since in reaction (2) hydroxide ion is a product, the pH dependence of reactions (1) and (2) was investigated. While the pseudo first order rate constants, k_{obs}, for reaction (1) were found to be inversely proportional to [OH⁻], the dependence of

k_{obs} on [OH⁻] for reaction (2) was found to be rather complex. A plot of $[IMID]_T/k_{obs}$ as a function of $1/[H^+]$ for reaction (1) is presented in Fig. 5.

Activation parameters for reactions (1) and (2) were also determined by Arrhenius plot. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ computed from the slope and intercept of such a plot are 18 ± 2 kcal and +12 ± 6 eu for reaction (1) and 22.4 ± 0.3 kcal and +11 ± 1 eu for reaction (2) respectively at 25 °C.

Studies at pH 6.6

Trends in spectral changes were similar to those at pH 10.0. The $(Cr(III)–P(H_2O)_2)$ species absorbs at 441 nm. As the titration with imidazole progresses, the isosbestic point observed initially at 445 nm disappears. At this point another isosbestic point was noted at 448.5 nm. These changes are attributed to

$$\begin{array}{c} H_2O \\ | \\ Cr(III)–P + IMID \\ | \\ H_2O \end{array} \overset{K_3}{\rightleftharpoons} \begin{array}{c} IMID \\ | \\ Cr(III)–P + H_2O \\ | \\ H_2O \end{array} \quad (3)$$

$$\begin{array}{c} IMID \\ | \\ Cr(III)–P + IMID \\ | \\ H_2O \end{array} \overset{K_4}{\rightleftharpoons} \begin{array}{c} IMID \\ | \\ Cr(III)–P + H_2O \\ | \\ IMID \end{array} \quad (4)$$

Equilibrium constants K_3 and K_4, computed from spectrophotometric data as described above, are 7900 ± 200 and 490 ± 20 respectively.

The kinetics of reaction (3) were investigated in the total imidazole concentration, $[IMID]_T$, range of 3.15×10^{-3} to 62.45×10^{-3} M. Though PIPES buffer was used, the pH in individual runs varied from 6.50 to 6.94. The reaction was monitored at 440 nm. The reaction was found to obey the rate law

$$\text{rate} = k_{obs}[Cr(III)P] = \frac{k'}{(H^+)^2 + H^+k'' + k'''}$$
$$[IMID]_T[Cr(III)–P(H_2O)_2]_T$$

The form of the rate expression is discussed below along with a possible mechanism for this reaction. The observed rate constants along with computed ones are presented in Table I.

Kinetics of reaction (4) were studied over a total imidazole concentration range of 4.96×10^{-3} to 50.3×10^{-3} M. Here again the pH in individual runs ranged from 6.50 to 7.0. Under these conditions, the reaction tends toward equilibrium. A plot of observed rate constants as a function of free imidazole concentration $[IMID]_F$, is presented in Fig. 6. The slope, which refers to the forward rate constant k_f, and the intercept, the reverse rate constant k_r, are $(1.21 \pm 0.05) \times 10^{-1}$ and $(1.7 \pm 0.4) \times 10^{-4}$, respectively.

Discussion

Reaction 1, as indicated earlier, follows a simple rate law of the form:

$$k_{obs} = k_f[IMID] + k_r$$

This behavior is in complete accord with an earlier study on cyanide substitution reactions [2]. Aside from that, no mechanistic inferences could be made on this reaction. Reaction 2 exhibits rate-saturation with increasing ligand concentration. This behavior could be indicative of S_N1 limiting [11] (or type D [12]) mechanism. Moreover, as noted earlier by Pasternack and Cobb [3], the observed positive $\Delta S^{\ddagger}$ values for the reactions 1 and 2 support the inference that these reactions indeed follow S_N1 pathways.

Such a dissociative process would warrant separation of hydroxide ion from the inner coordination sphere of chromium(III). But it is improbable to effect such a dissociation of charges. In the case of cobalt porphyrins [3], change in the basicity of the metal as a consequence of coordination by a ligand (SCN⁻) has been proposed. This results in abstraction of a proton by the bound hydroxide ion. In the

TABLE I. Comparison of the Experimentally Observed Pseudo First Order Rate Constants and Those Calculated Using Eq. 8 for Reaction (3).

$[Imidazole]_{Total} \times 10^3\,M$	pH	$k_o \times 10^3\,sec^{-1}$ Calculated	$k_o \times 10^3\,sec^{-1}$ Observed
3.15	6.50	1.76	2.39
4.96	6.60	4.12	4.20
6.29	6.58	4.82	6.16
9.92	6.60	8.23	7.78
12.60	6.71	16.0	13.2
19.83	6.63	18.5	16.3
25.16	6.80	44.8	34.6
37.74	6.82	72.1	57.4
49.58	6.61	42.8	43.8
62.45	6.69	73.7	69.7
62.90	6.53	39.5	40.8

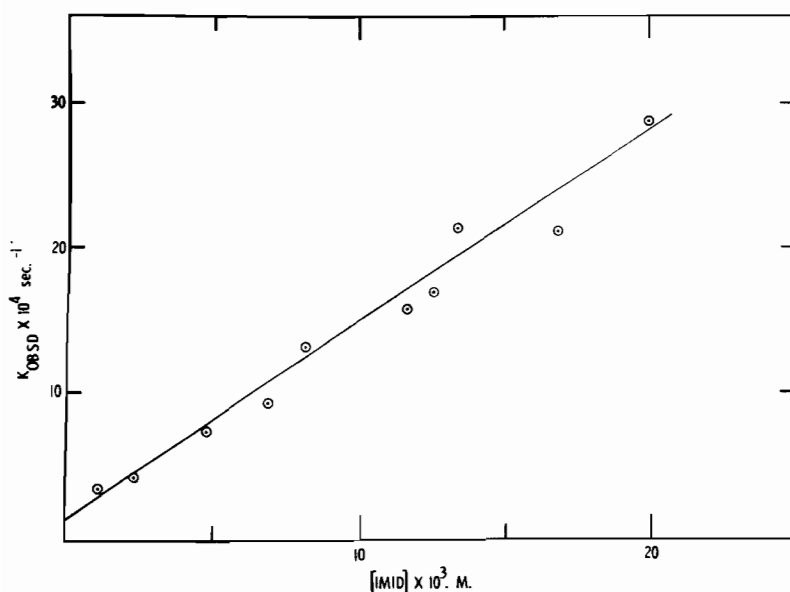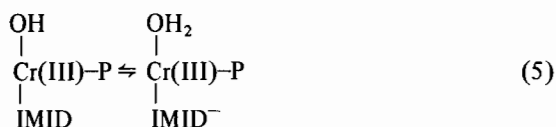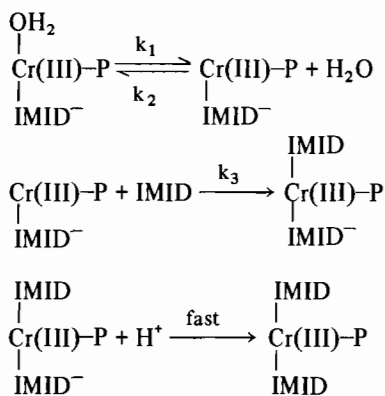Fig. 6. Dependence of k_{obs} on $(IMID)_F$, free imidazole concentrations, for reaction (4).

present case, the reacting species absorbs at 439 nm, while $[Cr(III)P(H_2O)(IMID)]$ absorbs at 447 nm. So we propose a tautomeric equilibrium as follows:

$$\begin{array}{ccc} OH & & OH_2 \\ | & & | \\ Cr(III)-P & \rightleftharpoons & Cr(III)-P \\ | & & | \\ IMID & & IMID^- \end{array} \quad (5)$$

Such an equilibrium is supported by the well documented fact that coordinated imidazole ionizes easily [13]. The proposed mechanism for reaction (2) is as follows:
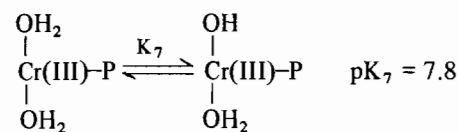
$$\begin{array}{ccc} OH_2 & & \\ | & k_1 & \\ Cr(III)-P & \xrightleftharpoons[k_2]{} & Cr(III)-P + H_2O \\ | & & | \\ IMID^- & & IMID^- \end{array}$$

$$\begin{array}{ccc} & & IMID \\ & & | \\ Cr(III)-P + IMID & \xrightarrow{k_3} & Cr(III)-P \\ | & & | \\ IMID^- & & IMID^- \end{array}$$

$$\begin{array}{ccc} IMID & & IMID \\ | & & | \\ Cr(III)-P + H^+ & \xrightarrow{fast} & Cr(III)-P \\ | & & | \\ IMID^- & & IMID \end{array}$$

Such a mechanism leads to a rate law:

$$k_{obs} = \frac{k_1 k_3 [IMID]}{k_2 + k_3 [IMID]}$$

A plot of $1/k_{obs}$ *versus* $1/[IMID]$ leads to a straight line of slope $k_2/k_1 k_3$ and intercept $1/k_1$.

From such a plot k_1 and k_2/k_3 were found to be $(2.0 \pm 0.2) \times 10^{-2}$ sec^{-1} and 0.32 ± 0.05 respectively.

As reaction 3 was investigated in solutions of pH 6.5 to 7.0, the following equilibria need to be considered as well:

$$HIMID^+ \underset{}{\overset{K_6}{\rightleftharpoons}} H^+ + IMID \qquad pK_6 = 7.12 \text{ [14]}$$

$$\begin{array}{ccc} OH_2 & & OH \\ | & K_7 & | \\ Cr(III)-P & \rightleftharpoons & Cr(III)-P \qquad pK_7 = 7.8 \\ | & & | \\ OH_2 & & OH_2 \end{array}$$

Assuming $[Cr(III)(OH)(H_2O)P]$ to be the only reactive species, the following expression for the rate law of reaction 3 is obtained:

$$\text{rate} = \frac{k_4 K_7 K_6}{[H^+]^2 + H^+[K_6 + K_7] + K_6 K_7}$$

$$[IMID]_T [Cr(III)P(H_2O)_2]_T$$

where k_4 is

$$[Cr(III)(OH)(H_2O)P] + [IMID] \xrightarrow{k_4}$$
$$[Cr(III)(OH)(IMID)P]$$
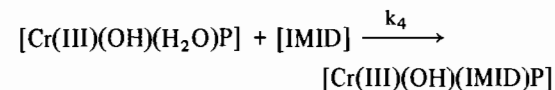
Therefore

$$k_{obs} = \frac{k_4 K_7 K_6}{(H^+)^2 + H^+(K_6 + K_7) + K_6 K_7} [IMID]_T \quad (8)$$

In Table I, the values of k_{obs} calculated according to (8) using known k_4, K_7 and K_6 are presented. The close agreement between calculated and observed
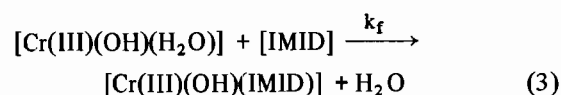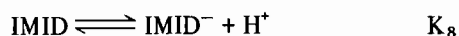
values upholds the assumption regarding the reactive species.

Labilization of a *trans*-ligand by hydroxide ion in substitution reactions is a well recorded phenomenon in chromium chemistry. In the aquation reactions of *trans*-$[Cr(III)(NH_3)_4H_2O(I)]^{+2}$, the rate constant, k_o, for the aquo form was found to be 1.75×10^{-4} sec^{-1} at 30 °C [15]. The corresponding rate constant, k_{OH}, for the hydroxo form *trans*-$[Cr(III)(NH_3)_4(OH)I]^+$ was 3.71 sec^{-1} at 30 °C. Similarly for the aquation of *trans*-$[Cr(III)(NH_3)_4(H_2O)Cl]$ and *trans*-$[Cr(III)(NH_3)_4(OH^-)Cl]$ the rate constants were 7.0×10^{-7} sec^{-1} and 1.0 sec^{-1} respectively [16]. Considering these, the rate constant, $k_f = 60.3$ sec^{-1}, obtained for reaction (1) is not too surprising. But if all this labilization can be accounted for as due to *trans* activation of hydroxide ion, it is surprising to note the absence of any observable labilization due to the porphyrin ligand in these reactions. Furthermore, this could presumably mean that the labilization of ligand substitution reactions observed for cobalt and iron porphyrins, arises from the involvement of easily available lower oxidation states.

In the case of a cobalt(III) porphyrin, the rate constant for substitution of SCN$^-$ *trans* to a OH$^-$ was found to be 50 times the rate constant for a similar reaction *trans* to a water molecule [4]. Such a *trans* labilization by [OH$^-$] for the substitution of pyridine was found to be 300 fold. In the light of this, the absence of any term corresponding to the diaquo Cr(III)–P pathway in the rate expression for reaction 3 seems reasonable.

Unlike the case of cobalt and iron porphyrins, the introduction of the second imidazole is considerably slower than that of the first imidazole. No unusual labilization due to bound imidazole is observed. Apparently, imidazole is a poor *trans* activator compared to hydroxide ion in chromium(III) complexes.

A plausible mechanism for the observed dependence of reaction 1 on hydrogen ion concentration is as follows:

$$IMID \rightleftharpoons IMID^- + H^+ \qquad K_8$$

$$[Cr(III)(OH)(H_2O)] + [IMID] \xrightarrow{k_f}$$
$$[Cr(III)(OH)(IMID)] + H_2O \qquad (3)$$

$$\text{rate} = k_f \left[\frac{(H^+)}{(H^+) + K_8} \right] [IMID]_T [Cr(III)P(OH)(H_2O)]_T$$

and therefore

$$k_{obs} = k_f \left[\frac{(H^+)}{(H^+) + K_6} \right] [IMID]_T$$

On rearranging

$$\frac{[IMID]_T}{k_{obs}} = \frac{1}{k_f} + \frac{K_8}{k_f} \frac{1}{[H^+]} \qquad (9)$$

The k_f (74 ± 6 M^{-1} sec^{-1}) obtained from the intercept of a plot of $[IMID]_T/k_{obs}$ *versus* $1/[H^+]$ (Fig. 5) is comparable to k_f (60.3 ± 0.8 M^{-1} sec^{-1}) obtained in the imidazole dependence study. The pK_8 obtained by computation from the slope is 11.76 ± 0.05. The literature value is 14.43 ± 0.04 at $\mu = 0$ and 25 °C [13].

In conclusion, a) no unusual labilization of ligand substitution of Cr(III) due to porphyrin ligand is observed; b) only imidazole, neither imidazolium nor anionic imidazole, appears to be the reactive species; c) *trans*-labilization by the bound ligand (imidazole) observed in other metalloporphyrins is not observed in this case of Cr(III) porphyrin.

Acknowledgement

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