double-layer corrections are not the sole explanation of the observed difference, then it is likely that solvation energy effects ($\Delta G^{\ddagger}_{os}$) or nonadiabatic factors (A) peculiar to these large molecules are responsible for their low electrochemical rate constants.

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Registry No. Fe(TPP)OPh, 76282-28-5; Fe(TPP)Br, 25482-27-3; Fe(TPP)Cl, 16456-81-8; Fe(TPP)F, 55428-47-2; Fe(TPP)OAc, 33393-26-9; Fe(TPP)OMe, 29189-59-1; Mn(TPP)Cl, 32195-55-4; Fe(TPP)ClO_4, 57715-43-2; Fe(TPP)$(py)_2^+$, 60542-64-5; Fe(TPP)$(Im)_2^+$, 52155-41-6; Fe(TPP)$(CN)_2^-$, 40988-77-0.

Contribution from the Department of Chemistry, Brown University, Providence, Rhode Island 02912

Kinetic Study of Halide Ionization from Cobalt(III) Porphyrin Complexes. Rate Enhancements Produced by Hydrogen Bonding to the Halide and by Steric Congestion from Coordinated 2-Substituted Imidazoles

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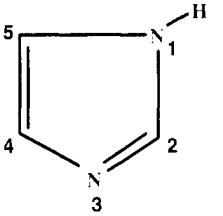
The reaction of Co(TPP)Cl and various imidazoles (RIm) has been investigated in acetone and dichloromethane solvents. Kinetic measurements at room temperature as well as low-temperature spectroscopic, conductivity, and kinetic studies show that Co(TPP)(RIm)Cl is rapidly formed and then slowly converts to $Co(TPP)(RIm)_2^+Cl^-$ in the presence of excess RIm. When the imidazole has a methyl or phenyl group at the N-1 position, the Co(TPP)(RIm)Cl intermediate reacts via rate-determining chloride ionization. With imidazoles bearing a hydrogen at the N-1 position, the chloride ionization is accelerated due to a hydrogen-bonding interaction with the *N*-H group. Although the cobalt porphyrin complexes react much more slowly than analogous iron porphyrins, the two metalloporphyrins follow the same detailed mechanism and display similar sensitivities to hydrogen-bonding interactions. The reaction of Co(TPP)Cl with imidazoles containing a 2-substituent was also studied in order to probe the effect of steric interactions in the intermediate Co(TPP)(RIm)Cl. When a 2-methyl or 2-phenyl substituent is present, the steric strain with the porphyrin ligand increases the lability of the trans chloride by a factor of at least 10; this may be related to "proximal strain" present in certain hemoproteins.

The substitution of cobalt for iron in iron porphyrins and hemoproteins has played an important part in the development of metalloporphyrin chemistry. Cobalt offers several distinct advantages over iron, such as (1) a paramagnetic M(II) state that allows bonding interactions to be probed by ESR and (2) a diamagnetic M(III) state that has a high NMR receptivity. The most important application of these properties has been (1) to probe $M-O_2$ bonding in proteins as well as model systems[4,5] and (2) to probe electronic interactions in cobalt(III) porphyrins via ^{59}Co NMR spectroscopy.[6,7] Of course, the hope is that information gleaned from work with cobalt systems will apply to the iron analogues; this is known to be at least qualitatively true in many cases. However, there are substantial differences between iron and cobalt porphyrins in the thermodynamics and kinetics of axial ligand binding/dissociation, which is related in part to the extra electron on cobalt and the propensity of iron to undergo spin-state changes.

This report concerns hydrogen bonding and steric interactions present in reaction 1, in which X is a halide or pseudohalide and RIm is an imidazole, substituted according to the numbering scheme in structure **2**. The six-coordinate complex Co(Por)-

$$Co(Por)(RIm)X + RIm \rightarrow Co(Por)(RIm)_2^+X^- \quad (1)$$



2

(RIm)X (**1**) is susceptible to two types of hydrogen-bonding interactions: from the coordinated (proximal) imidazole *N*-H (if present) to a base and from a proton donor to the coordinated halide. Hydrogen bonding from a proximal imidazole is believed to influence ligand binding, conformational changes, and redox potential regulation in hemoproteins.[8-17] Hydrogen bonding to

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the halide ligand is related to proposed distal interactions occurring in methemoglobin, metmyoglobin, certain peroxidases, and model systems.[11,17-29] It is also related to the stabilization of oxy-Hb and oxy-Mb via hydrogen bonding from the distal histidine to bound superoxide (Fe^{III}–O_2^-). The effect of introducing proximal steric strain in **1** can be investigated by using a 2-substituted imidazole. It has been shown with model iron complexes that the resultant steric interaction between the 2-substituent and the porphyrin ligand causes the metal to be displaced from the core, with the result that O_2 (and CO) affinities decrease.[4,5,22,30-32] This is suggested to be due to both an increased dissociation and a decreased association rate. Such proximal strain is also brought about in T-state hemoglobin via a tilting of the bound histidine. R-State hemoglobin does not have such tilting, and the O_2 affinity is increased, mostly because of a much smaller dissociation rate. Our results presented herein show that the rate of reaction 1 is significantly increased when RIm is sterically demanding and that this increase is entirely due to a lowering of $\Delta H^{\ddagger}$.

In a series of papers[23-29] we investigated in detail the chemistry of reaction 2. It was shown that the reaction proceeds stepwise according to eq 3 and 4, in which the high-spin Fe(Por)X is very

$$\mathrm{Fe(Por)X + 2RIm} \overset{\beta_2}{\rightleftharpoons} \mathrm{Fe(Por)(RIm)_2{}^+X^-} \qquad (2)$$

$$\mathrm{Fe(Por)X + RIm} \overset{K_1}{\rightleftharpoons} \mathrm{Fe(Por)(RIm)X} \qquad (3)$$

$$\mathrm{Fe(Por)(RIm)X + RIm} \overset{K_2}{\rightleftharpoons} \mathrm{Fe(Por)(RIm)_2{}^+X^-} \qquad (4)$$

rapidly (<1 ms) converted to the Fe(Por)(RIm)X intermediate, which was characterized as high-spin and six-coordinate for X^- = F^- and Cl^-. The intermediate itself is rapidly converted to the (low-spin) final product and at equilibrium is present at an insignificant concentration because $K_2 \gg K_1$. Mechanistically, reaction 2 proved to be very interesting because the rate and rate law depend markedly on the type of imidazole used. When RIm is substituted at N-1 (*N*-R imidazoles), the overall rate is relatively slow and the rate law reaches limiting zero order in RIm. When hydrogen is at N-1, the resulting *N*-H imidazoles react much more rapidly (ca. factor of 100) and follow second-order kinetics in RIm. The interpretation of these differences is straightforward. With *N*-R imidazoles the rate-determining step is unassisted dissociation of X^- from Fe(Por)(RIm)X, but with *N*-H imidazoles a hydrogen-bonding interaction of the distal type (Fe···X···H—N) causes a rate acceleration and a change in rate law.

Herein we present a study of reaction 5 in which X^- = Cl^- and Br^- and TPP is the dianion of tetraphenylporphyrin. The cobalt

$$\mathrm{Co(TPP)X + 2RIm} \overset{\beta_2}{\rightleftharpoons} \mathrm{Co(TPP)(RIm)_2{}^+X^-} \qquad (5)$$

system complements the iron porphyrin studies and offers several advantages. The important species in these reactions is the intermediate M(Por)(RIm)X; with cobalt it can be synthesized and isolated as a solid whereas with iron it has been studied as a transient in solution. This is due to a much larger K_1 with cobalt as well as a much slower rate of X^- dissociation. Most importantly, the overall stability constant (β_2) is also much larger with cobalt, and this meant that sterically congested imidazoles, which are difficult to study with Fe(Por)X, could be used. We also wished to determine if the pronounced hydrogen-bonding effects present in the iron reactions are equally evident with cobalt.

Experimental Section

Materials. Reaction 5 is very sensitive to small amounts of water or other protic materials, and great care was taken to remove them from reagents, solvents, and equipment. Molecular sieves (Baker 4A, 8–12 mesh) were activated by heating in a vacuum oven at 200 °C for several hours. They were cooled under vacuum, sealed, and stored under dry nitrogen. Particular care was taken to dry the solvent acetone. It was allowed to sit over activated molecular sieves for only 45 min (if longer, condensation products may become significant) and filtered under dry nitrogen in a glovebag. Just before use the predried acetone was freshly distilled under nitrogen and again dried over sieves for 45 min and filtered. Reagent grade dichloromethane was distilled under nitrogen from calcium hydride. Aldrich Gold Label 2,2,2-trifluoroethanol was dried over anhydrous calcium chloride. 1,10-Phenanthroline (Aldrich) was recrystallized from dichloromethane–pentane and dried in vacuo overnight.

The commercially available imidazoles were purified by vacuum sublimation (HIm, 2-MeIm, 2-EtIm, 2-PhIm, 4-PhIm) or by vacuum distillation (1-MeIm, 1,2-Me_2Im, 1-PhIm). 1-Me-2-PhIm was synthesized inside an argon glovebox by dissolving 0.5 mol of 2-PhIm in dry THF and slowly adding 0.5 mol of sodium hydride in small amounts with constant stirring. The solution was stirred until effervescence ceased and the reaction mixture cooled to room temperature. A white precipitate appeared on cooling. Next, 0.5 mol of methyl iodide was added with stirring and the precipitate dissolved to give a pale yellow solution. THF was removed with a rotary evaporator and dichloromethane added to dissolve most of the resulting solid. The sodium iodide in the product was extracted by shaking with water, and the dichloromethane layer was then separated and evaporated to yield the crude product as a yellow liquid. Purification was effected by vacuum distillation with a short-path column. The colorless liquid product solidified on standing: ^{1}H NMR ($CDCl_3$) δ 3.73 (3 H, s) 6.92 (1 H, s), 7.09 (1 H, s), 7.4 (5 H, br). Crystals of 1-Me-2-PhIm were readily obtained by slow cooling of a diethyl ether solution and structurally characterized by X-ray diffraction.[33]

The methylation of 4-PhIm by the above procedure gave, after vacuum distillation, a 3:1 mixture of 1-Me-4-PhIm and 1-Me-5-PhIm. Separation was effected via fractional crystallization by stirring 7.5 g of the mixture in 75 mL of diethyl ether for 30 min at room temperature. The undissolved solid was found to be 10:1 enriched in the 1-Me-4-PhIm isomer. Cooling the filtrate in an ice bath for 1 h produced mostly rod-shaped crystals with a small quantity of platelike crystals; the bulk solid was determined to be a 10:1 mixture in favor of 1-Me-4-PhIm. Cooling the remaining filtrate for an additional 30 min at −20 °C produced platelike crystals that consisted of pure 1-Me-5-phIm. The relative amount of each isomer was determined by ^{1}H NMR; in $CDCl_3$ the methyl groups give singlets at δ 3.64 (1-Me-5-PhIm) and 3.69 (1-Me-4-PhIm). Absolute assignment of the resonances was made by an X-ray structural study of one of the rod-shaped crystals, which was found to be 1-Me-4-PhIm.[33]

All of the 1-methyl-substituted imidazoles are hygroscopic and for this reason solutions of these materials were always prepared inside a glovebag or glovebox.

Co(TPP)Cl was prepared by a slight modification of a reported procedure.[34] Co(TPP) (0.3 g) was suspended in methanol (300 mL) containing 3 mL of concentrated hydrochloric acid. The suspension was stirred in the dark overnight. The solution, which had changed to a clear reddish color, was filtered through a fine frit and concentrated on a rotary

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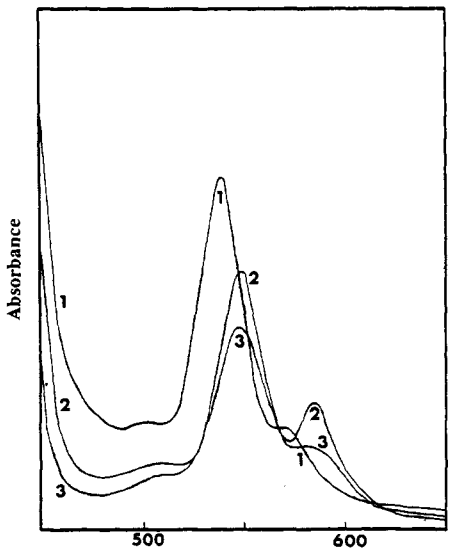

Figure 1. Optical spectra in dichloromethane at −90 °C: (1) Co(TPP)Cl; (2) Co(TPP)(1-MeIm)Cl; (3) Co(TPP)(1-MeIm)$_2$$^+Cl^-$.

evaporator at 50 °C to ca. 25 mL. The separated crystalline solid was then washed with 2:1 methanol–water three times and chromatographed on a neutral-alumina column with dichloromethane as the elutant. The first reddish purple band was collected and concentrated to yield crystals that were recrystallized by slow diffusion of pentane into a dichloromethane solution. The violet crystals of Co(TPP)Cl gave an electronic spectrum in methanol identical with that previously reported.[34] Co(TPP)Br was prepared by a similar procedure using concentrated hydrobromic acid instead of HCl. Some of the products of reaction 5, Co(TPP)(RIm)$_2$$^+X^-$, were prepared by reported methods.[6,7,35-37] Others were not isolated but merely characterized spectrally in situ (vide infra). The intermediate **1**, which occurs during reaction 5, was synthesized for RIm = HIm and 1-MeIm by slowly adding a ca. 10^{-4} M acetone solution of RIm to a Co(TPP)Cl solution of equal concentration and volume. The porphyrin solution immediately became green. Slow evaporation in the dark of ca. 90% of the reaction mixture produced a crystalline solid that was characterized by conductivity and optical spectroscopy (vide infra).

Kinetic Studies. All solutions were prepared inside a glovebag or glovebox (dry nitrogen or argon) to minimize the possibility of contamination by water. The kinetics of reaction 5 were followed with a Dionex stopped-flow spectrophotometer at 25 ± 0.5 °C or with a Gilford 250 spectrophotometer equipped with a temperature control accessory. The experiments were conducted under pseudo-first-order conditions with the imidazole concentration ranging from 5×10^{-4} to 0.35 M and a Co(TPP)X concentration of ca. 5×10^{-5} M. Standard log plots and least-squares-fitting routines were used to calculate the observed rate constants. Activation parameters were determined from a least-squares fit of the Eyring equation to rate constant data obtained over the temperature ranges +15 to +45 °C for Co(TPP)Cl and 1-MeIm and −45 to +25 °C for Co(TPP)Cl and 1-Me-2-PhIm.

Other Studies. Visible spectra were obtained on a Perkin-Elmer 552A spectrophotometer. Spectra at ca. −90 °C utilized a special previously described[26] optical cell that allowed cooling of reactant solutions separately prior to mixing. The coolant was a dichloromethane slush. Conductivity measurements were made with a Beckman RC-16B2 conductivity bridge. Measurements at other than ambient temperature were made with a previously described[26] cell that allows temperature equilibration and mixing of solutions without exposure to the atmosphere. The temperature was controlled by placing the cell in an FTS Multi-Cool refrigerated bath containing methanol and adjusted to the desired value. An Omega type T thermocouple probe was used to monitor the actual temperature in the reaction mixture.

Results and Discussion

Characterization of Co(TPP)(RIm)Cl and Co(TPP)(RIm)$_2$$^+Cl^-$. In both acetone and dichloromethane the addition of an imidazole to Co(TPP)Cl produces a very rapid color change from red to olive green. This is followed by a slow change to a red-green solution. At −90 °C the green intermediate persists indefinitely; Figures 1 and 2 show representative spectral changes. The low-temperature spectrum of the final product, Co(TPP)(RIm)$_2$$^+Cl^-$, was obtained by warming the green solution to room temperature and recooling after an appropriate amount of time. That the green species is the six-coordinate intermediate Co(TPP)(RIm)Cl (**1**) was established by observing that its spectrum is identical with that of a solution of **1** that was isolated from a 1:1 mixture of Co(TPP)Cl and RIm (see Experimental Section). By making conductivity measurements, it was possible to prove that the intermediate does not contain dissociated chloride or consist of a mixture of Co(TPP)Cl and Co(TPP)(RIm)$_2$$^+Cl^-$. At room temperature or low temperature, a solution of the intermediate, prepared by dissolving the isolated solid or prepared in situ, showed only background conductance. With excess RIm present and at room temperature, the conductivity slowly increased to that expected for Co(TPP)(RIm)$_2$$^+Cl^-$; this increase in conductivity was used in some cases to obtain rate constants (vide infra).

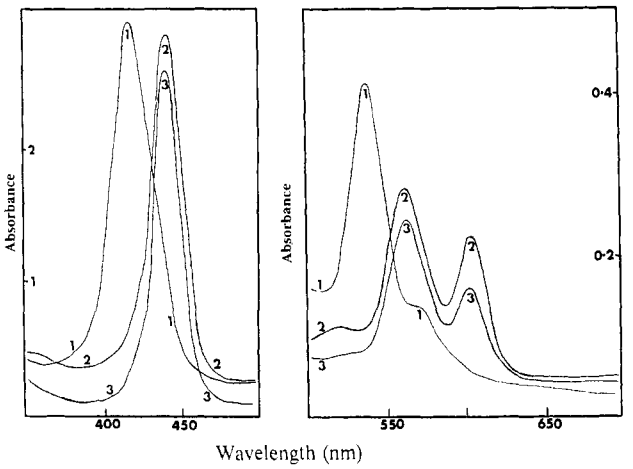

Figure 2. Optical spectra in dichloromethane at −90 °C: (1) Co(TPP)Cl; (2) Co(TPP)(2-PhIm)Cl; (3) Co(TPP)(2-PhIm)$_2$$^+Cl^-$.

The optical spectra of Co(TPP)(RIm)Cl and Co(TPP)(RIm)$_2$$^+Cl^-$ displayed rather different patterns for hindered versus unhindered imidazoles. Initially, the addition of unhindered imidazoles causes the Soret band to shift to 438 nm and the Q band to 548 nm with a second peak at 585 nm and a shoulder at 510 nm. Reaction to completion gives a product with decreased Q-band intensity, with a shoulder at 510 nm, principal peak at 545 nm, and a much diminished shoulder at ca. 580 nm (Figure 1). With hindered imidazoles the shifts upon coordination are to longer wavelengths than with unhindered ones, and the Q band is split much more equally into two peaks. Thus, on addition of 2-PhIm to Co(TPP)Cl in dichloromethane at −90 °C (Figure 2), the Soret band shifts to 445 nm; subsequent warming and recooling gives a slightly diminished Soret band at 443 nm. The intermediate **1** displays Q bands at 565 and 605 nm with a shoulder at 520 nm. Further reaction gives a product with decreased Q-band intensity, with wavelength positions virtually unchanged, but with the peak at 605 nm diminished relative to that at 565 nm. The corresponding 2-MeIm and 2-EtIm complexes display very similar changes, except that the Q-band maxima are at 560 and 600 nm.

Kinetics with Unhindered Imidazoles. In acetone, Co(TPP)Cl reacts very rapidly with 1-MeIm to give an intermediate, which then is slowly converted to Co(TPP)(1-MeIm)$_2$$^+Cl^-$ at a rate independent of the 1-MeIm concentration. Figure 3 shows the results at 25 °C with 1-MeIm and HIm, and Table I provides a summary of the rate data for these and other reactions. The rate constants in Figure 3 were determined spectrophotometrically; the reaction with 1-MeIm was also followed by conductivity (with 1-MeIm at 0.1 M) with the same result. For the reaction at six temperatures between 15 and 45 °C, the rate constant (k_1) for 1-MeIm was found to have $\Delta H^{\ddagger} = 15.4 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\ddagger}$

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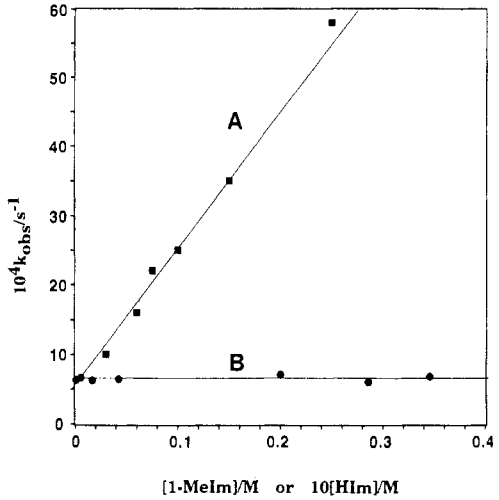


Figure 3. Rate constants in acetone at 25 °C for the reaction Co(TPP)Cl + 2RIm → $Co(TPP)(RIm)_2^+Cl^-$. Imidazole: (A) HIm; (B) 1-MeIm.

Table I. Rate Data for the Reaction of M(TPP)X with RIm[a]

M	X^-	RIm	solvent	k_1 or k_2[b]	$\Delta H^\ddagger$	$\Delta S^\ddagger$
Co	Cl^-	1-MeIm	Me_2CO	0.00065	15.4 ± 0.4	−20 ± 1
Co	Cl^-	1-MeIm	CH_2Cl_2	0.0085	11.3 ± 0.3	−29 ± 1
Co	Br^-	1-MeIm	Me_2CO	0.026		
Co	Cl^-	1-PhIm	CH_2Cl_2	0.0062		
Co	Cl^-	1-Me-2-PhIm	CH_2Cl_2	0.105	9.8 ± 0.5	−29 ± 2
Co	Cl^-	1-Me-5-PhIm	CH_2Cl_2	0.010		
Co	Cl^-	1,2-Me_2Im	CH_2Cl_2	0.30		
Co	Cl^-	HIm	Me_2CO	0.20		
Co	Cl^-	HIm	CH_2Cl_2	7[c]		
Co	Br^-	HIm	Me_2CO	1.55		
Co	Cl^-	4-PhIm	CH_2Cl_2	20[c]		
Co	Cl^-	2-PhIm	CH_2Cl_2	110[c]		
Co	Cl^-	2-MeIm	CH_2Cl_2	60[c]		
Co	Cl^-	2-EtIm	CH_2Cl_2	52[c]		
Co	Cl^-	2-EtIm	Me_2CO	1.0		
Fe	Cl^-	1-MeIm	Me_2CO	3.5	9.7 ± 0.5	−24 ± 4
Fe[d]	Cl^-	1-MeIm	Me_2CO	2.8	10.5 ± 0.5	−20 ± 2
Fe	Cl^-	1-MeIm	CH_2Cl_2	70		
Fe	Cl^-	HIm	Me_2CO	450		

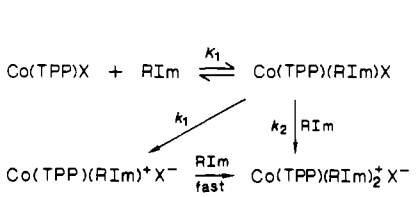
[a] All data refer to 25 °C. Data for the iron complexes are from ref 25–29. Units for $\Delta H^\ddagger$ are kcal mol^{-1} and for $\Delta S^\ddagger$ are cal deg^{-1} mol^{-1}. [b] k_1 refers to *N*-R imidazoles and k_2 to *N*-H imidazoles; refer to Scheme I. Units for k_1 are s^{-1} and for k_2 are M^{-1} s^{-1}. [c] These rate constants are approximate; see text. [d] The porphyrin is protoporphyrin IX dimethyl ester (PPIXDME).

= −20 ± 1 cal deg^{-1} mol^{-1}. Most of the experiments with 1-MeIm were performed by simply combining solutions of Co(TPP)Cl and the nucleophile, in which case a very rapid initial absorbance change occurred on the millisecond time scale; this was followed by the main reaction having a half-life of ca. 20 min. When Co(TPP)(1-MeIm)Cl was used as the starting material, an identical absorbance versus time change occurred except that the initial fast step was absent. It is likely that the initial absorbance change was due to the formation of Co(TPP)(1-MeIm)Cl. In dichloromethane the reaction with 1-MeIm was also found to be independent of nucleophile concentration, but the rate constant k_1 is about 13 times larger than in acetone. The activation parameters in dichloromethane were determined by measuring k_1 conductometrically at five temperatures between −25 and +25 °C: $\Delta H^\ddagger$ = 11.3 ± 0.3 kcal mol^{-1}, $\Delta S^\ddagger$ = −29 ± 1 cal deg^{-1} mol^{-1}. The addition of trifluoroethanol (TFE) markedly accelerated the reaction, and with 1-MeIm at 0.05 M in acetone, the rate constant k_{obsd} obeyed eq 6 at 25 °C.

$$k_{obsd}/s^{-1} = 0.00063 + 0.16[TFE] \quad (6)$$

Several other reactions were monitored with unhindered *N*-R imidazoles. These include Co(TPP)Br with 1-MeIm in acetone and Co(TPP)Cl with 1-PhIm and 1-Me-5-PhIm in dichloromethane (see Table I).

Scheme I



With unhindered imidazoles of the *N*-H variety the rate law obeyed eq 7. For example, with Co(TPP)Cl and HIm in acetone the data follow eq 8 at 25 °C (Figure 3). In dichloromethane

$$k_{obsd}/s^{-1} = k_0 + k_2[RIm] \quad (7)$$

$$k_{obsd}/s^{-1} = 0.0005 + 0.20[HIm] \quad (8)$$

the same reaction at 25 °C has k_0 = 0.01 s^{-1} and k_2 = 7 M^{-1} s^{-1}. HIm was found to react much more rapidly with Co(TPP)Br than with Co(TPP)Cl and in acetone k_0 = 0.026 s^{-1} and k_2 = 1.55 M^{-1} s^{-1} for the bromide complex. The other unhindered *N*-H imidazole studied was 4-PhIm which, due to rapid tautomerism,[38] undoubtedly has the phenyl substituent at the C-5 position when coordinated from N-3 to cobalt. All of these results are summarized in Table I.

The mechanism used to rationalize the results is given in Scheme I and is essentially identical with one previously postulated for analogous reactions of iron porphyrins.[23-29] In this mechanism the initial step is the rapid and reversible formation of the six-coordinate Co(TPP)(RIm)X, which then reacts with *N*-R imidazoles by rate-determining X^- ionization (k_1) followed by rapid addition of a second RIm to yield the product. With *N*-H imidazoles the k_1 pathway is also available, but the predominant pathway is a second-order one (k_2) in which RIm assists the X^- ionization via hydrogen bonding from the imidazole *N*-H to the departing X^- anion. All of the spectral evidence suggests that the initial equilibrium lies almost entirely to the right even when the concentration of RIm is quite small; i.e., $K_1[RIm] \gg 1$. With this assumption, the mechanism predicts eq 9 and 10 for the reaction of *N*-R and *N*-H imidazoles, respectively.

$$k_{obsd} = k_1 \quad (9)$$

$$k_{obsd} = k_1 + k_2[RIm] \quad (10)$$

The data conform to these rate laws. With 1-MeIm the activation entropy for k_1 is negative in acetone and even more so in the less polar solvent dichloromethane. This is expected[39] for an ionization process. With HIm the two-term rate law in eq 7 was found. From the mechanism, the k_0 term can be identified as k_1 (eq 10), and in agreement with this k_0 with HIm was found to be very close to k_1 for 1-MeIm. By careful absorbance measurements it was established that the intercept in eq 7 was not due to a lack of the overall reaction going to completion. *N*-H imidazoles react much more rapidly than *N*-R ones because of the second-order term in eq 10. Since this is postulated to be due to assisted ionization by hydrogen bonding, it should be possible to accelerate the reaction rates for *N*-R (and *N*-H) imidazoles by adding a good hydrogen bonder. Qualitatively, this is suggested by the sensitivity of the rates to small amounts of water. Quantitatively, it can be seen that the influence of TFE on the reaction of Co(TPP)Cl and 1-MeIm (eq 6) is analogous to the reaction with HIm (eq 8) and the respective slopes show that TFE and HIm are similar in their ability to hydrogen bond to the departing chloride in the transition state. The substantially greater rate constants (k_1, k_2) obtained in dichloromethane compared to those obtained in acetone also attests to the importance of hydrogen bonding in the chloride ionization step; the former solvent is a much better hydrogen bonder than the latter solvent.[40]

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N-H imidazoles are well-known[26] for their tendency to associate via intermolecular hydrogen bonding. This becomes more evident as the solvent polarity decreases. Such self-association had the effect of giving nonlinear k_{obsd} vs [RIm] plots for [RIm] greater than a certain value. In acetone the plots were quite linear up to [RIm] $\approx$ 0.03 M (Figure 3), after which there was a positive curvature. In dichloromethane the plots were linear only to [RIm] = 0.005 M. This meant that very good data sets could be obtained in acetone, so that the k_2 values listed are reliable. The k_2 constants for the reactions in dichloromethane are less reliable, and for this reason the numbers listed in Table I are best treated as reproducible to within ±50%. The positive deviation in the k_{obsd} plots with *N*-H imidazoles means that the associated species are more reactive than the monomers; this unsurprising result was also found with iron porphyrin reactions.[26]

The hydrogen-bonding arguments presented above are supported by the results for X^- = Cl^- compared to those for X^- = Br^-. Thus, for Co(TPP)Cl in acetone the ratio of k_2 for HIm to k_1 for 1-MeIm is 300:1; this ratio drops to 60:1 with Co(TPP)Br. Similarly, 1-MeIm in acetone reacts with Co(TPP)Br 40 times faster than with Co(TPP)Cl while HIm in acetone reacts only 8 times more rapidly with the bromide. This implies that hydrogen bonding from HIm is more important for X^- = Cl^- than for X^- = Br^-. This, of course, parallels the Brønsted basicities of these anions.

Kinetics with Hindered Imidazoles. The dependence of k_{obsd} on [RIm] for hindered imidazoles, i.e., ones containing a 2-substituent, was found to be the same as that seen with unhindered imidazoles. Thus, imidazoles of the *N*-R type rapidly reach a limiting rate (eq 9) while the *N*-H analogues obey eq 10. Considering first the *N*-R type imidazoles, Table I shows that the rate constant increases significantly when there is a 2-substituent. The relative values of k_1 in dichloromethane are in the order 1-PhIm (1) < 1-MeIm (1.4) < 1-Me-5-PhIm (1.6) < 1-Me-2-PhIm (17) < 1,2-Me_2Im (48). With *N*-H imidazoles an analogous but less pronounced rate acceleration was found: HIm (1) < 4-PhIm (3) < 2-EtIm (7.4) < 2-MeIm (8.6) < 2-PhIm (16).

In order to understand the role of the 2-substituent, it is necessary to estimate the relative importance of electronic and steric effects. The evidence suggests that the rate accelerations seen are not due to basicity changes. For example, the basicities of 1-MeIm and 1-PhIm are reported[38] to differ by 2 p*K* units, yet the k_1's for these imidazoles differ by very little (0.0085 and 0.0062 s^{-1}, respectively). Similarly, 1-MeIm and 1-Me-5-PhIm react at almost the same rates even though the former is ca. 1 p*K* unit more basic. Comparing 1-MeIm and 1-Me-2-PhIm, one would expect the greater basicity of 1-MeIm to be reflected in a weaker Co–Cl bond in the Co(TPP)(RIm)Cl intermediate, and hence a larger k_1 should obtain for 1-MeIm. The fact that the k_1 for 1-Me-2-PhIm is 12 times greater than that for 1-MeIm can reasonably be ascribed to the steric influence of the 2-Ph group. This steric effect can be viewed as an interaction between the 2-substituent and the porphyrin ligand, resulting in some displacement of the cobalt out of the porphyrin plane toward the imidazole in the six-coordinate intermediate, Co(TPP)(RIm)Cl. The thus weakened Co–Cl bond would lead to an increased rate of Cl^- ionization. The factor of 12 difference between k_1 for 1-MeIm and that for 1-Me-2-PhIm is probably *reduced* somewhat due to the greater basicity of 1-MeIm. Similarly, the factor of 35 difference between k_1 for 1-MeIm and that for 1,2-Me_2Im is probably not entirely due to steric effects since 1,2-Me_2Im is a better base by ca. 0.9 p*K* unit.[38]

The steric influence of the 2-substituent in Co(TPP)(RIm)Cl (RIm = 1-Me-2-PhIm, 1,2-Me_2Im) may also be relaxed by a tilting of the Co–N bond from the normal to the porphyrin core, much as seen in Co(TPP)(1,2-Me_2Im).[41] Of course, ruffling or doming of the porphyrin ligand may also be occurring as a way to alleviate the steric interactions. Molecular models indicate clearly that the phenyl ring in 1-Me-2-PhIm must be roughly parallel to the porphyrin "plane" in Co(TPP)(RIm)Cl, and this raises the possibility of π–π interactions that would help to stabilize the intermediate (and reduce k_1). Interestingly, the X-ray structure of 1-Me-2-PhIm shows that the 2-phenyl ring is rotated ca. 33° from the plane of the imidazole ring and the 1-methyl group is bent 0.15 Å out of the plane and away from the phenyl ring. In contrast, the 4-phenyl ring in 1-Me-4-PhIm is rotated only ca. 7° and the 1-methyl is in the imidazole plane.[33]

In view of the above discussion, we conclude that the steric effect of a 2-Ph or 2-Me substituent on the imidazole in Co(TPP)(RIm)Cl is to labilize the trans ligand by a factor of at least 10, and probably somewhat more. The activation parameters in Table I indicate that this steric acceleration is due to a lowering of $\Delta H^{\ddagger}$ for chloride ionization and is not due to a change in $\Delta S^{\ddagger}$.

The results with imidazoles of the *N*-H type also suggest significant steric effects. The 2-substituted bases are more reactive than HIm or 4-PhIm, but the rate increases are less than those seen with the *N*-R imidazoles. The reason for this reduced steric effect is unclear but may be analogous to the "buttressing effect" seen with substituted biphenyls.[42] The buttressing effect refers to a greater steric influence seen when three instead of two interacting centers are present. In our case, a complex like Co(TPP)(2-PhIm)Cl has two centers (TPP, 2-Ph group) while Co(TPP)(1-Me-2-PhIm)Cl has three (TPP, 2-Ph and 1-Me groups). Collman reported[43] a buttressing effect for 1,2-Me_2Im on the basis of variation in strength of O_2 binding to FeTpivPP compounds with substituted imidazoles. It may also be noted that the rate constants for *N*-H imidazoles reacting in dichloromethane are less reliable than those for *N*-R imidazoles due to self-association of the former bases at concentrations above ca. 0.005 M (vide supra). Although the trends listed for *N*-H imidazoles are unquestionably correct, there is a greater level of uncertainty than obtains with *N*-R imidazoles.

Walker has previously shown[8] that the thermodynamics of reaction 2 rather strongly reflect steric interactions. Invariably, a 2-substituent in the imidazoles lowers the overall equilibrium constant for reaction 2 by several powers of 10. In a separate paper we shall examine the mechanistic interpretation of these steric effects in iron porphyrins.[44] In the present paper we have shown how such steric interactions can influence the reactivity of analogous cobalt porphyrins.

Comparison of Cobalt and Iron Porphyrins. The reaction of M(TPP)Cl and RIm to give M(TPP)$(RIm)_2^+Cl^-$ is superficially quite different for cobalt and iron. However, an examination of the data shows that there are many more similarities than differences. Both metals react with imidazoles of the *N*-R and *N*-H types according to the mechanistic details in Scheme I. In general, the preequilibrium constant K_1 is much larger with cobalt, but the chloride ionization (k_1, k_2) is much larger with iron. Table I contains some comparative data for the two metals.

The spin states of a number of the relevant species in Scheme I differ for iron and cobalt, and this undoubtedly is reflected in the kinetic and thermodynamic data. Along the sequence M(TPP)Cl → M(TPP)(RIm)Cl → M(TPP)$(RIm)^+Cl^-$ → M(TPP)$(RIm)_2^+Cl^-$ the cobalt complexes almost certainly are all low-spin,[45] whereas the iron analogues change spin in the sequence hs → hs → hs → ls.[23-29] The rate-determining step does not involve a spin change for either metal but differs in that cobalt is low-spin and iron is high-spin. The activation parameters for the ionization of chloride from M(TPP)(1-MeIm)Cl in acetone (Table I) show that $\Delta S^{\ddagger}$ is within error the same for both metals and the 5000-fold smaller rate constant for cobalt is due mostly to a ca. 5 kcal larger

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$\Delta H^{\ddagger}$. When there is a spin change during the ionization step, as with Fe(TPP)(1-MeIm)N_3,[29] the $\Delta S^{\ddagger}$ value is very different from the values given in Table I.

Perhaps the most important comparison of cobalt and iron deals with the role of hydrogen bonding in the chloride ionization step. In this regard the two metals behave similarly. Changing the imidazole from 1-MeIm to HIm causes a large rate acceleration, and in acetone the rate constant ratio k_2/k_1 is 300 for cobalt and 130 for iron. The increase in the rate of reaction of M(TPP)(1-MeIm)Cl as the solvent is changed from acetone to dichloromethane is also ascribed to hydrogen bonding, and this increase is a factor of 13 for cobalt and 20 for iron.

Conclusions. Hydrogen bonding plays a major role in chloride ionization from Co(TPP)(RIm)Cl. While analogous iron complexes react much more rapidly, both metals follow the same mechanism and display similar sensitivities to hydrogen-bonding interactions involving the chloride. Imidazoles bearing a 2-Ph or 2-Me substituent exhibit steric interactions with the porphyrin ligand in Co(TPP)(RIm)Cl that result in a ca. 10-fold increase in the lability of the trans chloride.

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Registry No. 1-MeIm, 616-47-7; 1-PhIm, 7164-98-9; 1-Me-2-PhIm, 3475-07-8; 1-Me-5-PhIm, 2154-38-3; 1,2-Me_2Im, 1739-84-0; HIm, 288-32-4; 4-PhIm, 670-95-1; 2-PhIm, 670-96-2; 2-MeIm, 693-98-1; 2-EtIm, 1072-62-4; Co(TPP)Cl, 60166-10-1; Co(TPP)Br, 60166-11-2.

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Neutral Technetium(V) Complexes with Amide-Thiol-Thioether Chelating Ligands

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General methods for the preparation of ligands of the type $R'SCH_2CONHCH_2CH_2NHCOCH_2SR$, $H_2ema(R)(R')$, where R = alkyl, aminoalkyl, and carboxyalkyl and R' = H, benzoyl, acetamidomethyl, and benzamidomethyl are described. New methods for the protection and deprotection of thiols with triphenylmethyl and amidomethyl groups have been developed. These ligands have been reacted with $(Bu_4N)[TcOCl_4]$ and $Na[TcO(eg)_2]$ (eg = ethylene glycolato), and for the cases where R = Me, CH_2Ph, $(CH_2)_{10}COOH$, and $CH_2CH_2(NC_4H_8O)$, neutral complexes, [TcO(emaR)], have been isolated and characterized. The complex $[TcO(ema(CH_2CH_2NC_4H_8O))]$ was crystallized as a monohydrate, and a single-crystal X-ray structure determination was performed. For all of the $[TcO(ema(CH_2CH_2NR_2))]$ complexes, an intramolecular dealkylation occurred to cleanly form $[TcO(ema)]^-$, which can be isolated as the $AsPh_4^+$ salt. Furthermore, $[TcO(ema(CH_2Ph))]$ and [TcO(ema(Me))] were reacted with amines, water, and halides to give the dealkylated products. Crystal data for $C_{12}H_{20}N_3O_4S_2Tc\cdot H_2O$: monoclinic, a = 12.120 (1) Å, b = 7.172 (1) Å, c = 18.933 (2) Å, β = 94.29 (1)°, V = 1641.1 Å^3, space group = $P2_1/n$ (No. 14), Z = 4, R = 0.042, R_w = 0.055.

Introduction

The coordination chemistry of amide and thiolate ligands has a strong basis in both biology and chemistry, and reviews have been dedicated to the field.[2] We are particularly interested in this area of chemistry as it pertains to the preparation of new classes of chelate complexes of technetium that can direct the biodistribution of the radiotracer ^{99m}Tc (γ = 140 keV, $t_{1/2}$ = 6 *h*), for purposes in diagnostic nuclear medicine.[3] Similar strategies by ourselves and others have lead to useful radiopharmaceutical preparations of ^{99m}Tc complexes for imaging renal function,[4] cerebral perfusion,[5] myocardial perfusion,[6] and other purposes.[7]

Studying the chemistry of technetium, by using macroscopic quantities of the long-lived isomer, ^{99}Tc (β = 0.292 MeV, $t_{1/2}$ = 2.12×10^5 years) has been particularly fruitful and has provided a powerful tool for the design, preparation, and characterization of potential radiopharaceuticals.

Previous work with bis(amide)-bis(thiol) chelates, such as *N*,*N'*-ethylenebis(2-mercaptoacetamide) (H_4ema), showed that the oxotechnetium(V) square-pyramidal core is readily accessible either by reduction from pertechnetate or by ligand exchange from $(Bu_4N)[TcOCl_4]$ or $Na[TcO(eg)_2]$ (eg = ethylene glycolato) to give anionic "$TcON_2S_2$" complexes, which result from deprotonation of the thiol and amide groups on the ligand.[8,9] As these amide-thiol ligands are very amenable to derivatization and as other workers have shown that five-coordinate neutral oxotechnetium(V) complexes of bis(amine)-bis(thiol)[5b] and bis(amine)-bis(oxime)[5c,5d] chelates are extremely useful for evaluating cerebral perfusion and can aid in diagnoses of physiological disorders, we modified the chelate H_4ema to give a series of trianionic mono-S-alkylated derivatives, H_3emaR. These ligands react to give the five-coordinate neutral oxotechnetium(V) complexes [TcO(emaR)], and in some instances, when R = $CH_2CH_2NR_2$, these complexes react further to give the thioether-dealkylated product, $TcO(ema)^-$. The following report describes the preparation of the ligands and the corresponding complexes derived from their reaction with technetium(V).

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