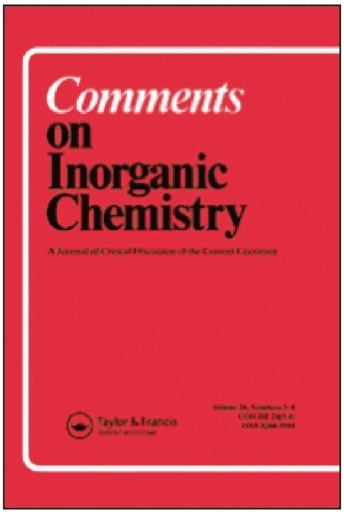

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Complexation and Demetalation Reactions of Porphyrins

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Complexation and Demetalation Reactions of Porphyrins

The mechanisms by which porphyrins form metal complexes in nature are of interest because of the importance of both the iron complexes, the active sites of hemoproteins, and the magnesium complexes, the chlorophylls. Currently there is interest in using chelated radioactive metal isotopes as diagnostic imaging and therapeutic agents; porphyrins are excellent candidates because of their extremely high stability constants with many metal ions. A great deal of effort has been invested to determine the reaction rates and examine implications of possible formation and decomposition mechanisms of metalloporphyrins: the subject has been periodically reviewed.[1-5] It is my intent in this Comment to choose a few of the most salient and personally interesting major trends that have been elucidated and to indicate some of the more troublesome unsettled questions.

COMPLEXATION

Typically, a chemist who would like to understand enzymatic porphyrin metalation mechanisms or synthesize a specific metalloporphyrin will immediately ask: "What is the rate-determining step?" For reactions that are relatively straightforward (i.e., those in which one step has a much higher activation energy than all other elemental steps under a great variety of conditions), knowledge of the rate-determining step can, of course, greatly simplify mechanistic interpretation and allow one to readily decide on appropriate synthetic conditions to efficiently obtain an acceptable product yield. Metalloporphyrin formation is, however, much more "interesting" than the simple case described above. The number of steps and the number of rapidly attained equilibria that appear

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to be involved cause the slow step to vary and to depend, sometimes in rather subtle ways, on temperature and environmental conditions such as the solvent, ionic strength, and nature of counterions present as well as concentrations.

Lewis Acid–Base Complexation

The type of reaction that has been most widely studied kinetically is the complexation of a metal ion with a porphyrin in which there is no oxidation–reduction reaction required.[6] For this type of reaction, a mechanism which is consistent with experiments by our group[7] and those of Hambright[8] and Tanaka[9] is:

Deformation (1)

$$H_2P \rightleftharpoons H_2P^*$$

Outer-Sphere Complexation (2)

$$ML_6 + H_2P^* \rightleftharpoons [L_6M,H_2P^*]^{2+}$$

Ligand Dissociation and First Metal-Nitrogen Bond Formation

$$[ML_6, H_2P]^{2+} \rightleftharpoons \underset{+\ L}{[ML_5{-}L{-}H_2P]^{2+}} \rightleftharpoons L_5M{-}H_2P^{2+} \qquad (3)$$

Second Metal–Nitrogen Bond Formation (Sitting-Atop Complex Formation)

$$L_5M{-}H_2P^{2+} \rightleftharpoons L_nM{=}H_2P^{2+} + (5 - n)L \qquad (4)$$

Metalloporphyrin Formation

$$L_nM{=}H_2P^{2+} \rightleftharpoons MP + L_n + 2H^+ \qquad (5)$$

SCHEME 1

In these studies, highly polar solvents (water or DMF) and divalent transition metal ions (as well as Zn^{2+} and Cd^{2+}) were employed.

The studies reported by these three groups demonstrate that ligand dissociation from the metal ion is extremely important in determining the overall reaction rate. As first pointed out by Hambright and Chock,[10] normalization of the overall rate to account for the rate of ligand dissociation, achieved by dividing the overall rate by the appropriate solvent exchange rate for each of the metal ions, reduces the range of rates for most of the metal ions studied (from Cu(II) at the most rapid to Ni(II) at the slowest) from 10^6 to about 10^2. Even in these well-designed studies, however, there is an anomaly. The complexation of Mn(II) is slower than that of Co(II) even though the exchange rate is faster. This anomaly in the correlation of exchange rates and metalation rates is consistent with studies of four quite different porphyrins in different solvents, tetrakis(p-methylpyridyl)porphyrin[10] and tetrakis(p-sulfophenyl)porphyrin[11] in water and tetraphenylporphyrin,[9b,12] and N-methyltetraphenylporphyrin[7] in DMF, so it appears to be due to properties of the metal ions rather than of the porphyrin or the medium. This anomaly can be rationalized if there is a metalloporphyrin intermediate with only a single metal–nitrogen bond in equilibrium with the uncomplexed porphyrin (specifically, the metal ion–porphyrin encounter complex or the precursor complex). In this event, the equilibrium toward bond formation might be expected to be less favorable for Mn(II) than for Co(II) or other transition metal ions because Mn(II) has no ligand field stabilization energy. Thus, most transition metal ions form more stable bonds to nitrogen, especially in the strong ligand field of a porphyrin, but high-spin Mn(II) binds well to oxygen instead. The overall reaction sequence for the complexation of a metal ion such as Cu(II) (which forms a metalloporphyrin complex that has no axial ligands) must involve the loss of all the ligands of the original first coordination sphere of the metal (e.g., six for $Cu(H_2O)_6^{2+}$ or $Cu(DMF)_6^{2+}$) and both of the protons from the nitrogen atoms of the free base porphyrin. Since so many species are involved, one must presume that the reaction could not occur as a single, highly concerted process, but rather that there are a number of separate steps with intermediates and there is no reason to assume *a priori* that all of these steps would be irreversible. At present, then, it is at least plausible that the Mn(II) anomaly is the consequence of pre-equilibrium differences between Mn(II) and the other metals studied. Interestingly, most of the information that has been gained about the reversible equilibria in the porphyrin metallation reaction sequence has resulted from kinetic studies of the reverse process, acid-promoted demetallation (*vide infra*).

In most of the other kinetic studies (several hundred to date) and in most practical situations in which one might wish to synthesize a metalloporphyrin, the picture is much less clear than in the studies of Hambright, Lavallee, and Tanaka. They were careful to define the situation as simply as possible, by making precursor metal complexes in which the first coordination sphere was composed of the same ligand as the solvent to be used (either water or DMF). They also used weakly coordinating counterions such as ClO_4^- or NO_3^-, took care to ensure that the porphyrin concentration was sufficiently dilute (to maintain the porphyrin in the monomeric state), and they checked for ionic strength effects. It is much more common to encounter studies in which relatively strongly complexing anions such as chloride or acetate are present, obscuring the identity of the metal complex that forms the encounter complex with the porphyrin. In many cases, solvents of low polarity have been employed. Although ion-pairing in these solvents may be extensive, making it crucial to understand the role of ionic strength and the nature of the counterions employed, rarely have these parameters been investigated. There are numerous examples of catalysis by Lewis bases and kinetic isotope effects and some reports of specific ion effects and proposed intermediates,[2-5] which, in light of more recent studies,[1] more likely involve changes in the nature of the reactive metal-ion-containing species than differences in the nature of the porphyrin precursor or of porphyrin–metal ion intermediates.

When considering the effects of bases as catalysts, it is important to realize that, with the sole exception of the tetrakis(pyridyl)porphyrins, it is very difficult to remove protons from the nitrogen atoms of free base porphyrins and only the free base form has been definitively demonstrated as a reaction precursor. On the other hand, many cases of general base catalysis of ligand exchange on metal ions have been reported and ligands are known to be able to affect the rate of exchange of other ligands in the first coordination sphere (i.e., *cis* and *trans* effects.) Metalloporphyrin formation is subject to either general or specific base catalysis. Deprotonation of a ligand such as H_2O or NH_3, which remains bound to the metal ion, can result in general base catalysis, which should show a dependence of the rate on the pK_b of the Lewis base. The replacement of a ligand in the first coordination sphere by the Lewis base and subsequent promotion of the rate of ligand release from the metal ion (a *cis* or *trans* effect) is a specific catalysis, not generally directly related to pK_b values. The lack of a change in the overall rate of metalation when proto- and deutero-forms of the porphyrin are used (i.e., H_2TPP and D_2TPP) but a significant isotope effect when the solvated form of the metal ion is different ($Zn(H_2O)_6^{2+}$ and $Zn(D_2O)(H_2O)_5^{2+}$,[13] for example) implies that the steps involving proton dissociation from the porphyrin–metal ion intermediate (the last step shown in Scheme 1)[14] are *not* rate determining in general.

The analysis of specific ion effects and of the identity of possible intermediates is of less general interest and requires elaboration that has been discussed sufficiently in the original literature.[15] It is adequate here to state that most current explanations of these effects are in terms of metal ion precursors rather than the porphyrin *per se*.

Although the nature of the metal-ion-containing precursor has been identified as a very important consideration in explaining *trends* in reaction rates, the *absolute* rates of metalation reactions depend strongly on other factors as well. Irrespective of the particular metal ion, complexation with typical porphyrins is many orders of magnitude slower than complexation with an open chain amine under the same conditions. For example, the rate constant for the complexation of Ni(II) and the linear polyamines, such as ethylenediamine, triethylenediamine, and tetraethylenediamine are all about 5×10^5 M^{-1} s^{-1} in water at 25 °C for the unprotonated forms of the ligands.[16] The rate-controlling step is apparently the formation of the first Ni(II)-to-nitrogen bond and the rate is determined by the loss of solvent (water) from the first coordination sphere of the Ni(II) atom. The rate constant for the analogous reaction with tetrakis(4-N-methylpyridyl)porphine is 5×10^{-5} M^{-1} s^{-1} at 22 °C (pH = 4, where this porphyrin is in the free base form).[10] Thus, though the division of the observed rate constant by the ligand dissociation rate provides a mechanistic rationale, the absolute amount by which these rate constants are smaller than normal (for Cu(II), Zn(II), Co(II) and Ni(II), $1-2 \times 10^{-9}$)[10] should not be overlooked. The great difference in rates, of course, must be due to a fundamental difference in the properties of the cyclic, and presumably less flexible, porphyrin ring system relative to other nitrogenous Lewis bases. Compared with open chain amines, the lone pairs of electrons on the porphyrin are both less accessible and, perhaps at least partially as a result, less basic. The extent to which the porphyrin ring must distort to expose these lone pairs sufficiently for a metal atom to bind is not known, but it is evident from studies of N-substituted porphyrins that distortion greatly increases the complexation rate. Under comparable conditions with corresponding porphyrins, the rates for N-substituted porphyrins are about 10^5 faster.[7,9b] The structures of a free base N-methylporphyrin (tetrakis(p-bromophenyl)porphine[17]) and closely related chloro-M(II) complexes of manganese, iron, cobalt and zinc[18] indicate that the N-substituted porphyrin ring system has a very similar topography and it seems quite plausible that much less distortion may be necessary during the metalation reaction (of course, a proton must be displaced in the process).

Porphyrins are generally much less basic than open chain amines (i.e., typical pK_a values are about 4 to 5 for porphyrins and 9 to 10 for the amines) and it might be reasonably supposed that the basicity difference is also an important factor that reduces the rates of metalloporphyrin formation reactions. Ademeyo *et al.* have shown that more basic porphyrins do, in fact, react faster.[19] The relation they deduced would account for a factor of about 10^3 to 10^4 due to the difference in basicity. (The porphyrins studied ranged in pK_3 values from about -1 to 5, extrapolation to pK_a values from the normal range of naturally derived and uncharged synthetic porphyrins, 4 to 5, to those of amines, 9 to 10, would give the increase in rate given above.) Since N-methyltetraphenylporphyrin and tetraphenylporphyrin differ in pK_3 values by only a factor of about 10–100 (depending on the nature of the solvent[20,21]), most of the rate differences for metalation reactions of these two species should be due to the conformational difference of the free bases. The data of Lavallee[7] and Tanaka[9b] show the relative rates to be about 10.[5] The combination of this factor with the basicity relation of Ademeyo *et al.* would, therefore, account for a factor of 10^8 to 10^9. The constants for the pre-equilibrium steps in Scheme 1 could be nearly unity (except for Mn(II), *vide supra*) to give the observed ratios of 10^9 to 10^{10}.

Having in mind the empirical results of the effects of distortion of the porphyrin ring and the effect of its basicity on observed reaction rates, it is interesting to speculate on their implications for the nature of the intimate processes involved in the metalation reaction. As the porphyrin ring distorts so that the nitrogen lone pairs can become accessible to an incoming metal atom, we might expect that the concommitant loss of resonance energy would continually reduce the probability of further distortion (i.e., small distortions involving relatively small losses in resonance energy would be likely, but the probability of large distortions would be much less). How can one estimate small and large in this case? Molecular structures deduced from x-ray diffraction studies and NMR and electronic spectrometric data are available for several N-substituted porphyrin complexes, for a free base and a monoprotonated species[23]; there is also a great deal of data for the comparable non-N-substituted porphyrins.[24] It is quite evident from a comparison of these data[23] (the N-substituted pyrrole ring is typically canted by about 40° while the other rings are canted by about 5° to 15°) that the pronounced distortion caused by N-substitution does not, in fact, greatly diminish the aromaticity of the ring system. For example, the positions of absorptions in the electronic spectra and the extinction coefficients are very similar (taking into account the lower symmetry and, therefore, the somewhat more complex spectra of the N-substituted species). Using the concept of ring current, the positions of the *b*-pyrrole proton resonances in the NMR spectra of diamagnetic porphyrins and complexes provide an indication of the aromaticity. Although the positions of the resonances of the N-substituent are very unusual, the *b*-proton resonances are very similar to the positions for non-N-substituted porphyrins[23] (in the region 7–8 ppm downfield from TMS), again demonstrating that the N-substituted porphyrins retain a high degree of aromatic character. Other types of porphyrin complexes demonstrating that aromaticity can be retained even when the porphyrin ring system is highly distorted have been summarized by Tsutsui.[25] An especially interesting case, a dimeric mercury(II) complex, has been described by Smith.[26] The complex reported by Smith involves complexation of two mercury(II) atoms, one on either side of a porphyrin ring, such that two opposed pyrrole rings of the porphyrin are bound to one mercury atom and the other two rings are bound to the other. The pyrrole rings are highly canted from the mean plane of the nitrogen atoms, yet the electronic spectrum indicates retention of aromatic character. Several of the porphyrin complexes with unusual structures that have been summarized by Tsutsui also involve highly canted pyrrole rings but retain aromatic characteristics in their electronic spectra. Although we can be quite confident that the porphyrin ring system can undergo large distortions and still remain highly aromatic, the sticking point is that we cannot as yet make any reliable quantitative estimates of how much energy is actually involved in these "minor" changes. The overall resonance energies of naturally derived porphyrins and tetraphenylporphyrin[27] are about 250 kcal mol^{-1}, so that if even a 5% loss in resonance energy were involved in the distortion needed to bind the metal atom (step 1 of Scheme 1), the pre-equilibrium constant would be about 10^{-4}. This loss of resonance energy would directly affect the overall rate constant by the same amount. An additional factor of 10^{-4} seems unreasonable in view of the deformation and basicity factors cited above. It is very unfortunate that no heats of atomization are available for highly distorted porphyrins so that this effect could be determined quantitatively. The high accuracy are excellent reproducibility of this type of experiment would provide a solid basis for mechanistic interpretation. The drawback to the experiment is that 1 to 2 grams of each compound must be provided as very pure crystalline material of a single crystal habit.

Porphyrins are not only weak bases compared to open chain amines, but the pK_a values for successive protonation of the two available nitrogen atoms in the porphyrin core are very similar (typically so close for porphyrins that they cannot be resolved in titrations), whereas the spacial proximity[27] might be expected to cause a larger difference. As pointed out by Fleischer,[28] the first protonation of a free base porphyrin may be very unfavorable due to the difficulty of distorting the porphyrin, but the second proton can add readily once the distortion has taken place to accomodate the first. The relatively high "innate" basicity of the pyrrole ring that was inhibited by the inaccessibility imposed by the remaining planar porphyrin ring system thus overcomes the normal inhibition for binding of a second proton that is incurred by the presence of the first positively charged proton in the same vicinity. The aspect of successive protonations is related to metalation because the overall process involves successive bond formation of the metal atom to the porphyrin nitrogen atoms. We assume in Scheme 1 that the metal binds first to the two unprotonated nitrogen atoms with at least the first bond formation being reversible. If we assume from Scheme 1 that the distortion required to allow the metal ion to form the first bond is difficult and that the second bond should be formed readily, we would assume that a relatively stable intermediate should be present once these two bonds have been formed. Formation of the second bond should involve a relatively small activation energy from the standpoint of the porphyrin,[29] but an additional metal–nitrogen bond would favor this step. Reversing the process would be analogous to the case of the stepwise dissociation of a chelating open chain amine. As discussed below in a section on acidic hydrolysis, there is evidence from metal atom dissociation reactions that forms of the complexes with more than one metal–nitrogen bond are much more stable than species with only a single metal–nitrogen bond. The most effective point at which to reverse the series of steps in which metal–nitrogen bonds are formed, then, should be after the formation of the first bond (step 3 of Scheme 1).

Until relatively recently, it had been thought that the final step of Scheme 1 was rate determining in general.[3] It now seems clear that this is not the case, since there is no isotope effect when D_2TPP and H_2TPP react with metal ions.[13] Certainly a pronounced isotope effect would be expected if proton dissociation occurs in the rate-determining step. If the activated complex resembles the product, one would also expect that the dissociation of metal ions would be promoted to the greatest extent by those metal ions that form the most stable products; Ni(II) would react nearly as fast as Cu(II) and Zn(II) would be slower than Cu(II), Ni(II) or Co(II). Finally, the dependence on porphyrin basicity found by Adeyemo *et al.*[19] shows that the more basic porphyrins are more reactive, which is opposite of the result that would be expected if proton dissociation were rate determining. Thus, it seems very reasonable that intermediates with two metal–nitrogen bonds and the porphyrin free base protons still bound (sitting-atop type complexes) are formed during the metalation reaction but that their decomposition is not generally rate determining.

One important practical aspect of porphyrin metalation reactions is not obvious from Scheme 1. Only the free base form of the porphyrin has been shown, whereas at pH values less than 4 or 5 or in organic solvents with small amounts of acid present, the major forms of the porphyrins will be protonated, cationic species. It is clear from numerous studies[1-4] that only the neutral, free base forms of the porphyrins are reactive (with few exceptions, deprotonated, anionic species are very difficult to form and are typically unimportant in metalation reactions). Solutions containing monoprotonated or diprotonated species may form complexes, of course, but only to the extent that equilibria with the free base form exist are established. Therefore, the actual rate of reaction in this case may depend strongly on the pH. For unbuffered solutions in which some water is present, rates for different metals will be affected by their hydrolysis constants. Fortunately, the absorption spectra for the free base and protonated forms of porphyrins are markedly different and it is easy to determine whether or not introduction of the metal ion into the solution of the porphyrin causes protonation.

The metalation of a porphyrin is generally fastest and most well behaved kinetically in acid-free, polar, rapidly exchangeable solvents. Typically the expected order of reaction rates (from Eigen's exchange data[31] and the exchange data of other workers[32]) would be: the alkali metals, the alkaline earths, Cu(II), Cd(II), Zn(II), Co(II), Mn(II), Fe(II), the lanthanides, Fe(III), In(III) and Al(III). The reactions of Ni(II) and Pd(II) would be expected to be feasible but relatively slow if the precursors are octahedral but considerably faster if the precursor complex is square where an associative mechanism may operate. This change in the nature of the mechanism may explain the observation by Longo[12] (which has been repeated in other laboratories) that Pd(II)-chloro complexes[33] react at relatively rapid rates—in the middle region of the series of divalent transition metal ions given above.

Unfortunately, thorough studies resulting in reliable, comparable kinetic data only pertain to Cu(II), Cd(II), Zn(II), Co(II), Mn(II), and Ni(II).[7-11] If reaction times for syntheses of other ions that react as solvated precursors are included,[34] the resulting relative rate series for polar solvents such as water and DMF is Cu(II) > Cd(II), Zn(II) > Co(II), Mn(II), Pd(II) > Fe(III), In(III) > Ni(II). The metalation reactions of these ions proceed much more rapidly, in general, in the more rapidly exchanging solvents methanol and acetonitrile, but few kinetic data in these solvents exist and low solubility of either the porphyrins or readily available metal salts may make these solvents less suitable than DMF, which has become the most widely used solvent for metalloporphyrin synthesis following the demonstration of its applicability by Adler *et al.*[35]

It is very important to note that the rate laws for the reactions of the metal ions cited above in either DMF or aqueous solution are second order: first order in the porphyrin and first order in metal ion concentration. Many other studies have been performed in acetic acid,[36] where dimeric forms of the transition metals can be formed. The conclusion has been drawn that the activated complex for porphyrin formation results from addition first of one metal ion from one side of the porphyrin plane that then accelerates addition from the other side, leading to a second-order dependence on metal ion.[9a] This is an overinterpretation of the rate law found in this solvent, which only demonstrates that there are two metal atoms present in the activated complex and does not shed light directly on the intimate process involved. The behavior of these metal ions in other solvents implies, instead, that a reaction order other than first order is due to the stoichiometry of the reactive form of the metal ion.

There exists only one kinetic study of the binding of lanthanide ions.[37] The data are very limited and do not yet allow generalization to the studies of other metal ions. The alkali metal and alkaline earth ions are difficult to study kinetically and no systematically obtained data are available. The transition metal ions classically studied kinetically to obtain information about ligand exchange mechanisms, Cr(III), Co(III) and Pt(II), react with porphyrins at exceedingly slow rates under conditions where kinetic data can be readily obtained. Again, the data are essentially nonexistent. It would, of course, be of interest to have data on these different types of metal ions to determine whether there are quite different mechanisms or rate dependences at different steps in the same overall sequence and to ensure that our conclusions are not too narrowly based on a series of rather similar metal ions (principally the divalent ions of the first transition series).

Other Mechanisms of Metal Complexation

A number of porphyrins have been synthesized by methods other than the direct Lewis acid–base adduct formation between a metal complex and the free base porphyrins.[34] One of the most important alternate mechanisms involves reduction of the core hydrogen atoms of the free base porphyrin, oxidation of the metal atom and complexation, in a process that is quite likely concerted. Some of the metal complexes which react with porphyrins in this manner (with the oxidation state of the product in parentheses) are: $Cr(CO)_6$, (Cr(III)); $Mo(CO)_6$, (Mo(V)); $Tc_2(CO)_{10}$, (Tc(I)); $Re_2(CO)_{10}$, (Re(I)); $[RuCl_2(CO)_3]_2$, (Ru(II)); $[Rh(CO)_2Cl]_2$, (Rh(III)); and $[Ir(CO)_2Cl]_2$, (Ir(III)). Typically these reactions are sluggish, requiring several hours reflux in relatively high boiling solvents. No kinetic data or mechanistic interpretations based on rate data are available for these reactions. It would be most interesting to find means of accelerating these reactions. For example, this synthetic procedure is the only means known for making technetium complexes of porphyrins, and technetium is currently the most important isotope for medical diagnosis.

It has been proposed that the lanthanides undergo complexation in DMF and other unspecified solvents by way of either the mono- or dianions of the porphyrin or the sodium–porphyrin complex.[37] Unfortunately, no data were presented in the article in which these intermediates were suggested. Under the conditions used for these reactions, it is quite possible that the sodium complexes are formed.[38] In this case the mechanism for the lanthanides could be very similar to that for transmetalation reactions, discussed below as one class of catalysis reactions of porphyrins. There is as yet no compelling evidence for the reaction of the anionic forms *per se*, i.e., as ions without a closely associated (and geometrically determined) cation. However, it must be stressed that the range of types of metal ion for which reliable, comparable data is available is very restricted and it is possible that the anionic form could be required. It would be interesting to have data for the case of a porphyrin anion with a large enough counterion (e.g., a quaternary ammonium cation) that specific distortion of the porphyrin by metal–nitrogen binding could be eliminated.

ACIDIC DEMETALATION

Buchler has presented a stability index ($100 \times Z \times E_N/r_i$, where Z is the ionic charge, E_N is the Pauling electronegativity and r_i is the ionic radius)[34] which correlates well the observed stability of porphyrins with respect to acidic demetalation. The qualitative behavior of metalloporphyrins when subjected to a variety of acidic media has long been the "rule of thumb" for discussing metalloporphyrin stability. Both the stability index and the procedures for empirically determining the stability classification of a particular metalloporphyrin are, of course, thermodyamic in nature and do not directly provide information about the length of time involved, nor do they provide parameters to predict in a quantitative manner the dissociation as a function of acid concentration. Major problems of instability of metalloporphyrins often arise as a result of hydrolysis. We are currently limited in large part to nonquantitative observations of the effects of water and of acid.

It is quite evident that the alkali metal and alkaline earth complexes of porphyrins are only stable in scrupulously dry solvents and that the metal ions are readily displaced by trace amounts of acid in nonaqueous solvents. These species are so unstable with respect to water that it would not be especially worthwhile to expend effort to obtain kinetic data and attempt to rationalize the intimate mechanism of these reactions.

A few metal ions, including high-spin Mn(II) and the filled-shell ions Zn(II), Cd(II) and In(III), are intermediate in stability against acidic demetalation, more stable than the alkali metals and alkaline earths and less stable than the transition metal ions with ligand field stabilization. Complexes of these ions can be formed in neutral, aqueous solution but they are very readily hydrolyzed by acid. They exhibit measurable equilibrium constants in aqueous solution and such equilibria are attained relatively rapidly. It is for these ions that the only quantitative data for metalloporphyrin hydrolysis reactions exist, with the principal work being produced by Hambright's group.[39] Berezin and co-workers have also published many reports of metalloporphyrin hydrolysis that include references to the timescale of the reactions but the nature of the media employed and the limited extent to which conditions are varied (acid concentration or temperature) often preclude mechanistic distinctions.[5] Hambright's data are very important because they not only provide a quantitative guide to the temporal stability of these particular complexes but because they provide information about the reverse reaction, complexation, and they have been used by Hambright and his co-workers to obtain the only quantitative stability constants for metalloporphyrins. Some of the most important conclusions to come from this work are[1,2]:

(1) Breaking of the last metal–nitrogen bond is typically the most difficult step in hydrolysis.
(2) Rate laws are typically mixed, with the rate proportional to a higher order concentration of hydrogen ion when the concentration is relatively low, indicating a succession of protonation equilibria.
(3) For those metal ions without ligand field stabilization, the speed of hydrolysis as well as the tendency for hydrolysis are greater the smaller the charge/radius ratio.
(4) Equilibria favor complexation when the porphyrin is more basic.

As is unfortunately the case for numerous aspects of metalloporphyrin reactions, the number and variety of metal ions for which reliable, comparable data have been obtained is severely limited.

There are several other ions for which the relative rates of acidic hydrolysis are so clearly consistent that general conclusions seem justified even though comprehensive kinetic results have not been reported. Highly charged, filled-shell ions (i.e., those which generally exhibit principally ionic bonding, such as Al(III), Fe(III) and the lanthanides) are less easily hydrolyzed than the divalent ions discussed above but are more readily hydrolyzed, in general, than metalloporphyrins formed from transition metal ions with ligand field stabilization. Because these ions readily produce acid from coordinated water, the major problem typically encountered in studying species is not the hydrolysis of the complexes but the interference of water with metalloporphyrin formation. If one attempts to avoid hydrolysis and consequent protonation of the porphyrin by making the solution slightly basic, these metal ions form unreactive precipitates.

Metal atoms are generally removed from their porphyrin complexes more readily in their reduced state (e.g., MnTPP > Mn(TPP)Cl, FeTPP > Fe(TPP)Cl, CoTPP > Co(TPP)Cl, etc.). These hydrolysis reactions are promoted, rather than catalyzed, when a reductant is added to a solution of the metalloporphyrin in the oxidized (generally air-stable) state. These reactions are typically not catalyzed because the reduced state is often the more stable state of the solvated metal atom. Thus, when the reduced metal atom is released from the porphyrin by acidic hydrolysis, a solvated metal atom is generated which is incapable of reducing a metal atom in the oxidized state in the metalloporphyrin. Reducing agents in stoichiometric amounts are typically required, then, to sustain the reaction.

CATALYSIS

Most examples of catalysis involve addition of a particular Lewis base (e.g., pyridine or acetate) or a change in the medium (especially the use of more basic conditions). Since extremely basic conditions would be required to form the porphyrin mono- or dianions as a precursor and since deprotonation of an intermediate complex between the metal atom and the free base form of the metalloporphyrin (the sitting-atop complex) is not likely to be rate determining, these means of catalysis are very likely due to alterations in the coordination sphere of the metal atom that make it more reactive. The complexity of the equilibria involved (the precursor responsible for the major reaction path could be present in low concentration but be readily available via rapidly established preequilibria) and the problem of detecting spectral changes for the metal atom chromophore in the presence of the porphyrin would make it difficult to obtain direct evidence for the mechanism of these reactions. It is quite possible in most cases to derive kinetically equivalent rate laws that are mechanistically divergent, i.e., based on either the acid–base equilibria of the porphyrin or of the metal ion. The use of titration or conductivity data to investigate these reactions has rarely been reported.

One interesting case of catalysis of metalloporphyrin formation that has unfortunately received little attention involved the use of a surfactant to form a microemulsion[11c] or a micellar medium.[40] Use of such media may provide the means for accomplishing complexation under mild conditions for porphyrins that are not water soluble and which have reactive substituents that would be affected by media such as acetic acid, pyridine or DMF that are generally employed.

A class of catalytic mechanism that is potentially very useful, originally described by Grant and Hambright,[41] involves transmetallation. They reported that Zn(II) reacts with tetraphenylporphinatolead(II) to form tetraphenylporphinatozinc(II) more rapidly than the direct reaction of Zn(II) with tetraphenylporphyrin. More recently Tanaka has demonstrated that prior complexation of tetrakis(p-trimethylanilium)porphyrin with Hg(II) increases the rate of formation of the Zn(II) complex by a factor of 4000.[42] Several large, filled-d-subshell ions can catalyze formation of more stable metalloporphyrins. Metal ions that form good transmetalation precursors include Hg(II), Cd(II) and Pb(II).[43] The metal atoms which displace these atoms well are Cu(II), Co(II), Ni(II) and Mn(II), in addition to Zn(II). In pyridine, the rate constants for formation of ZnTPP from precursors are 0.27 M^{-1} s^{-1} (HgTPP at 25 °C), 0.020 M^{-1} s^{-1} (CdTPP at 25 °C), 4.0×10^{-4} M^{-1} s^{-1} (PbTPP at 44 °C) and $<10^{-4}$ M^{-1} s^{-1} (H_2TPP at 25 °C).[42] In Tanaka's work, tetrakis(p-sulfophenylporphyrin) was used in water to form Mn(II) complexes via Hg(II) and Cd(II) catalysis and we have found that his conditions work well for the synthesis of complexes of hematoporphyrin in buffered aqueous solution, so the method may be quite general. In all cases reported to date, the species which catalyze complex formation by transmetalation are filled-d-subshell ions, which exhibit the tendency to form stable tetrahedral complexes. The structures of the complexes formed by these ions as the transmetalation intermediates are not known, but two possibilities seem likely. These metals may form bonds with only two of the pyrrollic nitrogen atoms, leaving the other free to bind to another metal atom (as in the structure of a Hg(II) porphyrin complex[26]). Another possibility that seems more reasonable is that the intermediates are monomeric with a domed shape wherein all four nitrogens are bound to the metal atom but in which the metal–nitrogen bonds are continually being broken and reformed. In this case, the complex could be attacked by another metal atom from the side opposite the complexed metal atom. The displacing metal could form a stronger bond to one nitrogen atom and "unzip" the others sequentially. The fact that the rate of the overall process for binding one metal atom (e.g., Hg(II)) and displacing it with a second metal atom (e.g., Mn(II)) is faster than the single process of binding a metal atom such as Mn(II) is intriguing. One drawback to this method is that the best catalysts are highly toxic metals, complicating its use for synthesis of metalloporphyrins for medical applications.

METALLOPORPHYRIN DECOMPOSITION

It is certainly tempting to propose that the great stability of the porphyrin ring system and the wide variety of catalytic roles of metalloporphyrins in nature would make them candidates for use as nonbiological chemical catalysts. Problems associated with their use are acidic, photochemical and oxidative decomposition. As discussed above, acidic conditions can lead to demetalation, but this problem involves relatively few metals. Photochemical and oxidative decomposition typically lead to modification of the porphyrin ring and consequent bleaching. The ultimate products of such reactions are profoundly different from the metalloporphyrin precursors and are unlikely to function catalytically. Although there have been some useful and important studies of the mechanisms of these reactions,[44] much remains to be done before they are well enough understood to design synthetically feasible porphyrins that avoid decomposition under conditions suitable for carrying out catalytic processes. Recently, several groups have found that metalloporphyrins are selective mono-oxidation catalysts. Generally, the porphyrins are decomposed rather rapidly under the reaction conditions, but recently Dolphin and Traylor and their co-workers have found that the highly hindered porphyrin tetrakis(2,6-dichloro)porphyrin is much more robust.[45] It is also known that the rate of decomposition of the hindered as well as unhindered metalloporphyrins is highly dependent on the metal ion. An understanding of the factors which lead to stability may provide the means for predicting the stability of new porphyrins that could be synthesized at a cost making their use feasible.

CONCLUSION

There are several areas of continuing interest to chemists in diverse fields which require an understanding of the kinetics and the parameters that affect the rates of metalloporphyrin reactions discussed in this Comment. The areas that are most prominent currently include the formation and decomposition of the active sites of metalloporphyrin-containing proteins, the application of metalloporphyrins in diagnostic imaging (using radioactive metal isotopes), and the use of metalloporphyrins as highly specific, stereoselective oxidation catalysts. Attempts to understand the mechanisms of novel synthetic schemes for metalloporphyrins and further effort to understand the mechanisms of metalloporphyrin decomposition should be especially important areas to pursue further.

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