Table II. Rate Constants and Activation Parameters

a. Low Water Concentrations

ester	solvent	k_1-(25 °C)/ M^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
ethyl[a]	ethanol	15.0	24 ± 2	−143 ± 19
ethyl[b]	ethanol	19.0	24 ± 4	−140 ± 29
methyl[b]	methanol	73.0	13 ± 1	−167 ± 13

b. High Water Concentrations in CH_3CN

ester	$[H_2O]$	k_{obsd}-(25 °C)/ s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
ethyl[a]	13.1	167.0	18 ± 1	−143 ± 3
n-pentyl[a]	19.1	96.0	15 ± 2	−156 ± 23
isopropyl[a]	13.1	2.9	29 ± 1	−140 ± 10
isopropyl[b]	24.0	4.2	29 ± 2	−136 ± 11

[a] Data obtained in region A; see Figure 1. [b] Data obtained in region B; see Figure 1.

evidence for hydrogen bonding between arsenate triesters and alcohols,[4] it seems reasonable to assume that some specific solvation of the esters by water can occur in a rapid prehydrolysis step; water molecules will also participate in solvent cage formation about the ester. Thus we can formulate Scheme I, where x represents the variable number of water molecules involved in specific solvation and cage formation, k_1' represents the step that obtains at low water concentration, and k_1'' represents the reaction at higher levels of water. A distinct first-order behavior for water obtains at low concentrations (step 5), but the order decreases as expected when water becomes a significant fraction of solvent (step 6).

Scheme I

$$xH_2O + OAs(OR)_3 \xrightleftharpoons{\text{rapid}} \underset{\text{I}}{xH_2O{\cdot}OAs(OR)_3} \quad (4)$$

$$\text{I} + H_2O \xrightarrow{k_1'} ROH + OAs(OH)(OR)_2{\cdot}xH_2O \quad (5)$$

$$\text{I} \xrightarrow{k_1''} ROH + OAs(OH)(OR)_2{\cdot}(x-1)H_2O \quad (6)$$

The activation parameters are reported in Table II. It should be noted that for reactions at higher water concentrations, k_{obsd} values were used in the ln (k/T) vs. $1/T$ plots without attempting to factor out the water dependence. The resultant error in the entropies of activation can be shown to be at most 25 J mol^{-1} K^{-1} in the positive direction. Given the large negative values found (from −136 to −167 J mol^{-1} K^{-1}), a correction of this magnitude does not influence interpretation at all. It may be noted that the values of ΔH^{*} are small (13 to 29 kJ mol^{-1}), which was also the case for pyroarsenate hydrolysis (49 kJ mol^{-1})[2] and arsenate ester–alcohol exchange (from −3 to 18 kJ mol^{-1}).[4] The entropies of activation are very negative, similar to that found for pyroarsenate hydrolysis (−107 J mol^{-1} K^{-1}) and the range obtained for ester–alcohol exchange (−153 to −226 J mol^{-1} K^{-1}). Further, the values of ΔH^{*} monotonically increase with increasing substitution on the carbon atom β to arsenic, undoubtedly due to increasing steric effects; comparable changes were found in the ester–alcohol exchange reactions.[4]

The experimental data are consistent with a highly associative mechanism and probable formation of a five-coordinate arsenic intermediate, $OAs(OR)_3(OH_2)$, where only the first coordination sphere is depicted. A similar mechanism was proposed for the arsenate ester–alcohol exchange reaction.[4]

There is a distinct deuterium isotope effect; when H_2O was replaced by D_2O in the ethyl arsenate hydrolysis in acetonitrile, the ratio $k_H/k_D = 1.86$ was found (see Table I). The exact role of the indicated proton transfer is open to conjecture.

The neutral hydrolysis of phosphate triesters is slow at 100 °C and complicated by C–O bond cleavage in some cases. Although it is not therefore possible to compare quantitatively the hydrolytic behavior of phosphate and arsenate triesters, it is clear that the latter hydrolyze many powers of 10 more rapidly.

Acknowledgment. We thank Anne L. Rieger and Thomas G. Richmond for experimental assistance and helpful discussions. This work was supported by Grant No. ES-00894 from the National Institute of Environmental Health Sciences.

Registry No. $OAs(OMe)_3$, 13006-30-9; $OAs(OEt)_3$, 15606-95-8; $OAs(O\text{-}n\text{-pentyl})_3$, 15063-75-9; $OAs(O\text{-}i\text{-Pr})_3$, 23060-61-9.

Contribution from the Department of Chemistry,
Hunter College, New York, New York 10021

Origin of the Hydrogen–Deuterium Kinetic Isotope Effect for Porphyrin Metalation

DAVID K. LAVALLEE* and GARY M. ONADY

Received August 6, 1980

It has been previously observed that the metalation of a porphyrin is slower in D_2O than H_2O. Discussion of this effect has focused on the role of dissociation of the hydrogen or deuterium atoms bound at the coordination site of the porphyrin. The importance of proton dissociation in determining the overall rate of porphyrin metalation is an essential feature of the intimate reaction mechanism. We have monitored the reaction of tetraphenylporphyrin with Zn(II) using protonated and deuterated forms of the porphyrin free base in dimethylformamide. The rates were found to be identical. The addition of either H_2O or D_2O increases the reaction rate, but the effect of H_2O is greater, leading to a k_H/k_D ratio of 2.3 at high $[H_2O]$ and $[D_2O]$. These results and the previously reported hydrogen–deuterium kinetic isotope effects found in aqueous solution can be explained by a mechanism involving a hydroxo complex of the metal ion. The isotope effect arises from a difference in the concentrations of reactive metal complexes, not from a difference in the reactivities of protonated and deuterated free-base porphyrins.

Introduction

Herein we report results of hydrogen–deuterium kinetic isotope effect experiments for metalloporphyrin formation. The data demonstrate that kinetic isotope effects observed for such reactions are due to changes in the reactive metal ion species rather than reactivity differences of protonated and deuterated free-base porphyrins.

The roles of metalloporphyrins and related complexes in respiration, photosynthesis, and electron-transfer processes have led to an interest in the mechanism of metalloporphyrin formation.[1-3] A prominent feature of proposed metalation

---

(1) F. R. Longo, E. M. Brown, W. G. Rau, and A. D. Adler in "The Porphyrins"; D. Dolphin, Ed.; Academic Press: New York, 1980; Vol. V, pp 459–481.

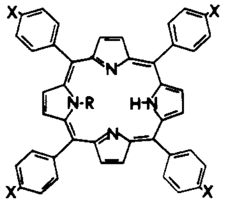


Figure 1. Structures of porphyrins discussed herein. For tetrakis(p-sulfophenyl)porphyrin, $X = SO_3^-$ and R = H, for tetrakis(p-trimethylaminophenyl)porphyrin, $X = N(CH_3)_3^+$ and R = H, for N-methyltetraphenylporphyrin, x = H and R = CH_3, and for tetraphenylporphyrin, X = H and R = H.

mechanisms is the importance of proton dissociation from the porphyrin.

Kinetic isotope effects (k_H/k_D) for rates of metalation of tetrakis(p-sulfophenyl)porphyrin (Figure 1) in H_2O and D_2O have been measured to be 2.2 for Zn(II)[4] and 1.4 for Cu(II).[5] The k_H/k_D kinetic isotope effect for tetrakis[p-(trimethylamino)phenyl]porphyrin reacting with Zn(II) in H_2O and D_2O is 2.4.[6] These kinetic isotope effects might be explained by partial bond-breaking in a concerted step, by dissociation in a predominantly bending mode or by difference in energies of deformation of free-base porphyrins preceding metal complexation.[4] As one part of a detailed study of metalation reactions of N-methyltetraphenylporphyrin, whose structure mimics that of the proposed distorted porphyrin precursor, we observed no isotope effect in its reaction with $Co(DMF)_6^{2+}$ in DMF.[7] We have now monitored the reaction of $Zn(DMF)_6^{2+}$ with H_2TPP and D_2TPP, and, surprisingly, we find no kinetic isotope effect (at 30.5 ± 0.1 °C, $k_H/k_D = 0.96 \pm 0.05$).

For deduction of the origin of previously observed kinetic isotope effects, rate constants for the reaction of Zn^{2+} with H_2TPP and D_2TPP were obtained for solutions containing different amounts of H_2O or D_2O in dimethylformamide.

Experimental Section

Preparation of Reagents. The Zn^{2+} solutions were prepared from anhydrous $Zn(ClO_4)_2$.[7] D_2TPP was obtained by two methods, the carbonate neutralization of $(D_4TPP)Cl_2$[7] and addition of a ~100-fold excess of CD_3OD to a solution of H_2TPP in DMF. The crystalline product of the first method was characterized by its infrared spectrum, which shows a shift of the band at 737 cm^{-1} assigned to an N-H bend.[8] Addition of CD_3OD to a solution of H_2TPP leads to very rapid exchange of the nitrogen-bound hydrogen atoms.[9] D_2TPP produced by both methods gave the same results.

Kinetic Measurements. A Varian 635D recording spectrophotometer thermostated with a Lauda K4/R circulating bath was used to obtain kinetic data.

Measurement of pH. A Radiometer Model 26 pH meter and Sargent combination electrode were used to measure H^+ and D^+ activities.

Results and Discussion

While it has been reported that the metalation of porphyrins is often accelerated at increased pH[2,3,6] and that the rates of metalation are faster in H_2O than D_2O,[4-6] it has not been determined whether these effects arise from the nature of the reactive metal complex or from the porphyrin itself. In previous discussion of the kinetic isotope effect of the metalation reaction, it has been assumed that the important determinant is the nature of the porphyrin, but our evidence from kinetic data in DMF/H_2O and DMF/D_2O solutions indicate that it is, in fact, the reactive metal ion complex, altered by the presence of exchangeable deuterium atoms, which causes the metalation rate difference.

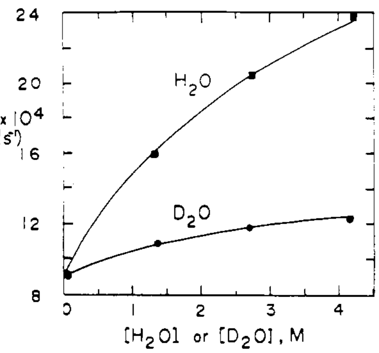
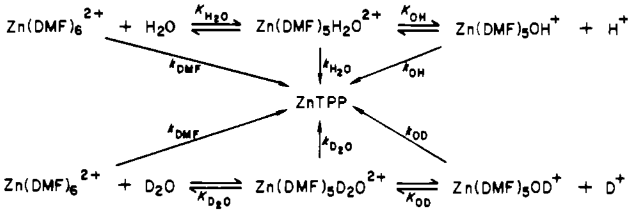


Figure 2. Dependence of the observed rate constant for the formation of ZnTPP. For all the kinetic runs with H_2O, H_2TPP was used, while for runs with D_2O (including the point at which $[D_2O] = 0$), the porphyrin was D_2TPP. The curves are fit for $K_{H_2O} = K_{D_2O} = 0.28$, and the limiting rates at high water concentration are 3.6×10^{-3} M^{-1} s^{-1} for the H_2O data and 1.6×10^{-3} M^{-1} s^{-1} for the D_2O data.

Scheme I



As is evident from Figure 2, H_2TPP and D_2TPP react at the same rate with $Zn(DMF)_6^{2+}$. Additionally, the general form of the dependence of the rate of metalation on the concentration of H_2O and D_2O (Figure 2) indicates similar rates as $[H_2O]$ and $[D_2O]$ approach zero. As the concentration of H_2O or D_2O increases, the rate constant increases. At the highest water concentrations studied (approaching the limit of solubility of the porphyrin), the isotope effect reaches a value of 2.0, showing that, as water replaces DMF in the coordination sphere, the difference between H_2O and D_2O manifests itself. A k_H/k_D ratio of 2.0 is far too large to be accommodated by the rate difference expected for the dissociation of OH_2 and OD_2 from a metal ion (on the basis of typical metal–oxygen stretching frequencies for aquo complexes[10] and the relative masses of OH_2 and OD_2, k_H/k_D is estimated to be 1.07). Similarly, such a large difference in rate would not be expected to arise from the dissociation of OH^- instead of OD^- from the zinc ion. A sizeable isotope effect is expected to result, however, for the dissociation of D^+ from D_2O bound to Zn^{2+} compared with dissociation of H^+ from H_2O bound to Zn^{2+} ($k_H/k_D \approx 7$). The processes involved in the reaction of Zn^{2+} to from ZnTPP in mixed media are summarized in Scheme I.

The rate expression for the isotope effect is

---

(2) P. Hambright In "Porphyrins and Metalloporphyrins"; K. M. Smith, Ed.; Elsevier: New York, 1975; pp 233–278

(3) Schneider, W. *Struct. Bonding (Berlin)* **1975**, *23*, 123–166.

(4) Cheung, S. K.; Dixon, F. L.; Fleischer, E. B.; Jeter, D. Y. M. Krishnamurty, M. *Bioinorg. Chem.* **1973**, *2*, 281–294.

(5) Johnson, N.; Krosropour, R.; Hambright, P. *Inorg. Nucl. Chem. Lett.* **1972**, *8*, 1063–1067.

(6) Thompson, A. N.; Krishnamurty, M. *J. Inorg. Nucl. Chem.* **1979**, *41*, 1251–1255.

(7) Bain-Ackerman, M. J.; Lavallee, D. K. *Inorg. Chem.* **1979**, *18*, 3358–3364.

(8) Boucher, L. J. Katz, J. J. *J. Am. Chem. Soc.* **1967**, *89*, 1340–1345.

(9) Strom, C. B.; Teklu, Y.; Sokloski, E. *Ann. N.Y. Acad. Sci.* **1973**, *206*, 631–634.

(10) Nakamoto, K. "Infrared Spectra of Inorganic and Coordination Compounds", 2nd ed.; Wiley-Interscience: New York, 1970; pp 166–169.

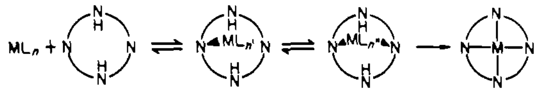
$$\frac{k_H}{k_D} = \{k_{DMF}[Zn(DMF)_6{}^{2+}] + k_{H_2O}[Zn(DMF)_5H_2O^{2+}] + k_{OH}[Zn(DMF)_5OH^+]\}/\{k_{DMF}[Zn(DMF)_6{}^{2+}] + k_{D_2O}[Zn(DMF)_5D_2O^{2+}] + k_{OD}[Zn(DMF)_5OD^+]\}$$

The rate ratio can be simplified considerably by using the assumptions that $k_{H_2O} \approx k_{D_2O}$ and $k_{OH} \approx k_{OD}$, arising from the small isotope effect expected for dissociation of relatively heavy species and two other assumptions that are experimentally justified. The equilibrium constants for replacement of DMF by H_2O or D_2O, K_{H_2O} and K_{D_2O}, are shown to be very similar from the fit of the curves in Figure 2. For a fit of the data for solutions containing H_2O, both K_{H_2O} and the limiting rate constant at high $[H_2O]$ were optimized. For a fit of the data for solutions containing D_2O, only the limiting rate constant was allowed to vary while K_{D_2O} was set equal to the K_{H_2O} value from the other curve. The excellent fit of the data for DMF/D_2O solutions support the assumption that $K_{D_2O} \approx K_{H_2O}$. The final assumption used in simplifying the rate expression is that K_{OH} and K_{OD} are $\ll 1$ in the DMF/aqueous media as they are in aqueous solution.[11] This assumption allows $[Zn(DMF)_5OH^+]$ to be expressed as $(K_{OH}/[H^+])[Zn(DMF)_5H_2O^{2+}]$ and $[Zn(DMF)_5OD^+]$ as $(K_{OD}/[D^+])[Zn(DMF)_5D_2O^{2+}]$, with $[Zn(DMF)_5H_2O^{2+}] \approx [Zn(DMF)_5D_2O^{2+}]$. This assumption is supported by the observation that, although the metalation reaction of Zn^{2+} with porphyrins is first order in Zn^{2+}, as $[H_2O]$ (or $[D_2O]$) is increased, the hydrogen ion (or deuterium ion) activity measured by a pH electrode for 0.10 M Zn^{2+} in DMF with 0.05–4.0 M H_2O is only the equivalent of 10^{-7} M, and it does not change measurably as the concentration of H_2O (or D_2O) is varied. Thus, in these solutions, $[H^+]$ (or $[D^+]$) is not changed by the change in $[Zn(DMF)_5H_2O^{2+}]$ (or $[Zn(DMF)_5D_2O^{2+}]$) and $[H^+] \ll$ Zn(II) total, so that K_{OH} (or K_{OD}) is $\ll 1$. With these assumptions, the simplified rate expression is

$$\frac{k_H}{k_D} = \left\{k_{DMF}[Zn(DMF)_6{}^{2+}] + k_{H_2O}[Zn(DMF)H_2O^{2+}] + \frac{k_{OH}K_{OH}}{[H^+]}[Zn(DMF)_5H_2O^{2+}]\right\} \Bigg/ \left\{k_{DMF}[Zn(DMF)_6{}^{2+}] + k_{H_2O}[Zn(DMF)_5H_2O^{2+}] + \frac{k_{OH}K_{OD}}{[D^+]}[Zn(DMF)_5H_2O^{2+}]\right\}$$

From this expression, the maximum value for k_H/k_D is $K_{OH}[D^+]/K_{OD}[H^+]$, and the actual value will depend on the importance of the path utilizing the hydroxo complex vs. the paths involving the aquo and DMF complexes. In aqueous solution Hambright and Chock have reported that $Zn(H_2O)_5OH^+$ reacts with $HTPPS_4$ 60 times as fast as does $Zn(H_2O)_6{}^{2+}$,[12] so it is to be expected that the hydroxo-complex path could dominate (the H^+ activity would not be expected to equal $[Zn(DMF)_5OH^+]$ since DMF is a basic solvent capable of decreasing $[H^+]$).

Scheme II



The ratio of limiting rates at high $[H_2O]$ which we have calculated for the Zn(II) metalation of H_2TPP and D_2TPP in DMF aqueous solutions is 2.3 which compares well with the values of k_H/k_D found for Zn(II) metalations of H_2TPPS_4[4] (2.2) and H_2TAPP[6] (2.4). Since we have shown that H_2TPP and D_2TPP react with Zn(II) at the same rate on the absence of added H_2O or D_2O and that k_{obsd} for the reaction depends on $[H_2O]$ and $[D_2O]$ in a manner consistent with equilibria involving hydroxo complex formation, we conclude that the origin of the kinetic isotope effect is the nature of the metal ion complex that reacts with the porphyrin and not the porphyrin itself. It should be noted that equilibria involving multihydrated complexes cannot be ruled out on the basis of the kinetic data but that the fit is consistent only for a complex with a single hydroxo ligand being present in the rate-determining step. The reaction sequences presented in Scheme I are the simplest ones consistent with the kinetic data.

The absence of a kinetic isotope effect due to the porphyrin free base but observation of a sizable effect attributable to changes in the reactivity of the complexing metal ion, combined with previously observed features of the metalation reaction,[1-3,7,13] leads to the following conclusions: (1) the dominant feature that causes large differences in rates of metalation for various metal ions is the loss of ligands from the reactive metal complex; (2) rate enhancement due to increased pH or addition of nitrogenous bases is due to changes in the nature of the reactive metal species;[14] (3) significant N–H bond-breaking during the rate-determining step is unlikely. Since the free-base porphyrin is commonly the reactive species[13,14] and N–H bond-breaking is not rate determining, it is reasonable to propose that a sitting-atop intermediate is formed and that its collapse to form the product metalloporphyrin is rapid with respect to the rate of its formation. Dissociation of a sitting-atop complex to reform the reactants, of course, may also be rapid. A reaction sequence of this type is illustrated in Scheme II.

Acknowledgment. We gratefully acknowledge support of this work by the CUNY BHE-PSC grants program.

Registry No. H_2TPP, 917-23-7; Zn^{2+}, 23713-49-7; D_2, 7782-39-0.

---

(11) Sillen, L. G.; Martell, A. E.; *Spec. Publ.-Chem. Soc.* **1964**, *No. 17.*

(12) Hambright, P.; Chock, P. B. *J. Am. Chem. Soc.* **1974**, *96* 3123–3131.

(13) Turay, J.; Hambright, P. *Inorg. Chem.* **1980**, *19*, 562–564.

(14) This conclusion relates to those porphyrins which require very strong bases to undergo proton dissociation to form anions (all the natural porphyrins, TPP, and phenyl-substituted *meso*-tetraarylporphyrins). More acidic porphyrins, such as tetrakis(*N*-methylpyridyl)porphyrin, may react via anionic forms in mildly basic solution: Hambright, P. *Inorg. Chem.* **1980**, *19*, 562–564.