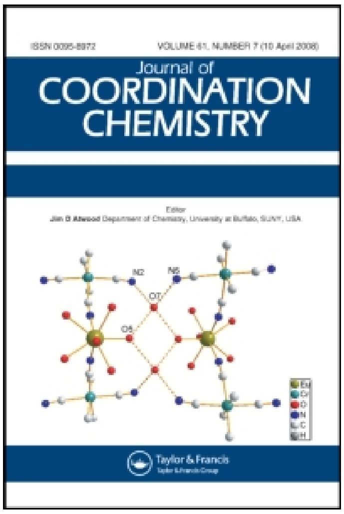

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ACID CATALYZED SOLVOLYSIS KINETICS OF ZINC(II), COBALT(II), COPPER(II) AND NICKEL(II)N-METHYL-TETRA-(4-SULFONATOPHENYL)PORPHYRINS

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A kinetic study of the acid solvolysis reactions of divalent nickel, cobalt, zinc and copper complexes of N-methyl-tetra(4-sulfonatophenyl)porphyrin was done at 25° C in aqueous solution. All reactions were first order in metalloporphyrin and first order in $[H^+]$. Only the Zn^{II} and Cu^{II} derivatives had a second term proportional to $[H^+][Ac^-]$. Calculated formation constants of the uncatalyzed reactions are in the order Ni > Cu ~ Zn > Co > Cd. The results show that kinetically N-alkylated metalloporphyrins require one less proton for acid solvolysis than do the corresponding metalloporphyrins.

KEYWORDS: porphyrins, acid catalyzed solvolysis, kinetics, zinc(II)

INTRODUCTION

Comparisons between the dynamic coordination chemistry of porphyrins and centrally N-alkylated porphyrins have been done in non-aqueous solvents primarily and the results often differ from studies in aqueous solutions.[1] Generally, N-alkylporphyrins are pre-deformed, more basic towards protons and react with metal ions faster than the corresponding porphyrin.[2,3] Such N-alkylated macrocycles stabilize the divalent Mn, Fe and Co oxidation states, while porphyrins tend to favor the trivalent forms.[4] In DMF, tetraphenylporphyrin (TPP) and N-methylated-TPP show different metallation rate laws[5,6] and in acetonitrile, the identity of the coordinated metal ion strongly influences the rate of nucleophilic displacement of the N-alkyl group.[7] The mechanism of migration of the methyl group from the porphyrin to the coordinated metal has been probed by pulse-radiolysis techniques with the water soluble Ni^{II} and Co^{II}-NMeP (NMeP = N-methyl-tetra(4-sulphonatophenyl)porphyrin) adducts,[8] and the kinetics of metal ion incorporation into NMeP are known.[9] For methanol/HCl solutions, the rate law for dissociation of zinc from etioporphyrin-III was third order in HCl at low acidities, while only second order for the N-methyl-etio.[10] We report the kinetics of the acid catalyzed solvolysis reactions of Ni^{II}, Co^{II}, Cu^{II} and Zn^{II} complexes of NMeP, and find different rate behavior from that shown in methanol. Our results are compared with

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the corresponding reactions of the unmethylated tetra(4-sulfonatophenyl)-porphyrin(H_2-TPPS).

In a slightly different context, cobalt(II) and nickel(II) chloride are superior low dose prophylactic anti-cyanide drugs in mice.[11] The Co(II) and Ni(II)-NMeP complexes have potential as less cardiotoxic metal ion delivery agents, capable of binding cyanide with the subsequent release of the fairly benign metal-cyano complexes at certain cyanide tensions in solution, while the toxic excess metal remains with the N-MeP. In contrast, cyanide does not cause loss of the metal from most metalloporphyrins, which themselves are rather poor *in vivo* cyanide scavengers. This current study indicates the stability of the metal in M^{II}-NMeP species to acid and ligand catalyzed solvolysis reactions, an important consideration in the design of metal containing anti-cyanide drugs.

EXPERIMENTAL

The N-methyl-tetra(4-sulfonatophenyl)porphyrin and its metal complexes were prepared by literature procedures[8,12] and the acids were standardized by conventional techniques. The kinetics were run at 25° C on a thermostatted Beckman DU-70 spectrophotometer, and the pH's monitored on a Radiometer PHM-64 pH meter. For simplicity, the abbreviations H-NMeP and H_2-TPPS do not indicate the four ionized -SO_3^- groups on the periphery of these porphyrins.

RESULTS

In 0.10 M $NaNO_3$ at pH 7.5 (1.0×10^{-4} M Tris buffer), H_2-NMeP$^+$ followed Beer's law from 4×10^{-5} to 3×10^{-8} M, indicating that the porphyrin behaves as a monomer. The acid dissociation constants of N-MeP were studied by spectrophotometric pH titrations from pH 1–13 at an ionic strength of 0.1 ($NaNO_3$) in unbuffered solutions, and the equilibria are defined as follows:

$$H_3\text{-NMeP}^{2+} \rightleftarrows H_2\text{-NMeP}^{+} + H^{+} \qquad K_4 \qquad (1)$$

$$H_2\text{-NMeP}^{+} \rightleftarrows H\text{-NMeP} + H^{+} \qquad K_3 \qquad (2)$$

The values of pK_4 and pK_3 were found to be 3.0 ± 0.1 and 9.1 ± 0.3 respectively, in excellent agreement (3.0, 8.8) with previous work.[9]

At an ionic strength of 1.0 ($HNO_3/NaNO_3$), the kinetics of nickel removal from Ni^{II}-NMeP$^+$($\sim 10^{-6}$ M) were cleanly first older in porphyrin over more than three half-lives, with a *pseudo* first order rate constant, k_{obs}. The product porphyrin retained the central N-Me group. Figure 1 shows that the reaction is also first order in [H^+] from 8.6×10^{-1} to 8.6×10^{-2} M. The specific rate constant, k_d, was (6.4 ± 0.2) $\times 10^{-4}$ $M^{-1}s^{-1}$. The Co^{II}-NMeP$^+$ was also first order in porphyrin and [H^+] from pH 2.7 to 3.9 at I = 0.1 ($NaNO_3$), using 2.0×10^{-2} M chloroacetic acid (pK_a = 2.6) as the buffer. No dependence of k_{obs} on the chloroacetate ion concentration was found, and k_d = 12. ± 1. $M^{-1}s^{-1}$.

The acid solvolysis reaction of Cu^{II}-NMeP$^+$ at I = 0.1 ($NaNO_3$) was first order in porphyrin and dependent on both the acid and acetate concentrations in acetic acid (2.0×10^{-2} M, $pK_a = 4.53$) buffers. Fig. 1 is a linear plot of ($k_{obs}/[H^+]$) *vs.* $[Ac^-]$, for the rate expression formulated as

$$k_{obs} = k_d [H^+] + k_{cd} [H^+] [Ac^-] \qquad (3)$$

Under the same conditions, the Zn^{II}-NMeP$^+$ reaction followed the same rate law, and the k_d and k_{cd} values are tabulated in Table 1.

DISCUSSION

Beer's law studies indicate that the mono-cation H_2-MeP$^+$ ($pK_3 = 9.1$, $pK_4 = 3.0$)

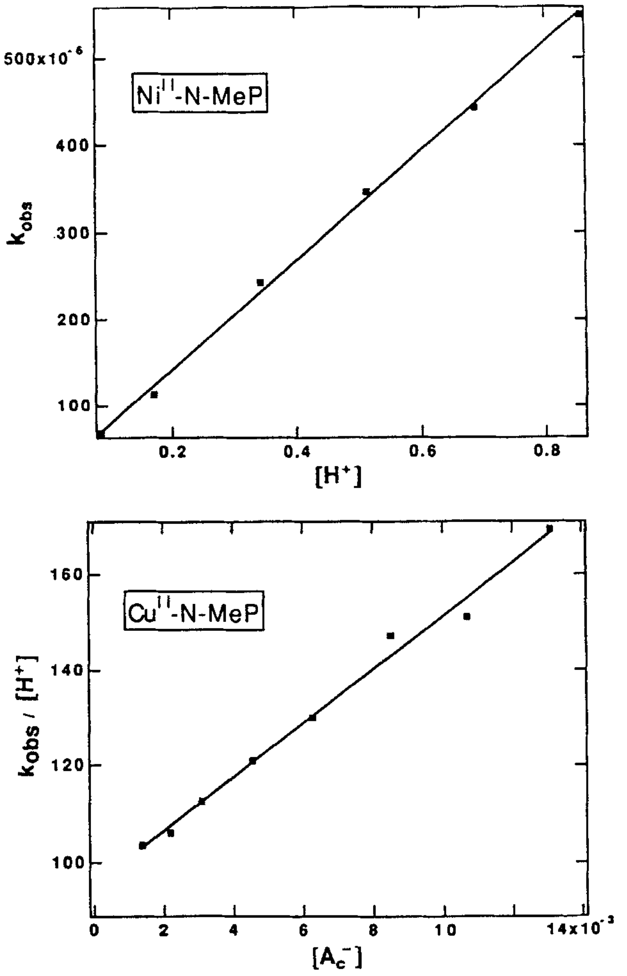

Figure 1 Top. First order dependence of k_{obs} on (H^+) for the acid solvolysis reaction of Ni^{II}-N-MeP. Bottom. Plot of [k_{obs} / (H^+)] vs. (Ac^-) indicating the acetate independent and dependent terms of the Cu^{II}-N-MeP acid solvolysis process.

Table 1 Rate constants for the acid and acetate catalyzed dissociation reactions of M^{II}-N-MePs, and H-N-MeP formation rate and equilibrium constants.

Metal	k_d ($M^{-1}\ s^{-1}$)	k_{cd} ($M^{-2}\ s^{-1}$)	k_f ($M^{-1}\ s^{-1}$)[a]	K_M (M^{-1})
Nickel(II)	$(6.4 \pm 0.1) \times 10^{-4}$		$\sim 3 \times 10^{-1}$	$\sim 5 \times 10^2$
Copper(II)	$(9.5 \pm 0.2) \times 10$	$(5.6 \pm 0.2) \times 10^3$	$\sim 1 \times 10^4$	$\sim 1 \times 10^2$
Cobalt(II)	$(1.2 \pm 0.1) \times 10$		1.9×10^2	1.6×10
Zinc(II)	$(5.3 \pm 0.3) \times 10$	$(2.7 \pm 0.3) \times 10^3$	5.0×10^3	9.4×10
Cadmium(II)[a]	1.9×10^7		2.3×10^5	1.2×10^{-2}

[a]Data from ref. 5, or estimated as noted in the text.

at pH 7.5 is monomeric below 4×10^{-5} M, whereas the less basic ($pK_3 = 4.7$, $pK_4 = 4.8$)[13] free base of H_2-TPPS at the same pH exhibits a concentration dependent monomer-dimer equilibrium.[14] In addition, resonance light-scattering techniques demonstrate that the di-acid H_4-$TPPS^{2+}$ is a large extended aggregate in acid, whereas H_3-$NMeP^{2+}$ shows no such behavior.[15] For both porphyrin types, kinetic studies reveal that only the free bases (not the protonated mono- or di-cations) are the major reactants in metal ion incorporation.[9,13] For Zn(II), the specific rate constants for Zn^{2+} and $Zn(OH)^+$ reactions with H-NMeP are 5.0×10^3 and $4.4 \times 10^4\ M^{-1}s^{-1}$, while for H_2-TPPS, the rate constants are substantially smaller, 1.2 and $3.1 \times 10^1\ M^{-1}s^{-1}$, respectively. Correlations have been made between the Zn^{2+} incorporation rate constants (k_f) for tetrasulfonated porphyrins[13] and the porphyrin basicity, pK_3. The prediction is that H-NMeP should have a k_f of 16 $M^{-1}s^{-1}$ based on its pK_3, substantially lower than the $5 \times 10^3\ M^{-1}s^{-1}$ result found. Thus, basicity alone does not account for the enhanced N-alkyl porphyrin reactivity. The N-MeP nucleus is deformed, since the proton and $-CH_3$ group cannot both fit into the central porphyrin cavity. For non N-alkylated species, the porphyrin nucleus must undergo an unfavorable deformational equilibrium process (K_D) before metal ion incorporation. The pre-deformed N-alkylporphyrins, in which the coordinated metal lies out of the plane (the crystal structures of the N-alkyl porphyrins,[16] both with and without the metal are similar) react faster with metal ions as a substantially smaller reorganization K_D is required. In addition, one less proton needs to be removed from the free base of the N-alkyl derivatives upon metalloporphyrin formation.

Table 1 is a list of the acid catalyzed solvolysis rate constants k_d, and acetate dependent k_{cd} terms. One possible mechanism of the reactions of the catalyzed Ni(II) and Cu^{II}-NMeP's is

$$M^{II}\text{-}NMeP^+ + Ac^- \rightleftarrows Ac\text{-}M^{II}\text{-}NMeP \qquad K \qquad (4)$$

$$M^{II}\text{-}NMeP^+ + H^+ \rightarrow \text{products} \qquad k_1 \qquad (5)$$

$$Ac\text{-}M^{II}\text{-}NMeP + H^+ \rightarrow \text{products} \qquad k_2 \qquad (6)$$

The dependence of k_{obs} on $[H^+]$ and $[Ac^-]$ would then be

$$k_{obs} = (k_1\ [H^+] + k_2\ K\ [H^+]\ [Ac^-])\ /\ (1 + K[Ac^-]) \qquad (7)$$

If $1 \gg K\ [Ac^-]$, then eq. 7 is of the same form as sq. 3, with $k_1 = k_d$ and $k_2K = k_{cd}$. In this context, acetate coordinates with the metal, and the reduced charge of the complexed ion facilitates its departure. Acetate also catalyzes the acid solvolysis reactions of Mg^{II}-TPPS.[17] However, a kinetic ambiguity arises in that the activated complex (H^+—AcM^{II}—NMeP)* has the same composition as (HAc—M^{II}—NMeP)*, and thus HAc could be the reactant with M^{II}-NMeP in the catalyzed pathway. The rate laws for both formulations are indistinguishable.

The equilibrium constants, K_M, for the reactions

$$M^{2+} + \text{H-NMeP} \rightleftarrows M^{II}\text{-NMeP}^+ + H^+ \qquad K_M \qquad (8)$$

are equal to the ratio of the formation and dissociation rate constants, k_f/k_d. The k_f values in Table 1 are based on the data of Tanaka and coworkers,[9] which were often measured at ionic strengths different from the 0.1 used in this study. In addition, based on results for tetra(N-methyl-4-pyridyl)porphyrin,[18] we assume that the Cu^{2+} / H-NMeP rate constant is the same as the reported $Cu(Ac)^+$ value and the k_f for Ni^{2+} was calculated from the single observation at pH 8. With such assumptions, the approximate K_M values, tabulated in Table 1, are in the order Ni > Cu ~ Zn > Co > Cd. Buchler[19] has defined a stability index S_i (= $100\ Z\ E_N/r_i$), where Z is the ion charge, r_i the effective ionic radii and E_N the Pauling electronegativity (a measure of covalence). The S_i constants are 6.88 (Ni) > 6.12 (Cu) > 5.78 (Co) > 4.46 (Zn) > 3.56 (Cd), a different sequence from the present K_M values. The relative acid dissociation rates of M^{II}-tetra(4-N,N,N-trimethylanilinium) porphyrins were shown to be faster[20] for lower values of S_i, while for the present M^{II}-NMeP's, the dissociation order is Cd > Cu > Zn > Co > Ni. These different orders may reflect difference between the square planar/square pyramidal geometries of the metalloporphyrins, in contrast to the basically tetrahedral structures in the metallo-N-alkylated derivatives.

For most divalent metalloporphyrins (Zn, Cd, Pb, Mg, Fe), the acid solvolysis kinetics are first order in porphyrin,[13] and either second order, or between first and second order in $[H^+]$. These observations are accommodated in the following scheme:

$$M^{II}\text{-P} + H^+ \rightleftarrows (M^{II}\text{-P-H}) \qquad k_3, k_{-3} \qquad (8)$$

$$(M^{II}\text{-P-H}) + H^+ \longrightarrow \text{products} \qquad k_4 \qquad (9)$$

With (M^{II}-P-H) as a steady state intermediate,

$$k_{obs} = k_3\,[H^+]^2 \,/\, ((k_{-3} \,/\, k_4) + [H^+]) \qquad (10)$$

For Zn-TPPS in water,[13] the second protonation step is rate limiting with $(k_{-3} / k_4) \gg [H^+]$ and $k_{obs} \alpha [H^+]^2$. For the present Zn-NMeP in water, perhaps only one proton is needed for solvolysis (eq. 9 need not occur) and $k_{obs} \alpha [H^+]$. The same phenomenon is noted in the methanol/HCl solvolysis reactions of zinc etioporphyrin-III complexes.[10] For the Zn-Etio, $k_{obs} = a[HCl]^3 / (b + [HCl])$, while for Zn-NMeEtio, $k_{obs} = c[HCl]^2/(d + [HCl])$, where a, b, c and d are constants. At high acidities, two protons are needed for solvolysis of Zn-P in methanol, while only one is required for Zn-NMeP species. Thus in both methanol and water, the N-methylated porphyrins require one less proton in the activated complex for acid solvolysis than do the corresponding porphyrins. The initial metalloporphyrins are four coordinate with respect to the metal, and in water, two proton addition gives $(M\text{-}PH_2)^*$, a sitting-atop type activated complex[21] of the cation on a free-base porphyrin. Crystal structures show that N-alkylated metalloporphyrins have three short M-N bonds and one longer and weaker M-N attachment to the formally sp^3 hybridized nitrogen bound to the alkyl group.[1] Thus, only one proton is needed to produce the sitting-atop (M-NMePH)* structure. This is consistent with the metalloporphyrin formation kinetics for both species, which also feature an activated complex containing the metal ion and free-base porphyrin.

The M^{II}-NMeTPPS acid solvolysis reactions appear faster than those of M^{II}-TPPS. For example Ni^{II} and Cu^{II} TPPS are stable for weeks in 1M H^+ while the half-lives for the corresponding M^{II}-N-MeTPPS complexes are ~18 min. and 7.2 ms, respectively. From the known rate laws, the rate ratio [(Zn-NMe-TPPS) / (Zn-TPPS)] = 2.4 / $[H^+]$. Thus at $[H^+]$ = 2.4 the solvolysis rates for the two porphyrins are predicted to be the same. Above 2.4 M $[H^+]$, Zn-TPPS is faster, while below 2.4 M, the Zn-NMeTPPS complex is more rapid, increasing by a factor of ten for each unit decrease in pH. Further studies on the unusual reactivities of metallo-NMeP's are in progress.

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