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# Kinetics and Mechanisms of Dealkylation Reactions of *N*-Methylporphyrin Complexes. 3. Effects of Porphyrin Ring Substituents and Reaction Media

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Copper(II) complexes of *N*-methylporphyrins react with nucleophiles under mild conditions to produce the corresponding non-N-alkylated metalloporphyrin and methylated nucleophile. Under similar conditions the rates for the reactions of Cu(II) complexes of *N*-methyltetraphenylporphyrin, *N*-methyltetrakis(*p*-sulfophenyl)porphyrin and *N*-methyldeuteroporphyrin IX dimethyl ester with di-*n*-butylamine in acetonitrile are quite similar. The reactions are first order with respect to the copper(II) *N*-methylporphyrin complexes but are only first order with respect to nucleophile concentration at relatively low concentration. Plots of the pseudo-first-order rate constants vs. nucleophile concentration show a negative deviation from linearity at high nucleophile concentrations. These results are consistent with a mechanism involving two first-order paths, one that involves two molecules of the nucleophile in the activated complex and has a smaller rate constant and another that has one molecule of nucleophile in the activated complex and predominates at low nucleophile concentration. The activation parameters for the path at low nucleophile concentration for the three reactions are similar ($\Delta H^{\ddagger}$ = 16.9 ± 1.0 kcal/mol, $\Delta S^{\ddagger}$ = −13.1 ± 2.9 eu, $\Delta G^{\ddagger}$ = 20.8 ± 1.9 kcal/mol; $\Delta H^{\ddagger}$ = 15.3 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = −20.2 ± 0.9 eu, $\Delta G^{\ddagger}$ = 20.8 ± 1.3 kcal/mol; $\Delta H^{\ddagger}$ = 15.6 ± 0.7 kcal/mol, $\Delta S^{\ddagger}$ = −17.6 ± 2.2 eu, $\Delta G^{\ddagger}$ = 21.3 ± 1.3 kcal/mol, respectively), indicating that even relatively large differences in ring substitutents have little effect on rates of dealkylation promoted by metal ions. The reactions of [*N*-methyltetrakis(*p*-sulfophenyl)porphinato]copper(II) with dialkylamines in $CH_3CN$ and $H_2O$ show that the highly polar aqueous medium substantially decreases the rate (by nearly 100-fold at low nucleophile concentration) and the dependence of the rate of nucleophile concentration is first order in aqueous solution even at high concentrations. In acetonitrile and dichloromethane, dialkylamines are better nucleophiles than pyridine. In $CH_3CN$, chloride is a poorer nucleophile than dialkylamines, and in water, no reaction is observed with $Cl^-$. In $CH_2Cl_2$, the rate is essentially independent of chloride concentration, indicating that the dealkylation involves a preformed ion pair.

## Introduction

N-Substituted porphyrins and corresponding metal ion complexes have received considerable attention recently, in part because of the discovery that *N*-alkylporphyrins are formed from the interaction of cytochrome P-450 with a variety of substrates.[1] The *N*-alkylporphyrins are also of interest because they can be used as synthetic precursors for the rapid synthesis of metal complexes of the corresponding non-N-alkylated porphyrins such as palladium-109 hematoporphyrin, which is currently being studied as an agent for specific lymphatic ablation.[2] Some complexes of *N*-alkylporphyrins are strong alkylating reagents, which may show selective cytotoxicity, and one complex, [*N*-methyltetrakis(*p*-sulfophenyl)porphinato]-copper(II), has shown reproducible activity in the P388 lymphocytic leukemia test system. An important property of these porphyrins is their relative stability (or, more properly in many cases, lability) with respect to dealkylation. Hambright first observed that an *N*-methyl metalloporphyrin, (*N*-methyletioporphinato)zinc(II), was slowly dealkylated in pyridine.[3] Subsequently, we reported the kinetics of dealkylation of *N*-methyltetraphenylporphyrin complexes of copper, nickel, manganese, and zinc with dialkylamines in acetonitrile.[4,5] Although the dependence of the dealkylation rate on the nature of the metal ion bound to the *N*-methylporphyrin has been investigated to some extent, the dependence of the rate of such important factors as the nature of the substituents on the porphyrin ring, the solvent, the alkyl leaving group, and the nucleophile are as yet relatively unexplored. In this report we discuss results pertaining to reactions of three disparate porphyrins, *N*-methyltetraphenylporphyrin (*N*-$CH_3$HTPP), *N*-methyltetrakis (*p*-sulfophenyl)porphyrin (*N*-$CH_3$HTPPS$_4$), and *N*-methyldeuteroporphyrin IX dimethyl ester (*N*-$CH_3$DP) in different solvents (water, acetonitrile, and dichloromethane) with di-*n*-butylamine, diethylamine, pyridine, and chloride ion as nucleophile.

## Experimental Section

The syntheses of *N*-methyltetraphenylporphyrin, *N*-methyltetrakis(*p*-sulfophenyl)porphyrin, and *N*-methyldeuteroporphyrin IX dimethyl ester have been reported previously.[6-8] The elemental analysis results for different preparations of the *N*-$CH_3$HTPPS$_4$ were inconsistent with any single formulation. Since the complex has a positively charged center and negatively charged periphery, it is possible that it can associate in different geometries that require different numbers of counterions and waters of crystallization. A sample used to obtain extinction coefficients gave an elemental analysis for the formulation $C_{45}H_{30}N_4S_4O_{12}Na_3Cl$. In all cases, thin-layer chromatograms using $CHCl_3$/MeOH (4:5) gave a single spot with an $R_f$ value of 0.71. The 300-MHz proton NMR spectrum of this material shows only a single series of peaks attributable to a para-sulfonated *N*-methylporphyrin—two doublets due to phenyl protons at 8.195 and 8.278 ppm with coupling constants of 7.8 Hz, β-pyrrolic hydrogen signals at 7.569 (assigned to the alkylated ring) and 8.984 ppm (assigned to the ring opposite to the alkylated ring), and doublets at 8.524 ($J$ = 4.5 Hz) and 8.743 ppm ($J$ = 4.5 Hz) assigned to the protons of other rings. The *N*-methyl proton resonance is at 4.00 ppm upfield from $Me_4Si$. (One note concerning all of these synthesis is in order. A powerful but possibly less dangerous methylating agent, methyl trifluoromethanesulfonate, can be substituted for methyl fluorosulfate without significant alteration in procedure or yield.) Copper complexes of the *N*-methylporphyrins are generally prepared in situ by mixing solutions of a Cu(II) salt in slight excess and the *N*-methylporphyrin in the presence of noncoordinating base such as 2,6-lutidine or 2,2,6,6-tetramethylpiperidine. They exhibit visible absorption spectra typical of *N*-methylporphyrin complexes.[8,9] The spectra of protonated

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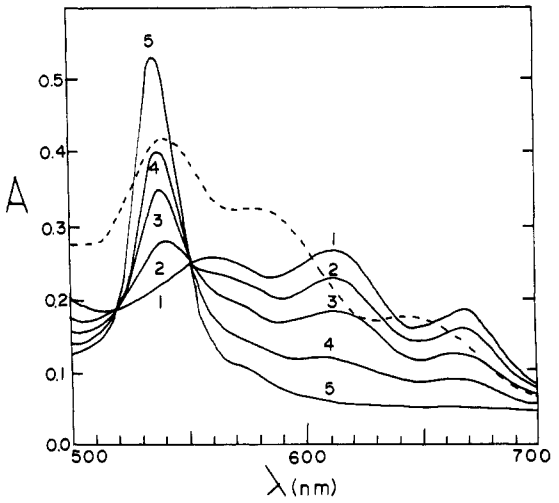


**Figure 1.** Spectra of the (*N*-methyltetraphenylporphinato)copper(II) cation in dichloromethane: before the addition of di-*n*-butylamine (the dashed line), just after addition (1), and after completion of the dealkylation reaction (5). The final spectrum (5) corresponds to that of (tetraphenylporphinato)copper(II).

**Table I.** First-Order Rate Constants for the Reaction of (*N*-Methyltetraphenylporphinato)copper(II) Cation with Di-*n*-butylamine in Acetonitrile at 45 °C[a,b]

| [amine], M | $10^3k$, $s^{-1}$ | [amine], M | $10^3k$, $s^{-1}$ |
|---|---|---|---|
| 0.0073 | 0.088 ± 0.001 | 0.112 | 1.64 ± 0.04 |
| 0.0182 | 0.302 ± 0.012 | 0.145 | 2.11 ± 0.03 |
| 0.0362 | 0.630 ± 0.007 | 0.216 | 2.46 ± 0.07 |
| 0.0530 | 0.808 ± 0.027 | 0.433 | 3.96 ± 0.04 |
| 0.0725 | 1.20 ± 0.020 | 0.868 | 5.92 ± 0.20 |
| 0.108 | 1.36 ± 0.06 | 1.30 | 7.42 ± 0.43 |

[a] Additional data obtained at 25 and 65 °C are presented in ref 4. [b] In this and subsequent tables in this article, the error limits are averaged deviations for two to six independent determinations of each rate constant. Typically the data for each kinetic run fit a first-order function for at least 4 half-lives with agreement between each calculated and observed absorbance value better than ±1%.

*N*-methylporphyrins resemble those of complexes;[8,9] however, spectra of the Cu(II) complexes not altered by the addition of a noncoordinating base such as 2,6-di-*tert*-butylpyridine or 2,2,6,6-tetramethylpiperidine. The trifluoromethanesulfonate salt of (methyltetraphenylporphinato) copper(II) was isolated and shows the expected visible absorption spectrum observed by Stinson and Hambright for the corresponding chloride salt.[10] Solvents and dialkylamines were purified by published procedures.[11] Pyridine (Fisher and Eastman spectral grade) was used without further purification. Tetraethylammonium chloride (Eastman) was recrystallized from ethanol and dried in vacuo.

Kinetic data were obtained with Beckman DU-8, Cary 14, and Varian 635-D spectrophotometers with self-contained solid-state temperature control and Lauda B-2 and Fisher Model 90 circulating constant-temperature baths, respectively. Data were analyzed by using statistics programs available with the PROPHET computing system. In all cases, nucleophiles were used in pseudo-first-order excess.

For reactions of the tetra-*n*-butylammonium salt of [*N*-methyltetrakis(*p*-sulfophenyl)porphinato]copper(II), stock solutions were prepared as follows: Solutions of $Cu(CF_3SO_3)_2 \cdot 6H_2O$ (2.5 mL, 1.11 × $10^{-3}$ M in $CH_3CN$) and *N*-$CH_3HTPPS_4(NBu_4)_4$ (2.5 ml, 1.03 × $10^{-3}$ M in $CH_3CN$) were added with 0.02 mL of 2,6-lutidine and diluted to 50.0 mL in a volumetric flask. Kinetic data were obtained at 596 nm. Stock solutions of Cu(*N*-$CH_3DP^+$) were obtained by mixing 0.64 mL of 8.4 × $10^{-5}$ M *N*-$CH_3DP$ in $CH_3CN$, 0.64 mL of 1.4 × $10^{-4}$ M, $Cu(CF_3SO_3)_2 \cdot 6H_2O$ in $CH_3CN$, and 1 mL of a solution of 2,2,6,6-tetramethylpiperidine (0.02 mL of tetramethylpiperidine in 25 mL of $CH_3CN$) and diluting to 10.0 mL with $CH_3CN$. Data were obtained at 393 nm. Isosbestic points are observed at 380 and 400 nm. In the reactions of the trifluoromethanesulfonate salt of Cu(*N*-$CH_3TPP)^+$ with di-*n*-butylamine and tetramethylammonium chloride in dichloromethane, isobestic points are observed at 518 and 550 nm. On addition of nucleophiles to Cu(*N*-$CH_3TPP(CF_3SO_3)$) in $CH_2Cl_2$ the color changes from brown to green (from peaks at 540, 588, and 650 nm to peaks at 560, 610, and 664 nm). Presumably the bathochromic shift is caused by axial ligation of amine. Spectra taken during the course of a reaction are shown in Figure 1.

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(11) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: London, 1966.

**Table II.** First-Order Rate Constants for the Reaction of (*N*-Methyltetrakis(*p*-sulfophenyl)porphinato)copper(II) Anion with Di-*n*-butylamine in Acetonitrile

| temp, °C | [amine], M | $10^3k$, $s^{-1}$ | temp, °C | [amine], M | $10^3k$, $s^{-1}$ |
|---|---|---|---|---|---|
| 25.3 | 0.070 | 0.251 ± 0.010 | 44.5 | 0.28 | 3.64 ± 0.16 |
| 25.3 | 0.14 | 0.430 ± 0.001 | 44.5 | 0.56 | 5.82 ± 0.33 |
| 25.3 | 0.28 | 0.744 ± 0.002 | 63.8 | 0.14 | 7.35 ± 0.09 |
| 25.3 | 0.56 | 1.14 ± 0.02 | 63.8 | 0.28 | 11.4 ± 0.4 |
| 44.5 | 0.14 | 2.08 ± 0.07 | | | |

**Table III.** First-Order Rate Constants for the Reaction of (*N*-Methyldeuteroporphyrin IV dimethyl ester)copper(II) Cation with Di-*n*-butylamine in Acetonitrile

| temp, °C | [amine], M | $10^3k$, $s^{-1}$ | temp, °C | [amine], M | $10^3k$, $s^{-1}$ |
|---|---|---|---|---|---|
| 25.4 | 0.125 | 0.151 ± 0.003 | 44.2 | 0.500 | 1.84 ± 0.05 |
| 25.4 | 0.250 | 0.233 ± 0.008 | 63.0 | 0.0625 | 1.63 ± 0.06 |
| 25.4 | 0.500 | 0.327 ± 0.008 | 63.0 | 0.125 | 2.84 ± 0.01 |
| 44.2 | 0.125 | 0.718 ± 0.009 | 63.0 | 0.500 | 7.93 ± 0.08 |
| 44.2 | 0.250 | 1.19 ± 0.002 | | | |

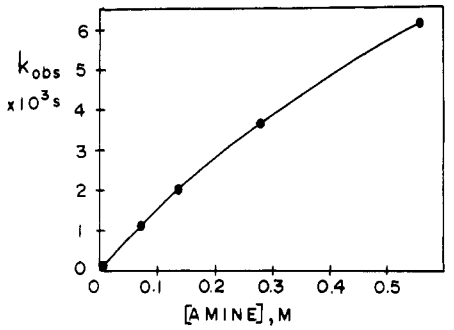



**Figure 2.** Plot of the observed pseudo-first-order rate constant for the reaction of the (*N*-methyltetrakis(*p*-sulfophenyl)porphinato)-copper(II) anion with di-*n*-butylamine in acetonitrile at 44.5 °C vs. the concentration of di-*n*-butylamine.

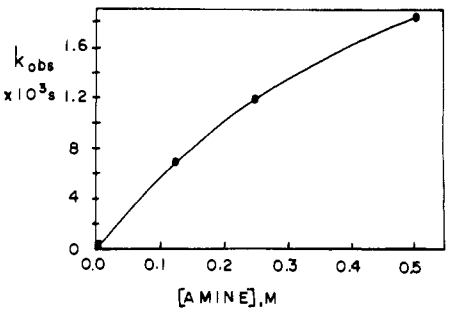



**Figure 3.** Plot of the observed pseudo-first-order rate constant for the reaction of (*N*-methyldeuteroporphyrin IX dimethyl ester)copper(II) with di-*n*-butylamine in acetonitrile at 44.2 °C vs. the concentration of di-*n*-butylamine.

## Results

Tables I–III contain data for the reactions of copper(II) complexes of *N*-methyltetraphenylporphyrin (Cu(*N*-$CH_3TPP)^+$), *N*-methyltetrakis(*p*-sulfophenyl)porphyrin (Cu-($N$-$CH_3TPPS_4)^{3-}$), and *N*-methyldeuteroporphyrin IX di-

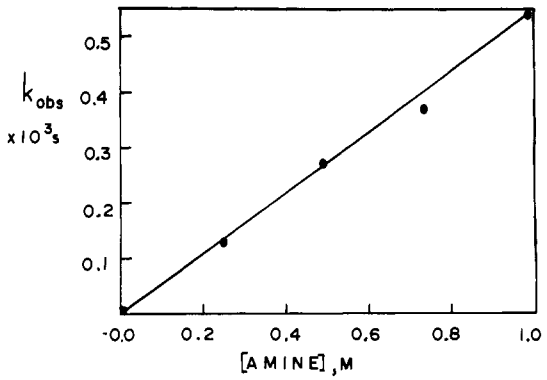



**Figure 4.** Plot of the observed pseudo-first-order rate constant for the reaction of (*N*-methyltetrakis(*p*-sulfophenyl)porphinato)copper(II) with diethylamine in aqueous solution at 45.1 °C vs. the concentration of diethylamine.

**Table IV.** First-Order Rate Constants for the Reaction of (*N*-Methyltetrakis(*p*-sulfophenyl)porphinato)copper(II) Anion with Diethylamine in Aqueous Solution

| temp, °C | [amine],[a] M | $10^3k$, s$^{-1}$ | temp, °C | [amine],[a] M | $10^3k$, s$^{-1}$ |
|---|---|---|---|---|---|
| 25.4 | 0.242 | 0.0101 | 45.1 | 0.242 | 0.123 ± 0.001 |
| 25.4 | 0.488 | 0.0219 | 45.1 | 0.488 | 0.273 ± 0.004 |
| 25.4 | 0.735 | 0.0332 | 45.1 | 0.735 | 0.361 ± 0.004 |
| 37.0 | 0.488 | 0.102 ± 0.001 | 45.1 | 0.982 | 0.540 ± 0.008 |

[a] Concentration determined on the basis of the dissociation constant of diethylammonium ion ($3.2 \times 10^{-11}$). No dealkylation is observed in aqueous solutions containing high concentrations of $OH^-$ but no amine. Therefore, $OH^-$ was not considered as a competing nucleophile in these reactions. The solutions were unbuffered.

methyl ester (Cu(*N*-$CH_3$DP)$^+$) with di-*n*-butylamine in acetonitrile. As will be discussed subsequently, these reactions are not simply first order with respect to the concentration of di-*n*-butylamine, as can be seen in Figures 2 and 3 for Cu(*N*-$CH_3$,TPPS$_4$)$^{3-}$ and Cu(*N*-$CH_3$DP)$^+$, respectively, and a similar plot in ref 4 for Cu(*N*-$CH_3$TPP)$^+$. For the comparison of activation parameters, presented in Table VIII, the initial linear segment of the plot of the observed pseudo-first-order rate constant vs. amine concentration (giving $k_1$) was employed.

Table IV contains data for the reaction of Cu(*N*-$CH_3$TPPS$_4$)$^{3-}$ with diethylamine in aqueous solution and Tables V and VI contain data for the reactions of Cu(*N*-$CH_3$TPP)$^+$ with di-*n*-butylamine and tetraethylammonium chloride, respectively, in dichloromethane. Activation parameters for reactions referred to in Tables I–V are presented in Table VIII. The reaction of Cu(*N*-$CH_3$TPPS$_4$)$^{3-}$ with diethylamine in aqueous solution is first order with respect to amine, as shown in Figure 4. The plot of the observed rate

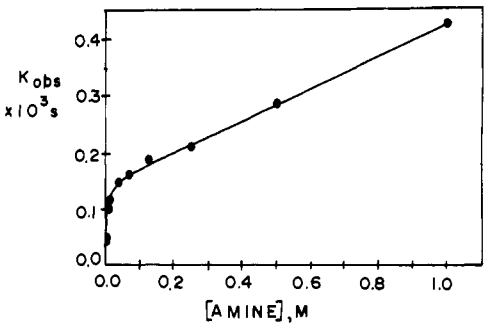
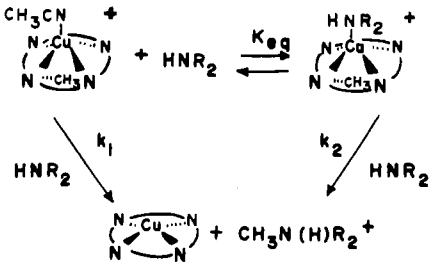



**Figure 5.** Plot of the observed pseudo-first-order rate constant for the reaction of (*N*-methyltetraphenylporphinato)copper(II) with di-*n*-butylamine in dichloromethane at 30.0 °C vs. the concentration of di-*n*-butylamine.

Scheme I




constant vs. nucleophile concentration for the reaction of Cu(*N*-$CH_3$TPP)$^+$ with di-*n*-butylamine in dichloromethane is shown in Figure 5. The reaction with tetraethylammonium chloride is nearly independent of its concentration. The low boiling point of dichloromethane and the relative slowness of the reactions prevented study of the reactions over a wide temperature range.

Table VII contains a summary of $k_1$, $k_2$, and $K_{eq}$ values. Since $k_2$ and $K_{eq}$ are coupled, statistical analysis results in a wide range of values.

## Discussion

In previous studies of the dealkylation of *N*-methyltetraphenylporphyrin complexes in acetonitrile, we found that the rate of dealkylation was not first order with respect to nucleophile concentration at relatively high concentrations of the nucleophile (di-*n*-butylamine) if the metal ion complexed with the *N*-methylporphyrin was either Cu(II) or Ni(II).[4,5] First-order behavior was exhibited, however, by Mn(II) and Zn(II) complexes.[5] A mechanism consistent with these observations was proposed (Scheme I). It involves concurrent $S_N2$ paths with either the solvent as axial ligand ($k_1$ path) or

**Table V.** First-Order Rate Constants for the Reaction of (*N*-Methyltetraphenylporphinato)copper(II) Cation with Di-*n*-butylamine in Dichloromethane

| temp, °C | [amine], M | $10^3k$, s$^{-1}$ | temp, °C | [amine], M | $10^3k$, s$^{-1}$ |
|---|---|---|---|---|---|
| 25.2 | 0.00125 | 0.0390 ± 0.0011 | 30.0 | 0.0625 | 0.0986 ± 0.0036 |
| 25.2 | 0.00625 | 0.0400 ± 0.0012 | 30.0 | 0.0125 | 0.122 ± 0.001 |
| 25.1 | 0.0188 | 0.0476 ± 0.0010 | 30.0 | 0.250 | 0.150 ± 0.001 |
| 25.1 | 0.0313 | 0.0504 ± 0.0006 | 30.0 | 0.500 | 0.241 ± 0.002 |
| 25.2 | 0.0625 | 0.0514 ± 0.0002 | 30.0 | 1.00 | 0.394 ± 0.014 |
| 25.2 | 0.125 | 0.0748 ± 0.0009 | 35.0 | 0.00125 | 0.0429 ± 0.0006 |
| 25.1 | 0.250 | 0.0852 ± 0.0004 | 35.0 | 0.00625 | 0.111 ± 0.003 |
| 25.2 | 0.500 | 0.153 ± 0.005 | 35.0 | 0.0312 | 0.142 ± 0.003 |
| 25.2 | 1.00 | 0.264 ± 0.005 | 35.0 | 0.0625 | 0.150 ± 0.001 |
| 30.0 | 0.00313 | 0.0530 ± 0.0080 | 35.0 | 0.125 | 0.186 ± 0.001 |
| 30.0 | 0.00625 | 0.0681 ± 0.0050 | 35.0 | 0.250 | 0.209 ± 0.008 |
| 30.0 | 0.0188 | 0.0731 ± 0.0040 | 35.0 | 0.500 | 0.285 ± 0.001 |
| 30.0 | 0.0313 | 0.0848 ± 0.0008 | 35.0 | 1.00 | 0.429 ± 0.017 |

Table VI. First-Order Rate Constants for the Reaction of (*N*-Methyltetraphenylporphinato)copper(II) Cation with Tetraethylammonium Chloride in Dichloromethane

| temp, °C | $[Et_4NCl]$, M | $10^3k$, $s^{-1}$ |
|---|---|---|
| 25.1 | 0.00919 | 0.0560 ± 0.0003 |
| 25.1 | 0.0122 | 0.0520 ± 0.0005 |
| 25.1 | 0.122 | 0.0462 ± 0.0010 |
| 30.0 | 0.00331 | 0.0992 ± 0.0050 |
| 30.0 | 0.00496 | 0.0955 ± 0.0010 |
| 30.0 | 0.0331 | 0.0855 ± 0.0040 |
| 30.0 | 0.165 | 0.0717 ± 0.0020 |
| 30.0 | 0.331 | 0.0646 ± 0.0030 |
| 35.0 | 0.00142 | 0.161 ± 0.008 |

the nucleophile as axial ligand ($k_2$ path), leading to the equation[12]

$$\frac{d[M(TPP)]}{dt} = \left(\frac{k_1 + k_2K_{eq}[HNR_2]}{1 + K_{eq}[HNR_2]}\right)[HNR_2][M(N\text{-}CH_3TPP)^+]$$

where M = Cu(II) or Ni(II) and to the equation

$$\frac{d[M(TPP)]}{dt} = k[HNR_2][M(N\text{-}CH_3TPP)^+]$$

for M = Mn(II) or Zn(II). The first-order behavior is attributed to less competition of the amine for the axial site, but it could also arise from nearly equal reaction rates along either path. Although the kinetics are more complex with Cu(II), the reaction rates are the fastest of the four metal ions studied, so we have chosen to use Cu(II) complexes of several *N*-methylporphyrins to study the effects of ring substituents, solvent media, and nucleophiles.

A typical plot of the concentration dependence of the pseudo-first-order rate constant for dealkylation of a copper(II) *N*-methylporphyrin complex is shown in Figure 2. The nonlinear concentration dependence of the rate constants was found for all three porphyrins studied (*N*-methyltetraphenylporphyrin, *N*-methyltetrakis(*p*-sulfophenyl)porphyrin, and *N*-methyldeuteroporphyrin IX dimethyl ester) in acetonitrile and for the reaction of $Cu(N\text{-}CH_3TPP)^+$ with di-*n*-butylamine in $CH_2Cl_2$. A linear dependence of the observed rate constant on nucleophile concentration was found, however, for the reaction of $Cu(N\text{-}CH_3TPPS_4)^{3-}$ with diethylamine in aqueous solution. The rate of the reaction of $Cu(N\text{-}CH_3TPP)^+$ with tetraethylammonium chloride in dichloromethane is nearly independent of nucleophile concentration.

**Porphyrin Ring Substituents.** Our first consideration is the effect of alteration of the substituents on the porphyrin ring of the dealkylation kinetics. The reaction of the cytochromes P-450 that produce *N*-alkylporphyrins in vivo involve the protoporphyrin ring system, not the tetraphenylporphyrin ring system whose dealkylation reactions were previously reported.[4,5] In order to deduce the effects of ring substituents for the naturally occurring porphyrins, we chose the deuteroporphyrin ring system because it is very closely related to protoporphyrin and the substitution of two hydrogen atoms for vinyl groups at the 2- and 4-positions avoids complications from photoreactions and hydrolysis reactions. Some properties of the *N*-alkylporphyrins, for example their basicities, are strongly affected by differences in peripheral ring substituents, especially the presence of phenyl groups in the meso positions.[6,13] The free base *N*-methyltetrakis(*p*-sulfophenyl)porphyrin and non-meso-substituted *N*-methylporphyrins such as *N*-methyldeuteroporphyrin have $pK_a$ values for monoprotonation of >13 while that of *N*-methyltetraphenylporphyrin is 4 (in DMF). From the data in Tables I–III, however, it is quite apparent that the absence of phenyl ring substituents or the presence of sulfonyl groups bearing a negative charge has relatively little effect on the rates of dealkylation. The data in Table VIII indicate that the activation parameters are also quite similar for reactions involving the same solvent and nucleophile. It appears, therefore, that the rates obtained for the dealkylation reaction of a particular synthetic *N*-methylporphyrin complex may be used to predict rates for naturally occurring porphyrins without meso substituents.

**Solvent Effects.** Comparison of reaction rates in acetonitrile, water, and dichloromethane (Tables I–V) shows that there is a much greater dependence of the rate on solvent than on ring substituents. Of special interest is the large decrease in rate in aqueous solution relative to the more poorly solvating media of acetonitrile and dichloromethane. The slower rate is consistent with greater stabilization of the reactants by the more strongly interacting aqueous solution. The linearity of the plot of the pseudo-first-order rate constant vs. nucleophile concentration for the reaction of $Cu(N\text{-}CH_3TPPS_4)^{3-}$ with diethylamine in aqueous solution and the nonlinearity for an analogous reaction in acetonitrile are consistent with the greater complexing ability of water vs. acetonitrile. Since water competes well for the axial binding site, we find no evidence involving reaction of a complex with dialkylamine bound to the copper(II) atom.

In dichloromethane, the concentration dependences of the kinetics for the reactions of di-*n*-butylamine and chloride ion are qualitatively as well as quantitatively different. A plot of $k_{obsd}$ vs. the concentration of di-*n*-butylamine (Figure 5) shows a steep rise at low amine concentration (<0.03 M) and a linear segment thereafter. Consistent with our proposed biphasic mechanism in aceonitrile media, we postulate that the amine has a higher binding constant in the more poorly solvating dichloromethane medium so that the $k_2$ path becomes predominant at a lower amine concentration in dichloromethane than in acetonitrile. With chloride ion as nucleophile, the dealkylation rate is nearly independent of its concentration (Table VI). Given the high affinity of a neutral species, di-*n*-butylamine, for the copper(II) *N*-methylporphyrin complex, which bears a 1+ charge, it is likely that the chloride ion forms an ion pair with a high binding constant. We attribute the fact that the dealkylation reaction of $Cu(N\text{-}CH_3TPP)^+$ with tetraethylammonium chloride is nearly independent of the nucleophile concentration in dichloromethane to ion-pair formation. If chloride ion readily associates with $Cu(N\text{-}CH_3TPP)^+$, addition of a large excess of chloride ion is not expected to increase the reaction rate.

**Effect of Nucleophiles.** The dealkylation reactions reported herein in acetonitrile and in aqueous solution indicate a bimolecular reaction. In previous studies,[4,5] we found that the di-*n*-butylamine and diethylamine exhibit essentially the same nucleophilicity for the reactions in acetonitrile and that pyridine is a much poorer nucleophile.

In acetonitrile, we find that reactions of $Cu(N\text{-}CH_3TPPS_4)^{3-}$ show pyridine to be a weaker nucleophile than di-*n*-butylamine (for [pyridine] = 2.38 M, $k_{obsd} = (6.9 \pm 0.1) \times 10^{-5}$ $s^{-1}$ at 54.6 °C) and $Cl^-$ is somewhat stronger than pyridine (for $[Et_4NCl]$

(12) An equation that is mathematically equivalent for a given nucleophile and reaction medium has been suggested by a reviewer:

$$\frac{d[MTPP]}{dt} = K_{eq}[HNR_2]\left[\frac{K_1 + k_2[HNR_2]}{1 + K_{eq}[HNR_2]}\right][M(N\text{-}CH_3TPP)^+]$$

This equation requires that changes in the shape of the plot of $k_{obsd}$ vs. [nucleophile] be due solely to changes in the relative values of $k_1$ and $k_2$, not in $K_{eq}$.

(13) Neuberg, A.; Scott, J. J. *Proc. R. Soc. London, Ser. A* **1952**, *213*, 307–9.

**Table VII.** Values of $k_1$, $k_2$, and $K_{eq}$ for Several Dealkylation Reactions of (*N*-Methylporphinato)copper(II) Complexes by Di-*n*-butylamine[a]

| complex | solvent | $T$, °C | $10^3k_1$, $M^{-1}$ $s^{-1}$ | $K_{eq}$ | $10^3k_2K_{eq}$, $M^{-1}$ $s^{-1}$ | $10^3k_2$,[b] $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|---|---|
| Cu(*N*-$CH_3$TPP)$^+$ | $CH_3CN$ | 25 | 2.94 ± 0.05 | 2.5 ± 0.2 | 0.75 ± 0.14 | 0.30 |
| | | 45 | 18.0 ± 0.10 | 3.0 ± 0.5 | 7.0 ± 2.4 | 2.3 |
| | | 65 | 151 ± 6 | 17 ± 2 | 210 ± 30 | 12 |
| Cu(*N*-$CH_3TPPS_4$)$^{3-}$ | $CH_3CN$ | 25.3 | 3.72 ± 0.13 | 1.5 ± 0.5 | 0.038 ± 0.84 | 0.025 |
| | | 44.5 | 17.3 ± 0.04 | 1.8 ± 0.5 | 8.7 ± 5.2 | 4.8 |
| | | 63.8 | 84.8 ± 1.4 | 6.0 ± 0.5 | 88 ± 18 | 15 |
| Cu(*N*-$CH_3$DP)$^+$ | $CH_3CN$ | 25.4 | 1.44 ± 0.17 | 1.6 ± 0.2 | −5.6 ± 0.8 | −3.5[c] |
| | | 44.2 | 7.30 ± 0.08 | 3.0 ± 0.5 | 3.8 ± 0.2 | 1.3 |
| | | 63.0 | 29.3 ± 0.7 | 4.3 ± 0.6 | 41 ± 8 | 9.5 |
| Cu(*N*-$CH_3$TPP)$^+$ [d] | $CH_2Cl_2$ | 25.1 | 86 ± 98 | 2000 ± 2300 | 440 ± 520 | 220 |
| | | 30.0 | 79 ± 18 | 1000 ± 300 | 330 ± 80 | 330 |
| | | 35.0 | 60 ± 10 | 400 ± 80 | 110 ± 20 | 270 |

[a] Values are calculated by using the equation $k_{obsd} = (k_1[A] + k_2K_{eq}[A]^2)/(1 + K_{eq}[A])$, where A is di-*n*-butylamine. Standard deviations are obtained from the nonlinear least squares statistical program of the PROPHET system. [b] Since the value of $k_2$ is coupled to that of $K_{eq}$, a wide range of values allows reasonable fits to be obtained. [c] Clearly, physically unreasonable, but the best-fit values obtained. [d] The sharp increase in the rate at very low nucleophile concentration, the volatility of $CH_2Cl_2$, and the slow rates at low nucleophile concentration make it difficult to obtain sufficient data for better determination of the rate parameters.

**Table VIII.** Activation Parameters for Dealkylation of Copper(II) Complexes of *N*-Methylporphyrins

| complex | nucleophile | solvent | $\Delta H^{\ddagger}$, kcal/mol | $\Delta S^{\ddagger}$, eu | $\Delta G^{\ddagger}_{298}$, kcal/mol |
|---|---|---|---|---|---|
| Cu(*N*-$CH_3$TPP)$^+$ | (*n*-$C_4H_9)_2NH$ | $CH_3CN$ | 16.9 ± 1.0[a] | −13.1 ± 2.9 | 20.8 ± 1.9 |
| Cu(*N*-$CH_3$DP)$^+$ | (*n*-$C_4H_9)_2NH$ | $CH_3CN$ | 15.3 ± 0.3[a] | −20.2 ± 0.9 | 21.3 ± 0.6 |
| Cu(*N*-$CH_3TPPS_4$)$^{3-}$ | (*n*-$C_4H_9)_2NH$ | $CH_3CN$ | 15.6 ± 0.7[a] | −17.6 ± 2.2 | 20.8 ± 1.3 |
| Cu(*N*-$CH_3TPPS_4$)$^{3-}$ | $(C_2H_5)_2NH$ | $H_2O$ | 23.6 ± 0.2 | 0.5 ± 0.6 | 23.4 ± 0.4 |
| Cu(*N*-$CH_3$TPP)$^+$ | $N(C_2H_5)_4Cl$ | $CH_2Cl_2$ | 19.7 ± 0.4 | −11.9 ± 1.3 | 23.2 ± 0.8 |
| ClCu(*N*-$CH_3$TPP) | $Cl^-$ | $CHCl_3$ | 24.4 ± 0.5[b] | +3.7 ± 1.1 | 23.3 ± 0.8 |

[a] In those cases in which the dependence of the observed rate constant in nucleophile concentration is nonlinear, the data from the initial portion of the plot (attributed to the path involving solvent as axial ligand; see text) have been used to determine activation parameters. [b] Reference 10.

= 0.5 M, $k_{obsd}$ = (5.1 ± 0.1) × $10^{-4}$ $s^{-1}$ at 55.0 °C). Limited experiments were performed with Cu(*N*-$CH_3TPPS_4$)$^{3-}$ in aqueous solution in this study, and the chloride ion is essentially unreactive.

The situation in the most poorly coordinating solvent studied, dichloromethane, is different. Although data for neutral nucleophiles such as di-*n*-butylamine indicate a bimolecular reaction and pyridine is a poorer nucleophile (for [pyridine] = 2.02 M, $k_{obsd}$ = (1.9 ± 0.1) × $10^{-5}$ $s^{-1}$ at 35.5 °C), the data for anionic $Cl^-$ indicate a unimolecular collapse of a strongly associated ion pair. This result is consistent with the results of Stinson and Hambright for a very similar reaction, that of spontaneous dealkylation of ClCu(*N*-$CH_3$TPP) in chloroform.[10] They also found first-order kinetics consistent with the reaction of an ion pair but not the bimolecular reaction of two ClCu(*N*-$CH_3$TPP) molecules. A bimolecular reaction would be expected if the chloride ion were specifically bound to the copper atom. It seems only reasonable to assume that the nucleophile must attack the methyl group from the same side of the porphyrin complex, and thus, a reactive ion pair that can collapse unimolecularly must differ from a complex in which the nucleophile is bound axially to the metal atom on the "wrong" side of the complex. Even though one might expect $Cl^-$ to bind exclusively to the axial site, the first-order kinetics are consistent with an ion pair in which the chloride ion spends some time randomly oriented so that it is in position to attack the methyl group. Second-order behavior would also be expected if free chloride were involved. In our study we have used the weakly coordinating trifluoromethanesulfonate ion as the counterion rather than the chloride ion and then added chloride in the form of the tetraethylammonium salt in order to initiate dealkylation. We have used a similar but not the same solvent and found a rate constant of 5.6 × $10^{-5}$ $s^{-1}$ at 25.1 °C whereas Stinson and Hambright found a rate of 1.54 × $10^{-4}$ $s^{-1}$ at 25.5 °C. Under similar conditions, we have found that the reaction of Cu(*N*-$CH_3$TPP)$^+$ with di-*n*-butylamine is slower in dichloromethane than in the polar acetonitrile (at 25 °C, $k_{obsd}$ = 1.5 × $10^{-4}$ $s^{-1}$ for [di-*n*-butylamine] = 0.50 M in $CH_2Cl_2$ and $k_{obsd}$ = 5.2 × $10^{-4}$ $s^{-1}$ for [di-*n*-butylamine] = 0.48 M in $CH_3CN$) so it is reasonable to expect that the rate in dichloromethane would be somewhat slower than in the more polar chloroform. An excess of noncoordinating ions has little effect on the rate; with excess tetrabutylammonium perchlorate (0.50 M), the rate constant is (7.8 ± 0.2) × $10^{-5}$ $s^{-1}$ at 30.0 °C compared with (9.9 ± 0.1) × $10^{-5}$ $s^{-1}$ at 30.0 °C in the absence of excess salt.

From these results and previous studies, it is evident that differences in dealkylation rates of orders of magnitude can result from variations in the coordinated metal ion and the attacking nucleophile. The reaction medium can also have a profound effect, changing the apparent mechanism in the case of dichloromethane and greatly affecting the rate in the case of aqueous solution. Ring substituents can be altered considerably, however, without causing large changes in the kinetics or mechanism of the dealkylation reactions.

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**Registry No.** Cu(*N*-$CH_3$TPP($CF_3SO_3$)), 84799-60-0; Cu(*N*-$CH_3TPPS_4$)$^{3-}$, 84752-34-1; Cu(*N*-$CH_3$DP)$^+$, 84774-86-7; (*n*-$C_4H_9)_2NH$, 111-92-2; $CH_3CN$, 75-05-8; $Cl^-$, 16887-00-6; $CH_2Cl_2$, 75-09-2; $(C_2H_5)_2NH$, 109-89-7.