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Kinetics of Dealkylation Reactions of *N*-Alkylporphyrin Complexes. 4. Effect of *N*-Alkyl and *N*-Aryl Substituents on the Dealkylation Process

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The dealkylation reactions of *N*-alkylporphyrins are of interest with respect to the formation of *N*-alkylporphyrins from the cytochrome P-450 prosthetic group and to the use of *N*-alkylporphyrins as intermediates for the rapid synthesis of non-N-alkylated porphyrin complexes. Previous work has demonstrated that the rate of dealkylation is strongly influenced by the nature of the metal ion, the nucleophile, and the solvent medium but that typical porphyrin ring substituents have little effect. In this report, we have examined the effect of the alkyl or aryl group on the dealkylation rate using Cu(II) complexes of monosubstituted 5,10,15,20-tetraphenylporphyrin in acetonitrile with di-*n*-butylamine as the nucleophile. The dealkylation reactions of Cu(II) complexes show biphasic kinetics, with the predominant path at low amine concentration being attributed to the reaction of the complex with solvent as axial ligand. At 25 °C (with the *N*-alkyl or *N*-aryl substituent in parentheses), the rate constants for this path are 2.94×10^{-3} M^{-1} s^{-1} (CH_3), 2.27×10^{-4} M^{-1} s^{-1} (CH_2CH_3), 0.271 M^{-1} s^{-1} (p-nitrobenzyl), and $<10^{-6}$ M^{-1} s^{-1} (phenyl). The activation parameters are as follows: $\Delta H^* = 16.9 \pm 1.0$ kcal/mol, $\Delta S^* = -13 \pm 3$ eu (CH_3); $\Delta H^* = 18.2 \pm 1.0$ kcal/mol, $\Delta S^* = -14 \pm 3$ eu (CH_2CH_3); $\Delta H^* = 14.8 \pm 1.0$ kcal/mol, $\Delta S^* = -12 \pm 3$ eu (*p*-nitrobenzyl). The rate constants for the path that is second order in amine are 3.0×10^{-4} M^{-1} s^{-1} (CH_3), 3.7×10^{-5} M^{-1} s^{-1} (CH_2CH_3), and 7.9×10^{-2} M^{-1} s^{-1} (*p*-nitrobenzyl). Thus, the alkyl group has a major effect on the rate, and the trend in rates suggests that good carbocation stabilization facilitates the reaction and steric hindrance has a significant but not as pronounced an effect. The rates are relatively slow for simple alkyl groups, suggesting that dealkylation of an N-alkylated protoheme intermediate in the decomposition of cytochrome P-450 would be an inefficient process.

Introduction

The discovery that heme in the liver is converted to *N*-alkylporphyrins by drugs with unsaturated side chains and certain dihydropyridines has aroused considerable interest in the chemistry of *N*-alkylporphyrin complexes.[1,2] It appears that there are different mechanisms leading to the formation of these *N*-alkylporphyrins. For example, in the case of 2-allyl-2-isopropylacetamide (AIA), a monooxygenated derivative of the drug becomes attached to one of the pyrrolic nitrogen atoms of protoporphyrin IX from cytochrome P-450,[3-5] and the sedative–hypnotic agent ethchlorvynol (1-chloro-3-ethyl-1-penten-4-yn-3-ol) alkylates the prosthetic heme via an oxidatively actiational acetylenic functionality,[6] while in the case of 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,4,6-trimethylpyridine (DCC), only the 4-methyl substituent is transferred to the pyrrolic nitrogen atom.[7-9] The inactivation of cytochrome P-450 by such drugs leads to disruption of the heme biosynthetic pathway, in some cases with effects analogous to porphyrins. *N*-methylprotoporphyrin IX has been shown to be a strong inhibitor of rat liver ferrochelatase.[10,11] Model studies for the in vivo transformation of cytochrome P-450 into the green pigment products. *N*-alkylporphyrins, have been reported by Callot et al.[12] Since *N*-alkylporphyrins appear to only be formed with a few of the many substrates for cytochrome P-450, we felt that it could be of interest to determine kinetic factors that are related to the decomposition of possible intermediates in the inactivation of cytochrome P-450. Until this report, however, there was no information about the reactivity of various N-substituents. Thus, we are investigating factors that favor dissociation of the alkyl group from an *N*-alkylporphyrin complex[13-15] and those that favor metal atom removal.[16] In the cases of cytochrome P-450 inactivation in which *N*-alkylporphyrins are produced, of course, iron atom removal predominates over dealkylation.

One of the porphyrins included in the study, *N*-phenylprotoporphyrin IX (Figure 1), is also of interest because it is the product of the reaction of phenylhydrazine with hemoglobin. Aspects of this chemistry have recently been elucidated by Ortiz de Montellano and co-workers.[17]

We are also interested in using *N*-alkylporphyrins to rapidly synthesize radiolabeled metalloporphyrins. Since *N*-alkylporphyrins form complexes much more rapidly than the corresponding non-N-alkylated porphyrins[18,19] and the alkyl group can be removed by an appropriate nucleophile, it is possible in some cases to form planar metalloporphyrins quite rapidly. An example of the application of this method is the synthesis of palladium-109 hematoporphyrin from *N*-methylhematoporphyrin for use as an agent for specific lymphatic ablation.[20] Metal ions that do not form especially stable and relatively planar metalloporphyrins tend to undergo sluggish *N*-metal dealkylation reactions. In other applications in which the specific properties of *N*-alkylporphyrin complexes, such as their

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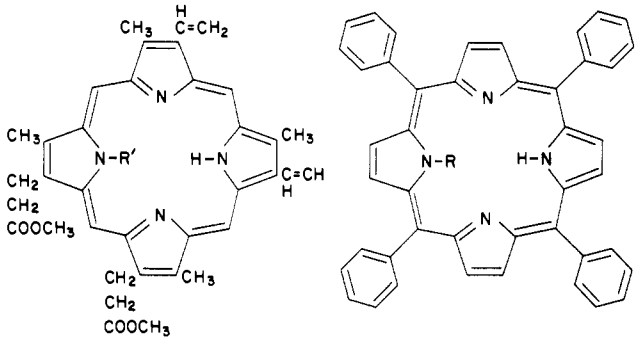

Figure 1. Structures of *N*-alkyltetraphenylporphyrin and *N*-arylprotoporphyrin IX dimethyl ester. Here we report studies of species where R = CH_3, C_2H_5, C_6H_5, and *p*-$CH_2C_6H_4NO_2$ and R′ = C_6H_5.

favorable reduction potentials[16,21] or spectroscopic properties,[22] may be of use, leaving groups that are more robust than the methyl group would be advantageous. Thus, in this study we have attempted to find groups that are more easily and those that are less easily dissociated than the methyl group.

In order to study the effect of the *N*-alkyl group, we have chosen to use Cu(II) complexes because of the easily monitored rate of dealkylation and because of the data on the magnitude of other effects that are available.[13-15,23] Since previous studies of the dealkylation reactions of Cu(II) *N*-methylporphyrin complexes have indicated that the dealkylation reaction may exhibit S_N1 as well as S_N2 characteristics, we have chosen to study *p*-nitrobenzyl and phenyl N-substituents to examine the effect of carbocation stabilization. We have chosen the ethyl substituent to examine the effect of its steric hindrance relative to that of the methyl group.

Experimental Section

Reagents. Solvents and di-*n*-butylamine were dried and distilled by using published procedures.[24] $Cu(CF_3SO_3)_2 \cdot 6H_2O$ was prepared by adding dilute trifluoromethanesulfonic acid to copper carbonate. It was recrystallized twice from methanol, washed with diethyl ether, and then dried in a vacuum oven and stored in a desiccator over P_2O_5. 2,2,6,6-Tetramethylpiperidine, $FSO_3C_2H_5$, benzyltriethylammonium chloride, and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Aldrich) and phenyllithium (Alfa) were used without purification.

Synthesis of *N*-Ethyl-5,10,15,20-tetraphenylporphyrin (*N*-C_2H_5-HTPP). Method A. Ethyl fluorosulfate was diluted in methylene chloride, this solution in a slight excess over a stoichiometric amount was slowly added drop by drop to a refluxing solution of tetraphenylporphyrin (H_2TPP; prepared by the method of Adler et al.[25]) in CH_2Cl_2, and the mixture was allowed to reflux for 2 days. The resulting green solution was neutralized with ammonia and dried over Na_2SO_4. The visible absorption spectrum and TLC indicate the presence of unreacted H_2TPP and more highly alkylated products as well as *N*-C_2H_5HTPP (using CH_2Cl_2/EtOAc, 5:1; the middle spot matches that of an authentic sample of *N*-C_2H_5HTPP). The mixture was purified on silica gel (Merck type 400–230 mesh) by using flash chromatography.[26] The H_2TPP was removed with CH_2Cl_2, and gradual addition of higher proportions of ethyl acetate afforded isolation of the product. Purity was ascertained by TLC and by NMR and UV–visible spectroscopy.[27] Yield: 14–15%.

Method B. The method of Callot[28] was used with few modifications. The N,N′-bridged porphyrin intermediate was conveniently purified by flash chromatography and must be stored cold to prevent decomposition to H_2TPP. Yield: 30–35%. The product was also purified by flash chromatography. Overall yield: 21%.

Synthesis of *N*-(*p*-Nitrobenzyl)-5,10,15,20-tetraphenylporphyrin. The method of Callot[28] was used and the product purified by flash chromatography. Purity was ascertained by TLC and by NMR and UV–visible spectroscopy.[29]

Synthesis of *N*-Phenyl-5,10,15,20-tetraphenylporphyrin. The method of Ortiz de Montellano et al.[30] was employed with phenyllithium rather than phenylmagnesium bromide to form the σ-phenyl FeTPP intermediate, which was used without further purification. The ClFeTPP was prepared by Fleischer's method[31] and recrystallized from CH_2Cl_2/CH_3CN or purchased from Strem Chemicals. In a typical preparation, 400 mg of ClFeTPP was dissolved in 80 mL of dry freshly distilled tetrahydrofuran under an argon atmosphere. After addition of 0.25 mL of phenyllithium solution (2.1 M in pentane) the reaction mixture became red and 20–25 mg of BHT was added. The formation of the μ-oxo Fe^{III}TPP dimer and a drastic reduction in yield of the σ-phenyl FeTPP occurred readily if the mixture was not strictly dry. The visible spectrum of the σ-phenyl FeTPP intermediate has peaks at 613 (sh), 531, 429 (sh), 417, and 396 (sh) nm. The mixture was added to an equal volume of methanol containing 5% H_2SO_4, the resulting mixture was stirred overnight, and the product was extracted with CH_2Cl_2, washed with $NaHCO_3$ solution, dried over Na_2SO_4, and purified by flash chromatography. Yield: 30–35%. The NMR spectrum matches literature values.[30]

N-Phenylprotoporphyrin IX was generously supplied by Dr. Paul Ortiz de Montellano of the University of California, San Francisco.

Synthesis of the Copper(II) Complexes. In a typical synthesis of (*N*-ethyl-5,10,15,20-tetraphenylporphinato)copper(II) trifluoromethanesulfonate, 45 mg of *N*-C_2H_5HTPP was dissolved in 100 mL of dry CH_3CN containing a 3-fold excess of $Cu(CF_3SO_3)_2 \cdot 6H_2O$. About 0.2 mL of 2,2,6,6-tetramethylpiperidine was added and the mixture allowed to stir for 1 h. From the visible absorption spectrum, formation of the desired complexes appears to be quantitative at this point. After it was filtered, the solution was evaporated by using a rotary flash evaporator. The excess Cu(II) salt was removed by washing with water, and the porphyrin complex was extracted into dichloromethane and dried over Na_2SO_4. The visible spectrum in the Soret region shows a small amount (~5%) of CuTPP. The complex was then purified by flash chromatography with 2–3% methanol in CH_2Cl_2 as eluent and recovered by using a flash rotary evaporator. It must be stored cold (i.e. in a standard freezer) to prevent CuTPP formation. Yield: 57%. UV–visible spectrum in CH_3CN, with absorptivities (M^{-1} cm^{-1}) in parentheses: 657 (4.0×10^3), 590 (7.0×10^3), 547 (9.0×10^3), 441 (1.2×10^5), 434 nm (1.1×10^5). Anal. Calcd for $CuC_{47}H_{33}N_4SO_3F_3$: C, 66.02; H, 3.86; N, 6.55. Found: C, 66.05; H, 4.12; N, 6.16 (Analytische Laboratorien, Engelskirchen, West Germany).

The (*N*-phenyl-5,10,15,20-tetraphenylporphinato)copper(II) trifluoromethanesulfonate complex was synthesized and purified in a similar manner. It is very stable at room temperature in the solid state or in solution. The UV–visible spectrum in CH_3CN, with absorptivities (M^{-1} cm^{-1}) in parentheses is 675 (5.5×10^3), 609 (9.8×10^3), 556 (10.2×10^3), 455 (1.3×10^5), and 440 nm (sh, 1.1×10^5). Anal. Calcd for $CuC_{51}H_{33}N_4SO_3F_3$: C, 67.89; H, 3.69; N,

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(27) The ^1H NMR spectrum ($CDCl_3$, 200 MHz; −4.43 (q, 2 H), −1.635 (t, 3 H), 7.5 (s, 2 H, the pyrrole ring bearing the alkyl group), 7.77–8.38 (m, 20 H, phenyl), 8.49 (d, 2 H, pyrrole ring adjacent to the alkylated ring), 8.7 (d, 2 H, pyrrole ring adjacent to the alkylated ring), and 8.81 ppm (s, 2 H, pyrrole ring opposite to the one bearing the ethyl group)), closely resembles that reported in ref 34b.
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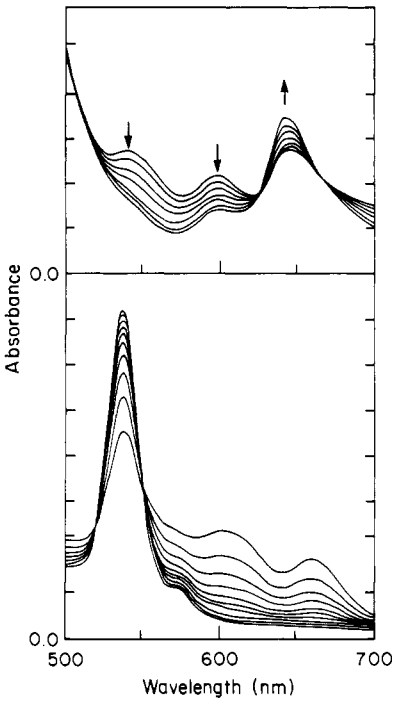

Figure 2. Top: Absorbance changes for (*N*-(*p*-nitrobenzyl)-5,10,15,20-tetraphenylporphinato)copper(II) in acetonitrile at 25 °C. The overlay interval was 90 min. Bottom: Absorbance changes for the reaction of (*N*-(*p*-nitrobenzyl)-5,10,15,20-tetraphenylporphinato)copper(II) with di-*n*-butylamine in acetonitrile, not showing the presence of the species in the spectrum above. The overlay interval was approximately 2 min.

6.21. Found: C, 67.88; H, 4.18; N, 5.89 (Analytische Laboratorien).

The (*N*-(*p*-nitrobenzyl)-5,10,15,20-tetraphenylporphinato)copper(II) complex is readily dealkylated to form CuTPP so that the isolation of pure solid material has not been accomplished. The material obtained after flash chromatography appeared pure but decomposed when isolation was attempted. Removal of solvent under vacuum results in considerable decomposition, leading to CuTPP. However, the spectral properties of the material formed in situ by the addition of a 2–3-fold excess of $Cu(CF_3SO_3)_2 \cdot 6H_2O$ to a solution of *N*-*p*-$CH_2C_6H_4NO_2$HTPP in dry CH_3CN with noncoordinating base (e.g. 2,2,6,6-tetramethylpiperidine; about 0.10 mL of a 0.02 M solution in CH_3CN added to 20 mL of the reaction mixture) are consistent with essentially quantitative formation of the Cu(II) complex. These stock solutions were stable for months when stored in a freezer. UV–visible spectrum (absorptivities in M^{-1} cm^{-1} in parentheses): 659 (7.3×10^3), 599 (1.09×10^3), 547 (1.38×10^3), 441 nm (1.73×10^5).

Kinetics Experiments. Absorbance data were obtained with Beckman DU-8, Cary 14, and Varian 6350 spectrophotometers with a self-contained Peltier solid-state temperature control, a Lauda B-2 circulating bath, and a Fisher Model 90 circulator, respectively. Data analyses were performed by using statistics programs available with the PROPHET computing system.[32] In all reactions the nucleophile, di-*n*-butylamine, was present in pseudo-first-order excess.

Stock solutions of Cu-*N*-$C_6H_5TPP^+$ were prepared by mixing $Cu(CF_3SO_3)_2 \cdot 6H_2O$ in 2–3-fold excess of *N*-C_6H_5HTPP in CH_3CN with approximately 0.10 mL of 0.02 M 2,2,6,6-tetramethylpiperidine added. The visible absorption spectra of these solutions matched those made by dissolving the analyzed solid (Cu-*N*-$C_6H_5TPP)(CF_3SO_3)$. Stock solutions are stable for months at room temperature. Similarly prepared stock solutions of Cu-*N*-*p*-$CH_2C_6H_4NO_2$TPP are stable over long periods when kept in the dark in a freezer, but they do undergo slow decomposition when kept in the light at room temperature. In this case the decomposition results in a new and as yet undefined species that is not CuTPP. In some cases we have obtained isosbestic points at 621 and 658 nm with new peaks appearing at 643 and 602 nm (sh)

(32) The PROPHET computing system is a multisite network, the CBIS system of NIH, which includes a wide array of statistics and structural simulation software. We are grateful to the NIH for the installation of the Hunter College facility.

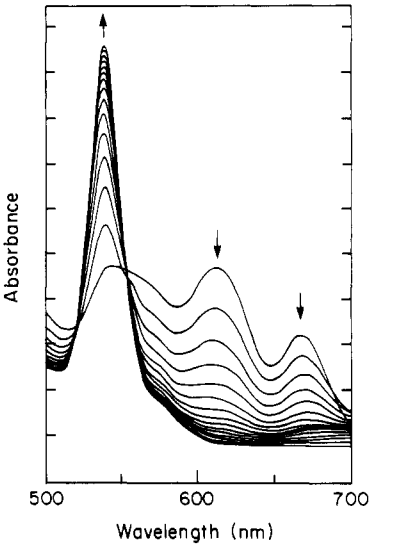

Figure 3. Absorbance changes for the reaction of (*N*-ethyl-5,10,15,20-tetraphenylporphinato)copper(II) with di-*n*-butylamine in acetonitrile at 49.2 °C. The interval time was approximately 2 min.

as shown in Figure 2. This species is then stable for several days. Addition of di-*n*-butylamine results in the formation of CuTPP. The time scale of the formation of this species is sufficiently slow that it does not interfere with the dealkylation kinetics experiments performed with added di-*n*-butylamine. The Cu-*N*-C_6H_5TPP and Cu-*N*-C_6H_5–protoporphyrin IX complexes were formed in situ in the same manner, and the stock solutions are very stable at room temperature. The kinetics of reactions performed by dissolving analyzed samples or with stock solutions made in situ were identical.

Product analysis for the reaction of Cu-*N*-C_2H_5TPP with di-*n*-butylamine was performed as previously reported for Cu-*N*-CH_3TPP.[13] The concentration of Cu-*N*-C_2H_5TPP was 6.5×10^{-3} M, and a 2-fold excess of di-*n*-butylamine was used. After visible absorbance changes indicated complete formation of CuTPP (2.5 days at 30–45 °C), the solution was made alkaline with solid NaOH. Analysis by gas chromatography was performed by using an HP Model 5700A and a 1% SP-1000 (Supeloco) column. Retention times of the amine products matched those of authentic samples of di-*n*-butylamine and di-*n*-butylethylamine, and there were no peaks unaccounted for. Analysis for the reaction of the *p*-nitrobenzyl complex was different because of the lower volatilityof di-*n*-butyl(*p*-nitrobenzyl)amine. A sample of di-*n*-butyl(*p*-nitrobenzyl)amine was prepared by the reaction of *p*-nitrobenzylbromide with di-*n*-butylamine and analyzed by NMR-spectroscopy. The products of a reaction of Cu-*N*-*p*-$CH_2C_6H_4NO_2TPP$ with a 2-fold excess of di-*n*-butylamine in CH_3CN had an NMR spectrum corresponding to di-*n*-butylamine and di-*n*-butyl(*p*-nitrobenzyl)amine. In addition, the products showed the same retention on TLC plates (CH_2Cl_2 as eluent) as the authentic samples. In all cases, the spectra of the metalloporphyrin products matched the visible absorption spectrum of CuTPP.

Results

The syntheses of the *N*-ethyl- and *N*-phenylporphyrins proceeded as expected from previously reported work. Purification by flash chromatography proves to be a great improvement over the column chromatography that has typically been used in the isolation of *N*-alkylporphyrins. An unexpected result was observed in the synthesis of the copper(II) complexes of the *N*-(*p*-nitrobenzyl)porphyrin. Although the stock solutions of this complex in acetonitrile are stable for weeks when stored in a freezer in the dark, solutions stored in the light at room temperature undergo a distinct color change. In some cases isosbestic points at 621 and 658 nm and new maxima at 602 and 643 nm are observed and there is no spectral evidence for CuTPP formation (e.g. Figure 2). Often some CuTPP is formed. We have found that the new species reacts very readily with nucleophiles to form CuTPP. The formation of this species is slow relative to dealkylation in the presence

Table I. First-Order Rate Constants for the Reaction of the (*N*-(*p*-Nitrobenzyl)-5,10,15,20-tetraphenylporphinato)copper(II) Cation with Di-*n*-butylamine in Acetonitrile

T, °C	[amine], M	10^3k,[a] s^{-1}
25.0	0.0125	2.33 ± 0.02
25.0	0.025	3.90 ± 0.05
25.0	0.050	6.37 ± 0.03
14.3	0.0125	0.982 ± 0.003
14.3	0.025	1.58 ± 0.01
14.3	0.050	2.62 ± 0.20
14.3	0.100	4.05 ± 0.14
6.8	0.0125	0.449 ± 0.002
6.8	0.050	1.03 ± 0.01
6.8	0.100	1.42 ± 0.01

[a] Averages with average deviations of two or three runs are reported. Each individual run gave a fit to first-order kinetics with a correlation coefficient better than 0.990, and the average $|OD_{obsd} - OD_{calcd}|$ is 0.003 or less. Similar fits were obtained for results given in Table II.

Table II. First-Order Rate Constants for the Reaction of the (*N*-Ethyl-5,10,15,20-tetraphenylporphinato)copper(II) Cation with Di-*n*-butylamine in Acetonitrile

T, °C	[amine], M	10^4k, s^{-1}
49.2	1.000	9.52 ± 0.02
49.2	0.500	6.39 ± 0.10
49.2	0.250	4.10 ± 0.05
49.2	0.125	2.42 ± 0.02
49.2	0.065	1.40 ± 0.02
49.2	0.03125	0.69 ± 0.03
37.2	1.000	3.79 ± 0.03
37.2	0.500	2.35 ± 0.01
37.2	0.250	1.60 ± 0.07
37.2	0.125	0.91 ± 0.01
37.2	0.0625	0.454 ± 0.001
37.2	0.03125	0.250 ± 0.001
25.0	1.000	1.11 ± 0.01
25.0	0.500	0.719 ± 0.015
25.0	0.250	0.420 ± 0.001
25.0	0.125	0.268 ± 0.014

of di-*n*-butylamine, and we observed isosbestic points in dealkylation reactions of the *N*-*p*-nitrobenzyl complex with di-*n*-butylamine that are not consistent with the presence of the slowly formed species. Thus, it does not appear that the species

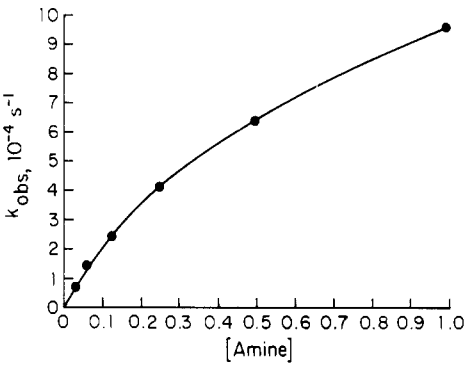

Figure 4. Plot of the pseudo-first-order observed rate constant for the dealkylation of (*N*-ethyl-5,10,15,20-tetraphenylporphinato)copper(II) by di-*n*-butylamine in acetonitrile at 49.2 °C as a function of the amine concentration.

is a principal intermediate in the dealkylation reaction we have studied.

A series of sequential spectra characterizing the dealkylation of (*N*-ethyltetraphenylporphinato)copper(II) by di-*n*-butylamine is shown in Figure 3. Isosbestic points are observed at 526 and 553 nm. Kinetics parameters obtained from absorbance changes at 536 nm with time are listed in Table I. The concentration dependence of the observed pseudo-first-order rate constant (Figure 4) is not linear, a result previously reported for the reaction of the corresponding *N*-methylporphyrin complex of Cu(II) and also that of Ni(II).[13,14] Sequential spectra for the reaction of the *N*-*p*-nitrobenzyl complex also show isosbestic points, in this case at 520 and 552 nm. The concentration dependence is also nonlinear. Observed rate constants and conditions for the dealkylation reaction of Cu*N*-$CH_2C_2H_6NO_2$TPP by di-*n*-butylamine in acetonitrile are listed in Table II. Values for the parameters of the rate law we propose (discussed later) are given in Table III, and activation parameters are listed in Table IV.

Discussion

The formation of *N*-alkylporphyrins in vivo from the decomposition of cytochrome P-450 is an intriguing process. During the interaction of a "suicide" substrate with the ferroprotoporphyrin prosthetic group, an alkylating moiety suf-

Table III. Values of Kinetics Parameters for Dealkylation Reactions of *N*-Methyl-, *N*-Ethyl- and (*N*-(*p*-Nitrobenzyl)-5,10,15,20-tetraphenylporphinato)copper(II) by Di-*n*-butylamine in Acetonitrile[a]

complex	solvent	*T*, °C	10^3k_1, M^{-1} s^{-1}	K_{eq}, M	$10^3k_2K_{eq}$, s^{-1}	10^3k_2, M^{-1} s^{-1}
Cu-*N*-CH_3TPP$^+$ [b]	CH_3CN	25.0	2.94 ± 0.05	2.5 ± 0.2	0.75 ± 0.14	0.30
		45.0	18.0 ± 0.10	3.0 ± 0.5	7.0 ± 2.4	2.3
		65.0	151 ± 6	17 ± 2	210 ± 30	12
Cu-*N*-C_2H_5TPP$^+$	CH_3CN	25.0	0.227 ± 0.004	1.6 ± 0.2	0.058 ± 0.015	0.037
		37.0	0.89 ± 0.05	3.2 ± 0.7	0.70 ± 0.21	0.22
		49.2	2.48 ± 0.05	2.7 ± 0.2	1.01 ± 0.02	0.38
Cu-*N*-$CH_2C_6H_4NO_2$TPP$^+$	CH_3CN	25.0	271 ± 12	58 ± 11	4600 ± 1100	79
		14.3	97.6 ± 3.5	31 ± 4	680 ± 140	22
		6.8	50.6 ± 0.4	38 ± 1	177 ± 91	467

[a] Observed rate constants have been fit by using the nonlinear least-squares program of the PROPHET system and the equation $k_{obsd} = (k_1[A] + k_2K_{eq}[A]^2)/(1 + K_{eq}[A])$. [b] Data from ref 13.

Table IV. Activation Parameters for Dealkylation of Copper(II) Complexes of *N*-(*p*-Nitrobenzyl)-, *N*-Methyl-, and *N*-Ethyl-5,10,15,20-tetraphenylporphyrin by Di-*n*-butylamine in Acetonitrile

	path 1[a]			path 2[b]		
complex	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}_{298}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}_{298}$, kcal/mol
Cu-*N*-$CH_2C_6H_4NO_2$TPP$^+$	14.8 ± 1.0	−11.6 ± 3.4	18.3 ± 2.0	24.9 ± 2.6	20.3 ± 9.0	18.9 ± 5.3
Cu-*N*-CH_3TPP$^+$ [c]	19.0 ± 1.6	−6.4 ± 5.1	20.9 ± 3.1	17.8 ± 0.4	−14.7 ± 1.4	22.2 ± 0.9
Cu-*N*-C_2H_5TPP$^+$	18.2 ± 1.0	−13.9 ± 3.3	22.4 ± 2.0	17.9 ± 5.0	−18.5 ± 16.4	23.4 ± 9.9

[a] The predominant path at low concentrations of di-*n*-butylamine. [b] The predominant path at high concentrations of di-*n*-butylamine. [c] Data from ref 13.

ficiently powerful to alkylate a porphyrin nitrogen atom must be produced. The carbon–nitrogen bond that is formed must be sufficiently stable to remain intact until the iron atom is removed. The free base *N*-alkylporphyrin (or more precisely the metal-free monoprotonated *N*-alkylprotoporphyrin, since the unprotonated free base has a pK_a value much greater than 7) is then released from the altered cytochrome. At least some of the *N*-alkylporphyrins produced in this manner interfere with heme biosynthesis.[10,11] Of related interest is the production of iron-free *N*-phenylprotoporphyrin from the reaction of phenylhydrazine with hemoglobin.[17]

In this work we have investigated the effect of the nitrogen atom substituent on the stability of *N*-alkyl- and *N*-arylporphyrin complexes. Metal-free *N*-alkylporphyrins are typically stable with respect to dealkylation except under drastic conditions (e.g., Ellingson and Corwin reported the dealkylation of *N*-methylethioporphyrin on heating at its melting point[33]). Metal complexes of *N*-alkylporphyrins can be dealkylated much more readily. Two different types of mechanism have been deduced—an oxidative-addition mechanism[34] and a bimolecular reaction involing nucleophilic displacement of the alkyl group.[13-15,35] This report concerns reactions of the latter type.

We have previously found that the rates of nucleophilic dealkylation reactions of *N*-alkylporphyrin complexes depend on several factors: the nucleophile, the reaction medium, the metal atom, and the substituents on the porphyrin ring.[13-15] Three features of the kinetics of these reactions are consistent with a bimolecular nucleophilic displacement mechanism: (1) the first-order dependence of the rate on nucleophile concentration, (2) a pronounced sensitivity to the nature of the nucleophile, and (3) the dependence on the solvent medium (slower reactions in more polar solvents). Those metal ions that form the more stable product (the corresponding non-N-alkylated metalloporphyrin) cause the faster dealkylation reaction, suggesting that the activated complex resembles the product. This indicates a large degree of N–C bond breaking and charge depletion of the alkyl group, i.e. significant S_N1 character of the reaction. In assessing the possible effect of the nitrogen-bound substituent on the dealkylation reaction rate, then, it is of interest to investigate both steric effects, of importance with respect to nucleophilic attack, and electronic effects, i.e. the tendency to accommodate the loss of electron density in forming the activated complex. We have chosen the methyl, ethyl, *p*- nitrobenzyl, and phenyl groups for comparison. To begin these investigations, we have made Cu(II) complexes because the reaction rates are suitable for acquiring data under comparable conditions and because the other factors discussed above have been analyzed principally for Cu(II) complexes.

The nucleophilic dealkylation of the *N*-methyltetraphenylporphyrin complex of Cu(II) by amines in acetonitrile proceeds by a competitive two-path mechanism. We have rationalized the kinetic data in terms of one path that involves a solvent molecule as the axial ligand of the copper complex (giving a first-order dependence on the concentration of amine) and a second path involving the amine as axial ligand (giving a second-order dependence of the dealkylation rae on amine concentration). The dealkylation rates for *N*-alkylporphyrin complexes are high dependent on the metal ion, varying by a factor of 10^4 from Cu(II) to Mn(II) under comparable conditions,[13,14] so it seems reasonable that a change in the axial ligand could cause a change in rate by a factor of 10. The following scheme outlines the proposed reaction sequence:

$$\text{path 1: S–Cu-}N\text{-RTPP}^+ + \text{nu} \xrightarrow{k_1} \text{CuTPP} + \text{S} + \text{R–nu}^+$$

$$\text{path 2: S–Cu-N-RTPP}^+ + \text{nu} \rightleftharpoons \text{nu–Cu-}N\text{-RTPP}^+ + \text{S} \quad K_{eq}$$

$$\text{nu–Cu-}N\text{-RTPP}^+ + \text{nu} \xrightarrow{k_2} \text{CuTPP} + \text{R–nu}^+ + \text{nu}$$

The rate law consistent with this scheme is

$$\frac{d[\text{CuTPP}]}{dt} = \left(\frac{k_1 + k_2K_{eq}[\text{nu}]}{1 + K_{eq}[\text{nu}]}\right)[\text{nu}][\text{Cu-}N\text{-RTPP}^+]$$

where nu signifies the nucleophile. The observed pseudo-first-order rate constants reported herein for the reactions of the *N*-ethyltetraphenylporphyrin and *N*-(*p*-nitrobenzyl)tetraphenylporphyrin complexes of Cu(II) are related to the concentration of amine in a manner consistent with this rate law. The activation parameters for these reactions (Table IV) are also consistent with a common mechanism. The dealkylation reaction for the *N*-phenyltetraphenylporphyrin complex of Cu(II) and for the copper(II) complex of *N*-phenylprotoporphyrin IX dimethyl ester are too slow ($t_{1/2} > 1$ week at 45 °C with [di-*n*-butylamine] = 1.0 M), for quantitative data to be obtained for comparison.

The dealkylation rate constants for the reactions of copper(II) *N*-alkylporphyrin complexes with *p*-nitrobenzyl, methyl, and phenyl substituents indicate the dramatic effect of the ability of the substituent to form a carbocation. The relative rates (in units of M^{-1} s^{-1}; with di-*n*-butylamine as nucleophile) at 25 °C for these groups, 100:1:$<10^{-4}$, indicate the importance of the shift of electron density from the nitrogen–carbon bond to the nitrogen–metal bond. Since a partial positive charge should be stabilized more by an ethyl group than a methyl group, one would expect the rate to be faster for the *N*-ethylporphyrin if carbocation formation predominantly determines the rate. Since the dealkylation reaction is, however, slower for the *N*-ethylporphyrin complex than for the *N*-methylporphyrin complex, we attribute retardation by the ethyl group to its greater steric hindrance. The effect (a factor of about 10 at 25 °C) is relatively small compared with the effect of other substituents. Previously, we found that the rate difference for nucleophiles of different size (diethylamine and di-*n*-butylamine) was also small.[13]

For rapid dealkylation, the nitrogen-bound substituent must provide excellent stabilization of positive charge. Even in the case of the *p*-nitrobenzyl substituent, dealkylation at moderate temperatures only occurs for the metal complex in the presence of a good nucleophile. We have previously shown that Fe(II) is not as effective as Cu(II) in promoting dealkylation. Although it is quite likely that Fe(III) would be a more effective dealkylation promoter than Fe(II), the oxidation is rather unfavorable, since N-alkylation increases the $Fe^{3+/2+}$ potential by about 0.7 V.[21a] It appears, therefore, that direct dealkylation of a nitrogen-bound substituent from an N-alkylated ferroprotoporphyrin intermediate would be very difficult. Preservation of the heme even after formation of an N-alkylated species may be possible, however, in those cases in which the nitrogen-bound substituent can migrate to the iron atom to form a dissociably bound species.[29,30,34a] For practical

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applications, it is desirable to be able to synthesize *N*-alkylporphyrin complexes of different stabilities with respect to dealkylation. We have shown that some non-N-alkylated metalloporphyrins can be made more rapidly by a two-step reaction sequence beginning with an *N*-alkylporphyrin than by the normal complexation reaction of the non-Nalkylated porphyrin. The rapid sequence has been used to make radioactive palladium-109 hematoporphyrin for selective lymphatic ablation to prevent the rejection of transplanted organs.[20,36] Synthesis of some other complexes by this method has not been possible because of the sluggishness of dealkylation of the appropriate *N*-methylporphyrin precursor. The high reactivity we have found for *N*-benzyl substituents greatly expands the possible applications of *N*-alkylporphyrins as synthetic precursors for rapid metalloporphyrins synthesis. On the other hand, *N*-arylporphyrin complexes such as the *N*-phenyl species or sterically hindered *N*-alkyl species may be of use as electrochemical catalysts where long-term stability is required.

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Registry No. Cu-*N*-$CH_3TPP^+CF_3SO_3^-$, 84799-60-0; Cu-*N*-$C_2H_5TPP^+CF_3SO_3^-$, 92396-64-0; Cu-*N*-*p*-$C_6H_4NO_2TPP^+CF_3SO_3^-$, 92366-26-2; Cu-*N*-$C_6H_5TPP^+CF_3SO_3^-$, 92396-66-2; di-*n*-butylamine, 111-92-2; cytochrome P-450, 9035-51-2.

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Contribution from the Department of Chemistry and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Metal Atom Synthesis of Metallaboron Clusters. 5.[1] Synthesis of the First (η^6-Arene)metallaborane and (η^6-Arene)metallaoxaborane Clusters. Structural Characterizations of 5-[η^6-$C_6(CH_3)_3H_3$]FeB_9H_{13} and 2-[η^6-$C_6(CH_3)_3H_3$]Fe-6-OB_8H_{10}

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The reaction of thermally generated iron atoms with decaborane(14) and mesitylene under rotary metal atom conditions was found to yield the first three reported examples of (η^6-arene)ferraborane complexes, 5-[η^6-$C_6(CH_3)_3H_3$]FeB_9H_{13} (I), 1-[η^6-$C_6(CH_3)_3H_3$]FeB_9H_9 (II), and 1-[η^6-$C_6(CH_3)_3H_3$]$FeB_{10}H_{10}$ (III). An analogous reaction employing toluene as a reactant resulted in the isolation of 5-[η^6-$C_6H_5CH_3$]FeB_9H_{13} (V) and 1-[η^6-$C_6H_5CH_3$]$FeB_{10}H_{10}$ (VI). A single-crystal X-ray study of I demonstrated that the compound is a decaborane(14) analogue, consistent with its $2n + 4$ skeletal electron count, in which the iron atom occupies the cage 5-position on the open face. Crystal data for I: space group $P2_1/c$; $Z = 4$; $a = 9.348$ (2) Å, $b = 9.842$ (1) Å, $c = 17.335$ (2) Å, $\beta = 90.70$ (2)°; $V = 1594.7$ Å^3. The structure was refined by full-matrix least squares to a final R of 0.049 and R_w of 0.049 for the 1755 reflections that had $F_o^2 > 3\sigma(F_o^2)$. Compounds II, III, and VI are each $2n$ skeletal electron systems and would be expected according to skeletal electron counting theory to adopt distorted polyhedral structures. The spectroscopic data for II, however, support a C_{3v} closo polyhedral structure, while the data for compounds III and VI are consistent with a closo octadecahedral geometry. In addition to the three (η^6-arene)ferraborane complexes produced in the mesitylene reaction, a fourth compound was isolated in trace amounts and was identified as 2-[η^6-$C_6(CH_3)_3H_3$]Fe-6-OB_8H_{10} (IV) by means of a single-crystal X-ray determination. The compound was shown to have a decaborane(14) structure in which the iron atom occupies the five-coordinate 2-position while the oxygen atom is in the 6-position on the open face. Compound IV is thus the first example of a polyhedral boron cage compound containing an oxygen atom in a cage vertex position. Crystal data for IV: space group $P2_1/c$; $Z = 4$; $a = 12.647$ (3) Å, $b = 13.437$ (2) Å, $c = 9.281$ (7) Å, $\beta = 104.57$ (3)°; $V = 1526.5$ Å^3. The structure was refined to a final R of 0.059 and $R_w = 0.065$ for the 1449 reflections that had $F_o^2 > 3\sigma(F_o^2)$.

Introduction

We have previously demonstrated that metal atom techniques can provide useful synthetic routes to (η^6-arene)-metallacarborane complexes,[1,3] and we have now used this method to prepare a variety of these species, including both two-carbon and four-carbon complexes, such as 1-[η^6-$CH_3C_6H_5$]Fe-2,3-$(C_2H_5)_2C_2B_4H_4$,[3] 1-[η^6-$C_6(CH_3)_6$]Fe-4,5,7,8-$(CH_3)_4C_4B_3H_3$,[1] and 2-[η^6-$CH_3C_6H_5$]Fe-6,7,9,10-$(CH_3)_4C_4B_5H_5$.[1] Others have also recently reported[4] the synthesis of (η^6-arene)metallacarboranes using different synthetic approaches.

Given the rapidly increasing number of (η^6-arene)metallacarborane complexes, it is indeed surprising that there has been heretofore no report of the synthesis of an (η^6-arene)metallaborane cluster. However, we have now found that metal atom reactions can be used to prepare these complexes, and we report here the synthesis of three different types of (η^6-arene)ferraborane cage systems, 1-(η^6-arene)$FeB_{10}H_{10}$, 1-

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