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The kinetic influence of increasing steric hindrance to metallation by zinc(II) which accompanies the inclusion of 5,10,15,20-*meso*(tetraphenyl)porphyrin into capped and quadruply bridged closely spaced bis-porphyrin structures

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Abstract

The solvent system toluene:acetic acid:methanol = 5:20:75% (vol./vol.) has been developed for metallation of porphyrins. This system is quite suitable for kinetic studies because it affords stable homogeneous solutions of porphyrins plus metal salts. In this solvent system, Zn^{2+} insertion into TPP ($\mathbf{IH_2}$) is more than 10^4 times faster than observed in DMF. Kinetics of Zn^{2+} incorporation into other porphyrins, C4-capped porphyrin ($\mathbf{IIH_2}$), cofacial bis-porphyrin ($\mathbf{IIIH_4}$) and spheroidal bis-porphyrin ($\mathbf{IVH_4}$), were then studied in this mixed solvent at 30.0 °C. It is found that Zn^{2+} insertion into $\mathbf{IIIH_4}$ is first order in both [Zn^{2+}] and [$\mathbf{IIIH_4}$]. The final kinetic product was characterized as $\mathbf{IIIZn_2}$. The mono Zn^{2+} insertion product ($\mathbf{IIIZnH_2}$) was separately synthesized and characterized. The kinetics of the stepwise Zn^{2+} insertion leading to $\mathbf{IIIZn_2}$ was followed by HPLC. The second order rate constants for the first and second insertion reactions are comparable (0.59 and 0.21 $s^{-1}\,M^{-1}$). Because both sides of the bis-porphyrin $\mathbf{IVH_4}$ are fully protected, the metallation was extremely slow. The relative rates of Zn^{2+} insertion into the four porphyrins ($\mathbf{IH_2}$, $\mathbf{IIIH_4}$, $\mathbf{IIH_2}$, $\mathbf{IVH_4}$) are 32 000 000:480 000:3 000:1.

Keywords: Kinetics and mechanism; Zinc complexes; Porphyrin complexes

1. Introduction

Metalloporphyrins are involved in a number of biological processes such as oxygen transport (hemoglobin, myoglobin), electron transport (cytochrome *c*) and detoxication (catalase, peroxidase, cytochrome P-450). Numerous model studies have been reported. The ease and mechanism of metallation of porphyrins is important and this topic comprises a subfield of porphyrin chemistry [1–3]. In order to better understand the mechanism of porphyrin metallation, we compare, in this report, the kinetics of incorporation of Zn^{2+} into (5,10,15,20)-tetraphenylporphyrin (TPP, $\mathbf{IH_2}$), bicyclo[2.2.2]octane-C4-capped tetraphenylporphyrin (capped porphyrin, $\mathbf{IIH_2}$) [4], quadruply-bridged cofacial dimeric tetraphenylporphyrin (cofacial bis-porphyrin, $\mathbf{IIIH_4}$) [5,6] and dual bicyclo[2.2.2]octane-C4-capped quadruply-bridged cofacial dimeric tetraphenylporphyrin (spheroidal bis-porphyrin, $\mathbf{IVH_4}$) [6] (Scheme 1). The choice of porphyrin structures has allowed the determination of important aspects of the metal insertion mechanism.

2. Experimental

Slow reactions (with half-lives 1 h or more) were monitored spectrophotometrically with a Perkin-Elmer 553 Fast Scan UV–Vis spectrophotometer with a 5-Cell programmer and a R100A recorder at the Soret band. Faster reactions (with half-lives between 1 min to 2 h) were monitored by use of a Cary-14 UV–Vis spectrophotometer interfaced with a Zenith computer employing OLIS (On-Line Instruments Systems Inc.) data acquisition and processing software.

(5,10,15,20)-Tetraphenylporphyrin (TPP, $\mathbf{IH_2}$) and zinc acetate dihydrate (98%) were obtained from Aldrich. Capped porphyrin ($\mathbf{IIH_2}$) [4], cofacial bis-porphyrin ($\mathbf{IIIH_4}$) [6] and spheroidal bis-porphyrin ($\mathbf{IVH_4}$) [6] were synthesized according to published procedures. All solvents were dried and distilled before use.

Melting points were obtained on a Baistolscope and are uncorrected. R_F values were obtained on E. M. Sciences 0.25 mm thick precoated glass-backed silica gel 60 F_{254} plates for non-porphyrin compounds. For porphyrins, the corresponding non-F_{254} plates were used in either analytic or preparative

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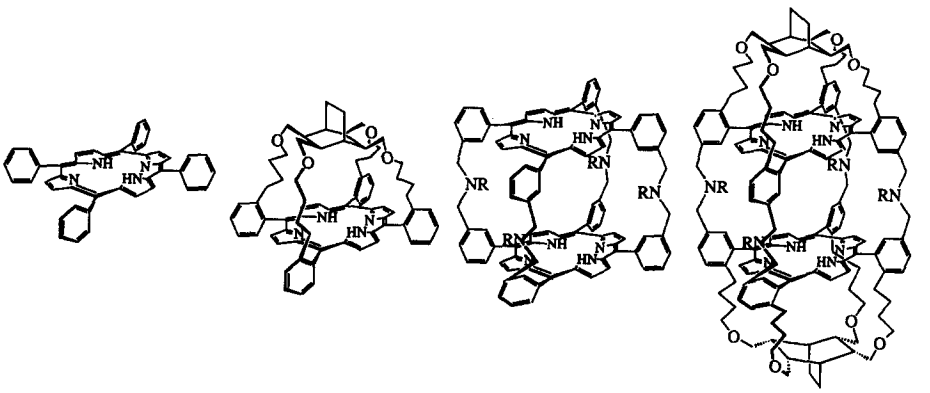


TPP IH_2 | Capped Porphyrin $IIIH_2$ | Cofacial bis-porphyrin $IIIH_4$ | Spheroidal bis-porphyrin IVH_4

Scheme 1.

TLC [1]. NMR experiments were recorded at 500 MHz on a General Electric GN-500 or at 200 MHz on a Varian Gemini-200 spectrometer at 25 °C in $CDCl_3$. Chemical shifts were reported relative to the signal of $CHCl_3$ (^1H, 7.240 ppm, and ^{13}C, 77.000 ppm). IR spectra were recorded on a Perkin-Elmer 1330 spectrophotometer and FT-IR on Galaxy 2020 with MacFirst software. Mass spectra were obtained by electron impact (EI) and fast atom bombardment (FAB) mass spectroscopy using *m*-nitrobenzyl alcohol as the matrix and a parallel run of cesium rubidium iodide for the reference. High resolution MS was obtained using PFK as a reference compound. HPLC was performed on a Hewlett Parkard 1050 pump and 1040 detector, a Gilson 231 Sample Injector with a 401 Dilutor, a Compaq computer interfaced with HP HPLC^{3D} ChemStation (Hewlett Packard) software. Column chromatography was performed with Fischer type 60 Å (200–425 mesh) silica gel. All reactions were carried out with purified reagents in dry, purified solvents under an atmosphere of argon.

2.1. Synthesis of 2-(3′-chloromethylphenyl)-1,3-dioxolane (2)

To a stirred solution of triphenyl phosphine (70.8 g, 0.27 mol), anhydrous 2,6-lutidine (40 ml, 0.34 mol) and 2-(3′-hydroxymethylphenyl)-1,3-dioxolane (**1**) (19.5 g, 0.108 mol) in 300 ml dry methylene chloride was slowly added carbon tetrachloride (29 ml, 0.30 mol) at 20 °C and stirring was continued for 2 h. Pentane (1200 ml) was then added and the precipitate removed by silica gel (60 g) filtration. The silica gel was washed with ether (200 ml) and the combined filtrates were concentrated. Column chromatography on silica gel (300 g), eluting with 10% ethyl acetate in hexanes, gave a product contaminated with 2,6-lutidine. The latter was removed via high vacuum to afford pure compound **2** in 85% yield (18.2 g) as a colorless liquid. $R_F = 0.37$ (10% ethyl acetate in hexanes). ^1H NMR (500 MHz): δ 4.00–4.15 (m, 4H, 4–H and 5–H), 4.581 (s, 2H, 3′–CH_2Cl), 5.801 (s, 1H, 2–H), 7.34–7.43 (m, 3H, aromatic), 7.495 (s, 1H, 2′–H) ppm. ^{13}C NMR (50 MHz): δ 45.8 (3′–CH_2Cl), 65.1 (4,5–C), 103.10 (2–C), 126.4 (2×C), 128.6, 129.1, 137.4, 138.4 (aromatic) ppm. IR: 2957, 2886, 1450, 1386, 1165, 1079, 966 cm^{-1}. MS: *m/z* (relative intensity) 200 (M^+, 8), 198 (M^+, 27), 197 ($(M-1)^+$, 100), 163 ($(M-Cl)^+$, 33), 73 (dioxolanyl, 88). HRMS: Calc. for $C_{10}H_{11}{}^{35}ClO_2$: (*M*) 198.0445. Found: 198.0447.

2.2. Synthesis of (5,10,15,20)tetrakis(α-chloro-m-tolyl)porphyrin (VH_2)

To a solution of 2-(3′-chloromethylphenyl)-1,3-dioxolane (**2**) (1.50 g, 7.56 mmol) and pyrrole (freshly distilled, 0.535 ml, 7.56 mmol) in chloroform (commercial, 750 ml) was added boron trifluoride etherate (1.4 ml, 11.3 mmol) in the dark and the reaction mixture was kept at such condition for 30 min before adding triethylamine (1.84 ml) to quench the reaction. DDQ (2,3-dichloro-5,6-dicyanoquinone, 0.5 g) was added and the mixture was immediately refluxed for 30 min when another 0.5 g of DDQ was added and refluxing continued for an additional 30 min. The whole reaction mixture was concentrated and passed through a short silica gel column (5 g) to clarify. Column chromatography on silica gel (50 g), eluted with 40% dichloromethane in pentane, afforded the product (0.64 g, 42%) as a purple solid: M.p. >300 °C. $R_F = 0.32$ (40% dichloromethane in pentane). ^1H NMR (500 MHz): δ −2.804 (s, 2H, NH), 4.866 (s, 8H, CH_2Cl), 7.743 (t, 4H, J=7.5 Hz, 5′–H), 7.760 (d, 4H, J=7.5 Hz, 6′–H), 8.166 (d, 4H, J=7.5 Hz, 4′–H), 8.230 (s, 4H, 2′–H), 8.832 (s, 8H, β-pyrrolic H). ^{13}C NMR (50

[1] We have previously reported [5a] that porphyrins can become ligated to zinc ion during TLC preparation and free base porphyrin can be recovered by treatment of the metallated porphyrin with trifluoroacetic acid at room temperature for 10 min. Also, others [7] have observed the same phenomenon and found that the zinc ion comes from fluorescent indicator coated with the silica gel on the plate. Therefore, for our preparative TLC and analytic TLC, no fluorescent indicator silica gel TLC plate was used.

MHz): δ 46.3 (CH_2Cl), 119.6 (*meso*-C), 127.1, 128.0, 134.5, 134.6 (aromatic C), 131.3 (β-pyrrolic C), 136.1 (3′–C), 142.5 (1′–C) ppm. IR: 3318 (NH), 1601, 1473 cm^{-1}. FAB MS: *m/z* 809 $(M+1)^+$, 808 $(M)^+$. UV–Vis (toluene): λ_{max} (log ε) 374.5 (4.38), 402 (sh, 4.89), 419.5 (5.63), 483 (3.53), 515 (4.28), 548.5 (3.88), 591 (3.72), 647 (3.53) nm.

2.3. Synthesis of zinc (5,10,15,20)tetrakis(α-chloro-m-tolyl)porphyrin (VZn)

To (5,10,15,20)tetrakis(α-chloro-*m*-tolyl)porphyrin (VH_2) (483 mg, 0.51 mmol) in a 100 ml round bottom flask was added 3 ml of toluene to dissolve the porphyrin followed by addition of 25 ml of acetic acid and zinc acetate dihydrate (483 mg, 2.2 mmol). The mixture was placed in a preheated bath at 100 °C. After 10 min, TLC shows that all starting material has been consumed and that there has been no exchange of chloro substituents for acetate substituents. The mixture was cooled down immediately, diluted with toluene and washed three times with water. After evaporating off the solvent, column chromatography on silica gel (15 g) with 50% dichloromethane in hexanes as a eluant gave pure **VZn** (503 mg, 97%) as a dark red solid. M.p. > 300 °C. $R_F = 0.20$ (50% dichloromethane in hexanes). ^1H NMR (500 MHz): δ 4.865 (s, 8H, CH_2Cl), 7.739 (t, 4H, $J = 7.5$ Hz, 5′–H), 7.804 (d, 4H, $J = 7.5$ Hz, 6′–H), 8.15–8.25 (m, 8H, 4′– and 2′–H), 8.935 (s, 8H, β-pyrrolic H). ^{13}C NMR (50 MHz): δ 46.4 (CH_2Cl), 120.5 (*meso*-C), 127.0, 127.8, 134.3, 134.5 (aromatic C), 132.1 (β-pyrrolic C), 135.9 (3′–C), 143.1 (1′–C), 150.2 (α-pyrrolic C) ppm. IR: 1600, 1481 cm^{-1}. FAB MS: *m/z* 872 $(M)^+$. UV–Vis (toluene): λ_{max} (log ε) 426 (5.63), 551 (4.27), 600 (3.58); (0.5% pyridine/toluene): 408 (4.65), 430 (5.81), 525 (3.54), 563 (4.33), 602 (3.93) nm.

2.4. Synthesis of bis-zinc cofacial bis-porphyrin (IIIZn$_2$)

To 5 mg of **IIIH$_4$** contained in a 10 ml round bottom flask was added 0.5 ml of toluene. After the porphyrin dissolved there were added 1 ml of acetic acid, 0.5 ml of methanol and 5 mg of zinc acetate dihydrate. The whole reaction mixture was placed in a preheated bath at 100 °C. After 20 min, the reaction mixture was cooled, diluted with toluene and washed three times with water. After evaporating off the solvent, preparative TLC, eluting with 5% diethyl ether in benzene, afforded 5 mg of pure **IIIZn$_2$** as a dark red solid. M.p. > 300 °C. $R_F = 0.16$ (5% diethyl ether in benzene). ^1H NMR (500 MHz): δ 0.171 (s, 36H, $4 \times SiMe_3$), 1.20–1.30 (m, 8H, $4 \times SiCH_2$), 3.25–3.35 (m, 8H, $4 \times CH_2SO_2$), 4.776 (s, 16H, benzylic H), 7.55–7.77 (m, 24H, aromatic H), 7.926 (d, 8H, $J = 7.5$ Hz, 4–H), 8.270 (s, 16H, β-pyrrolic H) ppm. FAB MS: 2178 (M^+) (Calc. for $C_{116}H_{116}N_{12}O_8S_4Si_4Zn_2$: 2177.7). HPLC: $T_R = 7.0$ min (immobile phase:silica gel; mobile phase:0.5% pyridine in toluene; flow rate: 0.75 ml/min; monitored at 419 nm). UV–Vis (toluene): λ_{max} (log ε) 418.5 (5.34), 551 (3.90) nm.

2.5. Synthesis and separation of mono-zinc cofacial bis-porphyrin (IIIZnH$_2$)

A 100 ml round bottom flask was dried by flame under high vacuum and argon was introduced. Cesium carbonate (450 mg, 1.38 mmol) was weighted into the flask and dried again. Trimethylsilylethanesulfonamide (93.9 mg, 0.518 mmol) [6,8] was placed into the flask. The flask was dried by hot-gun for 30 min and argon was charged. Dry DMF (predried over molecular sieves overnight and distilled at reduced pressure under argon) (15 ml) was charged and the mixture was stirred at 50 °C for 10 min. To this suspension was added slowly a solution of 5,10,15,20-tetrakis(α-chloro-*m*-tolyl)porphyrin (VH_2, 147 mg, 0.156 mmol) and zinc porphyrin **VZn** (157 mg, 0.156 mmol) in dry DMF (15 ml) via a syringe driver during 7 h at 57 °C. The solution was stirred overnight then most solvent was removed by rotavapor and the residue dissolved in dichloromethane. Column chromatography on silica gel (5% diethyl ether in benzene), followed by preparative thin layer chromatography (see Footnote [1] on p. 196) (100 × 200 × 0.50 mm, 5% diethyl ether in benzene) gave two fractions: the polar one is bis-zinc cofacial bis-porphyrin **IIIZn$_2$** (9.0 mg, 2.7%) and the nonpolar one is a mixture (20.4 mg, 6.2%) of free base cofacial bis-porphyrin **IIIH$_4$** and mono-zinc cofacial bis-porphyrin **IIIZnH$_2$** with a ratio of 40:60 by ^1H NMR. The two components are not separable on TLC even after developing several times but separable on silica gel column HPLC (T_R of **IIIH$_4$** = 6.0 and T_R of **IIIZnH$_2$** = 6.5 min when a mobile phase of 0.5% pyridine in toluene was used at a flow rate of 0.75 ml/min). The pure desired mono-zinc cofacial bis-porphyrin **IIIZnH$_2$** is then collected by this way. $R_F = 0.20$ (5% diethyl ether in benzene). ^1H NMR (500 MHz): δ −4.025 (s, 2H, NH), 0.122 (s, 36H, $4 \times SiMe_3$), 1.10–1.20 (m, 8H, $4 \times SiCH_2$), 3.13–3.25 (m, 8H, $4 \times CH_2SO_2$), 4.639 (s, 8H, benzylic protons of the phenyl groups on the free base porphyrin ring), 4.670 (s, 8H, benzylic protons of the phenyl groups on the zinc porphyrin ring), 7.127 (s, 4H, 2–H of the phenyl groups on the free base porphyrin ring), 7.186 (s, 4H, 2–H of the phenyl groups on the zinc porphyrin ring), 7.68–8.15 (m, 24H, aromatic), 8.306 (s, 8H, β-pyrrolic protons on the free base porphyrin ring), 8.331 (s, 8H, β-pyrrolic protons on the zinc porphyrin ring) ppm. FAB MS: 2114.0 (M^+) (Calc. for $C_{116}H_{118}N_{12}O_8S_4Si_4Zn$: 2114.3). UV–Vis (toluene): λ_{max} (log ε) 417.5 (5.81), 515.5 (4.40), 525.5 (4.02), 593 (3.91), 650 (3.68) nm.

3. Results and discussion

3.1. Selection of solvent system

A number of kinetic studies of metalloporphyrin formation have been reported and several reviews are available [2].

The majority of studies have been carried out in DMF [3] while other solvents which have been employed include pyridine [3b], acetic acid [9], chloroform/methanol [10] and acetic acid/ethanol [11]. When solubility has allowed, water [3a,12] has been employed as solvent. Although DMF serves well as a solvent for metallation of simple porphyrins [13], the reaction is relatively slow. Previous investigations have found that extended reaction times are accompanied by gradual absorption of porphyrin on the glass surface of the reaction vessel [14]. DMF suffers in this regard. A practical requirement of the metallation reaction is a shortening of the reaction time period. This requires the invention of a 'good' solvent system.

There is no single solvent which excels at dissolving both metal salts and tetraphenyl porphyrins. For good solvation of both parties of the reaction, it is a good idea to utilize miscible mixed solvents (two or more components) in which a nonpolar solvent participates in dissolving the hydrophobic porphyrin and a polar solvent helps by dissolving the metal salt. In order to find the best solvent components and the best ratio of these components, zinc incorporation into TPP (IH_2) was studied at 30.0 °C in the presence of a large excess (4350 folds) of zinc acetate. Compared to the sterically hindered capped porphyrin IIH_2, cofacial bis-porphyrin $IIIH_4$ and spheroidal bis-porphyrin IVH_4, TPP is the less sterically encumbered structure. One can imagine then that the rate constants for metallation of TPP (IH_2) would be the largest. A summary of a portion of the experimental results is shown in Table 1 where a solvent system of DMF/PhCl (20:80 (vol./vol.)) served as a standard.

From Table 1, the two best co-solvents are found to be acetic acid and methanol (entry 11 and 7). The contribution to the rate acceleration from methanol is smaller than that from acetic acid: the reaction is six times faster than in DMF (entry 20) if 10% of methanol was added while the reaction is at least 14 times faster if the same amount of acetic acid was added. Unfortunately, in the presence of acetic acid (even 0.2% acetic acid in 10% DMF with 90% PhCl) zinc acetate slowly precipitates from solution.

Table 1
Screening of co-solvents (10% of co-solvent, 10% of DMF, 80% of PhCl at 30.0 °C, $[Zn^{2+}] = 4.35 \times 10^{-2}$ M, $[IH_2] = 1 \times 10^{-6}$ M)

Entry	Co-solvent	k_{obs} ($1000\ s^{-1}$)	Relative rate
1	^{n}BuOH	1.95	4.0
2	^{t}BuOH	1.60	3.3
3	^{s}BuOH	1.77	3.6
4	^{i}PrOH	1.79	3.7
5	^{n}PrOH	2.47	5.0
6	EtOH	2.06	4.2
7	MeOH	3.02	6.2
8	DMSO	0.20	0.41
9	Et_3N	1.48	3.0
10	MeCN	1.14	2.3
11	HOAc	7.12 [a]	14.5
12	THF	0.83	1.7
13	Acetone	0.97	2.0
14	PhCl	1.03	2.1
15	CH3Cl	1.63	3.3
16	Pyridine	0.17	0.35
17	1,4-Dioxane	0.68 [a]	1.4
18	2,6-Lutidine	0.92	1.9
19	Ethyl acetate	0.97	2.0
20	DMF	0.49	1.0

[a] Precipitates formed.

For kinetic purposes the concentrations of porphyrin need not exceed 10 nM. Such low concentrations are sufficient because of the appreciable extinction coefficients of porphyrins and metalloporphyrins. At such low porphyrin concentrations it is not necessary to use a 80% PhCl solvent component; 5% of PhCl or toluene is sufficient. On the basis of experiments with varying ratios of methanol and acetic acid the ideal solvent for promoting the rate of metallation and solvation of the zinc salt was found to be 5% toluene, 20% acetic acid and 75% methanol. In this system the concentration of zinc can be as high as 0.16 M.

3.2. Kinetic studies of zinc incorporation into TPP (IH_2)

Fig. 1 shows the dependence upon $[Zn^{2+}]$ of the pseudo first-order rate constants (k_{obs}) for the metallation of IH_2 in the presence of a large excess of zinc acetate. The sequence of reactions depicted in Eqs. (1), (2) and (3) [3b,c] are now considered. The species $IH_2 \cdot \cdot Zn^{2+}$ is a complex or so

$$IH_2 + Zn^{2+} \overset{K}{\rightleftharpoons} IH_2 \cdot \cdot Zn^{2+} \quad (1)$$

$$IH_2 \cdot \cdot Zn^{2+} \overset{k_1}{\rightarrow} IZn + 2H^+ \quad (2)$$

$$IH_2 \cdot \cdot Zn^{2+} + Zn^{2+} \overset{k_2}{\rightarrow} IZn + Zn^{2+} + 2H^+ \quad (3)$$

called 'sitting-atop' intermediate which converts to the metalloporphyrin IZn via two pathways. The first consists of facially associated Zn^{2+} being ligated by the porphyrin on the later loss of two protons (Eq. (2)). This reaction may occur by stepwise ionization of IH_2 with each dissociation

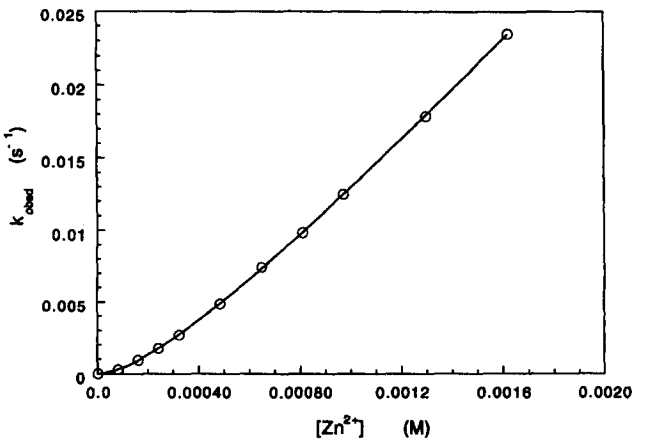


Fig. 1. Plot of k_{obs} vs. $[Zn^{2+}]$ for the reaction of TPP (IH_2) and zinc acetate in toluene/HOAc/MeOH (5:20:75 (vol./vol.)) at 30.0 °C. The circles are the observed data, and the solid line is calculated from Eq. (4) with $K = 2300\ M^{-1}$, $k_1 = 4.7 \times 10^{-4}\ s^{-1}$ and $k_2 = 18\ s^{-1}\ M^{-1}$.

being accompanied by pyrrole nitrogen anion association with Zn^{2+}. The second process involves a transient species composed of two metal ions (Eq. (3)). The derived rate law is shown as Eq. (4). Best values of K, k_1 and k_2 were determined by fitting plots of

$$k_{obs} = \frac{k_1 + k_2 [Zn^{2+}]}{1 + K [Zn^{2+}]} K [Zn^{2+}] \quad (4)$$

k_{obs} versus $[Zn^{2+}]$ to Eq. (4) by use of a non-linear least-squares program. The fitting of the points of Fig. 1 to Eq. (4) provides the constants $K = 2300\ M^{-1}$, $k_1 = 4.7 \times 10^{-4}\ s^{-1}$ and $k_2 = 18\ s^{-1}\ M^{-1}$.

3.3. Kinetic studies of zinc incorporation into the capped porphyrin (IIH_2)

Fitting of plots of the pseudo first-order rate constants (k_{obs}) for insertion of Zn^{2+} into IIH_2 required the use of Eqs. (1) and (2) only (Eq. (5) and Fig. 2). That the

$$k_{obs} = \frac{k_1 K [Zn^{2+}]}{1 + K [Zn^{2+}]} \quad (5)$$

metallation of IIH_2 is only first-order in $[Zn^{2+}]$ must be due to one face of the porphyrin ring being shielded from approach by a second Zn^{2+}. It is known that the cavity between bicyclo[2.2.2]octane cap and porphyrin face, in the energy minimized conformation of IIH_2, is only large enough to accommodate a water molecule [4]. Thus, results with IIH_2 firmly support the two Zn^{2+} moieties being associated with opposite faces of the porphyrin ring in the reaction of Eq. (3). The constants k_1 and K were determined to be $3.6 \times 10^{-4}\ s^{-1}$ and $6.5\ M^{-1}$, respectively. Comparison of the values of k_1 for IIH_2 and IH_2 establishes their near identity. On the other hand, the equilibrium constant (K) for association of Zn^{2+} with the porphyrin is 354-fold smaller for IIH_2 as compared to IH_2. Thus, although the side of the porphyrin ring protected by the bicyclo[2.2.2]octane cap is

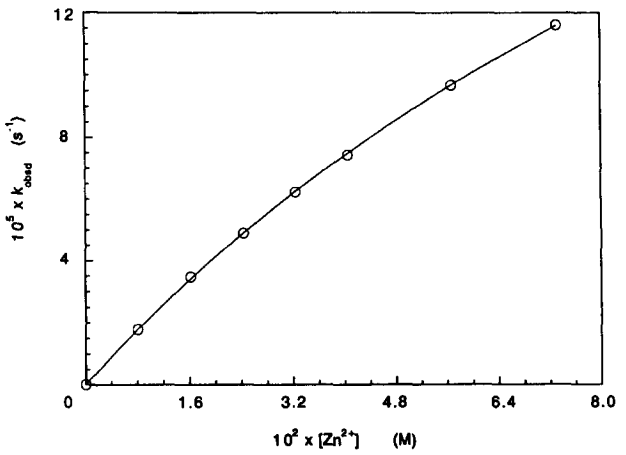


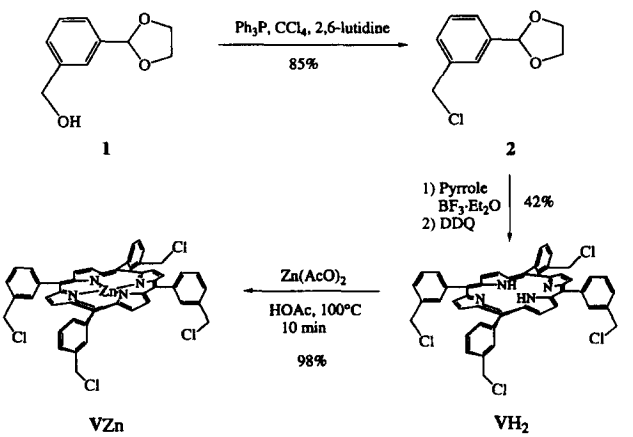
Fig. 2. Plot of k_{obs} vs. $[Zn^{2+}]$ for the reaction of capped porphyrin (IIH_2) and zinc acetate in toluene/HOAc/MeOH (5:20:75 (vol./vol.)) at 30.0 °C. The circles are the observed data, and the solid line is calculated from Eq. (5) with $K = 6.5\ M^{-1}$, $k_1 = 3.6 \times 10^{-4}\ s^{-1}$.

distal to the side undergoing complexation with Zn^{2+}, the presence of the cap has a large influence on the equilibrium constant for this complexation. In solution a porphyrin ring takes on a number of conformations due to its dynamic flexing motions. It is possible that the favored conformation for Zn^{2+} complexing with TPP is energetically less available when the TPP is encumbered by the bicyclo[2.2.2]octane cap. Once the $Zn^{2+} \cdot \cdot IH_2$ and $Zn^{2+} \cdot \cdot IIH_2$ complexes are formed there is equal ease for metal insertion. Apparently there is no steric hindrance to solvation of the departing $2H^+$ by the cap on insertion of the Zn^{2+}.

3.4. Synthesis of the mono-zinc ($IIIZnH_2$) and bis-zinc ($IIIZn_2$) derivatives of the cofacial bis-porphyrin ($IIIH_4$)

As shown in Scheme 2, compound **1** (2-(3′-hydroxymethyl)phenyl-1,3-dioxolane) [6,15] was converted into the corresponding substituted benzyl chloride (**2**) in 85% yield by treatment of **1** with triphenyl phosphine and carbon tetrachloride in the presence of 2,6-lutidine (to prevent the hydrolysis of the acetal group) [6]. Free base porphyrin VH_2 was then synthesized in 42% yield by treatment of acetal **2** with pyrrole and boron trifluoride etherate in chloroform followed by DDQ (2,3-dichloro-5,6-dicyanoquinone) oxidation [4,16]. Metallation of free base porphyrin VH_2 with zinc acetate in acetic acid at 100 °C for 10 min, monitored by TLC, afforded zinc porphyrin **VZn** in 97% yield. Elongation of reaction time would result in the substitution of chloro groups by acetates to form the corresponding mono- to tetra-acetate compounds.

Two molecules of the zinc porphyrin **VZn** were coupled [5a,6] with trimethylsilylethanesulfonamide (**3**) [6,8] in the presence of cesium carbonate in DMF at 60 °C to provide the bis-zinc cofacial bis-porphyrin $IIIZn_2$ which was collected by preparative thin layer chromatography (see Footnote [1] on p. 196) in 15% yield. In a like manner there was coupled with sulfonamide **3** one molecule of free base porphyrin (VH_2) and one molecule of the zinc porphyrin **VZn** (Scheme 3) to provide, in a combined yield of 6%, the mono-zinc cofacial bis-porphyrin ($IIIH_2Zn$) and free base cofacial



Scheme 2.

$$2\ \mathrm{VZn} \xrightarrow[\mathrm{Cs_2CO_3,\ DMF,\ 60°C}]{\mathrm{Me_3SiCH_2CH_2SO_2NH_2\ (3)}} \mathbf{IIIZn_2}$$

$$\mathrm{VH_2} + \mathrm{VZn} \xrightarrow[\mathrm{Cs_2CO_3,\ DMF,\ 60°C}]{\mathrm{Me_3SiCH_2CH_2SO_2NH_2\ (3)}} \mathbf{IIIH_2Zn}$$

$$\mathbf{IIIH_4} \xrightarrow[\mathrm{HOAc,\ 100°C}\ 10\ \mathrm{min}]{\mathrm{Zn(AcO)_2}} \mathbf{IIIZn_2}$$

Scheme 3.

bis-porphyrin $\mathbf{IIIH_4}$ in a ratio of 60:40. The two components were separated by HPLC on a silica gel column using 0.5% pyridine in toluene as a mobile phase (T_R of $\mathbf{IIIH_4}$ = 6.0 min, T_R of $\mathbf{IIIH_2Zn}$ = 6.5 min). There also could be isolated the bis-zinc cofacial bis-porphyrin $\mathbf{IIIZn_2}$ (T_R = 7.0 min) in 3% yield. The latter was also obtained from direct metallation of $\mathbf{IIIH_4}$ with zinc acetate in acetic acid at 100 °C for a few minutes.

3.5. Product analysis in the reaction of Zn^{2+} with the cofacial bis-porphyrin ($IIIH_4$)

Product analysis was carried out at a concentration of $\mathbf{IIIH_4}$ 8-fold greater than used for kinetic studies. About 5 mg of cofacial bis-porphyrin ($\mathbf{IIIH_4}$) was metallated by reaction with zinc acetate, and the pure product collected after diluting with toluene, washing with water four times and drying. Every step of the workup process was monitored by both HPLC and spectrophotometry to be certain that the product was not changed during separation. The product was identical to the known bis-metallated $\mathbf{IIIZn_2}$ in both spectroscopic features (FAB MS, ^{1}H NMR, UV–Vis, Fluorescent) and chromatographic (TLC, HPLC) characteristics. Therefore, the final product of metallation is clearly $\mathbf{IIIZn_2}$.

3.6. The order and means of incorporation of two Zn^{2+} into the cofacial bis-porphyrin ($IIIH_4$)

There are two porphyrin cores in the cofacial bis-porphyrin ($\mathbf{IIIH_4}$), each can bind one zinc ion. A stepwise mechanism for Zn^{2+} incorporation is provided in Eqs. (6)–(9), where H_2P–PH_2 stands for free base cofacial bis-porphyrin; H_2P–$H_2P\cdot\cdot Zn^2$ and $Zn^{2+}\cdot\cdot PH_2$–PZn stand for the metal–porphyrin complexes of free base and mono-zinc cofacial bis-

$$H_2P-PH_2+Zn^{2+} \overset{K_1}{\rightleftharpoons} H_2P-H_2P\cdot\cdot Zn^{2+} \quad (6)$$

$$H_2P-H_2P\cdot\cdot Zn^{2+} \overset{k_{11}}{\rightarrow} H_2P-PZn+2H^+ \quad (7)$$

$$H_2P-PZn+Zn^{2+} \overset{K_2}{\rightleftharpoons} Zn^{2+}\cdot\cdot PH_2-PZn \quad (8)$$

$$Zn^{2+}\cdot\cdot PH_2-PZn \overset{k_{12}}{\rightarrow} ZnP-PZn+2H^+ \quad (9)$$

porphyrin, respectively. Because kinetic saturation in Zn^{2+} was not observed, values of K_1 and K_2 could not be determined. In the presence of a large excess of zinc ion, all reactions monitored spectrophotometrically followed the first order rate law to completion of reaction (Fig. 3) and the values of k_{obs} were linearly dependent upon $[Zn^{2+}]$ as shown in Fig. 4. Thus, bimetallation is first order in both $[Zn^{2+}]$ and $[\mathbf{IIIH_4}]$ (Eq. (10)) and k was determined as 0.26 s^{-1} M^{-1}. Values of k_{obs} remained the same when using concentrations of $\mathbf{IIIH_4}$ between 10^{-7} to 10^{-5} M at given values of $[Zn^{2+}]$.

$$\frac{d[\mathbf{IIIZn_2}]}{dt} = k\,[Zn^{2+}]\,[\mathbf{IIIH_4}] \quad (10)$$

The stepwise nature of the bimetallation reaction was established by monitoring the reaction via HPLC analysis. In each experiment, the visible absorbance of the reaction solution at 419 nm was recorded prior to removal of small aliquots ($\sim$100 μl) for HPLC analysis. The samples were immediately cooled to −78 °C and solvents removed under high vacuum. Samples were taken up in toluene (50 μl) and sub-

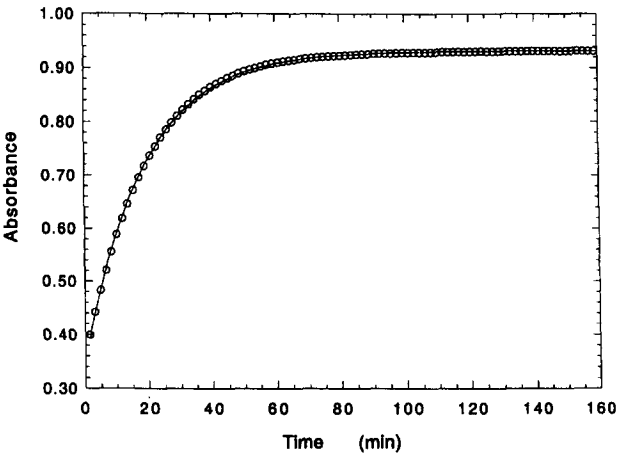


Fig. 3. The change in absorbance at 419 nm over time for the reaction of zinc acetate and cofacial bis-porphyrin ($\mathbf{IIIH_4}$) when $[Zn^{2+}]$ = 3.24 mM and $[\mathbf{IIIH_4}]$ = 1.3 μM. The observed data (circles) fits perfectly with the first-order rate equation.

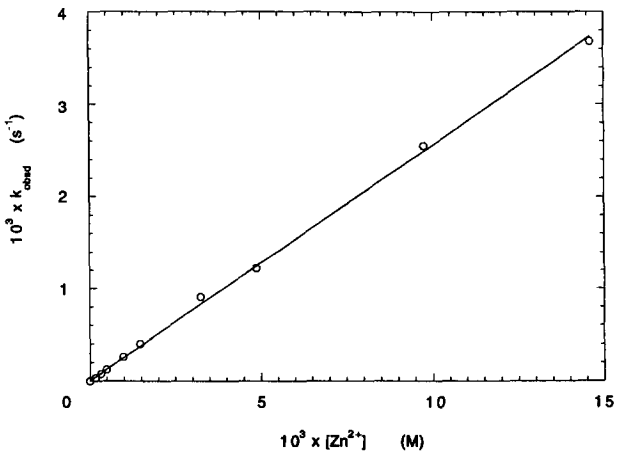


Fig. 4. Plot of k_{obs} vs. $[Zn^{2+}]$ for the reaction of cofacial bis-porphyrin ($\mathbf{IIIH_4}$) and zinc acetate in toluene/HOAc/MeOH (5:20:75 (vol./vol.)) at 30.0 °C. The circles are the observed data, and the solid line is calculated from Eq. (10) with k = 0.26 s^{-1} M^{-1}.

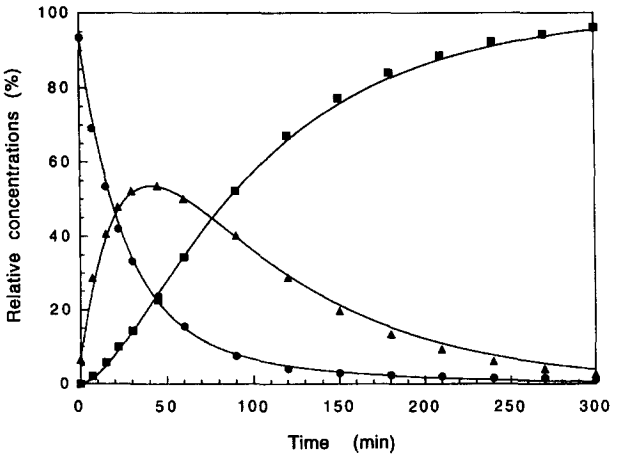


Fig. 5. Plot of concentrations of $\mathbf{IIIH_4}$ (●), $\mathbf{IIIH_2Zn}$ (▲) and $\mathbf{IIIZn_2}$ (■) over time in the reaction of cofacial bis-porphyrin ($\mathbf{IIIH_4}$) and zinc acetate in toluene/HOAc/MeOH (5:20:75 (vol./vol.)) at 30.0 °C when $[Zn^{2+}] = 3.24$ mM. The observed data points were obtained by HPLC analysis, and the solid lines are calculated from Eq. (11) via KINSIM program [17] with $k_{1obs} = 1.9 \times 10^{-3}$, $k_{-1obs} = 1.9 \times 10^{-4}$, and $k_{2obs} = 7.2 \times 10^{-4}\ s^{-1}$.

jected immediately to HPLC analysis. A sampling of the HPLC analysis is presented in Fig. 5. Examination of Fig. 5 shows that as the concentration of $\mathbf{IIIH_4}$ disappears the intermediate $\mathbf{IIIH_2Zn}$ accumulates and then gives way to the product $\mathbf{IIIZn_2}$. The experimental points were fit to the sequential first-order pathway of Eq. (11) by use of the program

$$\mathrm{A} \underset{k_{-1obs}}{\overset{k_{1obs}}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_{2obs}} \mathrm{C} \qquad (11)$$

KINSIM [17] Version 3.4 PC 900819. Under the pseudo first-order conditions of a large excess of Zn^{2+} the identities of Eqs. (12)–(14) hold. The values of k_{1obs}, k_{-1obs} and

$$k_{1obs} = k_1 \cdot [Zn^{2+}] \qquad (12)$$

$$k_{2obs} = k_2 \cdot [Zn^{2+}] \qquad (13)$$

$$k_{-1obs} = k_{-1} \cdot [H^+]^2 \qquad (14)$$

k_{2obs} were found to be 1.9×10^{-3}, 1.9×10^{-4} and 7.2×10^{-4} s^{-1}, respectively, when $[Zn^{2+}] = 3.24$ mM. The reverse reaction of A → B with k_{-1obs} can be explained by the acidic hydrolysis of metalloporphyrin. Under the conditions of the experiment ($[Zn^{2+}] = 3.24$ mM in 20% of acetic acid) the rate of the reverse reaction amounts to 10% of the forward reaction.

Fig. 6 shows the linear dependence of the pseudo first-order rate constants k_{1obs} and k_{2obs} upon the concentration of zinc acetate. The slope of the plots provide the second-order rate constants $k_1 = 0.59\ s^{-1}\ M^{-1}$ and $k_2 = 0.21\ s^{-1}\ M^{-1}$. These may be compared to the second-order rate constant ($k = 0.26\ s^{-1}\ M^{-1}$) determined by monitoring with time the change in absorbance of the total reaction solution at 419 nm.

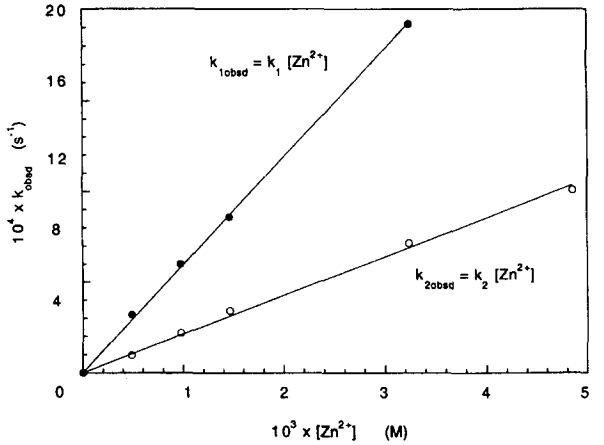


Fig. 6. Plot of k_{1obs} and k_{2obs} vs. $[Zn^{2+}]$ for the reaction of cofacial bis-porphyrin ($\mathbf{IIIH_4}$) and zinc acetate in toluene/HOAc/MeOH (5:20:75 (vol./vol.)) at 30.0 °C. The points (dots and circles) are observed data, the solid lines are calculated data with $k_1 = 0.59\ s^{-1}\ M^{-1}$ from Eq. (12) and $k_2 = 0.21\ s^{-1}\ M^{-1}$ from Eq. (14).

3.7. Kinetic studies of zinc incorporation into the spheroidal bis-porphyrin (IVH_4)

The reaction of zinc acetate and $\mathbf{IVH_4}$ is extraordinarily slow. The rate constant was estimated via the initial rate method [18] and the assumption that the reaction steps resemble those for $\mathbf{IIIH_4}$. In the first 1% or so of reaction it may be assumed that the concentration of reactants have not changed (Eq. (15)).

$$\frac{dP}{dt} \simeq k\,[\mathbf{IVH_4}]_0[Zn^{2+}]_0 \qquad (15)$$

Therefore:

$$k = \frac{1}{[\mathbf{IVH_4}]_0[Zn^{2+}]_0}\frac{dP}{dt} \qquad (16)$$

$$k = \frac{1}{[\mathbf{IVH_4}]_0[Zn^{2+}]_0}\frac{1}{1 \cdot \epsilon}\frac{dA}{dt} \qquad (17)$$

$$k = \frac{1}{[Zn^{2+}]_0}\frac{1}{A_p^{\infty}}\frac{dA}{dt} \qquad (18)$$

where dP stands for the concentration change of product, ϵ is the extinction coefficient of product, dA/dt is the absorbance change ($\Delta 419$ nm) during a given time, $[Zn^{2+}]_0$ is the initial concentration of Zn^{2+}, A_p^{∞} is the final absorbance of the product. $A^{\infty}{}_p$ was determined by heating the reaction mixture at 100 °C until no further change in absorbance occured. The rate constant was estimated as $5 \times 10^{-7}\ s^{-1}\ M^{-1}$. No further kinetic data for zinc incorporation into $\mathbf{IVH_4}$ can be obtained. However, FAB MS established that two zinc ions were inserted to provide $\mathbf{IVZn_2}$.

4. Conclusions

Because of the differences in the kinetic expressions of metal insertion into the four porphyrins studied, comparisons

Table 2
Comparison of the results of the kinetics of zinc ion incorporation into porphyrins

Porphyrin	K (M^{-1})	k_1 (s^{-1})	k_2 ($M^{-1}s^{-1}$)	k ($M^{-1}s^{-1}$)	k_{obs} (s^{-1})	Relative rate	Ref.	Notes
IH_2	2.3×10^3	4.7×10^{-4}	18		1.3	3.2×10^7	this work	
IIH_2	6.5	3.6×10^{-4}	0		1.2×10^{-4}	3.0×10^3	this work	
$IIIH_4$				0.26	1.9×10^{-2}	4.8×10^5	this work	
IVH_4				5×10^{-7}	4×10^{-8}	1	this work	
IH_2	1.2×10^3	1.6×10^{-5}	9.7×10^{-4}		8.6×10^{-5}	2.2×10^3	[3a]	DMF, 25 °C
IH_2	7.2×10^2	3.5×10^{-5}	8.6×10^{-4}		9.6×10^{-5}	2.4×10^3	[3c]	DMF, 25 °C
IH_2	3.6×10^2	2.1×10^{-4}	0		2.0×10^{-4}	5.0×10^3	[3b]	Py, 25 °C

of efficiency cannot be made by examination of specific rate constants. One is left with the comparison of pseudo first-order rate constants (k_{obs}) at a given concentration of zinc acetate. For instance, when $[Zn^{2+}] = 0.073$ M, k_{obs} of TPP (IH_2), cofacial bis-porphyrin ($IIIH_4$), capped porphyrin (IIH_2), and spheroidal bis-porphyrin (IVH_4) are 1.3, 1.9×10^{-2}, 1.1×10^{-4}, and 4×10^{-8} s^{-1}, respectively (Table 2), corresponding to the rate ratios of 32 000 000:480 000:3 000:1. Therefore, the rate of zinc incorporation into the spheroidal bis-porphyrin is 32 million times slower than that of TPP. Also, compared with known [3a–c] studies on Zn^{2+} incorporation into TPP at 25 °C, the rate of Zn^{2+} insertion in the condition employed here ($PhCH_3$:HOAc:CH_3OH = 5:20:75, 30.0 °C) is about 14 000 times faster than in DMF at 25 °C.

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