# Acid Solvolysis Kinetics of Lanthanide Porphyrins

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The kinetics of the acid solvolysis reactions of twelve water-soluble lanthanide tetrakis(*N*-methyl-4-pyridyl)porphyrins (Ln–P) follow rate = $k_1$ [Ln–P] $[H^+]^2/\{(k_{-1}/k_2) + [H^+]\}$ at 25 ° C, $I$ = 0.8 M ($LiNO_3/HNO_3$) indicating that two protons are required for solvolysis, and since log $(k_1k_2/k_{-1}) = 45.0R_0 - 39.4$ ($R_0$ is the ionic radius in Å), a 0.1 Å change in radius has a 32 000 fold rate effect.

The tumour-localizing ability of certain porphyrin molecules complexed with paramagnetic metal ions[1] makes water-soluble lanthanide porphyrins attractive candidates as *in vivo* magnetic resonance imaging agents for malignant tissues.[2] Since nothing is quantitatively known about the *in vitro* stability of lanthanide porphyrins in aqueous solution, we report the kinetics of the acid solvolysis reactions of twelve lanthanide tetrakis-(*N*-methyl-4-pyridyl)porphyrins (M–TMPyP). These are the only trivalent metalloporphyrin rections that need not be investigated in concentrated acids,[3] and as such allow for a comparison with solvolysis rate laws found for divalent derivatives.

The $Ln^{III}$–TMPyP compounds were made from the disodium salt of tetra(4-pyridyl)porphyrin and lanthanide acetates in refluxing dimethylformamide (DMF) after the procedure of Adler and co-workers,[4] followed by *N*-methylation in chloroform with methyl iodide.[5]† They could also be prepared directly from $H_2$–TMPyP and the lanthanide acetates in imidazole melts[6] at 120 °C. The kinetics were followed spectrophotometrically at 25 °C at an ionic strength of 0.8 M ($LiNO_3/HNO_3$).‡

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† For HO-$Lu^{III}$–TMPyP$I_4$·$3H_2O$, satisfactory elemental analyses were obtained; at pH 6, $\lambda_{max.}$/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$): 426.5 ($1.9 \times 10^5$), 517.0 (sh, $3.5 \times 10^3$), 554.5 ($1.7 \times 10^4$), and 590.0 (sh, $4.3 \times 10^3$).

‡ The solutions were unbuffered below pH 1, while 10 mM dichloroacetic acid (p$K_{a1}$ 1.5) was used between pH 1 and 2, and 10 mM monochloroacetic acid (p$K_{a1}$ 2.5) was added for pH values between 2 and 3.5. The kinetics studies were carried out on a stopped-flow apparatus.

**Table 1.** Acid solvolysis rate constants for lanthanide porphyrins.

| M in $M^{III}$–TMPyP[a] | $k_1$/dm$^3$ mol$^{-1}$ s$^{-1}$ | $(k_{-1}/k_2)$/mol dm$^{-3}$ | $(k_1k_2/k_{-1})$ /dm$^6$ mol$^{-2}$ s$^{-1}$ |
|---|---|---|---|
| Lutetium | $(1.3 \pm 0.1) \times 10^{-2}$ | $(9.5 \pm 1.3) \times 10^{-2}$ | $(1.4 \pm 0.2) \times 10^{-1}$ |
| Ytterbium | $(5.6 \pm 0.3) \times 10^{-2}$ | $(2.5 \pm 0.2) \times 10^{-1}$ | $(2.2 \pm 0.2) \times 10^{-1}$ |
| Thulium | $(1.1 \pm 0.1) \times 10^{-1}$ | $(1.2 \pm 0.1) \times 10^{-1}$ | $(9.6 \pm 0.6) \times 10^{-1}$ |
| Erbium | $(3.1 \pm 0.2) \times 10^{-1}$ | $(1.9 \pm 0.1) \times 10^{-1}$ | $1.6 \pm 0.1$ |
| Holium | $(2.5 \pm 0.2) \times 10^{-1}$ | $(2.6 \pm 0.4) \times 10^{-2}$ | $9.5 \pm 1.4$ |
| Dysprosium | $(2.2 \pm 0.7) \times 10^{-1}$ | $2.8 \pm 0.2$ | $7.7 \pm 0.4$ |
| Terbium | $(9.0 \pm 0.2) \times 10^{1}$ | $2.1 \pm 0.1$ | $(4.2 \pm 0.2) \times 10^{1}$ |
| Gadolinium | — | — | $(2.5 \pm 0.2) \times 10^{2}$ |
| Europium | — | — | $(2.0 \pm 0.2) \times 10^{3}$ |
| Samarium | — | — | $(1.1 \pm 0.2) \times 10^{4}$ |
| Neodymium | $(2.7 \pm 0.1) \times 10^{3}$ | $(8.4 \pm 0.1) \times 10^{-3}$ | $(3.2 \pm 0.4) \times 10^{5}$ |
| Praseodymium | $(2.3 \pm 0.1) \times 10^{4}$ | $(3.9 \pm 0.1) \times 10^{-3}$ | $(6.0 \pm 0.1) \times 10^{6}$ |

[a] $T = 25$ °C, $I = 0.8$ M ($LiNO_3/HNO_3$).

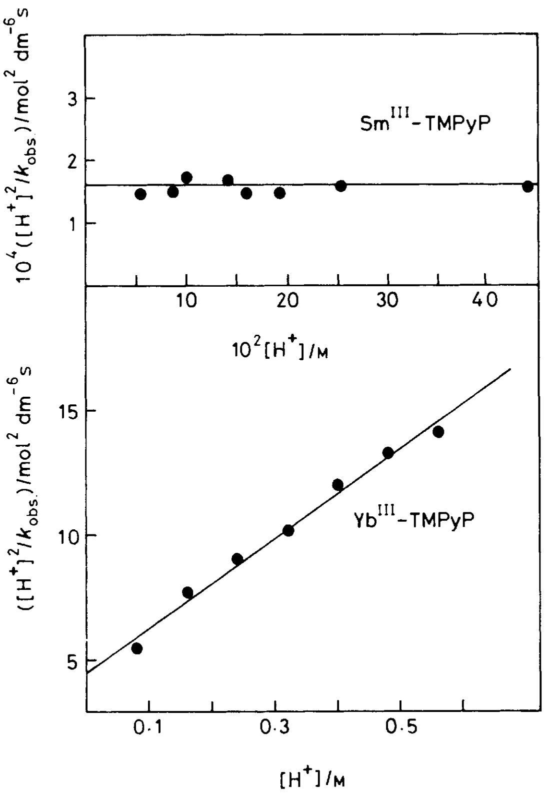

**Figure 1.** Plots of $[H^+]^2/k_{obs.}$ *vs.* $[H^+]$ for the acid solvolysis reactions of $Sm^{III}$–TMPyP and $Yb^{III}$–TMPyP indicating the two types of rate behaviour found.

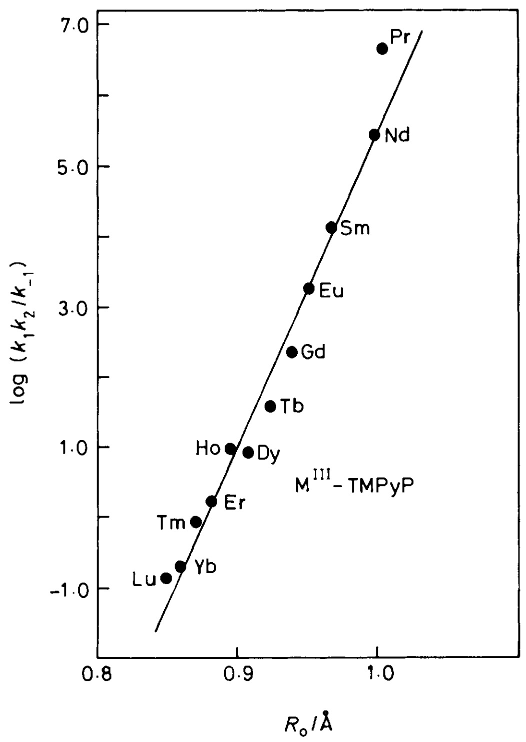

**Figure 2.** Plot of log $(k_1k_2/k_{-1})$ *vs.* the ionic radii of the lanthanide ions, $R_0$.

The lanthanides are postulated to be eight-co-ordinated in porphyrin complexes,[7] with four bonds to the porphyrin and four to other ligands. The large lanthanide ions sit well out of the mean porphyrin plane. Crystal structure results[7] with octaethylporphyrin (OEP) complexes show that the M–$N_4$ distances are *ca.* 1.4 Å for $Eu(OEP)_2$, 1.37 Å for $Ce(OEP)_2$, and 1.3 Å for $Ce_2(OEP)_3$. $^1H$ N.m.r. work on metalloporphyrins[6] indicates the following distances of the metal ion to the porphyrin plane: 1.6 Å for $Tm^{III}$, 1.8 Å for $Eu^{III}$, and 1.6 Å for $Yb^{III}$. We find no evidence of an equilibrium between free lanthanide ions and $H_2$–TMPyP, as has been noted previously[8—10] for $Pb^{II}$, $Cd^{II}$, and $Zn^{II}$ porphyrins. Preliminary results indicate that the acid hydrolysis p$K_a$ values of the Ln–TMPyP derivatives are above pH 5, and since our kinetic work is below pH 4, the presumed tetra-aquo $(H_2O)_4$–$Ln^{III}$–P is the reactant.

In all cases, the reactions were first order in porphyrin concentration over three half-lives, with a pseudo-first-order rate constant, $k_{obs.}$. The simplest mechanism consistent with the data is that in equations (1) and (2). With $[Ln^{III}–P–H^+]$ as a steady-state intermediate, the expected rate law is of the form in equation (3). Thus plots of $[H^+]^2/k_{obs.}$ *vs.* $[H^+]$ should be linear, and Figure 1 shows that this is the behaviour found. For Gd, Eu, and Sm, only $(k_1k_2/k_{-1})$ could be obtained, while for the other complexes, both $k_1$ and $(k_{-1}/k_2)$ were accessible. The results are in Table 1. To compare all the lanthanides, Figure 2 shows a linear plot of log $(k_1k_2/k_{-1})$ *vs.* the ionic radii $R_0$ of the metal ions (in Å), in accord with the equation

$\log (k_1k_2/k_{-1}) = 45.0R_0 - 39.4$. A similar linear relationship holds between $\log k_1$ and $R_0$, where $\log k_1 = 36.9R_0 - 32.9$.

$$\mathrm{Ln^{III}\text{–}P} + \mathrm{H^+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\mathrm{Ln^{III}\text{–}P\text{–}H^+}] \quad (1)$$

$$[\mathrm{Ln^{III}\text{–}P\text{–}H^+}] + \mathrm{H^+} \xrightarrow{k_2} \mathrm{Ln^{III}} + \mathrm{H_2\text{–}P} \quad (2)$$

$$k_{\mathrm{obs.}} = k_1\,[\mathrm{H^+}]^2/\{(k_{-1}/k_2) + [\mathrm{H^+}]\} \quad (3)$$

The same two-proton rate law that we find for the trivalent lanthanides has been demonstrated before for acid solvolysis reactions of water soluble $\mathrm{Zn^{II}}$,[8,11] $\mathrm{Cd^{II}}$,[9] $\mathrm{Pb^{II}}$,[10] $\mathrm{Fe^{II}}$,[12] $\mathrm{Mn^{II}}$,[13] and $\mathrm{Mg^{II}}$ (ref. 12) porphyrins. The divalent derivatives also give a $\log k$ *vs.* $R_0$ correlation,[12] and the porphyrin nucleus deformations postulated for metal ion removal have been discussed.[14] At high $[\mathrm{H^+}]$ {where $k_{\mathrm{obs.}} \propto [\mathrm{H^+}]$}, $\mathrm{Pr^{III}\text{–}TMPyP}$ reacts about $10^7$ times faster than does the $\mathrm{Lu^{III}}$ complex, and a 0.1 Å increase in the ionic radius of the co-ordinated metal ion leads to a remarkable 32 000 fold increase in the rate parameters. At low $[\mathrm{H^+}]$ {where $k_{\mathrm{obs.}} \propto [\mathrm{H^+}]^2$}, a 0.1 Å increase leads to a rate constant enhancement of 4900. This is consistent with previous qualitative observations indicating that (a), the heavier lanthanide porphyrins are more stable to solvolysis,[6,15] and (b), a larger divalent ion in a metalloporphyrin is solvolysed much more rapidly than the same ion in its smaller trivalent state.[13] Under similar conditions,[12] for example, $\mathrm{Mg^{II}\text{–}P}$ [$R_0 = 0.72$ Å (six-co-ordinate), $k_d = 1.9 \times 10^6\ \mathrm{dm^6\ mol^{-2}\ s^{-1}}$] and $\mathrm{Fe^{II}\text{–}P}$ [$R_0 = 0.61$ Å (low spin, six-co-ordinate), $k_d = 55\ \mathrm{dm^6\ mol^{-2}\ s^{-1}}$] both show rate $= k_d[\mathrm{M\text{–}P}][\mathrm{H^+}]^2$. The observed ratio of $(k_{\mathrm{Mg}}/k_{\mathrm{Fe}})$ is $3.5 \times 10^4$, and that calculated is $1.1 \times 10^4$.

In conclusion, the paramagnetic lanthanide derivatives of the tetrapositively charged TMPyP from $\mathrm{Eu^{III}}$ onwards are of sufficient stability to protons at pH 7.4 that they could be useful magnetic resonance imaging contrast agents. As expected for $\mathrm{H^+}$/positive porphyrin interactions, the solvolysis rate constants decrease with a decrease in ionic strength.§ In preliminary work, we note that ethylenediaminetetra-acetate (edta) is able to remove the lanthanide ions from their porphyrin complexes, a reaction not shown by most other metalloporphyrins.¶ The rates of such trans-metallations parallel the lanthanide stability sequence found here for the acid solvolysis processes.

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§ For $\mathrm{Sm^{III}\text{–}TMPyP}$, $\log (k_1k_2/k_{-1}) = 2.1 + 4.4\,[I^{1/2}/(1 + I^{1/2})]$, where $I/\mathrm{M}$ is the ionic strength.

¶ At pH 8, with 10 μM M–P and 25 mM edta, the $\mathrm{Ni^{II}}$, $\mathrm{Mn^{III}}$, $\mathrm{Cu^{II}}$, $\mathrm{Rh^{III}}$, $\mathrm{In^{III}}$, $\mathrm{Zn^{II}}$, $\mathrm{VO^{IV}}$, $\mathrm{Fe^{III}}$, $\mathrm{Al^{III}}$, $\mathrm{Cr^{III}}$, $\mathrm{Pd^{II}}$, and $\mathrm{Sn^{IV}}$ porphyrins were unchanged after 25 h in the dark.