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 di-sodium 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}–TMPyPI$_4$·3H$_2$O, satisfactory elemental analyses were obtained; at pH 6, $\lambda_{max.}$/nm (ε/dm^3 mol^{-1} cm^{-1}): 426.5 (1.9 × 10^5), 517.0 (sh, 3.5 × 10^3), 554.5 (1.7 × 10^4), and 590.0 (sh, 4.3 × 10^3).

‡ The solutions were unbuffered below pH 1, while 10 mM dichloroacetic acid (pK_{a1} 1.5) was used between pH 1 and 2, and 10 mM monochloroacetic acid (pK_{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 ± 0.1
Holium	$(2.5 \pm 0.2) \times 10^{-1}$	$(2.6 \pm 0.4) \times 10^{-2}$	9.5 ± 1.4
Dysprosium	$(2.2 \pm 0.7) \times 10^{-1}$	2.8 ± 0.2	7.7 ± 0.4
Terbium	$(9.0 \pm 0.2) \times 10^{1}$	2.1 ± 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 ($LiNO_3/HNO_3$).

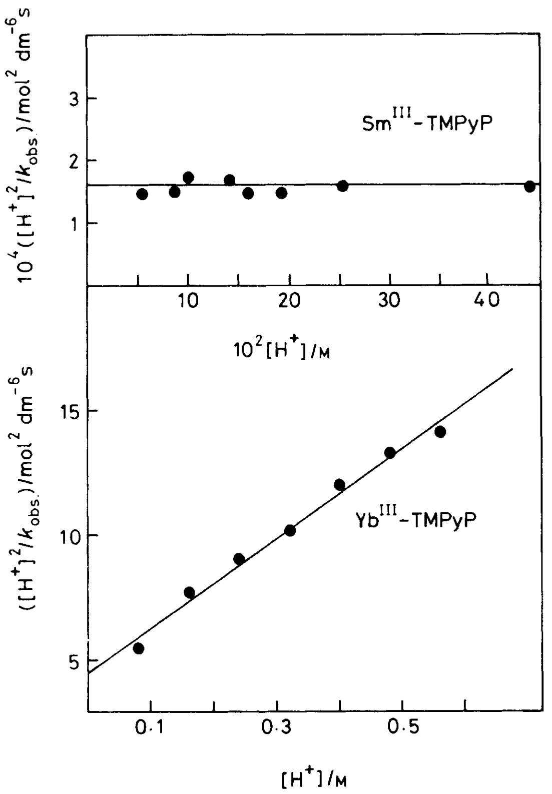

Figure 1. Plots of $[H^+]^2/k_{obs.}$ *vs.* $[H^+]$ for the acid solvolysis reactions of Sm^{III}–TMPyP and Yb^{III}–TMPyP indicating the two types of rate behaviour found.

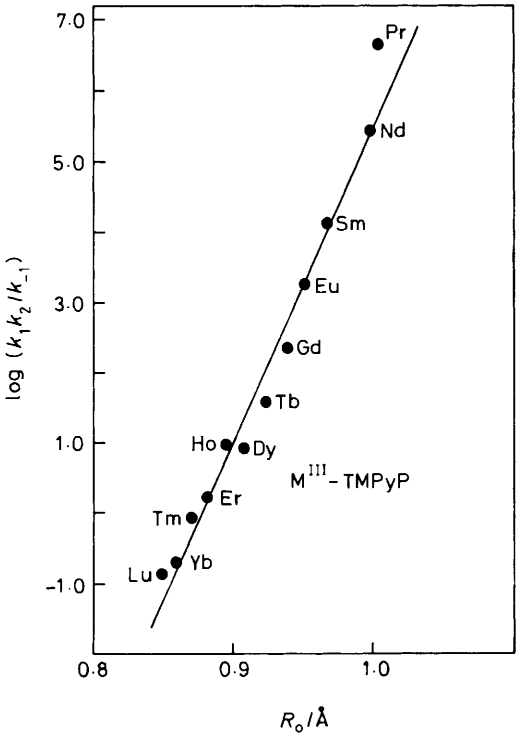

Figure 2. Plot of log (k_1k_2/k_{-1}) *vs.* the ionic radii of the lanthanide ions, R_0.

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 pK_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 $k_1 = 36.9R_0 - 32.9$.

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

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

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

The same two-proton rate law that we find for the trivalent lanthanides has been demonstrated before for acid solvolysis reactions of water soluble Zn^{II},[8,11] Cd^{II},[9] Pb^{II},[10] Fe^{II},[12] Mn^{II},[13] and 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 [H$^+$] {where $k_{\mathrm{obs.}} \propto [\mathrm{H^+}]$}, Pr^{III}–TMPyP reacts about 10^7 times faster than does the Lu^{III} complex, and a 0.1 Å increase in the ionic radius of the co-ordinated metal ion leads to a remarkable 32000 fold increase in the rate parameters. At low [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, Mg^{II}–P [R_0 = 0.72 Å (six-co-ordinate), $k_d = 1.9 \times 10^6$ dm^6 mol^{-2} s^{-1}] and Fe^{II}–P [R_0 = 0.61 Å (low spin, six-co-ordinate), $k_d = 55$ 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 3.5×10^4, and that calculated is 1.1×10^4.

In conclusion, the paramagnetic lanthanide derivatives of the tetrapositively charged TMPyP from 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 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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References

1 J. Winkelman, *Cancer Res.*, 1962, **22**, 589; P. Hambright, R. Fawwaz, P. Valk, J. McRae, and A. J. Bearden, *Bioinorg. Chem.*, 1975, **5**, 87.

2 R. Lyon, P. Faustino, J. Cohen, A. Katz, F. Mornex, D. Colcher, S. Koenig, and P. Hambright, *Magn. Reson. Med.*, 1987, **4**, 24; N. Patronas, J. Cohen, R. Knop, A. Dwyer, D. Colcher, J. Lundy, F. Mornex, P. Hambright, M. Sohn, and C. Myers, *Cancer Treat. Rep.*, 1986, **70**, 395.

3 For Fe^{III}, see A. Reynolds, K. Kooda, B. Fluorine, N. Johnson, and T. Thielman, *Int. J. Chem. Kinet.*, 1980, **12**, 97. For In^{III}, see P. Hambright, *J. Coord. Chem.*, 1983, **12**, 297; W. Reynolds, P. Gall, and P. Arndt, *Int. J. Chem. Kinet.*, 1982, **14**, 849.

4 A. Adler, W. Newman, M. Mulvaney, and J. Paine, in 'Porphyrin Chemistry Advances,' ed. F. R. Longo, Ann Arbor Science, 1979, ch. 20.

5 P. Hambright and E. B. Fleischer, *Inorg. Chem.*, 1970, **9**, 1757.

6 W. DeW. Horrocks and E. Hove, *J. Am. Chem. Soc.*, 1978, **100**, 4338; W. DeW. Horrocks and C-P. Wong, *ibid.*, 1976, **98**, 7157.

7 J. Buchler, A. de Cian, J. Fischer, M. Kihn-Botulinski, and R. Weiss, *Inorg. Chem.*, 1988, **27**, 339, and references therein.

8 P. Hambright, *Inorg. Chem.*, 1977, **16**, 2987; J. Nwaeme and P. Hambright, *ibid.*, 1984, **23**, 1990; M. Tabata and M. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1985, 43.

9 A. Shamim and P. Hambright, *Inorg. Chem.*, 1984, **23**, 564.

10 S. Haye and P. Hambright, *Inorg. Chem.*, 1984, **23**, 4777.

11 S. Cheung, F. Dixon, E. Fleischer, D. Jeter, and M. Krishnamurthy, *Bioinorg. Chem.*, 1973, **2**, 281.

12 A. Valiotti, A. Adeyemo, and P. Hambright, *Inorg. Nucl. Chem. Lett.*, 1981, **17**, 213.

13 R. Langley and P. Hambright, *Inorg. Chem.*, 1985, **24**, 1367; K. Morehouse and P. Neta, *J. Phys. Chem.*, 1984, **88**, 3118; P. Hambright, *Inorg. Nucl. Chem. Lett.*, 1977, **13**, 403.

14 D. K. Lavallee, *Coord. Chem. Rev.*, 1985, **61**, 55; P. Hambright, in 'Porphyrins and Metalloporphyrins,' ed. K. M. Smith, Elsevier, Amsterdam, 1975, ch. 6.

15 T. Srivastava, *Bioinorg. Chem.*, 1978, **8**, 61; C.-P. Wong and G. Bisset, *Inorg. Synth.*, 1984, **22**, 156.

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

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