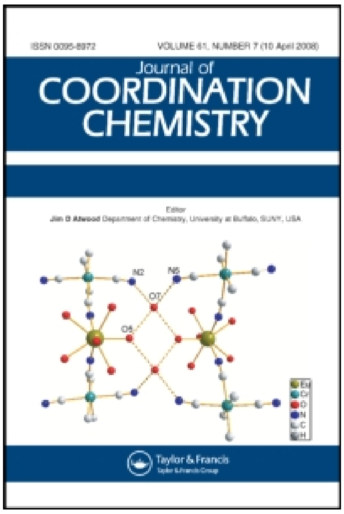

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KINETICS OF THE DEMETALLATION OF WATER SOLUBLE LANTHANIDE PORPHYRINS BY ETHYLENEDIAMINETETRAACETIC ACID

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The kinetics of the demetallation of six water soluble trivalent lanthanide tetrakis (*N*-methyl-4-pyridyl)-porphyrins (Lu, Yb, Dy, Gd, Sm and Nd-TMPyP) by EDTA (ethylenediaminetetraacetic acid) were studied at 25°C between pH 5 and 10. The reactions were first order in porphyrin, and the kinetics indicated complexation between the HY^{3-} form of EDTA and the monohydroxylanthanide porphyrin. The rate determining step was either the dissociation of this complex into products (k_1), or, if the complex was a dead-end intermediate, the reaction between the uncomplexed reactants, k_2. The rate laws for either pathway were the same, and thus the mechanisms kinetically indistinguishable. For all of the lanthanide porphyrins, an equation of the form $\log (k_2) = 44.9 (R_o) - 39.4$ described the results, with R_o the ionic radii of the lanthanide ions in Ångstroms. A linear relationship was also found between $\log (k_2)$ for EDTA and $\log (k_{H^+})$ for the acid catalyzed solvolysis reactions of the complexes.

Keywords: lanthanide porphyrins, EDTA, exchange kinetics, lanthanides

INTRODUCTION

The coordination chemistry of water soluble lanthanide porphyrins, in which the metal sits 1.2 to 1.8 Ångstroms above the mean porphyrin plane, is a relatively unexplored area.[1] In contrast to smaller first row transition metal ions, Gd(III)[2] [and Pb(II)[3]] can be displaced from the porphyrin by chelating agents. We report the kinetics of the removal of six lanthanide ions from their tetrakis (*N*-methyl-4-pyridyl)-porphyrin (TMPyP) complexes by ethylenediaminetetraacetic acid (EDTA). A comparison is made between the present results for EDTA and those found for the proton catalyzed dissociation of lanthanides from TMPyP derivatives.[4] Such stability data on highly paramagnetic complexes are of value in designing porphyrin based drugs[5-7] that show selective tissue localization properties *in vivo*, leading to organ visualization by magnetic resonance imaging (MRI) procedures.

EXPERIMENTAL

The metalloporphyrins were samples from a previous study.[4] The kinetics were followed at 25.0°C on a Beckman DU-70 spectrophotometer, or a Durrum-Gibson stopped flow apparatus, with at least a forty fold excess of EDTA to porphyrin. The solutions were buffered with 1 mM acetic acid in the pH range 4–5.5, Pipes (5.5–7.5), Hepes (7–8) and Tris between 8 and 10. None of the buffers caused demetallation,

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and the observed rates changed by no more than 5% at pH 7.5 when the total buffer concentration was diluted by a factor of ten, or when the Sm-TMPyP concentration was varied from 7×10^{-2} μM to 5.0 μM. An ionic strength of 0.1 was maintained with $NaNO_3$, and the EDTA was standardized with zinc.

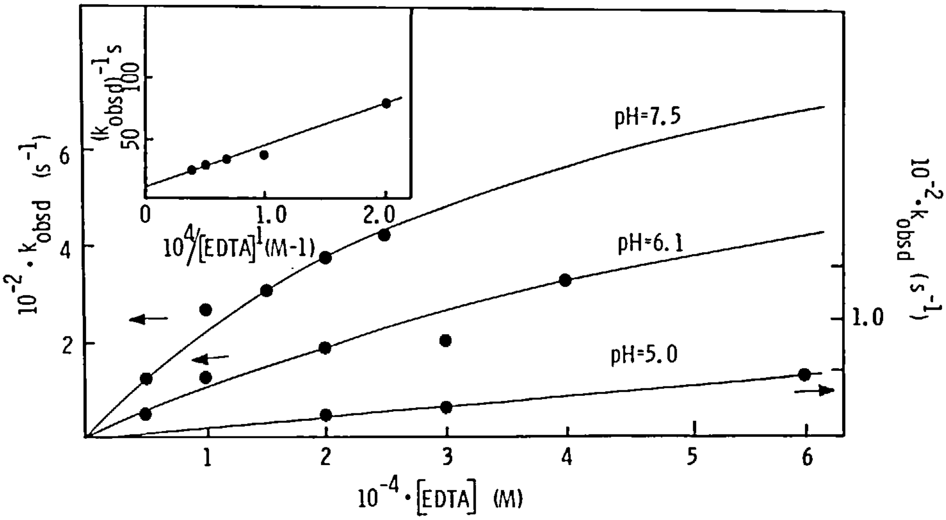

FIGURE 1 Plots of the observed rate constants k_{obsd} *vs* the total EDTA concentration at various pH values for the reaction of Gd(III)–TMPyP and EDTA. The insert shows $(k_{obsd})^{-1}$ *vs* $(EDTA)^{-1}$ for the reaction at pH 7.5. The circles are the observed data, and the solid lines are calculated from (*6*).

RESULTS AND DISCUSSION

For Gd(III)–TMPyP (Gd–P), the kinetics of demetallation by EDTA were studied from pH 4.5 to 9.5, by following the decrease with time of the 555 nm Gd–P peak. Isosbestic points were found at 664, 632, 586, 538, 488 and 425 nm, as the Gd–P was cleanly transformed into the free-base, H_2–P. The reactions were first order in porphyrin concentration over three half lives. The pseudo first order rate constant is referred to as k_{obsd}. As seen in Figure 1, the reactions appear to be first order in total EDTA from 50 to 600 μM, at pH 5.0, whereas at pH 6.1 and 7.5, it is clear that the specific rate constants over the same range are first order in EDTA at low concentrations, and become independent of EDTA at higher values. From low concentration data, where the reactions are first order in EDTA, Figure 2 shows the dependence of $k_{obsd}/[EDTA]$ on pH. The specific rates go through a maximum at pH ~ 7.5. In the pH ranges considered, EDTA exists in various protonated forms,[8] with the dissociation constant of H_2Y^{2-} into HY^{3-} having $pK_3 = 6.12$, and for HY^{3-} into Y^{4-}, $pK_4 = 10.3$ at $I = 0.1$. Gd–P itself (Table I) has $pK_{a1} = 4.9$ and $pK_{a2} = 8.7$. One explanation for the overall kinetic behaviour assumes a complex (K_I) is formed between monohydroxy-Gd–P and HY^{3-}. The slow step of the reaction is either the dissociation of this adduct into products (k_1), or if the complex acts as an unreactive intermediate, the rate determining step, k_2, would be the

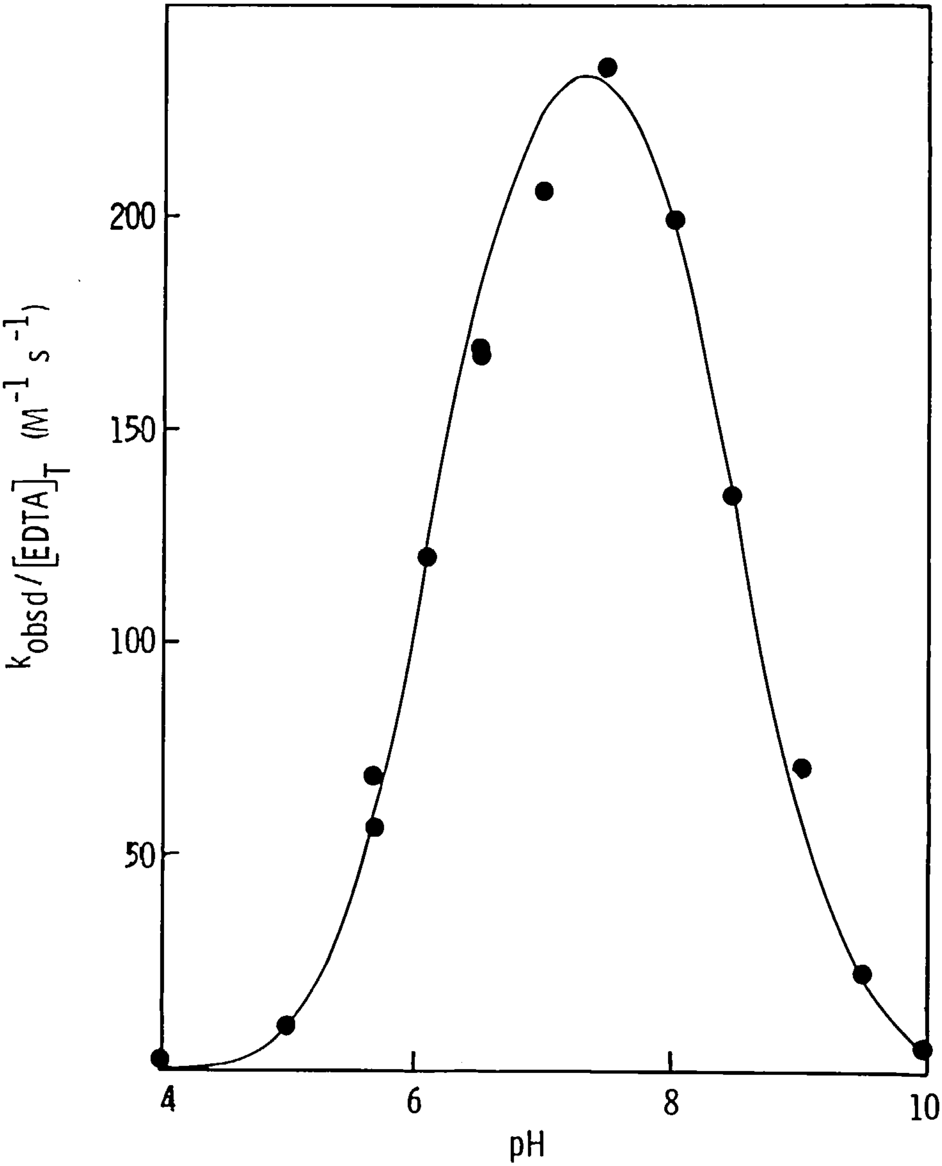

FIGURE 2 pH profile of the Gd–TMPyP/EDTA reaction. The circles are the experimental points, and the solid line is calculated from (*6*).

reaction of the uncomplexed reactants. The overall charge of $(H_2O)_2$–Gd(III)–TMPyP is 5+. Thus,

$$\text{Gd–P}(H_2O)_2^{5+} \rightleftharpoons \text{Gd–P}(H_2O)(OH)^{4+} + H^+ \qquad K_{a1} \qquad (1)$$

$$\text{Gd–P}(H_2O)(OH)^{4+} \rightleftharpoons \text{Gd–P}(OH)_2^{3+} + H^+ \qquad K_{a2} \qquad (2)$$

$$\text{Gd–P(H}_2\text{O)(OH)}^{4+} + \text{HY}^{3-} \rightleftharpoons [\text{Gd–P(H}_2\text{O)(OH)--HY}]^{+} \qquad K_{II} \qquad (3)$$

and, then, either:

$$[\text{Gd–P(H}_2\text{O)(OH)--HY}]^{+} \rightarrow \text{Products} \qquad k_I \qquad (4)$$

or

$$\text{Gd–P(H}_2\text{O)(OH)}^{4+} + \text{HY}^{3-} \rightarrow \text{Products} \qquad k_2 \qquad (5)$$

and, thus,

$$k_{obsd} = J(\text{HY}^{3-}) / [Q + K_I(\text{HY}^{3-})] \qquad (6)$$

The constant $J = k_1K_I$, when k_1 is rate determining, and $J = k_2$ for the dead-end mechanism. $Q = [1 + (H^+)/K_{a1} + K_{a2}/(H^+)]$. At pH 7.5, $Q \sim 1$ and $(\text{HY}^{3-}) \sim [\text{EDTA}]$. From (*6*) at this pH, a plot of $(k_{obsd})^{-1}$ *vs* $(\text{EDTA})^{-1}$ should be linear, with a slope of J^{-1} and intercept of K_I/J. The insert in Figure 1 shows such a linear graph, from which $K_I = (2.4 \pm 0.2) \times 10^3 M^{-1}$ and $k_2 = (2.7 \pm 0.1) \times 10^2 M^{-1}s^{-1}$. With J and K_I known, (*6*) can be used (with the EDTA dissociation constants) to calculate theoretical values of k_{obsd} / [EDTA] *vs* pH over the entire pH range, and Figure 2 shows the satisfactory agreement between the observed and calculated data. The results for the various lanthanide porphyrins studied are shown in Table I.

TABLE I

pK_a and kinetic reactivity results.

Metal–TMPyP	pK_{a1}	pK_{a2}	$k_1/(s^{-1})$	$k_2/(M^{-1}s^{-1})$	$K_I/(M^{-1})$
Lutetium[a]		8.0	$(1.2 \pm 0.2) \times 10^{-5}$	$(1.2 \pm 0.1) \times 10^{-2}$	$(1.0 \pm 0.1) \times 10^3$
Ytterbium	4.0	8.0	$(4.2 \pm 0.7) \times 10^{-5}$	$(8.0 \pm 0.6) \times 10^{-2}$	$(1.9 \pm 0.2) \times 10^3$
Dysprosium	4.7	8.5	$(5.4 \pm 0.8) \times 10^{-3}$	$(1.3 \pm 0.1) \times 10^{-1}$	$(2.4 \pm 0.2) \times 10^3$
Gadolinium	4.9	8.7	$(1.1 \pm 0.2) \times 10^{-1}$	$(2.7 \pm 0.1) \times 10^{-2}$	$(2.4 \pm 0.2) \times 10^3$
Samarium	5.0	8.4	(5.9 ± 1.1)	$(7.1 \pm 0.5) \times 10^{-3}$	$(1.2 \pm 0.1) \times 10^3$
Neodymium	5.1	8.6	$(2.5 \pm 0.6) \times 10^{-1}$	$(3.5 \pm 0.3) \times 10^{-4}$	$(1.4 \pm 0.2) \times 10^3$

[a] No pK_{a1} was found for Lu–TMPyP. The reported pK values are ±0.1 units.

Similar reactions were run with Gd(III)–TMPyP and other chelates. For CyDTA (cyclohexylenediaminetetraacetic acid), $k_2 = (4.0 \pm 0.1) \times 10^1\ M^{-1}s^{-1}$ and $K_I = (7.6 \pm 0.4) \times 10^3 M^{-1}$, while for NTA (nitrilotriacetic acid), $k_2 = (2.4 \pm 0.1) \times 10^1 M^{-1}s^{-1}$ and $K_I = (3.1 \pm 0.1) \times 10^2 M^{-1}$. Over a 24 hour period at pH 7.5, no demetallation was found with 10 mM IDA (iminodiacetic acid) or en (ethylenediamine).

The main term in the rate law for the reaction between EDTA and Gd–TPPS [tetra(4-sulfonatophenyl)porphyrin] where both reactants are negatively charged was first order in HO(H_2O)–Gd–P and HY^{3-} with no kinetic evidence for a complex.[2] In the present case of a reaction between positive TMPyP porphyrins and negatively charged EDTA, a complex forms between HO(H_2O)–Gd–TMPyP and HY^{3-}. Kinetics cannot distinguish whether the rate determining step is the dissociation of this complex k_1, or the reaction between the uncomplexed reactants, k_2, since the observed rate laws are the same under equilibrium conditions. A similar complex formation was found[9] for Co(III)–TMPyP reductions by $Fe(EDTA)^{2-}$, and was absent in the corresponding reactions of the negatively charged Co(III)–TPPS with the same reductant. This is consistent with the negatively charged reactants having substantially smaller values for K_I than found in the positive–negative cases. The same form of the rate law for EDTA was noted for CyDTA and NTA, where the lower charge of NTA produced lower values of k_1 and K_I. The fact that en and IDA were unreactive could indicate that four coordination is required for such lanthanide-porphyrin exchange reactions.

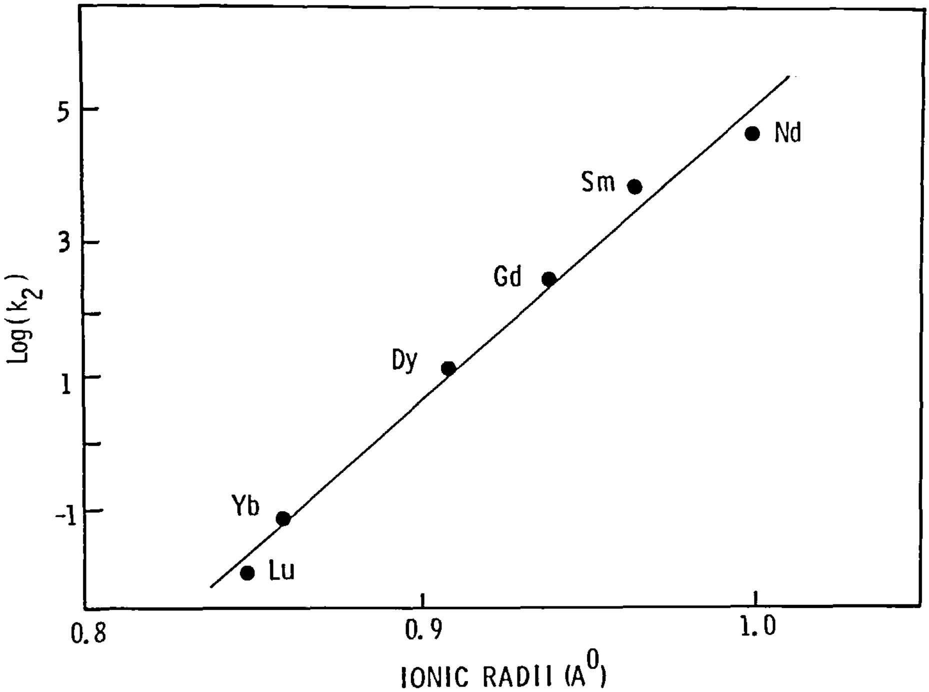

FIGURE 3 The relationship between the logarithms of the specific rate constants for the Ln(III)–TMPyP/EDTA reaction and the Ln(III)–TMPyP/H^+ acid catalyzed solvolysis reaction.

It is remarkable that with the variety of hydrolyzed forms of the metalloporphyrin and EDTA in the pH ranges studied, the major pathway for both positive and negative porphyrins has an activated complex of composition {P–Gd-(H_2O)OH--HY}. This is kinetically equivalent to {P–Gd-$(H_2O)_2$--Y} and {P–Gd-$(OH)_2$--H_2Y}, and thus kinetics cannot identify the nature of the actual reactants. With Co(III) and Cr(III) porphyrin anation reactions,[10–12] the water molecule is labilized more rapidly in the [P–M-(H_2O)(OH)] species containing a coordinated hydroxide than in the diaquo complex, and the dihydroxy adduct is particularly inert to substitution. For the lanthanide porphyrins, rapid proton transfer in the activated complex could produce {P–Gd-(H_2O)(OH)--HY}, in which the H_2O could be lost in a dissociative step, leading to a series of bond making and bond breaking steps with ultimate removal of the metal from the macrocycle.[13] The only other work in this area[3] concerns the reaction of EDTA with Pb(II)–TMPyP. That study gave no indication of a K_I type complex, and while Y^{4-} was about equally reactive with the aquo and mono-hydroxo lead porphyrins, HY^{3-} interacts with the aquo- and not the HO–PbP species.

The kinetics of the acid catalyzed demetallations of these lanthanide porphyrins have been reported.[4] For the acid solvolysis reactions, a linear relationship was found between log (k_{H^+}) and the ionic radius (R_o), and it was noted that a 0.1 Å increase in R_o at low acidities produces a 3.2×10^4 rate enhancement. Similar behaviour is found for the EDTA system, where an equation of the form Log (k_2) = $44.9\,R_o - 39.4$ is applicable. The neodymium-TMPyP complex is demetallated by EDTA 10^6 times faster than the lutetium derivative, and a 0.1 Å increase in radius leads to a 3.1×10^4 rate increase. Figure 2 shows the linear relationship between Log (k_2[EDTA]) and log (K_{H^+}). Thus, the smaller the lanthanide metal ion, the more stable is the ionic metalloporphyrin in both H^+ or EDTA type demetallation reactions. Gd–TMPyP shows MRI relaxivity values similar[14] to the only clinically approved imaging agent $[Gd(DTPA)(H_2O)]^{2-}$ (DTPA is diethylenetetraminepenta-acetic acid), and is found to be a better tumor relaxation agent than Gd(DTPA) or Mn(III)–TPPS. The present results tend to support speculations[7,14] that chelating agents in the blood might remove the Gd from Gd–TMPyP *in vivo*. The fact that the half-life for acid catalyzed dissociation of Gd–TMPyP at pH 7.5 is 5×10^4 years certainly argues against a proton assisted dissociation mechanism.[4]

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