

A Lanthanum Macrocycle catalysed Hydrolysis of a Phosphate Triester

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A lanthanum macrocycle is shown to be an effective catalyst for the hydrolysis of the phosphate triester 2,4-dinitrophenyl diethyl phosphate, at pH 9 the rate enhancement using $2.5 \times 10^{-3} \text{ mol dm}^{-3}$ catalyst at 25°C being ca. 10^3 -fold; the reaction is shown to be catalytic rather than stoichiometric, and possible mechanisms are considered to account for the catalysis.

In recent years there has been growing interest in the metal ion promoted hydrolysis of phosphate esters as model systems for metallo-phosphatase enzymes and as potential catalysts for the detoxification of anticholinesterase agents used in chemical warfare.¹⁻⁷ Early studies by Butcher and Westheimer⁸ indicated that lanthanum hydroxide gels promoted the hydrolysis of esters such as β -methoxyethyl and β -aminoethyl phosphates at pH 8.5 and 78°C . Bamann⁹ also noted that the hydroxides of La^{3+} , Ce^{3+} , and Th^{3+} promoted the hydrolysis of α -glycerophosphate in the pH range 7–10 and suggested that the reaction could be regarded as a model for the metal-containing alkaline phosphatases which cleave phosphate esters around pH 9. In view of the heterogeneous nature

of these reactions it is difficult to come to firm mechanistic conclusions; however, it seems likely that metal-bound hydroxide nucleophiles are involved. For this reason we have investigated the activity of the lanthanum complex of the macrocycle (1) as a potential catalyst for the hydrolysis of the water-soluble triester (2).

There has been considerable interest in the synthesis of lanthanide macrocycles and the topic has recently been reviewed;¹⁰ however the catalytic potential of these complexes has not been previously studied. The complex $[\text{La}(\text{NO}_3)_3\text{L}]$ was prepared as previously described.¹² The crystal structure establishes twelve-co-ordination of the metal ion to the six macrocyclic nitrogen atoms and to three bidentate nitrate ions. Conductivity measurements show that in aqueous solution the complex exists mainly as $[\text{LaL}(\text{H}_2\text{O})_n]^{3+}$. The macrocyclic ligand remains undissociated in water and is kinetically stable to dissociation. Furthermore, the complex gives no precipitate on addition of KF or KOH.

The triester 2,4-dinitrophenyl diethyl phosphate provides a useful water-soluble substrate of low toxicity. Hydrolysis to diethyl phosphate is readily monitored at 360 nm owing to the release of 2,4-dinitrophenolate. The reaction is first order in the phosphate ester and excellent pseudo-first-order kinetics were observed in the presence of millimolar concentrations of the complex. In order to avoid complications due to buffer catalysis the metal complex was employed as the buffer system

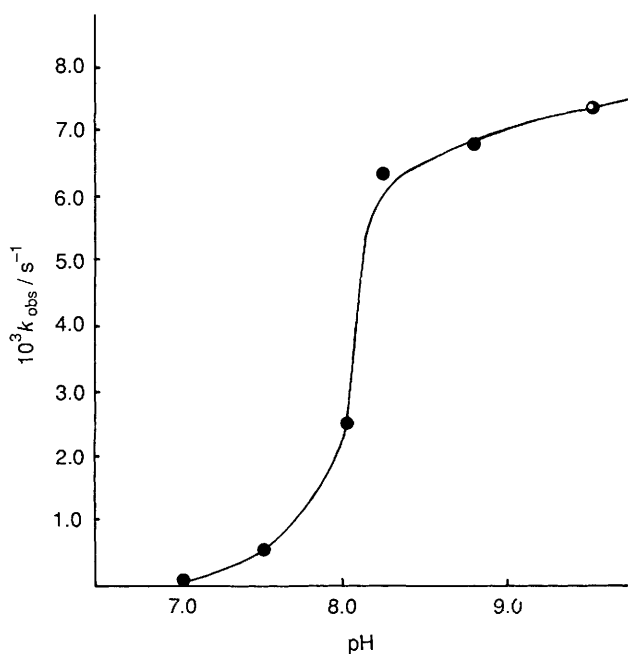
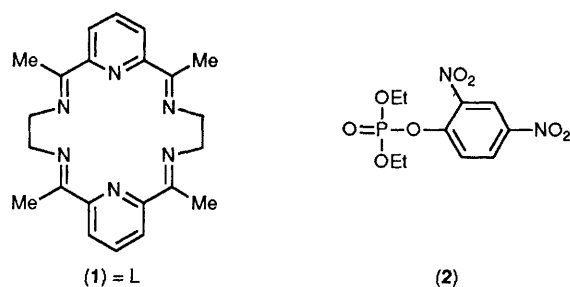


Figure 1. The pH-rate profile for the lanthanum macrocycle catalysed hydrolysis of 2,4-dinitrophenyl diethyl phosphate at 25°C and $I = 0.1 \text{ mol dm}^{-3}$.

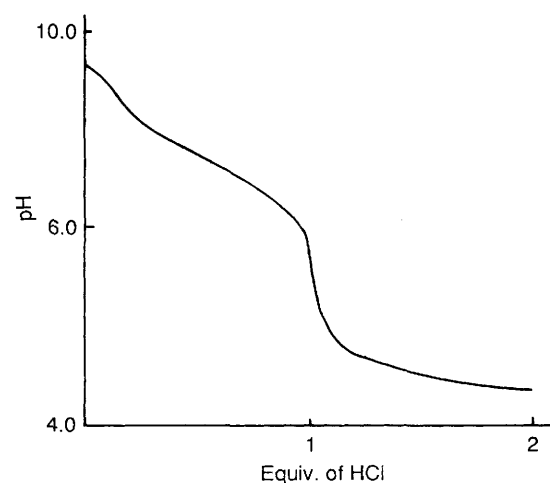
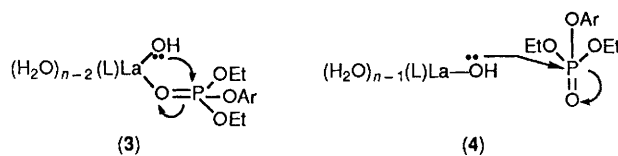


Figure 2. Potentiometric titration of $[\text{La}(\text{NO}_3)_3\text{L}]$ in aqueous solution with hydrochloric acid.

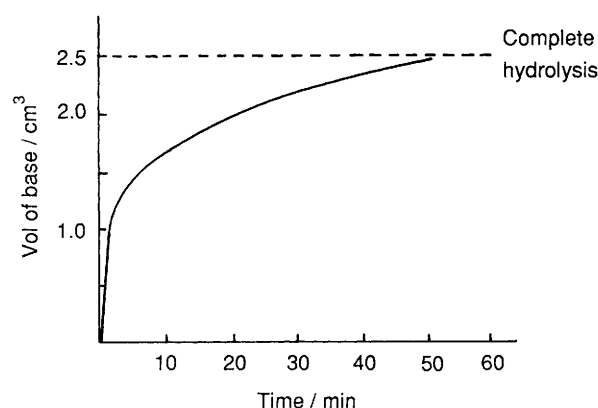


Figure 3. A pH-stat trace for the hydrolysis of 2,4-dinitrophenyl diethyl phosphate at pH 8.50 and 25 °C. The concentration of 2,4-dinitrophenyl diethyl phosphate was $5 \times 10^{-4} \text{ mol dm}^{-3}$ and that of the lanthanum macrocycle $5 \times 10^{-5} \text{ mol dm}^{-3}$.

and the pH was adjusted by the dropwise addition of hydrochloric acid. The pH dependence of the catalysis was studied over the pH range 7.00–9.50 (Table 1). The reaction displays a sigmoidal pH-rate profile of the type seen in a number of phosphate ester hydrolyses promoted by copper(II)² and cobalt(III)^{12,13} complexes (Figure 1). Such profiles are indicative of the involvement of metal-hydroxo complexes and the data suggest that intermediates of the type (3) and (4) are probably involved in the reaction. Potentiometric titration of $[\text{La}(\text{NO}_3)_3\text{L}]$ in aqueous solution with hydrochloric acid gives the titration curve shown in Figure 2. A pronounced end point is observed after addition of one equivalent of hydrochloric acid consistent with protonation of a $\text{La}-\text{OH}$ species. The apparent pK for the equilibrium is *ca.* 7.4.

For base hydrolysis of 2,4-dinitrophenyl diethyl phosphate, $k_{\text{OH}} = 0.65 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25 °C and $I = 0.1 \text{ mol dm}^{-3}$ ($\Delta H^\ddagger = 50.7 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger_{298} = -78.8 \text{ J K}^{-1} \text{ mol}^{-1}$).¹⁴ At pH 9, k_{obs} for the base hydrolysis of the triester to diethyl phosphate is given by the expression $k_{\text{obs}} = k_{\text{OH}}[\text{OH}^-] = 8.5 \times 10^{-6} \text{ s}^{-1}$.[†] The rate enhancement at pH 9 is thus *ca.* 10^3 -fold using a catalyst concentration of $2.5 \times 10^{-3} \text{ mol dm}^{-3}$.

A true catalytic system should exhibit turnover. Turnover experiments were carried out using a Radiometer Titrablab system interfaced with an Apple IIe computer. A solution containing $5 \times 10^{-4} \text{ mol dm}^{-3}$ 2,4-dinitrophenyl diethyl

Table 1. The lanthanum macrocycle promoted hydrolysis of 2,4-dinitrophenyl diethyl phosphate at 25 °C and $I = 0.1 \text{ mol dm}^{-3}$ (KNO_3).^a

pH	$k_{\text{obs}}/\text{s}^{-1}$	pH	$k_{\text{obs}}/\text{s}^{-1}$
7.00	6.25×10^{-5}	8.25	6.30×10^{-3}
7.50	5.22×10^{-4}	8.80	6.70×10^{-3}
8.00	2.45×10^{-3}	9.50	7.28×10^{-3}

^a Hydrolysis monitored spectrophotometrically at 360 nm. Concentration of $[\text{LaL}(\text{NO}_3)_3]$ employed = $2.5 \times 10^{-3} \text{ mol dm}^{-3}$; concentration of 2,4-dinitrophenyl diethyl phosphate = $4 \times 10^{-5} \text{ mol dm}^{-3}$.

phosphate and $5 \times 10^{-5} \text{ mol dm}^{-3}$ $[\text{La}(\text{NO}_3)_3\text{L}]$ was adjusted to pH 8.50 at 25 °C and the release of H^+ due to ester hydrolysis monitored by the automatic addition of 0.002 mol dm^{-3} sodium hydroxide solution. The initial slope of the plot (Figure 3) gives a release rate for H^+ of $1.9 \times 10^{-4} \text{ mol min}^{-1}$, with a turnover of $1.9 \times 10^{-4}/5 \times 10^{-5} = 3.8$ turnovers min^{-1} . At pH 8.50 and 25 °C, ten moles of ester are hydrolysed by one mole of catalyst in *ca.* 50 min. At this pH the half-life of the free triester is 71.5 h.

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† The hydroxide ion concentration was calculated from the pH using an activity coefficient of 0.772 and $pK_w = 13.9965$.

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