Catalytic hydrolysis of phosphate triesters by lanthanide(III) cryptate (2.2.1) complexes†

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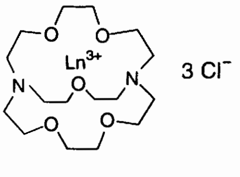
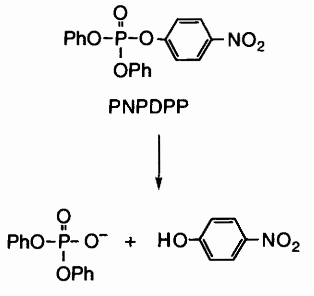
Lanthanide(III) cryptate (2.2.1) chlorides [Ln(2.2.1)Cl$_3$; Ln = La, Ce, Eu] are effective in catalysing the hydrolysis of 4-nitrophenyl diphenyl phosphate. Kinetic studies reveal that the europium(III) (2.2.1) chloride catalyses the hydrolysis efficiently (k = 1.8 × 10^{-2} s^{-1} at 1.6 mmol dm^{-3}, turnover number = 12 at pH 9.00 and 25 °C). The reactivity of the cerium(III) complex is enhanced by the presence of molecular oxygen. Analysis of the products of the hydrolysis shows that the selectivity toward yielding 4-nitrophenol against phenol is unusually high (ratio = 17 : 1).

The chemistry, such as hydrolysis, of phosphate esters has been investigated extensively because such processes occur in many enzymes and their control would have wide applicability.[1] In particular, hydrolysis of phosphate triesters attracts considerable attention for its relevance to the detoxification of insecticides and nerve gases.[2]

Considerable enhancement of the rates of reaction has been achieved for the hydrolysis of phosphate triesters with transition metal complexes,[3,4] iodosobenzoates[5] and a protease mimic.[6] Moreover, synergistic enhancement can be achieved when the above catalysts are applied in the form of microemulsions.[7] Recently, catalysts with comparable reactivity have been developed by utilizing the desirable properties of lanthanide ions.[8–10] Here we report the catalytic activity of lanthanide(III) cryptate (2.2.1) complexes **1a–c** for the hydrolysis of 4-nitrophenyl diphenyl phosphate (PNPDPP) with remarkable enhancement of the rate [eqn. (1)].



1 a Ln = La
1 b Ln = Ce
1 c Ln = Eu



(1)

Experimental

All chemicals were purchased from the Aldrich Chemical Co. and Strem Chemical Co., unless otherwise stated. The lanthanide (2.2.1) complexes were synthesized under anhydrous conditions,[11] and handled and weighed in an N$_2$-filled glovebox. The high purity of 4-nitrophenyl diphenyl phosphate was confirmed by ^{1}H NMR spectroscopy and melting point measurement [mp 49.5–50.0 °C (lit.,[12] mp 49–51 °C)]. Kinetic traces were recorded on a Perkin-Elmer Lambda 15 UV–VIS spectrophotometer equipped with a temperature-controlled cell holder. ^{1}H NMR spectra were recorded on a Bruker AM300 spectrometer operating at 300 MHz. IR spectra were recorded on a Bomem MB-102 FTIR spectrometer. High performance liquid chromatography (HPLC) was performed on a Spectra-Physics's SP8800 equipped with a SP4200 integrator and a SP8450 UV–VIS detector. A Brownlee C$_{18}$ column (220 × 4.6 mm) and a Brownlee guard column (30 × 4.6 mm) were used.

Buffers were made up from TRIS (Sigma) or BIS-TRIS (Sigma) and standardized HCl and NaOH in deionized water (18 MΩ cm^{-1}). The concentration of the buffers was fixed at 0.010 mol dm^{-3}. The ionic strength of the buffers was maintained at 0.100 mol dm^{-3} (NaCl). The pH of the buffers was measured at 25 °C with a Corning M220 pH meter fitted with Corning 4765030 combination electrodes. The concentration of the PNPDPP was fixed at 4.00 × 10^{-5} mol dm^{-3} except for the cases for measuring turnover numbers. An aqueous solution of the metal complexes was syringed into a cell thermostatted at 25 °C containing PNPDPP in acetonitrile. Typically, the volume ratio between the aqueous solution and the acetonitrile solution is 9 : 1, but for the turnover experiment this was changed to 1 : 1 to dissolve a large excess of PNPDPP. The solution was mixed rapidly, and the absorbances at 400 nm were recorded automatically at preset intervals. For the hydrolysis under argon atmosphere, the solutions are completely degassed through freeze–pump–thaw cycles, filled with purified argon and finally mixed in a closed UV–VIS cell designed for handling air sensitive compounds.

Changes of absorbance were recorded in the presence of an excess of catalyst to meet the conditions for a pseudo-first-order rate equation [eqn. (2)]. Plotting ln ($A_\infty - A$) against the reaction time (t) resulted in strict linear plots, the slopes of which gave the pseudo-first-order constants (k_{p1}). The formation of phenol as a minor product was observed, but the conclusion drawn from the kinetic experiments is not affected by the concurrent competitive process.[4b]

$$\text{Rate} = k_{p1}\,[\text{PNPDPP}] \qquad (2)$$

$$\ln(A_\infty - A) = -k_{p1}t + \ln A_\infty \qquad (3)$$

Samples were analysed by reversed-phase HPLC, and products were identified by comparison of their retention times with those of authentic samples. After excess acetonitrile was added to the reaction mixture, the resulting solution was filtered to remove precipitates. The filtrate was evaporated to dryness

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† Lanthanide(III) salts of 4,7,13,16,21-pentaoxa-1,10-diazabicyclo-[8.8.5]tricosane.

Table 1 The pseudo-first-order rate constants ($k_{p1}/10^{-4}$ s^{-1}) of the hydrolysis of PNPDPP at 25 °C (H_2O–CH_3CN, 9 : 1)

Catalyst[a]	pH 7.00	7.50	8.00	8.50	9.00
1a	0.48	1.5	5.9	17	38
1b	0.20	5.9	25	54	72
1c	0.11	3.2	16	40	76
1a–argon		1.3			
1b–argon	0.63	2.0	13	28	66
1c–argon		3.0			

[a] Concentration of the catalyst is 4.0 × 10^{-4} mol dm^{-3}.

Table 2 The pseudo-first-order rate constants (k_{p1}) *vs.* concentration at pH 9.00, 25 °C, and in air

Concentration/ mmol dm^{-3}	**1a**/10^{-2} s^{-1}	**1b**/10^{-2} s^{-1}	**1c**/10^{-2} s^{-1}
0.10		0.058	0.044
0.20	0.060	0.11	
0.30			0.27
0.40	0.38	0.73	0.77
0.80	0.45	0.89	0.91
1.00		1.17	
1.20	0.95	1.29	1.26
1.60	1.09	1.75	1.80

while the temperature of the solution was maintained below room temperature. The samples were redissolved by adding a small amount of the eluent [TRIS buffer solution of pH 8.0: methanol = 1 : 1 (v/v)]. Compounds were detected at 260 nm. The relative ratio of phenol and 4-nitrophenol was determined by use of a calibration curve obtained at pH 8.0.

Results and discussion

When the rate constants are measured at pH 7.00–9.00, it is found that the rate constants increase with the pH of the reaction medium (Table 1). The pH dependence of the rate constants is similar to that observed for the hydrolysis of 4-nitrophenyl phosphate in the presence of the catalyst.[9] Under the conditions used, the reactivity order of the metal complexes (La < Eu < Ce) is not that which would be expected given the size of the metal ions and the Brønsted acidity of the coordinated water ligands. To discover the effect of molecular oxygen, the solutions were totally degassed by a series of freeze–pump–thaw cycles and filled with argon. Under these conditions, the reactivity of the cerium complex was lowered, while the reactivity of the other two complexes remained unchanged. As a result, the reactivity order under the inert atmosphere is in accord with expectations (La < Ce < Eu).

The enhanced reactivity of the cerium complex under molecular oxygen is reminiscent of Chin's observation[10a] that the cerium(III) ion can be activated by molecular oxygen to cleave DNA in a hydrolytic manner. Hydrogen peroxide was added to increase the reactivity of the lanthanide complex further, but only an acceleration of the rate of demetallation was observed.

As shown in Fig. 1, the europium complex effectively catalyses the hydrolysis with a turnover number of 12 at pH 9.0 and 25 °C. Also, the cerium complex at the ambient condition produces 10 equiv. of 4-nitrophenol. Reduced catalytic activities with time are observed, and can be rationalized by the inhibitory nature of the products, diphenyl phosphate (DPP) and 4-nitrophenyl phenyl phosphate (NPPP). The products not only compete with PNPDPP, but also induce decomplexation of the lanthanide complexes.[9] Therefore, the rate of the mature stage deviates from extrapolation based on the initial rate.

The concentration of the metal complexes was varied to elucidate the molecularity of the hydrolysis. As shown in Fig. 2, the rate constants are linear up to a concentration of 1.6 mmol dm^{-3}, which indicates that one lanthanide metal centre is involved (Table 2). The precise measurement of the rates at the higher concentration was hampered by complicated phenomena, for example, formation of precipitates presumably due to association of the metal complexes. For the europium case, the maximal rate constant (k_{p1}) of 1.8 × 10^{-2} s^{-1} (k_{bi} = 11 dm^3 mol^{-1} s^{-1}) is observed at pH 9.00 and 25 °C. Because the measured rate constant for the uncatalysed hydrolysis is 2.6 × 10^{-6} s^{-1} under these conditions, a 6900-fold enhancement of the hydrolysis rate is achieved with 1.60 mmol dm^{-3} of **1c**. The enhancement is of the same order of magnitude as that for 4-nitrophenyl phosphate. It is interesting to note that the effectiveness of the catalysts is constant for two different types of substrate, *i.e.* a neutral PNPDPP and an anionic 4-nitrophenyl phosphate.‡

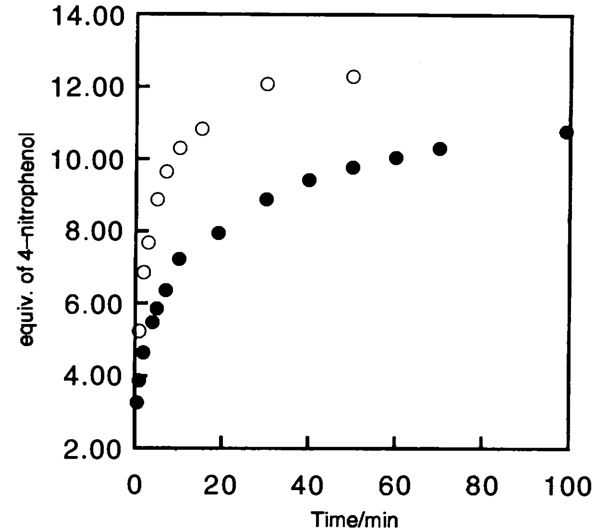

Fig. 1 Catalytic turnover numbers against time when **1b** (●) and **1c** (○) are employed at pH 9.00 and 25 °C (H_2O–CH_3CN, 1 : 1). 2.0 × 10^{-2} mol dm^{-3} PNPDPP was used for the experimental runs.

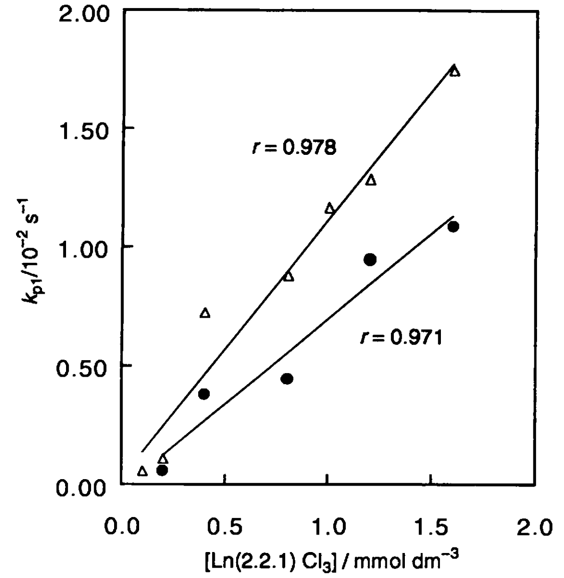

Fig. 2 Concentration of the metal complexes *vs.* k_{p1} at pH 9.00 and 25 °C for **1a** (●) and **1b** (△) in air. In order to avoid overlap in the figure, points for **1c** are omitted, and can be fitted by a linear equation, $y = 1.0822x + 0.0477$ ($r = 0.972$).

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‡ A referee notes the mechanistic difference of the uncatalysed reactions for the anionic 4-nitrophenyl phosphate and the triester: for the anionic substrate the hydrolysis is spontaneous, while for the triester the reaction is hydroxide-catalysed.

Table 3 Product composition from the hydrolysis of 4-nitrophenyl diphenyl phosphate (PNPDPP) in aqueous acetonitrile (H_2O–CH_3CN, 9 : 1) at pH 8.00 and 25 °C

Catalyst	NP/P
1a	9.7
1b	14
1c	17

The hydrolysis was quenched at three half-lives by pouring the reaction mixture into acetonitrile, at which point the dissolved catalyst precipitated from solution. With analytical HPLC, it is found that the ratio (R) of 4-nitrophenol (NP) to phenol (P) varies from 9.7 to 17 (Table 3). The observed selectivity toward 4-nitrophenol is unusually high when it is compared with the other metal-catalysed hydrolyses (R = 3.8–5.5 for Zn^{II} complexes).[3b,4b]

Acknowledgements

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