Activation of Acyl Phosphate Monoesters by Lanthanide Ions: Enhanced Reactivity of Benzoyl Methyl Phosphate

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Abstract: Acyl phosphate monoesters are intermediates in many biochemical acylation reactions, such as those involving aminoacyl adenylates. Benzoyl methyl phosphate, a typical acyl phosphate monoester, is slowly hydrolyzed in neutral solutions but reacts rapidly with amines. Since biochemical processes of acyl phosphate monoesters involve accelerated reactions with oxygen-centered nucleophiles, we sought catalysts for hydrolysis and methanolysis of benzoyl methyl phosphate to mimic the biochemical outcome. Lanthanide ions are particularly effective catalysts, accelerating reactions much more than comparable levels of magnesium ion. Detailed kinetic analysis of the hydrolysis reactions reveals formation of a 1:1 complex, followed by rapid reaction with a nucleophile. The hydroxide-dependent hydrolysis rate in the europium complex is about 10^5 times that of free substrate with hydroxide. A mechanism that accounts for the data and observed behavior involves bidentate coordination of the metal ion by the acyl phosphate through phosphate and carbonyl oxygens, lowering the energy of the tetrahedral addition intermediate and the associated transition states. The dependence of the metal ion catalyzed process on the concentration of hydroxide ion is consistent with coordinated hydroxide acting as a nucleophile. The reaction of benzoyl methyl phosphate with methanol to form methyl benzoate and methyl phosphate is 30 000 times more rapid in the presence of 0.0001 M lanthanum triflate (in the absence of the metal ion $k_{obs} = 2.1 \times 10^{-7}$ s^{-1}, at 25 °C). Thus, the combination of acyl phosphate esters and lanthanide salts appears to be a promising method for biomimetic acylation of hydroxyl groups.

Metabolic acyl transfer reactions require initial enzymatic catalysis to convert carboxylic acids to activated acylating agents. An important example is ribosomal protein synthesis, in which amino acids are converted to anhydrides with AMP from ATP prior to transferring the aminoacyl moiety to a terminal hydroxyl of tRNA specified by its anticodon. It occurred to us that acyl phosphate monoesters might also be biomimetic acylating agents. They hydrolyze very slowly in neutral solutions but react rapidly with amines to form amides.[1,2] It would be especially useful also to have these compounds acylate hydroxyl groups, emulating the reaction that leads to the formation of aminoacyl tRNAs. However, since the compounds are inherently unreactive toward hydroxyl groups, we needed to find catalysts for such a process. Since hydrolysis involves the attack of an oxygen-centered nucleophile, we initially examined pathways of ionic catalysis.

We have previously reported that some divalent cations increase the rate of hydrolysis of acyl phosphate monoesters but the acceleration is not large.[3] We reasoned that a more powerful, water-stable Lewis acid could be a better catalyst. In particular, since the primary coordination site of metal ions is the phosphate oxygen atoms and the reaction site is the carbonyl carbon, a larger catalyst should connect these sites more easily. Recently, Neverov and Brown reported that lanthanide ions accelerate reactions of other activated acyl derivatives with methanol.[4-6] Lanthanide ions have also been reported by Komiyama and co-workers to promote the hydrolysis of peptides,[7,8] alkyl esters, and amides.[9] These are promising indications for the potential use of lanthanides in enhancing the reactivity of acyl compounds in general toward oxygen-centered nucleophiles. Therefore, we examined the effects of lanthanide ions upon the hydrolysis of the acyl phosphate monoester benzoyl methyl phosphate (BMP) and the reaction of BMP with methanol. Our results indicate that lanthanide salts dramatically increase the reactivity of acyl phosphates toward oxygen-centered nucleophiles.

Experimental Section

Materials and Methods. Commercial reagents were used as received. NMR spectra were recorded at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 121.5 MHz for ^{31}P. Benzoyl methyl phosphate (BMP) was

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prepared by the general procedure reported for acyl phosphate esters.[10] Sodium dimethyl phosphate was prepared by the reaction of sodium iodide in acetone with trimethyl phosphate.[10,11] Benzoyl chloride (14.0 g, 0.1 mol) and sodium dimethyl phosphate (14.8 g, 0.1 mol) were suspended in dry tetrahydrofuran (60 mL, under nitrogen) and refluxed for 10 h. The solution was cooled and filtered to remove sodium chloride. Removal of the solvent left benzoyl dimethyl phosphate (**1**) as a colorless oil (19 g, 96%). ^{1}H NMR (CDCl$_3$) δ 3.89 (6H, d, J_{P-H} = 11.7 Hz), 7.40 (2H, tt, J_1 = 7.24 Hz, J_2 = 1.3 Hz), 7.57 (1H, tt, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 7.93−8.0 (m).

31P NMR (CDCl$_3$) δ −4.50. ESI MS calculated 215.1, found (*m/z*) 215.
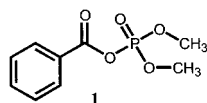
Benzoyl dimethyl phosphate was dissolved in acetone and an acetone solution of an equimolar amount of sodium iodide was added. The solution stood overnight, leading to crystallization of the product, the sodium salt of benzoyl methyl phosphate (BMP) in 71% yield, mp > 260 °C. ^{1}H NMR (D$_2$O) δ 3.55 (3H, d, J_{P-H} = 11.6 Hz), 7.27 (1H, t, J_1 = 7.9 Hz), 7.45 (1H, br d, J = 8.8 Hz), 7.74−7.82 (2H, m).

^{31}P NMR (D$_2$O) δ −4.47. MS (negative FAB) calculated 229.1, found (*m/z*) 229.
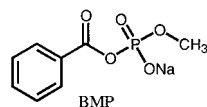
Kinetic Studies. The hydrolysis of benzoyl methyl phosphate (BMP) to give methyl phosphate and benzoic acid parallels the change in absorbance at 240 nm due to the difference in absorbance of BMP and benzoate. All rates were determined at 25 °C, pH 7 (0.01 M EPPS buffer) unless noted otherwise. Fresh solutions of buffer and inorganic materials were prepared and the pH was adjusted at 25 °C. Before each kinetic run, the buffer and salt solutions were transferred into spectrometer cells and brought to a volume of 2.85 mL by addition of water. The cells were then kept in a water-jacketed compartment at 25 °C for a minimum of 30 min. A stock solution (0.001 M) of BMP was prepared immediately before each kinetic run and 0.15 mL was transferred to give a final BMP concentration of 5 × 10^{-5} M and a final reaction volume of 3 mL. At least three kinetic runs were performed for each set of experimental conditions. The data were fit to the equation for a single-exponential decay to determine the observed first-order rate coefficients.

The dependence of rate on lanthanide concentration was determined over a range 0.001−0.008 M for neodymium and europium triflates, 0.001−0.009 M for europium chloride, and 0.001−0.010 M for ytterbium triflate. (The concentration was limited by the solubility of the individual lanthanides in water at pH 7.) A solution 0.001 M in lanthanide salt was used for studying rate variation due to changes in buffer, salts, and acidity. The effects of magnesium ion concentration on the rate of BMP hydrolysis were determined by the method of initial rates due to the very slow hydrolysis. The second-order rate constant (k_{Mg}) was determined from the linear dependence of the observed first-order rate coefficients on magnesium ion concentrations between 0.05 and 0.4 M. The magnesium ion dependence was studied under conditions where the ionic strength was allowed to vary with the concentration of magnesium and also with ionic strength maintained at $I = 1$ with potassium chloride. The second-order rate constant for specific acid catalysis was also determined by initial rates over the

range 0.1−0.8 M HCl. The rate coefficients for BMP hydrolysis at high acid concentrations are affected by the ionic strength of the solution, so the ionic strength was maintained to the equivalent of 1 M by addition of potassium chloride.

The pH dependence of the lanthanide ion-catalyzed hydrolysis of BMP was determined by extrapolation of buffer plots to zero concentration for four pH values. MES buffer was used at pH 5.5, 6, and 6.7, and EPPS buffer was used at pH 7. At higher pH values, water-insoluble lanthanide hydroxide species form, interfering with kinetic determinations.[4,12−17] The dependence of rate on hydroxide of the lanthanide free reaction was determined at concentrations of added hydroxide ion ranging from 0.002 to 0.008 M in the absence of buffer. Ionic strength was maintained at 1 M (KCl) for these studies.

Mass Spectral Analysis. BMP is a mixed anhydride and the same products result from addition of water to either the phosphoryl or carbonyl group. Acyl phosphate monoesters in general are much more reactive at their carbonyl group.[1,18] However, since the lanthanide ions in principle could accelerate reactions at either site, we conducted a lanthanide-catalyzed hydrolysis of BMP using ^{18}O-enriched water. A stock solution of 0.02 M EPPS and 0.01 M EuCl$_3$ was prepared with doubly distilled, deionized water. One milliliter of this solution was mixed with 1 mL of 10 atom % ^{18}O-enriched water in which 25 mg of BMP had been dissolved, to give a final solution that is 0.01 M in EPPS buffer, 0.005 M in EuCl$_3$, and about 0.05 M in BMP, with the water containing 5 atom % [18]O. The reaction was stirred at room temperature for 24 h, acidified, and then extracted three times with ether. The solution was dried over magnesium sulfate, filtered, and concentrated to give a white powder. The same procedure was repeated with doubly distilled deionized water in place of the 10 atom % [18]O water to provide a standard. The masses and relative abundance of the resulting benzoic acid products were analyzed by mass spectrometric measurements of the intensities of parent ions. We note that the exchange of water into benzoic acid is an extremely slow process, even in strongly acidic solutions at high temperatures,[19,20] so that the isotopic oxygen incorporation we observe in benzoic acid does not arise from exchange into this product.

Methanolysis. The rates of methanolysis of BMP were determined by monitoring the decrease in UV absorbance at 240 nm, 25 °C. For the methanol reactions, all stock solutions were prepared in 99.8% methanol. Apparent first-order rate coefficients were determined with the assumptions of initial rates and pseudo-first-order conditions. Lanthanide salts were added to the methanolic solutions and the rates were observed as in the reactions in water. Lanthanum triflate stock solution (0.001 M) was used. The solution was prepared simply by dissolving the lanthanum salt in methanol. The formation of methyl benzoate was confirmed by HPLC analysis of the reaction mixtures with a co-injection of authentic methyl benzoate. UV scans of the product mixtures show a shift of λ_{max} to 227 nm, which is the λ_{max} of methyl benzoate in methanol.

Methanolysis was followed by high-performance liquid chromatography (HPLC) analysis, detected at 230 nm on a C18 reverse-phase column, eluting with a 90:10 mixture (v/v) of water and acetonitrile. Methanolic solutions of 0.01 M La(OTf)$_3$ and 0.1 M triethylamine were

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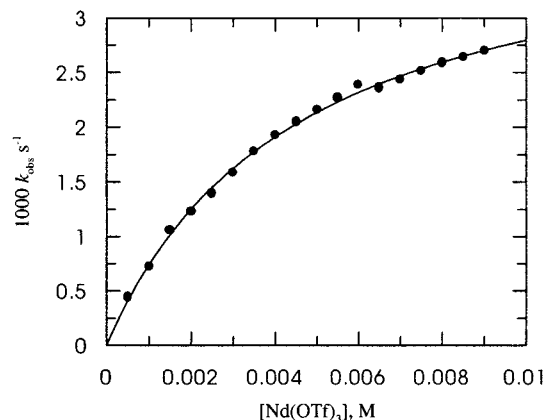(15) Jurek, P. E.; Jurek, A. M.; Martell, A. E. *Inorg. Chem.* **2000**, *39*, 1016−1020.
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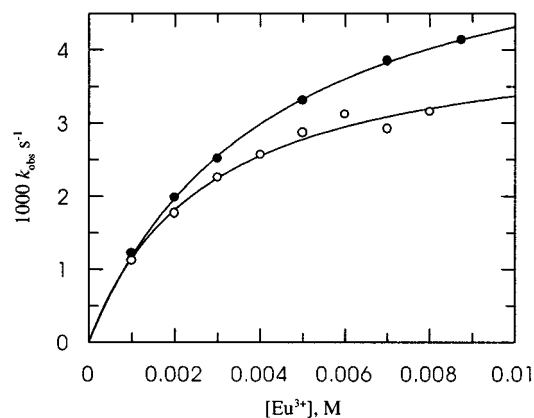(17) Briggs, P. J.; Satchell, D. P. N.; White, G. F. *J. Chem. Soc. B* **1970**, 1008−1012.
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Figure 1. Saturating dependence of the observed first-order rate coefficient for hydrolysis of BMP on the concentration of neodymium ion, 25 °C, pH 7, 0.01 M EPPS.


Figure 2. Effects of europium chloride (●) and europium triflate (○) concentration on the observed first-order rate coefficient for hydrolysis of BMP, 25 °C, pH 7, 10 mM EPPS buffer.

prepared. Increasing amounts of these solutions were added to methanol to give a final volume of 0.5 mL. Then 0.5 mL of 0.001 M BMP in methanol was added to the reaction mixture and immediately subjected to HPLC analysis.

Results

Metal Ion Catalysis. The addition of lanthanide salts significantly accelerates the hydrolysis of BMP (which is pseudo-first-order in BMP). The magnitude of the observed first-order rate coefficient is dependent on the lanthanide ion at low concentrations but the dependence decreases at higher metal ion concentrations (Figures 1−3). The data fit the general Michaelis−Menten catalytic scheme (Scheme 1), where lanthanide ion is a catalyst, permitting separation of the association (K_1) and catalysis (k_2) parameters. The reaction conducted in ^{18}O-enriched water resulted in incorporation of the of ^{18}O into the resulting benzoic acid as evidenced by enhancement of the parent ion + 2 peak in the mass spectrum of benzoic acid (m/z 124) to the extent of isotopic enrichment of the water. Therefore, the lanthanide ions accelerate C−O cleavage, indicating that these ions promote reaction at the carboxyl group of BMP.

The derived values for the catalytic rate constants, k_2, and association constants for the substrate lanthanide complexes, K_1, were obtained by a computer-generated least-squares fit of k_{obs} to eq 1. The second-order rate constant for magnesium-promoted BMP hydrolysis is 8.1×10^{-6} M^{-1} s^{-1}. The magnesium dependence is independent of ionic strength and
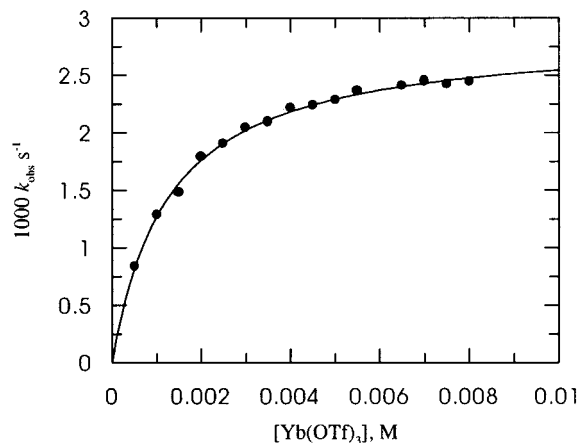
Figure 3. Dependence of the observed first-order rate coefficient for hydrolysis of BMP on the concentration of ytterbium ion, 25 °C, pH 7, 0.01 M EPPS.

Scheme 1

$$BMP + Ln^{+++} \underset{}{\overset{K_1}{\rightleftharpoons}} Ln\text{-}BMP \xrightarrow{k_2} P$$
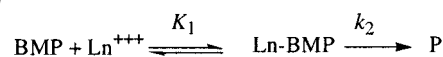
Table 1. Rate and Equilibrium Constants Associated with the Lanthanide-Catalyzed Hydrolysis of BMP[a]

catalyst	k_2, s^{-1}	K_1, M^{-1}	k_2K_1, M^{-1} s^{-1}
Nd(OTf)$_3$	$(4.0 \pm 0.1) \times 10^{-3}$	$(2.2 \pm 0.2) \times 10^2$	0.88
Eu(OTf)$_3$	$(4.3 \pm 0.4) \times 10^{-3}$	$(3.7 \pm 1) \times 10^2$	1.6
EuCl$_3$	$(6.1 \pm 0.2) \times 10^{-3}$	$(2.2 \pm 0.2) \times 10^2$	1.3
Yb(OTf)$_3$	$(2.9 \pm 0.1) \times 10^{-3}$	$(8.0 \pm 0.6) \times 10^2$	2.3
MgCl$_2$			8.1×10^{-6} [b]

[a] Based on a Michaelis−Menten mechanism, 25 °C, pH 7, 0.01 M EPPS buffer. [b] Second-order rate constant determined from the linear correlation of the observed first-order rate coefficient for BMP hydrolysis and magnesium concentration.

shows no sign of curvature at 0.4 M metal. This shows that the interaction of magnesium ions with BMP is very weak compared to the interaction with lanthanide ions, which saturates at 0.01 M metal. Table 1 contains a summary of the derived rate constants under conditions of lanthanide ion catalysis, as well as the measured second-order rate constant for magnesium catalysis:

$$k_{obs} = K_1 k_2 [Ln]/(1 + K_1 [Ln]) \tag{1}$$

Salt Effects. Increasing concentrations of the EPPS buffer do not promote the rate of hydrolysis of benzoyl methyl phosphate in the presence of metal ions. In fact, we observe that increased EPPS slows the rate of the reaction with inhibition saturating at approximately 0.5 M EPPS. Sensitivity of metal-catalyzed reactions to buffer concentration has been observed for other reactions involving coordination to phosphorus oxygens.[16,21]

The rate of the lanthanide-promoted hydrolysis of BMP is subject to a nonspecific depressing salt effect. The effect of mono- and divalent cations is a linear function of Debye−Hückel ionic strength parameters from a plot of log k_{obs} values vs the Debye−Hückel term, $\sqrt{I}/(1 + \sqrt{I})$ at constant lanthanide concentration (see Figure 4 and eq 2).[22] This is consistent with the expectation that the catalytically active species (lanthanide

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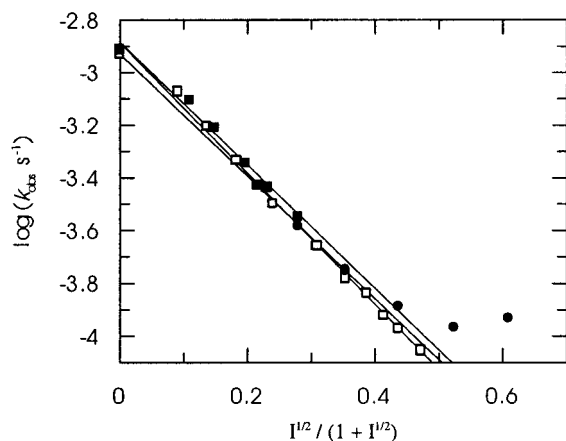
Figure 4. Observed first-order rate coefficients as a function of ionic strength: 1×10^{-3} M EuCl$_3$ ($\square$, Li$^+$; $\blacksquare$, Mg^{2+}; $\bullet$, Ca^{2+}; 25 °C, pH 7, 0.010 M EPPS).
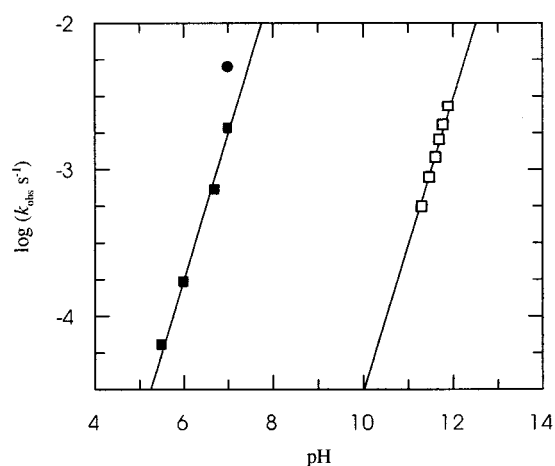

Figure 5. Dependence on pH (indicating measured value or $14 + \log$ [hydroxide]) of the observed first-order rate coefficients for the hydrolysis of BMP, 25 °C. ($\blacksquare$) 1×10^{-3} M europium, ($\bullet$) saturating europium, ($\square$) no europium, $\mu = 1$ (KCl).[30]

chelate, see Discussion) dissociates in the presence of other ions, as they provide electrostatic stabilization of the unassociated species.

$$\log k = \log k_0 + m\left(\frac{\sqrt{I}}{1 + \sqrt{I}}\right) \qquad (2)$$

Acid and Base Catalysis. The hydrolysis of BMP is subject to specific hydronium ion catalysis with a second-order rate constant of 3.1×10^{-6} M^{-1} s^{-1} (obtained from the linear dependence of the observed first-order rate coefficients on the concentration of added acid in solutions of 0.1 M HCl and higher, at constant ionic strength, $I = 1$). At these high acidities, lanthanide ion does not promote the hydrolysis of BMP, indicating that the proton is a superior catalyst under these conditions. The hydrolysis in the absence of metal ions is promoted by hydroxide, $k_{OH} = 3.4 \times 10^{-1}$ M^{-1} s^{-1}. In the case of the europium ion-promoted reaction, the hydroxide-dependent reaction is much faster ($k_{OH} = 1.9 \times 10^4$ M^{-1} s^{-1}), with a second-order rate constant that is 5 orders of magnitude greater than that for the dissociated species (Figure 5).

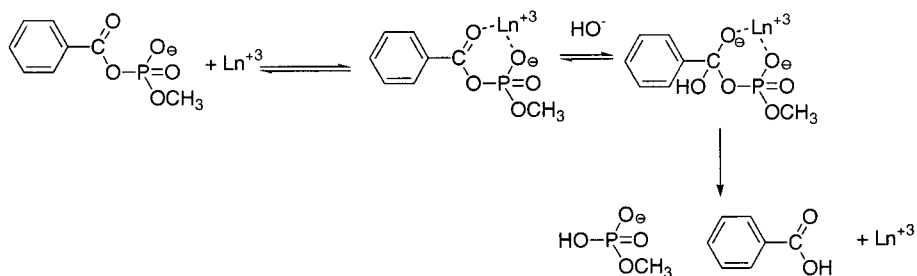(23) Schneider, H. J.; Theis, I. *J. Org. Chem.* **1992**, *57*, 3066−3070.
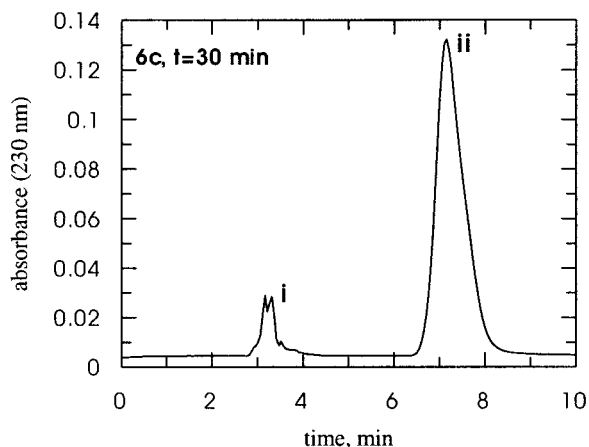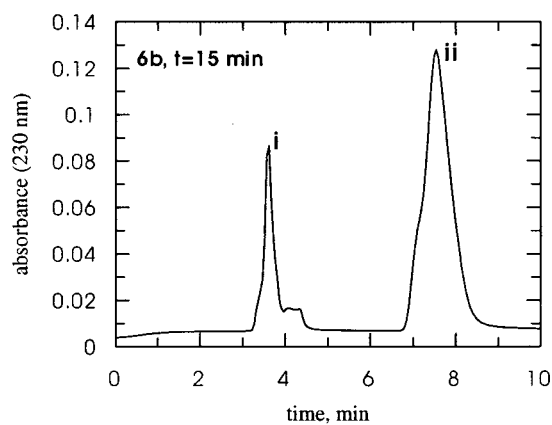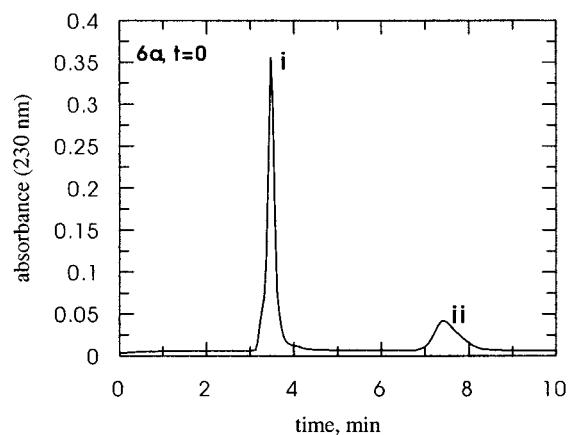
Figure 6. HPL chromatograms for the reaction of BMP in methanol. The peak for BMP is indicated by i, and the methanolysis product, methyl benzoate, is indicated by ii. Conditions: 0.0005 M BMP in methanol with 0.005 M La(OTf)$_3$, 25 °C.
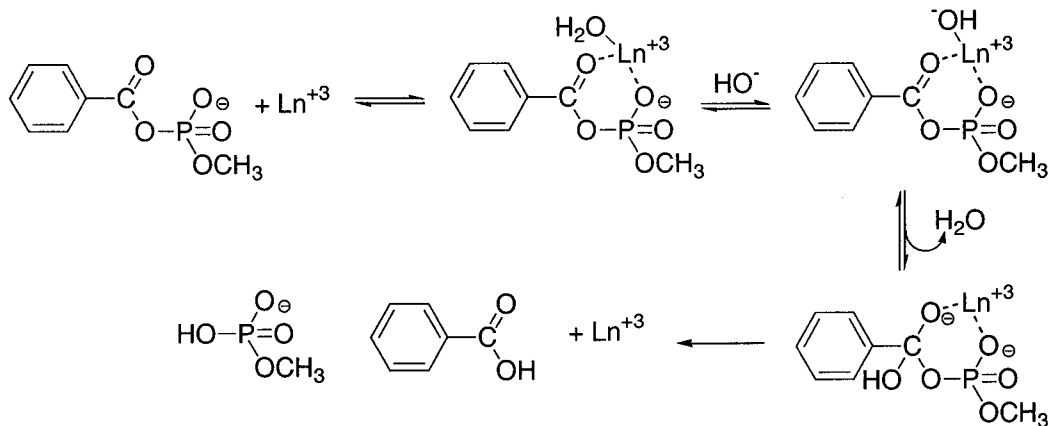
Methanolysis. Since we undertook these studies with the objective of using acyl phosphate esters for biomimetic acylation of hydroxyl groups, we examined the effects of lanthanum triflate in methanol on the formation of methyl benzoate from BMP. The initial first-order rate coefficient for uncatalyzed methanolysis of BMP at 25 °C is 2.1 ($\pm$ 0.7) $\times 10^{-7}$ s^{-1}. This slow rate of methanolysis of BMP is dramatically accelerated by lanthanide ions. We find that low concentrations of La(III) have a very large catalytic effect. Addition of 0.0001 M lanthanum triflate gives an observed initial first-order rate of formation of methyl benzoate that is accelerated 30 000-fold ($k_{obs} = 7.7$ ($\pm$ 0.3) $\times 10^{-3}$ s^{-1}). We observe greater accelerations at higher lanthanide concentrations and in more basic

Scheme 2

Scheme 3

solutions, but the reactions are kinetically complex, (presumably due to changes in speciation at different lanthanide concentrations and $_s^s$pH).[4−6,24]

HPLC analysis of reaction solutions of BMP in methanol permits direct observation of the formation of methyl benzoate, clearly showing the large catalytic effect of lanthanide ions. In the absence of lanthanide, the system does not detect a significant amount of methyl ester present after 22 h. However, in the presence of 5.0×10^{-3} M La(OTf)$_3$ (Figure 6), after 15 min in methanol, more than half of the BMP is converted to the methyl ester. When we increase the basicity of the solution by the addition of triethylamine (0.001 M), the reaction is faster, with 95% conversion of BMP to methyl benzoate at the initial injection.

Discussion

Lanthanide ions are powerful catalysts for the hydrolysis and methanolysis of BMP in neutral solutions. Our detailed kinetic studies focus on the hydrolysis reactions. The saturating dependence of the observed first-order rate coefficients for hydrolysis upon lanthanide concentration indicates that catalysis occurs through initial formation of a complex between the ion and BMP. Since metal ions normally coordinate at phosphate oxygens, we could expect a similar coordination structure to form between lanthanides and BMP. However, such coordination would not have a significant effect on the specific reactivity of the carbonyl center. On the other hand, bidentate coordination via the carbonyl and phosphate oxygens could lead to stabilized tetrahedral intermediates from addition of water or hydroxide ion to the carbonyl, as well as in the associated transition states (Scheme 2). Such a pattern is analogous to those Sigel found for association of acetyl phosphate and divalent metal ions.[25−27]

The acyl phosphate dianions form bidendate complexes via the carbonyl group and phosphate, producing six-membered chelate rings whose formation is promoted by low solvent polarity. This is consistent with our observation that increasing ionic strength slows the reaction involving lanthanide ion. Since BMP is monoanionic, the carbonyl will compete more effectively with the phosphate as a coordinating site than in unesterified acyl phosphate dianion derivatives. Furthermore, lanthanide ions are superior to smaller divalent metal ions for this mode of coordination, on the basis of size, charge, and oxophilicity. The importance of the high charge-to-size ratio of the metal ions in the catalysis of acyl phosphate monoester hydrolysis is illustrated by the trend in association constants within the lanthanide series (formation of the catalytically active complex increases with the charge density of the lanthanides).

A further mode of activation that is likely to be provided by the lanthanide ion is ionization of coordinated water, producing a nucleophilic hydroxide species that is positioned within the chelate for reaction with the carbonyl center (Scheme 3). In the scheme we show only the ionizing water ligand in the lanthanide hydration sphere. Although the pK_a of water is depressed by about 7 units upon binding to a lanthanide ion,[28] it is still 1−2 units higher than would be necessary to have it be 50% dissociated under the conditions of our measurements (pH 7). Hydroxide ion would act as a Brønsted base, accepting the proton of the lanthanide-bound water. This mechanism accounts for both the first-order hydroxide dependence and the acceleration provided by the lanthanide of the base-catalyzed process.

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The activation toward hydrolysis of the acyl phosphate monoester that is provided by complexation with the lanthanide ions is very significant, indicating that this can be a productive system for utilizing the otherwise stable acyl phosphate monoesters as acylating agents in biomimetic chemistry. Lanthanide ions have already proven to be catalysts in the alcoholysis of phosphodiesters,[29] esters,[6] and amides.[4,5] The rates for the uncatalyzed hydrolysis, with $k_{hydr} = 8.6 \times 10^{-7}$ s^{-1} (obtained by extrapolation of the linear magnesium ion dependence) and methanolysis ($k_{MeOH} = 2.1 \times 10^{-7}$ s^{-1}) of BMP are similar. The rate enhancement of methanolysis achieved by 10^{-4} M lanthanum triflate is greater than the rate enhancement of hydrolysis achieved by a 10-fold higher concentration of lanthanide. This suggests that alcoholysis may be a preferred process in mixed solvents in the presence of lanthanides. On the basis of our observation of a facilitated reaction with metal ions, we have begun a complete study of lanthanide catalysis in the reactions of alcohols with acyl phosphate monoesters and with aminoacyl phosphate esters. We are currently developing systems that target hydroxyl groups in complex biological molecules.

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