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La^{3+}-Catalyzed Methanolysis of Phosphate Diesters. Remarkable Rate Acceleration of the Methanolysis of Diphenyl Phosphate, Methyl *p*-Nitrophenyl Phosphate, and Bis(*p*-nitrophenyl) Phosphate

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The interaction of La^{3+} with diphenyl phosphate, methyl *p*-nitrophenyl phosphate, and bis(*p*-nitrophenyl) phosphate (**4**, **5**, and **3**) and the ensuing catalysis of methanolysis has been studied in methanol under completely homogeneous conditions of known ${}^{s}_{s}pH$. ^{31}P NMR shows that phosphates **3** and **4** are each associated with La^{3+} as a rapidly interconverting mixture of complexes having 2:1, 1:1 (or 2:2), and 1:2 stoichiometry. At $[La^{3+}] > 2 \times 10^{-4}$ M, the kinetically dominant species in the ${}^{s}_{s}pH$ regions of interest are phosphate-bound La^{3+} dimers having 2−5 associated methoxides. Potentiometric titration reveals that 4 mM La^{3+} alone in MeOH exhibits two apparent ${}^{s}_{s}pK_a$s at 7.86 and 10.44 consuming 1 and 1.5 CH_3O^- per metal, the suggested structures being La^{3+} dimers with first two and then five associated methoxides. In the presence of 0.5 equiv of **4** the potentiometric titration reveals strong complexation of **4** to La^{3+} and a profile with apparent ${}^{s}_{s}pK_a$s at 7.8 and 11.1 consuming 1 and 1.5 CH_3O^- per metal corresponding to phosphate-bridged La^{3+} dimers with first two and then five associated methoxides. Methanolysis of **3**−**5** is strongly accelerated by La^{3+}. At ${}^{s}_{s}pH$ 8.9 or 11.1, respectively, as little as 5×10^{-4} M $La(OTf)_3$ accelerates the methanolysis of **3** or **4** by 10^{10}-fold relative to the background reaction. Detailed kinetic studies of the methanolysis of **5** at varying $[La^{3+}]$ and ${}^{s}_{s}pH$ indicate that both La^{3+} monomers and dimers with associated methoxides are reactive species. The rate constants for La^{3+} monomer and dimer catalysis of the methanolysis of **5** are dependent on ${}^{s}_{s}pH$, the slopes of the log plots being 0.35 and 0.5, respectively. A scheme is proposed to account for the non-first-order dependence on $[CH_3O^-]$ wherein the $La^{3+}(CH_3O^-)_x + \mathbf{5} \rightleftarrows La^{3+}\text{-}(CH_3O^-)_x{:}\mathbf{5}$ and $(La^{3+})_2(CH_3O^-)_y + \mathbf{5} \rightleftarrows \mathbf{5}{:}(La^{3+})_2(CH_3O^-)_y$ equilibria are driven to the left with increasing numbers of associated methoxides and that attack on these complexes, whether by external or metal-associated methoxide, is slower due to the reduced net positive charge on the complex.

Introduction

In Nature many enzymes that promote the hydrolysis of phosphate esters have active sites containing two or more metal ions.[1] These include enzymes cleaving phosphate monoesters[2] (alkaline phosphatase, inositol phosphatase, and purple acid phosphatase) and those cleaving phosphate diesters[3] (such as the RNAse from HIV reverse transcriptase,[3a] 3’−5’ exonuclease from DNA polymerase I,[3b] and P1 nuclease[3c]). Due to its obvious biological relevance pertaining to the storage of genetic information in DNA and RNA, much attention has been focused on hydrolysis of phosphodiesters mediated by metal ions.[4] Among the metal ions, lanthanides exhibit the most dramatic accelerations, particularly under basic conditions as their metal−hydroxo forms. One of the general stumbling blocks in understanding metal ion catalysis of any hydrolytic process is the fact that above the pK_a’s of metal−aquo complexes, formation of precipitates or gels of poor definition often complicates mechanistic evaluation.[5] In some cases the problem has been ameliorated by complexing the metal ions to stabilizing ligands[4] including cyclodextrins[4i] and macrocycles,[4h,4k] or inserting them in micelles,[4e] but even so, homogeneity problems usually make it difficult to study the reaction under highly basic conditions.

Recently we have shown that certain metal ions including Zn^{2+}, Co^{2+}, and La^{3+} are soluble in methanol throughout the ${}^{s}_{s}pH$ region where ionization of the $M^{x+}(CH_3OH)_n$ occurs, thus making it possible to study the metal ion promoted methanolysis

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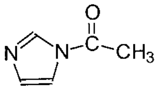
of the simple substrate, acetylimidazole (**1**), and its ligand exchange inert complex $(NH_3)_3Co^{III}-AcIm$ (**2**).[6] While the two transition metals studied exist as monomers throughout the $^{s}_{s}\mathrm{pH}$ range from 7 to 11 where ionization of the $M^{2+}(CH_3OH)_n$ occurs to give catalytically inactive $M^{2+}(CH_3O^-)_2$, the La^{3+} behaves quite differently, existing as a catalytically active dimer held together by two methoxides above its first $^{s}_{s}\mathrm{p}K_a$.

These findings, and the recent reports of Bosch and coworkers[7] concerning the measurement and control of $^{s}_{s}\mathrm{pH}$ in methanol, suggest that it should be possible to undertake studies of a variety of metal-promoted acyl and phosphoryl transfer reactions in methanol as simply as one does in water without the attendant metal alkoxide precipitation problems. Among organic solvents, methanol is closest to water in terms of structure and properties. However, there are important differences attributable to its reduced dielectric constant (31.5 vs 78.5 at 25 °C)[8] which may be important for metal ion/anion interactions and therefore relevant to phosphate ester cleavages occurring in the reduced polarity of a metalloenzyme's interior.[9] In this report we focus on a study of the methanolysis of bis(*p*-nitrophenyl) phosphate (**3**), diphenyl phosphate (**4**), and methyl *p*-nitrophenyl phosphate (**5**) promoted by $La^{3+}(^-OTf)_3$. Our results indicate that there are various phosphate/La^{3+} complexes formed in equilibrium in methanol, these being dependent on both $[La^{3+}]$ and $[CH_3O^-]$, and that the methanolysis of **3**−**5** can be accelerated by as much as 10^{10}-fold by as little as 5×10^{-4}M $[La^{3+}]$ at 25 °C. Further, a combination of kinetic, titration, and ^{31}P NMR data indicate that kinetically active phosphate:$(La^{3+})_2(CH_3O^-)_x$ complexes are formed throughout the $^{s}_{s}\mathrm{pH}$ region from 7 to 12.



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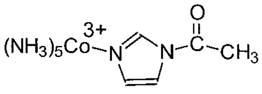

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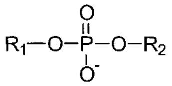

3 $R_1=R_2$ = *p*-nitrophenyl
4 $R_1=R_2$=phenyl
5 R_1=*p*-nitrophenyl, $R_2=CH_3$

Experimental Section

Materials. Methanol (99.8% anhydrous), sodium methoxide (0.5 M), $HClO_4$ (70%, BDH), $La(CF_3SO_3)_3$, bis(*p*-nitrophenyl) phosphate (**3**), and diphenyl phosphate (**4**) were all purchased from Aldrich and used without any further purification. Methyl *p*-nitrophenyl phosphate (**5**) was synthesized as described.[10]

$^{s}_{s}$pH Measurements. The $CH_3OH_2^+$ concentration was determined using a Radiometer GK2322 combination (glass/calomel) electrode calibrated with Fisher Certified Standard aqueous buffers (pH = 4.00 and 10.00). Values of $^{s}_{s}\mathrm{pH}$ were calculated by adding a correction constant of 2.24 to the experimental meter reading ($^{s}_{w}\mathrm{pH}$). This method was first described by Bates[11] for a molality scale (correction constant 2.34) and later by Bosch et al.[7] for a molar correction constant of 2.24 units. The $^{s}_{s}\mathrm{p}K_a$ values of buffers used for the present kinetic studies were obtained from the literature[7] or measured at half neutralization of the bases with 70% $HClO_4$ in MeOH.

$^{s}_{s}$pKa Determination. The general procedures for potentiometric titrations of the La^{3+}-containing solutions in methanol, performed using a Radiometer Vit 90 Autotitrator under anaerobic conditions (Ar) at 25 °C, are described in our recent publications.[6]

The concentrations of metal salts and sodium methoxide titrant (prepared from stock 0.5 M sodium methoxide provided in a Sure Seal bottle) were $(1.00-4.33) \times 10^{-3}$ M, and $(0.019 - 0.225)$ M, respectively. The latter was calibrated by titrating standardized HCl with the endpoint taken to be $^{s}_{s}\mathrm{pH} = 8.38$. The values of the dissociation constants ($^{s}_{s}\mathrm{p}K_a$) were calculated using the computer program PKAS.[12] The $^{w}_{w}\mathrm{p}K_w$ in the program was replaced by the autoprotolysis constant for methanol at 25 °C ($^{s}_{s}\mathrm{p}K_{MeOH} = 16.77$).[7]

Kinetic Measurements. The rates of methanolysis of **3** and **5** in buffered methanol solutions were followed by monitoring either the appearance of *p*-nitrophenolate at 400 nm or the complex of *p*-nitrophenolate with La^{3+} at 355 nm or by monitoring the disappearance of starting material at 285 nm with an OLIS modified Cary 17 UV−vis spectrophotometer at 25.0 ± 0.1 °C. Reactions were generally monitored under pseudo-first-order conditions with metal ion in the range of 1×10^{-5} M to 2×10^{-3} M and were initiated by addition of an aliquot of a 2.5×10^{-2} M stock solution of **3** or **5** in CH_3CN to 2.5 mL of the buffered reaction mixture. At the lowest $[La^{3+}]$ of $(1-2) \times 10^{-5}$ M the kinetics monitored as above are not strictly under pseudo-first-order conditions. However, kinetics monitored varying **5** through the range of $(0.2-1.2) \times 10^{-4}$ M at these metal concentrations gave identical rate constants showing the true catalytic nature of the system. Reactions with **3** did not give good first-order kinetics as expected since two sequential processes are involved in the methanolysis, and in this case initial rate experiments were performed. However, **5** displayed good first-order behavior, and the pseudo-first-order rate constants (k_{obs}) for its methanolysis were determined by NLLSQ fitting of the absorbance vs time traces to a standard exponential model. *N*-methylimidazole ($^{s}_{s}\mathrm{p}K_a = 7.60$), *N*-ethylmorpholine ($^{s}_{s}\mathrm{p}K_a = 8.28$), trimethylamine ($^{s}_{s}\mathrm{p}K_a = 9.80^{7b}$), triethylamine ($^{s}_{s}\mathrm{p}K_a = 10.78^{7b}$), and diisopropylamine ($^{s}_{s}\mathrm{p}K_a = 11.45^{7b}$) buffers, partially neutralized with $HClO_4$, were used to control the $^{s}_{s}\mathrm{pH}$. Total buffer concentrations varied between $(1-4) \times 10^{-2}$ M and, for technical reasons, ionic strength was not controlled, but held approximately constant by the ionic form of the buffer and added metal salts. $^{s}_{s}\mathrm{pH}$ measurements were performed before and after each experiment, and in all cases, values measured were consistent to within 0.05 units. Tables of k_{obs} values vs $[La^{3+}]$ at various $^{s}_{s}\mathrm{pH}$ values for the methanolysis of **5** are given in the Supporting Information.

Initial rate measurements for methanolysis of **5** in the absence of La^{3+} were done at a constant $[NaOCH_3]$ of 0.1−0.5M using an experimental extinction coefficient for *p*-nitrophenylate in methanol of ϵ_{400}=14310 ± 20 M^{-1}. The k_{obs} constant at a given $[CH_3O^-]$ was computed by linear regression of the concentration vs time plot, with the second-order rate constant for methoxide attack being given as $k_{obs}/[CH_3O^-]$.

The kinetics for methanolysis of **4** were monitored under conditions described above by initial rate methods, observing the rate of appearance of phenol at 279 nm using an $\epsilon_{279} = 1390 \pm 3\ M^{-1}cm^{-1}$. No binding of the phenol product to La^{3+} was observed.

NMR Kinetics. The methanolyses of 0.025 M solutions of **3** and **4** in 80% CD_3OD/CH_3OH were investigated by ^1H NMR at 25 °C in the presence of 0.053 M $La(OTf)_3$ and 0.089 M $NaOCH_3$ for **3** and 0.04 M $La(OTf)_3$ and 0.1 M $NaOCH_3$ for **4**. The reaction was followed by monitoring the appearance of the proton signals attributable to the free

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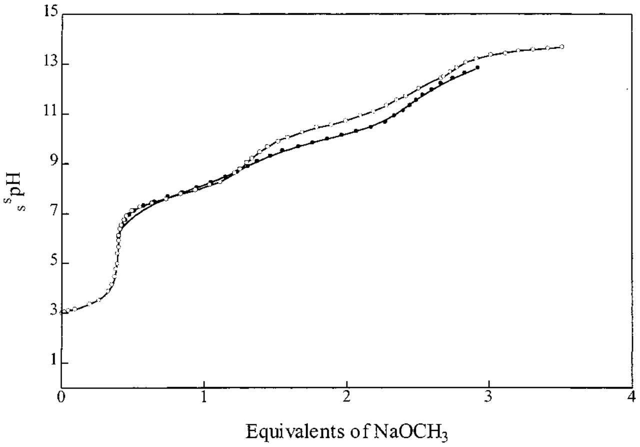


Figure 1. Titration curve for 4 mM La(OTf)$_3$ alone (●) and in the presence of 2 mM of diphenyl phosphate (○) in methanol at 25 °C. Titration curve for La(OTf)$_3$ alone shifted right by 0.5 equiv of NaOCH$_3$ to compensate for the presence of acidic proton in diphenyl phosphate.

phenol product. In both cases two molecules of the phenol product are released during the reaction, and in order to simplify the analysis, the initial rates for appearance of product were monitored. The so-determined k_{obs}values for La^{3+}-promoted methanolysis under these conditions were 6.6×10^{-5} s^{-1} for **4** and about 5.4×10^{-4} s^{-1} for **3**.

^{31}P NMR Study of Phosphate Diester Complexation by La(OTf)$_3$ in Methanol. ^{31}P NMR spectra of 0.005 M solutions of **3** in methanol containing 10% CD$_3$OH and 0.04 M *N*-ethylmorpholine buffer at pH = 9.5, T = 25 °C, were determined at 161.97 MHz using a Bruker Avance-400 NMR spectrometer with an external standard of 70% phosphoric acid in water. In the absence of La^{3+}, a single ^{31}P signal at δ −11.39 ppm was observed. Addition of 1.0 equiv of La(OTf)$_3$ caused an immediate formation of a white precipitate, and no ^{31}P signals were observed. Addition of a second equivalent of La(OTf)$_3$ followed by sonication for 10 min led to a clear solution exhibiting a ^{31}P signal at δ −14.96 ppm, and no signal at δ −11.39 ppm. Addition of a third and fourth equivalent of La(OTf)$_3$ only slightly changed the ^{31}P signal to δ −15.025 and −15.167, respectively. During the time taken for the above sets of spectra, a new signal was observed in the solution at δ −7.55 ppm, attributable to the intermediate product, methyl *p*-nitrophenyl phosphate. Authentic dimethyl phosphate product with 2 equiv of added La^{3+} gives a ^{31}P signal at δ −0.88 ppm.

The ^{31}P NMR spectrum of a 0.005M solution of **4** in methanol containing 10% CD$_3$OD and 0.04 M *N*-ethylmorpholine buffer at $^{s}_{s}$pH = 9.5, T = 25 °C, contained a single peak at δ −9.336 ppm. Addition of 2 equiv of La(OTf)$_3$ caused a shift in the peak position to δ −13.432 ppm and slight broadening, similar to the situation observed with **3** above. When the experiment was determined at lower $^{s}_{s}$pH (0.01 M *N*-methylimidazole, $^{s}_{s}$pH = 6.7), or higher $^{s}_{s}$pH (0.04 M triethylamine buffer, $^{s}_{s}$pH =11.5), no signals were observed in the ^{31}P spectrum following addition of the La(OTf)$_3$, suggesting a close-to-coalescence dynamic equilibrium. At −80 °C, pH 6.7 (*N*-methylimidazole buffer, 2 equiv of La(OTf)$_3$), the spectrum exhibits three distinct signals: a major one at δ −13.140, a second at −21.490 ppm, and a minor one at −19.359 ppm corresponding to three different La^{3+}/**4** complexes. Also observed in the ^{31}P NMR spectrum is a peak at δ −17.515 of uncertain origin.

A final series of ^{31}P NMR experiments with 0.005 M **4** in unbuffered, $^{s}_{s}$pH∼6, CH$_3$OH containing 20% CD$_3$OD was conducted as a function of added La(OTf)$_3$ at −80 °C. The ^{31}P spectra at [La^{3+}]/[**4**] = 0.5, 1.0, 2.0, and 3.0 are shown in Figures 2a−d.

Results and Discussion

1. Titration of La^{3+} in the Presence and Absence of Phosphate Diester. Shown in Figure 1 is the titration curve at 25 °C for a 4 mM solution of La^{3+}($^{-}$OTf)$_3$ in MeOH that indicates two events tied to the consumption of a total of 2.5 equiv of CH$_3$O$^-$ per La^{3+} occurring between $^{s}_{s}$pH 6 and 11. The first, having an apparent $^{s}_{s}$pK_a of 7.86, involves 1 equiv of CH$_3$O$^-$/La^{3+} and the second, centered at $^{s}_{s}$pH 10.44 (the $^{s}_{s}$pH of half neutralization), consumes 1.5 equiv of CH$_3$O$^-$/La^{3+}. The nonstoichiometric consumption of methoxide, taken in conjunction with kinetic data presented in our earlier study of the La^{3+}-promoted methanolysis of **1** and **2**,[6] is explained by the process shown in Scheme 1 where La^{3+} dimers are formed, which, following ionization, are first associated with two methoxides ($^{s}_{s}$p$K_{a(1,2)}$ 7.86, eq 2), and then five ($^{s}_{s}$p$K_{a(3-5)}$ ∼10.44, eq 3).

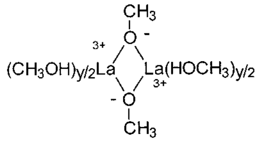
Scheme 1

$$2\mathrm{La}^{3+}(\mathrm{CH_3OH})_n \underset{K_d}{\rightleftharpoons} \mathrm{La}_2^{3+}(\mathrm{CH_3OH})_x \tag{1}$$

$$\mathrm{La}_2^{3+}(\mathrm{CH_3OH})_x \overset{{}^s_sK_{a(1,2)}}{\underset{2\mathrm{H}^+}{\rightleftharpoons}} \mathrm{La}_2^{3+}(\mathrm{CH_3O^-})_2(\mathrm{CH_3OH})_y \tag{2}$$

$$\mathrm{La}_2^{3+}(\mathrm{CH_3O^-})_2(\mathrm{CH_3OH})_y \overset{{}^s_sK_{a(3-5)}}{\underset{3\mathrm{H}^+}{\rightleftharpoons}} \mathrm{La}_2^{3+}(\mathrm{CH_3O^-})_5(\mathrm{CH_3OH})_z \tag{3}$$

We suggest that these dimers contain bridging CH$_3$O$^-$ ligands as in **6** or **7a**,**b** with an uncertain number of associated solvent molecules. Double-bridged structures are known for La^{3+} in solution and were suggested for La$_2$Cl$_6$(CH$_3$OH)$_{10}$[13] (with bridging chloride ions) and a La^{3+}−peroxide complex (with bridging peroxide dianions).[14] From a study of the hydrolysis of an RNA model dimer promoted by La^{3+} in water, Hurst, Takasaki, and Chin[15] proposed a similar catalytically active structure having two lanthanide ions bridged by five HO$^-$.



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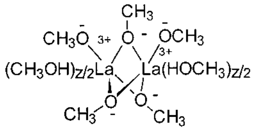

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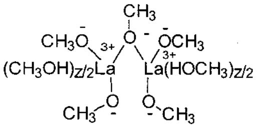

7b

Also in Figure 1 is a titration curve for 4 mM La^{3+}($^{-}$OTf)$_3$ in methanol containing 2 mM diphenyl phosphate (**4**). This curve is similar to that of La^{3+}($^{-}$OTf)$_3$ alone but with two notable differences. In methanol, diphenyl phosphate has a single $^{s}_{s}$pK_a of 3.95 which is lowered to 3.0 ± 0.1 in the presence of La^{3+}($^{-}$OTf)$_3$, suggesting strong complexation of the phosphate monoanion to La^{3+}. Continued titration leads to the consumption of one CH$_3$O$^-$/La^{3+} having an apparent $^{s}_{s}$pK_a of 7.8, indicating that the presence of phosphate only slightly perturbs the first $^{s}_{s}$pK_as of the dimeric lanthanide-bound methanol. Further titration leads to the consumption of 1.5 equiv of CH$_3$O$^-$/La^{3+} with an apparent $^{s}_{s}$pK_a of 11.1, perturbed upward by ∼0.7 units by the presence of the phosphate. We propose dimeric structures **8**−**10a**,**b** (with an unspecified number of associated solvent molecules) to explain the sequential binding of the

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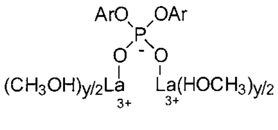
diphenyl phosphate to the metal ions, followed by consumption of first 1 and then 1.5 equiv of CH_3O^-/La^{3+}. There are other possibilities, but the methoxide stoichiometry and symmetry considerations require that **9** contains an even number of bridging methoxides (0 or 2), and **10** contains an odd number (1, 3, or 5). Similar phosphate bridged dimers have been identified;[16] for example, a $La^{3+}{}_2(^-OH)_5$:RNA analogue,[15] two $(Co^{III}$:maclocycle$)_2(^-OH)_2$:phosphate diester systems,[17] and two dinuclear Cu^{2+}:phosphate systems.[18,19] Such has also been proposed for a (bisTris-$La^{3+})_2(^-OH)_4$:diphenyl phosphate complex as the active species in the hydrolysis of bis(*p*-nitrophenyl) phosphate.[20]



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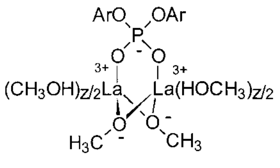

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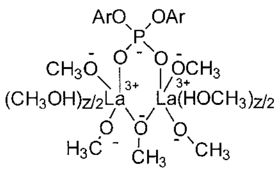

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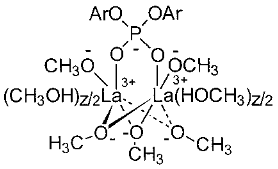

10b

2. ^{31}P NMR

(i) Bis(*p*-nitrophenyl) Phosphate (3) and La^{3+}. The room temperature ^{31}P NMR of a methanol solution of 5 mM **3**, buffered with 0.04 M *N*-ethylmorpholine at $^{s}_{s}$pH 9.5, shows a single peak at δ −11.390 ppm which, in the presence of 2 equiv of $La^{3+}(^-OTf)_3$, generates a slightly broadened peak at δ −14.96 ppm. Addition of a third and fourth equivalent of La^{3+} does not shift the peak markedly, but due to the time required for the series of spectra (~2 h), a second peak (roughly 1:1 intensity with **3**) centered at δ −7.55 was observed which is attributable to the intermediate methanolysis product, NO_2-Ph-P(=O)(O^-)-OCH_3 (**5**). Further information was sought with a less reactive substrate, **4**.

(ii) Diphenyl Phosphate (4) and La^{3+}. The room temperature ^{31}P NMR spectra of **4** in methanol containing 0.01 M *N*-methylimidazole, $^{s}_{s}$pH 6.7, and in methanol containing 0.04 M *N*-ethylmorpholine, $^{s}_{s}$pH 9.5, show single peaks at δ −9.175 and δ −9.336 ppm, respectively. Addition of 2 equiv of $La^{3+}(^-OTf)_3$ to the $^{s}_{s}$pH 9.5 solution shifts the peak to δ −13.432 ppm with slight broadening; however, addition of 2 equiv of La^{3+} to the solution at $^{s}_{s}$pH 6.7 and another at $^{s}_{s}$pH 11.5 (triethylamine [buffer] = 0.04 M) produced no visible ^{31}P signals. Taken together, these data suggest a dynamic process occurring at the fast exchange limit at $^{s}_{s}$pH 9.5 and near-coalescence at lower and higher $^{s}_{s}$pH values at 25 °C.

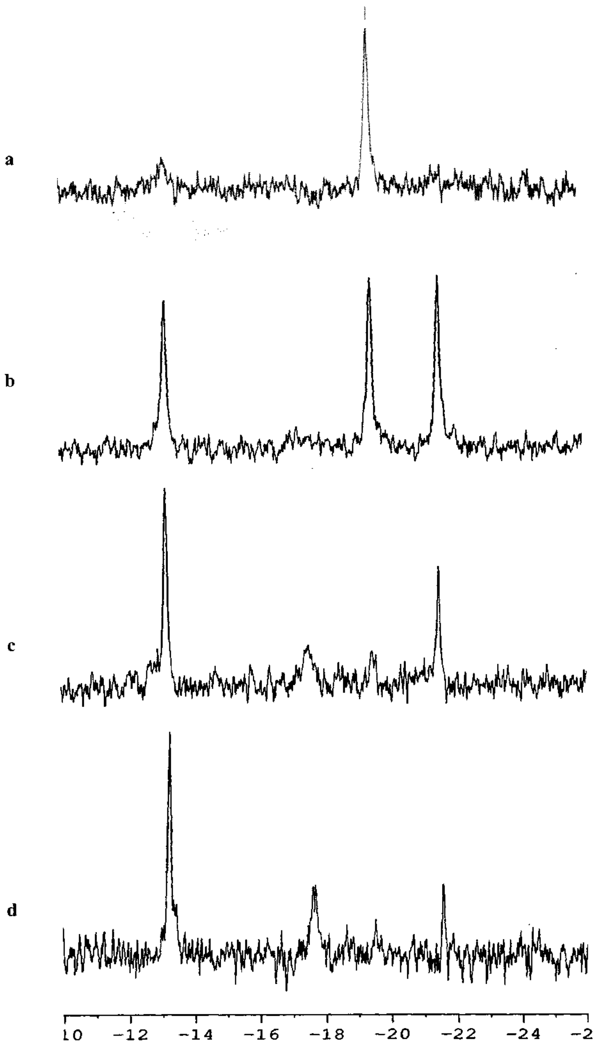

Figure 2. ^{31}P NMR spectra of 0.005 M **4** in methanol at −80 °C containing different $[La^{3+}]/[\mathbf{4}]$ ratios, referenced to 70% phosphoric acid in water. Top to bottom spectra at $[La^{3+}]/[\mathbf{4}]$ ratios of 0.5, 1, 2, and 3. Peak at δ −17.63 at the two highest $[La^{3+}]/[\mathbf{4}]$ ratios is of unknown origin, possibily higher under aggregates.

At −80 °C, the ^{31}P NMR spectrum of the *N*-methylimidazole $^{s}_{s}$pH 6.7 solution containing a $[La^{3+}]/[\mathbf{4}]$ ratio of 2 exhibits signals at δ −13.140, −19.359, and −21.490 ppm in an approximate 5/1/3 ratio, suggesting the presence of three distinct **3**:La^{3+} complexes of different stoichiometry in slow exchange. To cast light on the stoichiometry of these complexes, we obtained the −80 °C ^{31}P NMR spectra of 0.005 M **4** in unbuffered methanol ($^{s}_{s}$pK~6) containing $[La^{3+}]/[\mathbf{4}]$ ratios of 0.5, 1, 2, and 3 which are shown in Figure 2. At a ratio of 0.5, a dominant signal is present in the ^{31}P spectrum (Figure 2, top) centered at δ −19.450 ppm attributable to a 1:2 La^{3+}:**4** complex with a second small peak observed at δ −13.14 due to a 2:1 La^{3+}:**4** complex, the ratio of these being roughly 7/1. At a $[La^{3+}]/[\mathbf{4}]$ ratio of 1.0, three peaks of approximate 1/1/1 intensity are observed at δ −13.129, −19.439, and −21.439 ppm attributed, respectively, to the 2:1 La^{3+}:**4** complex, the 1:2 La^{3+}:**4** complex, and a 1:1(or possibly 2:2) La^{3+}:**4** complex. Increasing the $[La^{3+}]/[\mathbf{3}]$ ratio to 2 alters the relative intensity of the peaks at δ −13.132 (2:1 complex), −19.44 (1:2 complex), and −21.48 ppm (1:1 or 2:2 complex) to a 13/2/8 ratio. Notably, this spectrum is nearly identical to that obtained at −80 °C under

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(16) (a) Schepers, K.; Bremer, B.; Krebs, B.; Henkel, G.; Althous, E.; Mosel, B.; Müller-Warmuth, W. *Angew Chem Int Ed. Engl.* **1990**, *29*, 531. (b) Uhlenbrock, S.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1647 and references therein. (c) Suzuki, M.; Kanatomi, H.; Murase, I. *Chem. Lett.* **1983**, 185. (d) Tomoaki, T.; Watton, S. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 9401.

(17) (a) Williams, N. H.; Chin, J. *J. Chem. Soc., Chem. Commun.* **1996**, 131. (b) Wahnon, D. Lebuis, A.−M.; Chin, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2412.

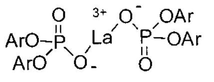
(18) Wall, M.; Hynes, R. C.; Chin, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *33*, 1633.

(19) Young, M. J.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 10577.

(20) Oh, S. J.; Choi, Y.-S.; Hwangbo, S.; Bae, S. C.; Ku, J. K.; Park, J. W. *J. Chem. Soc., Chem. Commun.* **1998**, 2189.

buffered conditions (*N*-methylimidazole, ${}^{s}_{s}$pH 6.7) containing a [La^{3+}]/[**4**] ratio of 2. At the highest [La^{3+}]/[**3**] ratio of 3, the 1:2 complex is not detected and only peaks attributable to the 2:1 and 1:1(2:2) complexes are observed, the ratio being 11/4.[21]

The above NMR experiments indicate that **4** has a high propensity to associate with La^{3+} in solution, even at millimolar concentrations, and that there are several complexes in dynamic equilibrium, the relative concentrations of which are controlled by the [La^{3+}]/[**4**] ratio. From the NMR experiments it is not possible to say with certainty what the structures of these are or how many associated methoxides are present. However, combination of the NMR and titration data, determined under approximately similar concentrations of La^{3+} and **4**, support structure **9** for the 2:1 complex in the ${}^{s}_{s}$pH 6.7 solution. Possible structures **11** and **12** are suggested for the 1:2 and 2:2 complexes, the exact number of associated solvent and methoxide molecules being omitted for lack of data.



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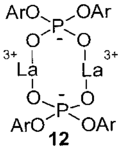

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3. UV−vis Kinetics for Methanolysis of 3 and 5 in the Presence and Absence of La^{3+}. Methanolysis of bis(*p*-nitrophenyl) phosphate (**3**) is strongly catalyzed by La^{3+} with the release of 2 equiv of *p*-nitrophenol. Since this is an A → B → C process as in eq 4 with different rate constants for the first and second step, we resorted to initial rate experiments to determine the first rate constant for methanolysis. Experiments at 25 °C with 2×10^{-5} M **3** at ${}^{s}_{s}$pH 7.7 in *N*-methylimidazole buffer containing 10^{-3} M added $La^{3+}(^{-}OTf)_3$ gives an observed pseudo-first-order rate constant of 2×10^{-4} s^{-1}. A second experiment with 4×10^{-5} M 3 at ${}^{s}_{s}$pH 8.9 in *N*-ethylmorpholine buffer containing 5×10^{-4} M $La^{3+}(^{-}OTf)_3$ gives an observed rate constant of 4.8×10^{-4} s^{-1}. Rate measurements at [CH_3O^-] = 0.1 M give a second-order rate constant for its reaction with **3** $k_{CH_3O^-}{}^{\mathbf{3}} = 2.5 \times 10^{-6}$ M^{-1}s^{-1} which is close to the reported rate constant determined for attack of hydroxide in water, $k_{HO^-}{}^{\mathbf{3}} = 5.8 \times 10^{-6}$ M^{-1} s^{-1}.[22] The acceleration of methanolysis of **3** afforded by La^{3+} can be judged by comparison with the solvent reaction at the appropriate ${}^{s}_{s}$pH assuming that the latter is entirely attributable to methoxide attack on **3**,[23] the so-computed accelerations being 9.4×10^{10}-fold at ${}^{s}_{s}$pH 7.7, and 1.4×10^{10}-fold at ${}^{s}_{s}$pH 8.9.[24] These impressive accelerations merit further study, but since the simplified process given in eq 4 is complicated by the sequential methanolyses we turned to detailed study of the La^{3+}-promoted methanolysis of **5**.

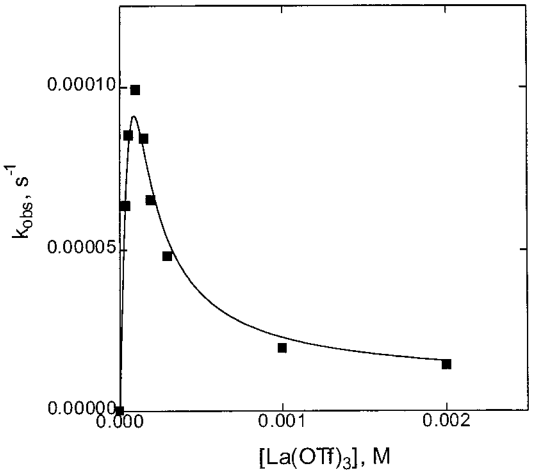

Figure 3. Plot of pseudo-first-order rate constant for the methanolysis of **5** (2×10^{-5} M) vs [La(OTf)$_3$] at 25 °C; ${}^{s}_{s}$pH = 9.5 (0.04 M *N*-ethylmorpholine buffer).

$$\underset{\mathbf{3}}{(ArO)_2P(=O)O^-} \xrightarrow[\substack{CH_3OH \\ k_1}]{La^{3+}} \underset{\mathbf{5}}{(ArO)(CH_3O)P(=O)O^-} \xrightarrow[\substack{CH_3OH \\ k_2}]{La^{3+}} (CH_3O)_2P(=O)O^- \quad (4)$$

Initial rate experiments at high [CH_3O^-] give a second-order rate constant for methoxide attack on **5** in methanol ($k_{CH_3O^-}{}^{\mathbf{5}}$) of $(7.9 \pm 0.6) \times 10^{-7}$ M^{-1} s^{-1} at 25 °C, a value which is close to that for the hydroxide reaction in water, 4.7×10^{-7} M^{-1} s^{-1}.[25] We have also determined the pseudo-first-order rate constants for methanolysis of **5** with varying [La^{3+}] (1×10^{-5} M to 3×10^{-3} M) at ${}^{s}_{s}$pH values ranging from 7.5 to 12.7 (Tables 1S to 10S, Supporting Information). These are ${}^{s}_{s}$pH values close to the first ${}^{s}_{s}$pK_a (7.86) and bracketing the second ${}^{s}_{s}$pK_a (10.44) of the metal bound methanols so that the dominant forms of the La^{3+} in solution are associated with first a single methoxide, and then with 2.5 methoxides per metal, probably as dimers as discussed above. It is also important to point out that the same number of associated methoxides is obtained for the diphenyl phosphate-bound La^{3+} dimers according to the titration data and that such complexes are probably kinetically important with **5** as well.

Plots of the k_{obs} vs [La^{3+}] data for methanolysis of **5** are highly unusual. For example, in Figure 3 one can see the catalytic effect of [La^{3+}]$_t$ changes suddenly to an inhibitory effect with further increases in concentration suggestive of changes in speciation of La^{3+}. Typically all such plots show three domains of interest which are ${}^{s}_{s}$pH dependent as illustrated in Figure 3 (${}^{s}_{s}$pH 9.5) and Figure 4 (${}^{s}_{s}$pH 11.1). In general there is a linear acceleration of k_{obs} from 1×10^{-5} M < [La^{3+}] <1×10^{-4} M, which gives rise to a nonlinear second-order dependence on further increases in [La^{3+}]. At low ${}^{s}_{s}$pH (as shown in Figure 3) there is a dramatic decrease in observed rate constant with increasing [La^{3+}], while at higher ${}^{s}_{s}$pH (as shown in Figure 4) the rate constant increases. In all cases, the plots plateau at high [La^{3+}], indicating saturation phenomena

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[21] In the ^{31}P NMR spectra of diphenyl phosphate at La^{3+}/**4** ratios of 2 and 3, a minor peak at −17.63 ppm is observed. We have monitored the spectrum for several hours to determine that it does not arise from products of methanolysis. Its origin, while uncertain at present, is probably due to higher order La^{3+}/**4** aggregates.

[22] Ketelaar, J. A. A.; Gersmann, H. R. *Rec. Trav. Chim. Pays-Bas* **1958**, *77*, 973.

[23] Assuming that the solvent reaction in the ${}^{s}_{s}$pH region from 7.5 to 12.5 is attributed exclusively to methoxide, the solvent reaction for **3** or **5** can be computed as $k_{solvent} = k_{CH_3O^-}{}^{\mathbf{3}\text{ or }\mathbf{5}} \times [CH_3O^-]$, the autoprotolysis constant of methanol being $10^{-16.77}$ at 25 °C.[7]

[24] We have not determined whether the methanolysis reaction of **3** in the neutral ${}^{s}_{s}$pH region contains a spontaneous term, but this is possible based on the analogous hydrolysis reaction. Hurst, Takasaki, and Chin[15] have reported a spontaneous hydrolysis pseudo-first-order rate constant of 1.1×10^{-11} s^{-1} for the water reaction with **3**. Should a similar spontaneous methanolysis term be present with **3**, the computed accelerations afforded by La^{3+} at ${}^{s}_{s}$pH 7.7 and 8.9 would be 1.8×10^{7}-fold and 4.3×10^{7}-fold, respectively.

[25] Chin, J. Private communication. Values of 4×10^{-7} M^{-1} s^{-1} and 1.5×10^{-6} M^{-1} s^{-1}, respectively, can be estimated from the Brönsted plot given in Figure 1 of ref 4b, or the data given in ref 28.

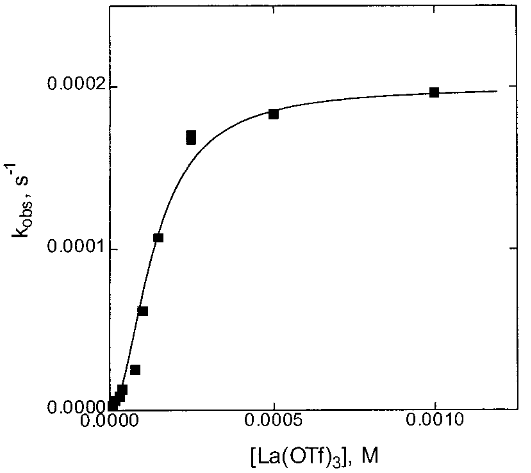
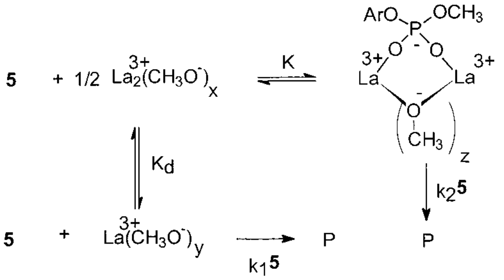


Figure 4. Plot of pseudo-first-order rate constant for the methanolysis of **5** (2×10^{-5} M) vs [La(OTf)$_3$] at 25 °C; ^s_spH = 11.1 (0.02 M triethylamine buffer).

Scheme 2



where **5** is completely bound to a La^{3+} dimer as a kinetically competent species.

Given in Scheme 2 is a simplified mechanism that accounts for the kinetic behavior and has two independent pathways having first- and second-order dependencies on [La^{3+}]. In the scheme solvating methanol is omitted for clarity, K_d refers to dissociation of the $La_2^{3+}(CH_3O^-)_x$ dimer into a $La^{3+}(CH_3O^-)_y$ monomer where the subscripts x, y, and z refer to the number of associated methoxides (1−5 depending on the pH and structure), $k_1^{\mathbf{5}}$ and $k_2^{\mathbf{5}}$ are conditional, and probably composite, rate constants which incorporate [CH_3O^-] for reaction of the monomeric and dimeric La^{3+} species with **5**, and P is the $(CH_3O)_2PO_2^-$ methanolysis product. Derived from that kinetic scheme and the equations for conservation of mass is the expression given in eq 5 relating the k_{obs} to the total [La^{3+}], (for derivation, see Supporting Information). NLLSQ fitting of the k_{obs} vs $[La^{3+}]_t$ data at ^s_spH 9.5 and 11.1 to eq 5 gives the lines shown in Figures 3 and 4 which fit the experimental points acceptably given the admittedly simplified nature of the scheme.

$$k_{obs} = (2k_1^{5}K((1 + 8[La^{3+}]_t/K_d)^{0.5} - 1) + k_2^{5}(4[La^{3+}]_t/K_d - (1 + 8[La^{3+}]_t/K_d)^{0.5} + 1))/(8K/K_d + 4[La^{3}]_t/K_d - (1 + 8[La^{3+}]_t/K_d)^{0.5} + 1) \quad (5)$$

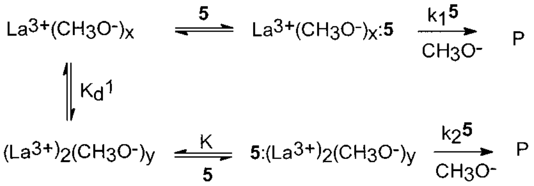
Unfortunately, the NLLSQ fits of the complete k_{obs} vs [La^{3+}] data at each ^s_spH do not provide reliable values for $k_1^{\mathbf{5}}$, $k_2^{\mathbf{5}}$, K, and K_d because the various rate and equilibrium values are heavily correlated. Since the second-order rate constant for La^{3+} monomer mediated methanolysis ($k_1^{\mathbf{5}}$) and the pseudo-first-order rate constant for reaction of the **5**:$(La^{3+})_2(CH_3O^-)_z$ dimer ($k_2^{\mathbf{5}}$) are of most interest, these were evaluated separately at each ^s_spH from analysis of the linear sections of the k_{obs} vs [La^{3+}] data at low and high metal concentrations.

Table 1. ^s_spH Dependence of the Second-Order Rate Constants for the Reaction of **5** with Monomeric La^{3+} ($k_1^{\mathbf{5}}$) and Pseudo-First-Order Rate Constants for Methanolysis of **5**:$(La^{3+})_2(CH_3O^-)_z$ ($k_2^{\mathbf{5}}$); T = 25.0 °C

^s_spH	$k_1^{\mathbf{5}}$ ($M^{-1}s^{-1}$)	($k_1^{\mathbf{5}}/k_{CH_3O^-}{}^{\mathbf{5}}$)[a]	^s_spH	$10^4k_2^{\mathbf{5}}$ (s^{-1})[b]	($k_2^{\mathbf{5}}/k_{solvent}{}^{\mathbf{5}}$)[c]
7.60	0.09 ± 0.01	114 000	8.5	0.075	1.7×10^9
8.00	0.14 ± 0.03	177 000	8.9	0.125	1.2×10^9
8.50	0.26 ± 0.01	329 000	9.5	0.14	3.3×10^8
8.90	0.37 ± 0.01	468 000	10.2	0.71	3.3×10^8
9.45	0.56 ± 0.03	709 000	11.2	1.9	8.9×10^7
10.14	0.74 ± 0.03	937 000	11.63	2.7	4.7×10^7
11.10	0.33 ± 0.02	418 000	12.14	7.5	4.0×10^7
11.63	0.39 ± 0.02	493 000	12.7	9.0	1.4×10^7

[a] $k_{CH_3O^-}{}^{\mathbf{5}} = (7.9 \pm 0.6) \times 10^{-7}$ M^{-1} s^{-1}. [b] Error does not exceed ±10% of quoted value. [c] Assuming the solvent reaction at the indicated ^s_spH is entirely attributable to methoxide attack on **5**.

Scheme 3[a]



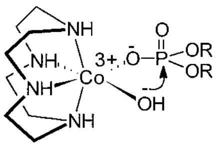
[a] x, y assume values from 1 to 5 depending on ^s_spH.

Given in Table 1 are the so-determined $k_1^{\mathbf{5}}$ and $k_2^{\mathbf{5}}$ values as a function of ^s_spH. There are two general features of note, namely (a) the impressive rate accelerations afforded to methanolysis by the monomeric and the dimeric forms of La^{3+}, and (b) a somewhat peculiar ^s_spH dependence of both rate constants. The effectiveness of catalysis by La^{3+} monomer can be judged by comparing the second-order $k_1^{\mathbf{5}}$ rate constants at each ^s_spH with that for attack of methoxide on **5** ($k_{CH_3O^-}{}^{\mathbf{5}} = 7.9 \times 10^{-7}$ M^{-1} s^{-1}).[23] The $k_1^{\mathbf{5}}/k_{CH_3O^-}{}^{\mathbf{5}}$ from 100 000 to 940 000 between ^s_spH 7.6 and 11.6, apparently maximizing at ~ ^s_spH 10.1. Comparison of the $k_2^{\mathbf{5}}$ and solvent reaction rate at each ^s_spH indicates that in its bound form of **5**:$(La^{3+})_2(CH_3O^-)_z$, methyl p-nitrophenyl phosphate is subject to even more impressive rate accelerations of 1.7×10^9 to 1.4×10^7 fold between ^s_spH 8.5 and 12.7.

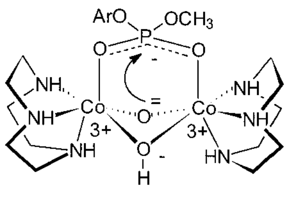
Plots of log $k_1^{\mathbf{5}}$ and log $k_2^{\mathbf{5}}$ vs ^s_spH give approximately straight lines, indicating that the rate constants incorporate terms dependent on [CH_3O^-]. Neither plot displays an integer dependence on ^s_spH, the slopes of these being approximately 0.35 and 0.5, respectively, and in the case of log $k_1^{\mathbf{5}}$ vs ^s_spH there is a serious drop in activity at high ^s_spH. The less than first-order dependence on [CH_3O^-] of these plots is at first hard to understand until one realizes that there are drastic changes in speciation of the La^{3+} that occur as a function of ^s_spH as determined by potentiometric titration. Shown in Scheme 3 is slightly modified form of Scheme 2 involving a series of La^{3+} monomers and dimers differing in the number of associated methoxides (x or y which can vary from one to five depending on the ^s_spH) along with the equilibria that interconnect them and the association and rate constants for their reaction with **5**. No transient complexes of **5** with La^{3+} monomers have been detected kinetically since there is no observable saturation of k_{obs} at low [La^{3+}]. Being far from saturation, the $k_1^{\mathbf{5}}$ rate constants can then be redefined to incorporate the equilibrium constants for association of the various $La^{3+}(CH_3O^-)_x$ forms with **5** making the $k_1^{\mathbf{5}}$ terms in Scheme 3 consistent with the kinetics derived from Scheme 2. Each dimeric form can also associate with **5** to form complexes (observed kinetically), which then react with rate constants $k_2^{\mathbf{5}}$.

The kinetic data indicate that the reaction rates respond to both changes in [La^{3+}] and [CH_3O^-], but in a complex way suggestive of combinations of competing processes. Scheme 3 contains several species of inferred La^{3+} and CH_3O^- stoichiometry supported by the combination of the titration, ^{31}P NMR, and kinetic data. Disappointingly, exact analysis of the kinetic importance of each of these is impossible due to the large number of equilibrium and rate constants that likely contribute to the overall reaction. However, qualitatively one can rationalize the less than first-order dependence on [CH_3O^-] for the monomeric and dimeric La^{3+} reactions by invoking counterbalancing effects wherein the $La^{3+}(CH_3O^-)_x + \mathbf{5} \rightleftarrows La^{3+}(CH_3O^-)_x{:}\mathbf{5}$ and $(La^{3+})_2(CH_3O^-)_y + \mathbf{5} \rightleftarrows \mathbf{5}{:}(La^{3+})_2(CH_3O^-)_y$ equilibria are driven to the left with increasing numbers of associated methoxides and that attack on these complexes, whether by external or metal-associated methoxide, is slower due to the reduced net positive charge on the complex.

As is the case with most metal ion mediated acyl and phosphoryl transfer reactions, it is difficult to ascertain whether base-promoted methanolysis of the monomeric or dimeric $La^{3+}{:}\mathbf{5}$ complexes involves attack of external CH_3O^- or a La^{3+}-coordinated CH_3O^-. Williams, Takasaki, Wall, and Chin, in an authoritative analysis of the possible roles of metal ion catalysis,[4b] point out that the metal-coordinated hydroxide in **13**[26] can be a very effective nucleophile in promoting hydrolysis of a bound phosphate containing good or poor leaving groups. They also point out[4b] that $^-$OH bridged between two metal centers as in **14**[17b,27] is a much poorer nucleophile than when associated with only one metal center, and intramolecular attack involving a bridged hydroxide can only occur when it is further deprotonated as a bridging oxide.



13 R=Ar, CH$_3$



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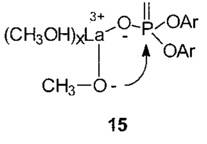
Extending these findings to the case of the La^{3+}-promoted methanolysis of **5**, it is possible that the monomeric forms could act by delivery of coordinated methoxide as in **15**. In the case of the La^{3+}dimers the doubly bridged methoxides cannot be



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considered effective nucleophiles which may account for the limited reactivity of $(La^{3+})_2(CH_3O^-)_2{:}\mathbf{5}$ in the neutral $_{s}^{s}$pH regions (structure **9** above). For the latter, methanolysis can only occur by attack of external methoxide or if **9** undergoes equilibrium opening of a methoxy bridge to expose a singly coordinated and now nucleophilic methoxide. Forms such as **10** formed at higher $_{s}^{s}$pH and having additional methoxides singly coordinated to either La^{3+} could be expected to be reactive.

4. Combined ^{1}H NMR and UV Kinetics with Bis(*p*-nitrophenyl) Phosphate (3) and Diphenyl Phosphate (4). Due to the fact that La^{3+} is soluble in MeOH at concentrations at least as high as 5×10^{-2} M throughout the $_{s}^{s}$pH domain where ionization of $La^{3+}(CH_3OH)_x$ occurs ($_{s}^{s}$pH 7−12.5), it is as convenient to monitor the methanolysis reactions of **3** and **4** by ^{1}H NMR as by UV/visible kinetics. This allows expansion of the concentration range of both substrate and metal ion and comparison of the rate constants for metal ion catalysis determined in both ways. In nonbuffered 80/20 CD_3OD/CH_3OH at 25 °C containing 5.3×10^{-2} M $La(OTf)_3$, (1 equiv), 1.7×10^{-2} M **3** (0.32 equiv), and 8.9×10^{-2} M $NaOCH_3$ (1.36 equiv + 0.32 equiv), $_{s}^{s}$pH 9.8, the ^{1}H NMR spectrum of the aromatic protons was monitored as a function of time. These are conditions where the titration and UV kinetic data indicate that the phosphate is primarily bound as $\mathbf{3}{:}(La^{3+})_2(CH_3O^-)_2$, possibly containing additional methoxides. After 20 min. 0.95 equiv of *p*-nitrophenol (out of the two possible equivalents) was observed, and after 140 min, 1.9 equiv of *p*-nitrophenol was observed. Although the methanolysis process contains two steps as in eq 4, the approximate half-time of 21 min can be used to derive a lower estimate of 5.4×10^{-4} s^{-1} for the pseudo-first-order rate constant for the overall appearance of *p*-nitrophenol. That value is close to that determined in the initial rate UV experiments under slightly different conditions (4×10^{-5} M **3**, $_{s}^{s}$pH 8.9 *N*-ethylmorpholine buffer, 5×10^{-4} M $La^{3+}(^-OTf)_3$, $k_{obs} = 4.8 \times 10^{-4}$ s^{-1}). This represents an acceleration in methanolysis of **3** of 2×10^9-fold relative to the solvent reaction, assuming that the latter is entirely attributable to methoxide at that $_{s}^{s}$pH.[23]

As expected on the basis of leaving group ability, diphenyl phosphate (**4**) is less susceptible to nucleophilic attack by methoxide than is **3**. Due to the extreme slowness of this reaction, we have been unable to experimentally determine a $k_{CH_3O^-}^{\mathbf{4}}$ from initial rate experiments at high [CH_3O^-]. However, based on literature data for the reaction of HO^- with **4**[28] one can infer that the methoxide reaction would be ∼10^4 slower than the reaction with **3**, leading to an estimated rate constant of $k_{CH_3O^-}^{\mathbf{4}} \sim 2 \times 10^{-10}$ M^{-1} s^{-1}. In nonbuffered 80/20 CD_3OD/CH_3OH at 25 °C containing 4.0×10^{-2} M $La(OTf)_3$, (1 equiv), 2×10^{-2} M 4 (0.5 equiv), and 0.1 M $NaOCH_3$ (2.0 equiv + 0.5 equiv), $_{s}^{s}$pH 11.6 (controlled by the $La^{3+}(^-OCH_3)_x$), the ^{1}H NMR spectrum of the aromatic protons was monitored as a function of time. This $_{s}^{s}$pH is slightly above the midpoint of the second La^{3+} ionization where the titration data indicate that **4** is completely bound a by La^{3+}dimer as a mixture of $\mathbf{4}{:}(La^{3+})_2(CH_3O^-)_2$ and $\mathbf{4}{:}(La^{3+})_2(CH_3O^-)_y$, with $y = 3$, 4, and

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(28) (a) Kirby, A. J.; Younas, M. *J. Chem. Soc. B* **1970**, 501 have shown that diphenyl phosphate exhibits no detectable hydrolysis in the neutral pH region and have provided evidence that the hydrolysis of diphosphates with monosubstituted aryl leaving groups throughout the entire pH domain is controlled by the acid and base terms. (b) Schneider, Rammo, and Hettich[4l] used the correlations described by Kirby and Younas[28a] and an enthalpy of activation for hydrolysis of 30 kcal/mol, extrapolated a rate constant for spontaneous diphenyl phosphate hydrolysis at pH 7 of $k_o = 3.6 \times 10^{-12}$ s^{-1} at 70 °C. (c) Gomez-Tagle and Yatsimirsky[4m] quote a value of 5×10^{-15} s^{-1} for the hydrolysis of **4** at pH 9, $T = 25$ °C. Given that this is controlled entirely by the [HO^-] reaction, the computed second-order rate constant for hydroxide reacting with **4** would be 5×10^{-10} M^{-1} s^{-1} at 25 °C. They also quote a value of 5.8×10^{-11} s^{-1} for the hydroxide reaction with **3** at pH 9.

Table 2. Values of $k_2^{\mathbf{4}}$ Determined from Analysis of the Plateau Region of Plots of Pseudo-First-Order Rate Constants[a] for Methanolysis of 1×10^{-4} M **4** vs $[La^{3+}]_t$, in Buffered Media, $T = 25$ °C[a]

${}^{s}_{s}pH$[b]	$10^5\ k_2^{\mathbf{4}}\ (s^{-1})$	$(k_2^{\mathbf{4}}/k_{solvent})$[c]
10.22	0.33 ± 0.04	5.8×10^{10}
11.0	0.55 ± 0.07	1.6×10^{10}
11.64	1.6 ± 0.3	1.1×10^{10}
12.08	1.85	4.5×10^{9}

[a] Determined from analysis of the abs. vs time plots for appearance of phenol at 279 nm, $\epsilon_{max} = 1390\ M^{-1}\ cm^{-1}$. Original data given in Tables 11S−15S, Supporting Information. [b] 0.02 M buffers of NEt_3 (${}^{s}_{s}pH$ 10.22) and i-Pr_2NH (${}^{s}_{s}pH$ 11.0−12.08). [c] Assuming $k_{solvent}$ at the indicated ${}^{s}_{s}pH$ is entirely attributable to methoxide attack on **4**, $k_{CH_3O^-}{}^{\mathbf{4}} = 2 \times 10^{-10}\ M^{-1}\ s^{-1}$.

5. The observed pseudo-first-order rate constant for methanolysis of $(6.6 \pm 0.1) \times 10^{-5}\ s^{-1}$ represents an acceleration of 5×10^{10}-fold relative to the CH_3O^- reaction at that ${}^{s}_{s}pH$!

Additional UV kinetic experiments were conducted for the methanolysis of **4** promoted by La^{3+} under buffered conditions (0.02 M NEt_3 or i-Pr_2NH), ${}^{s}_{s}pH$ 10.22−12.08, 10^{-4} M **4**, $T = 25$ °C). A plot of k_{obs} vs $[La^{3+}]_t$ at ${}^{s}_{s}pH$ 12.08 (not shown) exhibits the same general features as the similar plot for methanolysis of **5** shown in Figure 4, suggesting that the same features of the mechanism apply. The plateau regions of the plots at $[La^{3+}]_t$ sufficiently high to fully complex **4** (4×10^{-4} M to 2×10^{-3} M) were evaluated to give the pseudo-first-order $k_2^{\mathbf{4}}$ rate constants for methanolysis of **4**:$(La^{3+})_2(CH_3O^-)_x$ given in Table 2 (original data in Tables 11S−14S, Supporting Information). Aside from the very high rates of catalyzed methanolysis of **4** relative to the solvent reaction, there are two points of note. First, as is the case with **5**, the $k_2^{\mathbf{4}}$ rate constant for decomposition of **4**:$(La^{3+})_2(CH_3O^-)_x$ has a less than first-order dependence on $[CH_3O^-]$. Second, k_{obs} obtained at ${}^{s}_{s}pH$ 11.64 under UV conditions is ∼4-fold lower than that determined under NMR conditions. To investigate the effects of concentration changes of the reactants, three sets of UV kinetic experiments were conducted under nonbuffered conditions at ${}^{s}_{s}pH$ 11.6 in pure methanol commencing with the NMR concentrations of 4.0×10^{-2} M $La(OTf)_3$, (1 equiv), 2×10^{-2} M **4** (0.5 equiv), and 0.1 M $NaOCH_3$ (2.0 equiv + 0.5 equiv) and then diluting this 4- and 8-fold (original data given in Table 15S, Supporting Information). The k_{obs} vs concentration plot (not shown) shows a linear dependence, the slope being $(6.0 \pm 0.1) \times 10^{-4}\ M^{-1}\ s^{-1}$, and the intercept $1.0 \times 10^{-5}\ s^{-1}$. The latter value is gratifyingly close to the value of $(1.6 \pm 0.3) \times 10^{-5}\ s^{-1}$ given for that constant in Table 2 at ${}^{s}_{s}pH$ 11.64. The observed acceleration of the methanolysis at higher concentrations of complex requires that there is an additional pathway for methanolysis which involves catalysis by a second molecule of the reactive complex. At these high concentrations one may envision a process wherein the second molecule of complex acts as a nucleophile to deliver methoxide to the phosphate diester coordinated to the first.

Conclusions

The finding that La^{3+} is soluble in methanol throughout the entire accessible ${}^{s}_{s}pH$ range confers a special advantage to studying its catalysis of the methanolysis of acyl and phosphoryl derivatives including phosphate diesters such as **3**−**5**. Our present and previous[6] studies have shown that in methanol, at concentrations as low as $(1-5) \times 10^{-4}$ M, La^{3+} assembles into active dimers with 2−5 associated methoxides, depending on the ${}^{s}_{s}pH$, without the need for stabilizing ligands which have proven to be essential for comparable studies in water. A combination of NMR, titration, and rate data allows us to study the interaction of these phosphates with La^{3+} in solution and undertake detailed kinetic studies of the methanolysis process as a function of both ${}^{s}_{s}pH$ and $[La^{3+}]$. It is clear from this study that both La^{3+} monomers and dimers are capable of accelerating the methanolysis and that even at relatively low concentrations of metal, phosphate diesters are completely bound as kinetically important complexes with dimeric La^{3+}. It is also clear that the overall reactivity increases with ${}^{s}_{s}pH$, indicating a kinetic dependence on [methoxide]. What is not as clear is the less-than-first order dependence on [methoxide] for both the monomer- and dimer promoted reactions, but the available data indicates this is probably associated with the changes in reactivity of the metal:phosphate complex as the number of La^{3+}-coordinated methoxides increases. More work will be required to address these mechanistic uncertainties.

The catalysis of methanolysis of **3**−**5** is among the highest cited for La^{3+}-promoted phosphoryl transfer, with accelerations as high as 50 billion-fold being observed. These impressive rate accelerations invite study of the methanolysis and alcoholysis of more biologically relevant phosphate diesters promoted by La^{3+} and other lanthanide ions, and our findings with these will be reported in due course.

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Supporting Information Available: Tables of kinetic data for k_{obs} vs $[La^{3+}]_t$ for the methanolysis of **5** and **4**, and derivation of eq 5 based on process shown in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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