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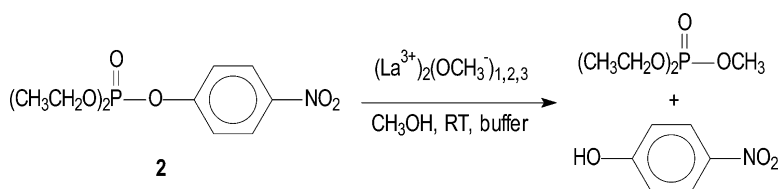# Billion-fold Acceleration of the Methanolysis of Paraoxon Promoted by La(OTf) in Methanol

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Billion-fold Acceleration of the Methanolysis of Paraoxon Promoted by La(OTf)$_3$ in Methanol

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Abstract: The methanolysis of the insecticide paraoxon (**2**) was investigated in methanol solution containing varying [La(OTf)$_3$] (OTf = $^-$OS(O)$_2$CF$_3$) as a function of ^s_spH at 25 °C. Plots of the pseudo-first-order rate constants (k_{obs}) for methanolysis as a function of [La(OTf)$_3$]$_{total}$ were obtained under buffered conditions from ^s_spH 5.15 to 10.97, and the slopes of the linear parts of these were used to determine the second-order rate constants (k_2^{obs}) for the La^{3+}-catalyzed methanolysis of **2**. Detailed analysis of the potentiometric titration data of La(OTf)$_3$ in methanol through fits to a multicomponent equilibrium mixture of dimers of general stoichiometry La$^{3+}_2$($^-$OCH$_3$)$_n$, where n assumes values of 1−5, gives the equilibrium distribution of each as a function of ^s_spH. These data, when fit to a second expression describing k_2^{obs} in terms of a linear combination of individual rate constants $k_2^{2:1}$, $k_2^{2:2}$.....$k_2^{2:n}$ for the dimers, allow one to describe the overall catalytic profile in terms of the individual contributions. The most catalytically important species are the three dimers La$^{3+}_2$($^-$OCH$_3$)$_1$, La$^{3+}_2$($^-$OCH$_3$)$_2$, and La$^{3+}_2$($^-$OCH$_3$)$_3$. The catalysis of the methanolysis of **2** is spectacular: a 2 × 10^{-3} M solution of [La^{3+}]$_{total}$, at neutral ^s_spH, affords a 10^9-fold acceleration relative to the base reaction ($t_{1/2} \approx 20$ s at ^s_spH 8.2) with excellent turnover. A mechanism of the catalyzed reaction involving the La$^{3+}_2$($^-$OCH$_3$)$_2$ species is proposed.

Introduction

Activated organophosphate, phosphinate, and phosphonate esters of the general form **1** are potent acetylcholinesterase inhibitors.[1] As such, these have important uses as animal and crop protectants[2] and, more regrettably, as chemical warfare agents.[3] This family includes the insecticides parathion (RO═Z═OEt; X═S; Y═OC$_6$H$_4$NO$_2$) and paraoxon (RO═Z═OEt; X═O; Y═OC$_6$H$_4$NO$_2$), as well as the alkylphosphonofluoridate nerve G-agents, for example, Soman (RO═(CH$_3$)$_3$CCH(CH$_3$)O; Z═CH$_3$; X═O; Y═F) and Sarin (RO═(CH$_3$)$_2$CHO; Z═CH$_3$; X═O; Y═F) and finally the V-agents such as VX (Z═Et; X═O; Y═SCH$_2$CH$_2$N(CH(CH$_3$)$_2$)$_2$). Due to their toxicity and the attention drawn to them by the 1992 Chemical Weapons Convention Treaty,[4] requiring total destruction of chemical weapons stockpiles by the signatories, considerable effort has been directed toward methods of facilitating the controlled decomposition of organophosphorus materials, particularly through hydrolysis and oxidation.[3,5] Although some very ef-

fective methods for destruction of organophosphorus materials are available, none is applicable to all situations or classes of compounds thus spurring research into alternative methods for their destruction.
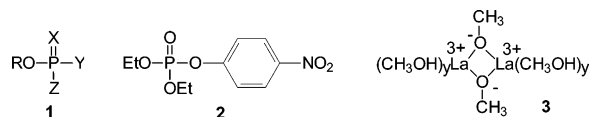
In this report, we focus on a new method for controlled decomposition of the pesticide paraoxon (**2**, often used as a simulant for the G-agents), namely its catalytic methanolysis promoted by La^{3+} in a methanol medium. The La^{3+}(OCH$_3$$^-$) system is one that we have previously reported to promote the methanolysis of esters[6] and activated amides such as acetyl imidazole and its pentamino-Co^{III} derivative.[7] Transition metal ions and lanthanides have been shown to catalyze the hydrolysis of neutral phosphate and/or phosphonate esters,[8] and Pt and Pd metallocycles were recently shown to be efficacious for thiophosphate pesticide hydrolysis;[9] but, as far as we are aware, little attention has been directed to the metal ion promoted alcoholysis of phosphate triesters.[10] Alcoholysis of organophosphates such as paraoxon should lead to relatively nontoxic

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products,[11] and the greater hydrophobicity of the alcoholic medium may also be advantageous to improve decontamination methods because of the enhanced solubility of the organophosphorus substrates.[3a] In certain cases, alcoholysis may proceed with a different selectivity than hydrolysis as is known to be the case for the uncatalyzed methanolysis of the V-agents, where the reaction with alkoxide proceeds largely to displace the SR^- group leading to phosphonate oxyesters.[3,12,13]

In our previous studies, we proposed that the active form of the catalyst was a dimer, $La^{3+}_2(OCH_3)_2$, having the dimethoxy bridged structure **3**.[6,7] Interestingly, a very recent X-ray structure of a phosphotriesterase (PTA) isolated from the soil dwelling bacterium *Pseudomonas diminuta* shows the active site as having two Zn^{2+} ions. These are bridged by a water or hydroxide and a carboxylated lysine, the metal ions being further ligated to the protein by four histidine imidazoles and an aspartate COO^-.[14] The dinuclear enzyme core, a feature seen in other enzymes that mediate the hydrolysis of phosphate diesters[15] and monoesters,[16] embues on the organism a catalytic efficiency for the hydrolysis of **2**, its preferred substrate, for which the k_{cat}/K_M value is $\sim 10^8$ M^{-1} s^{-1}.[17]

The putative dinuclear La^{3+} species, **3**,[6,7] cannot be claimed to be a "biomimetic" for the active site of the previously mentioned PTA. However, its dinuclearity, which is spontaneously adopted in methanol without the need for sophisticated

complexing ligands, its demonstrated efficacy in promoting transesterifications of unactivated carboxylic esters that do not contain a metal binding site, and the fact that the core of the PTA enzyme can be substituted with other metal ions such as Cd^{2+}, Ni^{2+}, Co^{2+}, and Mn^{2+} without loss of catalytic activity[17] suggested to us that $La^{3+}_2(^-OCH_3)_2$ might be able to promote the methanolysis of neutral phosphate and phosphonate esters. Herein, we report our preliminary findings that this goal is realized in the case of paraoxon (**2**) where as little as 10^{-3} M of **3** can, at 25 °C, promote the methanolysis reaction by $\sim 10^9$-fold relative to the background reaction at a neutral ${}^s_s$pH of ~ 8.5.

Experimental Section

A. Materials. Methanol (99.8% anhydrous), sodium methoxide (0.5 M solution in methanol), $La(CF_3SO_3)_3$, and paraoxon were purchased from Aldrich and used without any further purification. $HClO_4$ (70% aqueous solution) was purchased from BDH.

B. Methods. ^{1}H NMR spectra were determined at 500 MHz and referenced to the CD_2H peak of D_4 methanol appearing at δ 3.31.

The $CH_3OH_2^+$ concentration was determined using a Radiometer Vit 90 Autotitrator equipped with a Radiometer GK2322 combination (glass/calomel) electrode calibrated with Fisher Certified Standard aqueous buffers (pH = 4.00 and 10.00) as described in our recent papers.[6,7,18] Values of ${}^s_s$pH[19] were calculated by adding a correction constant of 2.24 to the experimental meter reading as reported by Bosch et al.[20] The ${}^s_s pK_a$ values of buffers used for the present kinetic studies were obtained from the literature[20] or measured at half neutralization of the bases with 70% $HClO_4$ in MeOH.

C. Kinetics. UV kinetics of methanolysis were monitored at 25 °C by observing the rate of loss of **2** at 268 nm or by the rate of appearance of *p*-nitrophenol at 313 or 328 nm at [**2**] = 2.04×10^{-5} M using an OLIS-modified Cary 17 UV–vis spectrophotometer. The [$La(OTf)_3$] was varied from 8×10^{-6} M to 4.8×10^{-3} M. All reactions were followed to at least three half-times and found to exhibit good pseudo-first-order rate behavior. The pseudo-first-order rate constants (k_{obs}) were evaluated by fitting the absorbance versus time traces to a standard exponential model.

The kinetics were determined under buffered conditions. Buffers were prepared from *N,N*-dimethylaniline (${}^s_s pK_a$ = 5.00), 2,6-lutidine (${}^s_s pK_a$ = 6.70), *N*-methylimidazole (${}^s_s pK_a$ = 7.60), *N*-ethylmorpholine (${}^s_s pK_a$ = 8.60), and triethylamine (${}^s_s pK_a$ = 10.78). Due to the fact that added counterions can ion pair with La^{3+} ions and affect its speciation in solution,[21] ionic strength was controlled through neutralization of the buffer. The total [buffer] varied between 7×10^{-3} M and 3×10^{-2} M, and the buffers were partially neutralized with 70% $HClO_4$ to keep the [ClO_4^-] at a low but constant value of 5×10^{-3} M, which leads to a reasonably constant ionic strength in solution. With [La^{3+}] > 5×10^{-4} M at ${}^s_s$pH > 7.0, the metal ion was partially neutralized by adding an appropriate amount of NaOMe to help control

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(13) Three organophosphonothioates were shown to react with methoxide to give 93−96% P−S cleavage, while, under similar hydroxide concentrations in water, P−S cleavage proceeds to the extent of 74−88%.[12] In the case of hydrolysis, the reaction products from P−S cleavage (RP(=O)O−(SR′)) are toxic in their own right and relatively resistant to further reaction, while P−S cleavage in the methanolysis reactions yields RP(=O)OCH₃(SR′) which undergoes further reaction to give RP(=O)(OCH₃)₂.
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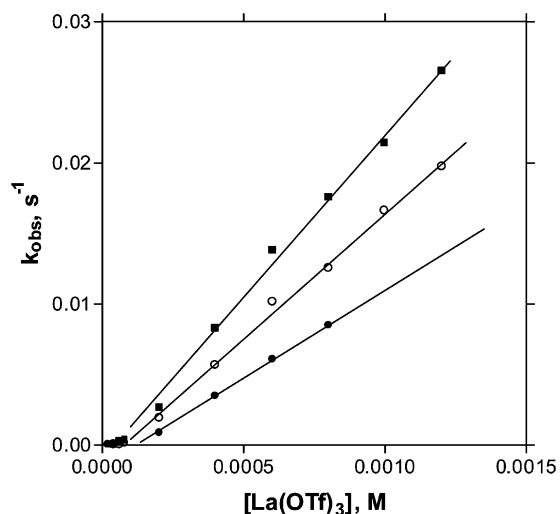(21) Gibson, G.; Neverov, A. A.; Brown, R. S. *Can. J. Chem.* In press.

Figure 1. Plot of k_{obs} vs [La(OTf)$_3$] for the La^{3+}-catalyzed methanolysis of paraoxon (2.04×10^{-5} M) at 25 °C, ^s_spH 8.96, (■); ^s_spH 8.23, (○); and ^s_spH 7.72 (●).

the ^s_spH at the desired value. ^s_spH measurements were performed before and after each experiment, and in all cases, the values were consistent to within 0.1 units.

D. ^{31}P NMR Experiment to Ascertain Turnover. To 2 mL of dry methanol at ambient temperature was added *N*-ethylmorpholine (25.5 μL or 23 mg), half neutralized with 11.4 M HClO$_4$ (8.6μL) so that the final total buffer concentration was 0.1 M. To this was added 16.0 mg of paraoxon. The ^{31}P NMR spectrum showed a single signal at δ −6.35 ppm. To the resulting mixture was added 12.9 mg of La(O$_3$SCF$_3$)$_3$ and 40 μL of 0.5 M NaOCH$_3$ in methanol solution. At this point, the concentration of paraoxon was 0.057 M and that of La(O$_3$SCF$_3$)$_3$ was 0.011 M, and the measured ^s_spH of the methanol solution is 8.75, essentially neutrality. The solution was allowed to stand for 10 min, after which time the ^{31}P NMR spectrum indicated the complete disappearance of the paraoxon signal and the appearance of a new signal at δ 0.733 ppm. The ^{1}H NMR spectrum of the same solution also indicated the complete disappearance of the starting material and full release of free *p*-nitrophenol.

Results

A. Kinetics. Shown in Figure 1 are three representative plots of the pseudo-first-order rate constants (k_{obs}) for the methanolysis of **2** as a function of added [La(OTf)$_3$] at ^s_spH 7.72, 8.23, and 8.96. As was observed in our earlier studies of the La^{3+}-catalyzed methanolysis of esters[6] and acetyl imidazole,[7] these plots exhibit two domains, a nonlinear one at low [La^{3+}] suggestive of a second-order behavior in La^{3+}, followed by a linear domain at higher [La^{3+}]. Following the approach we have used before,[6,7] we used the linear portion of these plots to calculate the observed second-order rate constants (k_2^{obs}) for the La^{3+}-catalyzed methanolysis of **2** at the various ^s_spH values. These are tabulated in Table 1 and graphically presented in Figure 2 as a log k_2^{obs} versus ^s_spH plot, which is seen to have a skewed bell-shape, maximizing at ^s_spH $\approx$ 9. (For original k_{obs} vs [La^{3+}] kinetic data, see Tables S1−S11, Supporting Information).

B. ^{31}P and ^{1}H NMR Turnover Experiments. A 2 mL aliquot of methanol NMR solution containing 0.1 M *N*-ethylmorpholine buffer and 0.057 M paraoxon was formulated as described in the Experimental Section. The ^{31}P NMR spectrum of this showed a single signal at δ −6.35 ppm. To the resulting mixture was added La(O$_3$SCF$_3$)$_3$ and NaOCH$_3$, so

Table 1. Observed Second-Order Rate Constants for the La^{3+}-Catalyzed Methanolysis of **2** at Various ^s_spH Values, $T = 25$ °C

^s_spH	k_2^{obs},[a] M^{-1} s^{-1}
5.15	0.065 ± 0.002
5.58	0.11 ± 0.01
5.82	0.28 ± 0.02
6.69	1.07 ± 0.04
7.10	2.4 ± 0.1
7.30	5.6 ± 0.1
7.72	11.3 ± 0.5
8.23	17.5 ± 0.5
8.96	23.2 ± 0.9
10.34	11.4 ± 0.8
10.97	5.4 ± 0.4

[a] k_2^{obs} determined from slope of the k_{obs} vs [La^{3+}]$_{total}$ plots at higher [La^{3+}] at each ^s_spH.
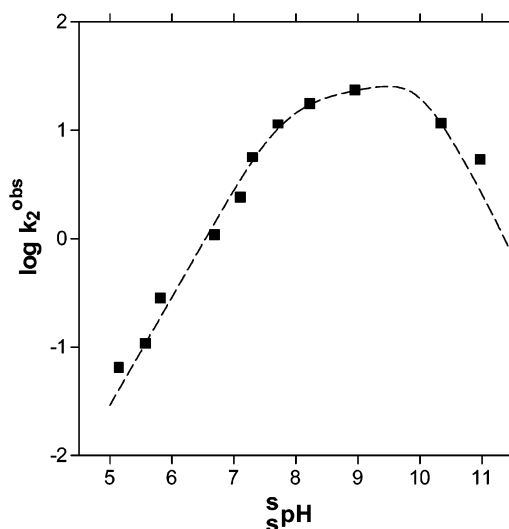

Figure 2. Plot of the log k_2^{obs} vs ^s_spH for the La^{3+}-catalyzed methanolysis of **2** at 25 °C. Dashed line through the data was computed on the basis of speciation and rate constants derived for various active species; see text.

that the final concentration of lanthanum ion was 0.011 M and the measured ^s_spH was 8.75, essentially neutrality.

After 10 min, the ^{31}P NMR spectrum indicated the complete disappearance of the paraoxon signal and the appearance of a new signal at δ 0.733 ppm, attributed to diethyl methyl phosphate, and the ^{1}H NMR spectrum indicated the full release of free *p*-nitrophenol.

The previously mentioned experiment shows that 10 turnovers of **2** occurred relative to the La dimers formed in situ, thus indicating the true catalytic nature of those species.

C. Speciation of La^{3+} in Methanol. Recently, we presented a study of the potentiometric titration of nine lanthanide metal ions as well as Zn^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, and Ti^{4+} in methanol solution.[21] In the case of La^{3+}, the titration data were obtained under various conditions from 1×10^{-3} M $\leq$ [La(OTf)$_3$] $\leq$ 3×10^{-3} M, which is within the concentration range where the kinetic plots of k_{obs} versus [La^{3+}] in this study are linear. The potentiometric titration data were successfully analyzed with the computer program Hyperquad[22] through fits to the dimer model presented in eq 1 where *n* assumes values of 1−5, to give the various stability constants ($^s_s K_n$) that are defined in

(22) The potentiometric data are fit using the computer program Hyperquad 2000 (version 2.1 NT). Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996** *43*, 1739.
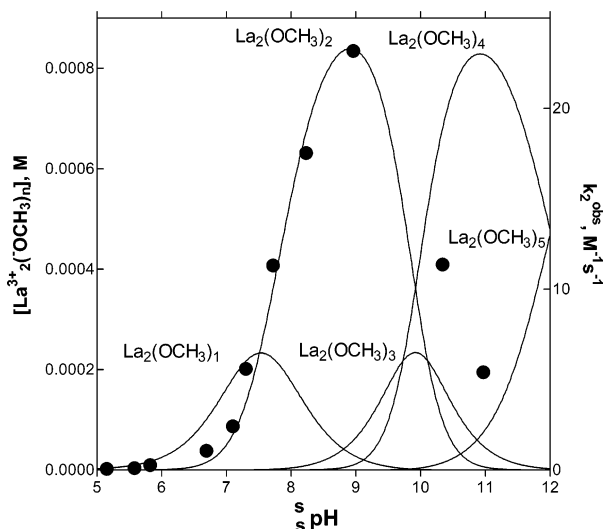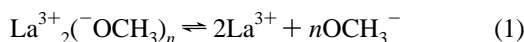
Figure 3. Speciation diagram for the distribution of $La^{3+}_2(^-OCH_3)_n$ forms, $n = 1-5$, as a function of ^s_spH. Speciation calculated[22] for $[La(OTf)_3] = 2 \times 10^{-3}$ M. Data represented as (●) correspond to second-order rate constants (k_2^{obs}) for the La^{3+}-catalyzed methanolysis of **2** presented in Table 1.

eq 2.[21] On the basis of the five computed stability constants, $\log\,^s_sK_{1-5} = 11.66 \pm 0.04$, 20.86 ± 0.07, 27.52 ± 0.09, 34.56 ± 0.20, and 39.32 ± 0.26, we constructed the speciation diagram shown in Figure 3 which presents the distribution of the various $La^{3+}_2(^-OCH_3)_n$ forms as a function of ^s_spH at $[La(OTf)_3]_{total} = 2 \times 10^{-3}$ M.

$$La^{3+}_2(^-OCH_3)_n \rightleftharpoons 2La^{3+} + nOCH_3^- \qquad (1)$$

$$^s_sK_n = [La^{3+}_2(^-OCH_3)_n]/[La^{3+}]^2[OCH_3^-]^n \qquad (2)$$

Also included in Figure 3 as (●) are the k_2^{obs} data for the La^{3+}-catalyzed methanolysis of **2** which predominantly coincide with the ^s_spH distribution of $La^{3+}_2(^-OCH_3)_2$ but with an indication that higher order species such as $La^{3+}_2(^-OCH_3)_3$ and/ or $La^{3+}_2(^-OCH_3)_4$ have some activity. To determine the activities for the various $La^{3+}_2(^-OCH_3)_n$, we analyze the k_2^{obs} data as a linear combination of individual rate constants (eq 3) where $k_2^{2:1}$, $k_2^{2:2}$......$k_2^{2:n}$ are the second-order rate constants for the methanolysis of **2**

$$k_2^{obs} = (k_2^{2:1}[La^{3+}_2(^-OCH_3)_1] + k_2^{2:2}[La^{3+}_2(^-OCH_3)_2] + ... \qquad (3)$$

$$k_2^{2:n}[La^{3+}_2(^-OCH_3)_n])/[La(OTf)_3]_t$$

promoted by the various dimeric forms. Given in Table 2 are the best-fit rate constants produced by fitting under various assumptions.

Discussion

In the absence of La^{3+}, the methoxide promoted reaction of **2** proceeds with the second-order rate constant, $k_2^{OCH_3}$, of 0.011 M^{-1} s^{-1} determined from 1×10^{-2} M $\leq [NaOCH_3] \leq 4 \times 10^{-2}$ M.[23] The methanolysis of **2** is markedly accelerated in

Table 2. Computed Second-Order Rate Constants for Various Dimeric Forms, $La^{3+}_2(^-OCH_3)_n$, Catalyzing the Methanolysis of **2** as Determined from Fits of k_2^{obs} Data in Table 1 to Equation 3, $[La(OTf)_3]_{total} = 2 \times 10^{-3}$ M, T = 25 °C

fit no.	$k_2^{2:1}$ (M^{-1} s^{-1})	$k_2^{2:2}$ (M^{-1} s^{-1})	$k_2^{2:3}$ (M^{-1} s^{-1})	$k_2^{2:4}$ (M^{-1} s^{-1})	R^2
1[a]	15.9 ± 3.2	49.8 ± 2.2	67.2 ± 36.0	8.8 ± 11.2	0.9976
2[b]	18.4 ± 5.4	47.2 ± 2.4	110.4 ± 11.8		0.9861
3[c]		51.4 ± 2.8	103.4 ± 17		0.9664

[a] Including all dimeric forms except $La^{3+}_2(^-OCH_3)_0$ and $La^{3+}_2(^-OCH_3)_6$. Computed value of $k_2^{2:5} = -3.4 \pm 10.8$ $M^{-1}s^{-1}$. [b] Computed without the involvement of $k_2^{2:4}$ and $k_2^{2:5}$. [c] Computed without the involvement of $k_2^{2:1}$, $k_2^{2:4}$, and $k_2^{2:5}$.

the presence of $[La^{3+}]$ with an observed second-order rate constant, k_2^{obs}, of $\sim$17.5 M^{-1} s^{-1} at the near neutral ^s_spH of 8.23 (see Table 1). When it is assumed that the methoxide reaction persists at ^s_spH 8.23, the acceleration afforded to the methanolysis of paraoxon at that ^s_spH by a 2×10^{-3} M solution of $La(OTf)_3$ is an impressive 1.1×10^9-fold[24] having a $t_{1/2}$ of 20 s.

In the absence of additional information, the previous data do not explicitly point to the nature of the catalytic species other than its requiring La^{3+}. As shown in Figure 2, the reactivity of the catalytic species increases with ^s_spH up to $\sim$9.0 indicating the involvement of at least one methoxide, although the general shape of the plot suggests the catalytic involvement of more than one species, vide infra. Since the second-order k_2^{obs} values for the La^{3+}-catalyzed reactions in the neutral ^s_spH region are some 1000- to 2300-fold larger than the methoxide $k_2^{OCH_3}$, the role of the metal ion is not to simply decrease the $^s_spK_a$ of any bound CH_3OH molecules that act as nucleophiles. This points to a dual role for the metal, such as acting as a Lewis acid and source of the nucleophile, as was suggested in our earlier work.[6,7]

Detailed mechanistic evaluation of our kinetic data requires additional information such as the stoichiometries and concentrations of various La^{3+}-containing species that are formed as a function of both ^s_spH and $[La^{3+}]$. Recent reports from Jurek, Jurek, and Martell[25] and Gómez−Tagle and Yatsimirski[26] deal with the pH-dependent speciation in multicomponent equilibria involving metal ions as well as the catalytic viability of the species. In that work, as well as in the work reported here, computer fitting of potentiometric titration data[21,22] to various models allows one to determine the concentration of metal-containing species as a function of both pH and $[M^{x+}]$. We have chosen to analyze the titration data[21] for a $[La^{3+}]_{total}$ of 2×10^{-3} M, which is in the general concentration range where the kinetic behavior of the methanolysis of **2** is linearly dependent on $[La^{3+}]$ and, thus, largely controlled by dimeric species. The titration data are satisfactorily fit to the series of equilibria shown in eq 1 where there are five proposed dimers of general form $La^{3+}_2(^-OCH_3)_n$, $n = 1-5$.[21] According to this model, which generates the speciation diagram shown in Figure 3, the two dominant species have even numbers of attached methoxides; $La^{3+}_2(^-OCH_3)_2$ between ^s_spH 8 and 10 (maximum concentration of $\sim$80% at ^s_spH 8.9), and $La^{3+}_2(^-OCH_3)_4$ between ^s_spH 10

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(23) The pseudo-first-order rate constants for the reaction of **2** with 1.00, 2.00, and 4.00×10^{-2} M $NaOCH_3$ are 9.65×10^{-5}, 2.09×10^{-4}, and 4.50×10^{-4} s^{-1} at 25 °C.

(24) Neutral ^s_spH in methanol is $\sim$8.4, and the accelerations at lower and higher ^s_spH values are also impressive, being 2.3×10^9-fold at ^s_spH 7.72 and 2.7×10^8-fold at ^s_spH 8.96.

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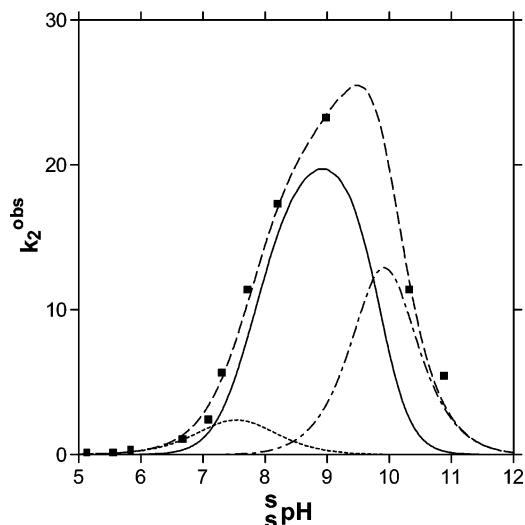(26) Gómez-Tagle, P.; Yatsimirsky, A. K. *Inorg. Chem.* **2001**, *40*, 3786.

Figure 4. Plot of the predicted k_2^{obs} vs. $_s^s pH$ rate profile for the La^{3+}-catalyzed methanolysis of **2** (— — —) based on the kinetic contributions of La^{3+}($^-$OCH$_3$)$_1$ (- - -); La$^{3+}_2$($^-$OCH$_3$)$_2$ (——); and La$^{3+}_2$($^-$OCH$_3$)$_3$ (· - · - · -) computed from the $k_2^{2:1}$, $k_2^{2:2}$, and $k_2^{2:3}$ rate constants (Table 2) and their speciation (Figure 3). Square data points (■) are experimental k_2^{obs} rate constants from Table 2.

and 12 (maximum concentration of ~80% at $_s^s pH$ 11). La dimers with odd numbers of methoxides, La$^{3+}_2$($^-$OCH$_3$)$_1$ and La$^{3+}_2$($^-$OCH$_3$)$_3$, are also present to a lesser extent, and their maximum concentration of ~25% each is reached at respective $_s^s pH$ values of 7.5 and 10.

Having established the species distribution as a function of $_s^s pH$, we analyzed the kinetic data by fitting the k_2^{obs} for the La^{3+}-catalyzed methanolysis of **2** (Table 1) to eq 3 to determine best fit rate constants ($k_2^{2:n}$) for each of the La$^{3+}_2$($^-$OCH$_3$)$_n$ species. In Table 2 are presented the best-fit constants along with the R^2 values for three fits of varying restriction. Fit #1 includes all species and has the best correlation coefficient but generates values for $k_2^{2:5}$ and $k_2^{2:4}$ which are, respectively, negative and with excessive error, such that one can reasonably exclude La$^{3+}_2$($^-$OCH$_3$)$_5$ and La$^{3+}_2$($^-$OCH$_3$)$_4$ as being catalytically important. Fit #2 omits those terms generating three kinetic constants for the La$^{3+}_2$($^-$OCH$_3$)$_1$, La$^{3+}_2$($^-$OCH$_3$)$_2$, and La$^{3+}_2$-($^-$OCH$_3$)$_3$, while Fit # 3 considers only the La$^{3+}_2$($^-$OCH$_3$)$_2$ and La$^{3+}_2$($^-$OCH$_3$)$_3$ terms, omitting $k_2^{2:1}$ as a trial because of its relatively large uncertainty from Fit #2. Fits #2 and #3 become progressively worse than Fit #1, at least on the basis of the decreasing R^2 value, but each agrees that the two kinetically dominant forms are La$^{3+}_2$($^-$OCH$_3$)$_2$ and La$^{3+}_2$($^-$OCH$_3$)$_3$.

In Figure 4 are presented kinetic plots for all three species (La$^{3+}_2$($^-$OCH$_3$)$_1$, La$^{3+}_2$($^-$OCH$_3$)$_2$, and La$^{3+}_2$($^-$OCH$_3$)$_3$) based on their second-order rate constants for the catalyzed methanolysis of **2** and their concentrations as a function of $_s^s pH$. Their combined reactivities as a function of $_s^s pH$ give the predicted log k_2^{obs} versus $_s^s pH$ profile shown as the dashed line in Figure 4. The computed line is also presented on the log k_2^{obs} versus $_s^s pH$ plot in Figure 2. Included in Figure 4 as ■ symbols are the actual experimentally determined values which fit on the computed profile with remarkable fidelity, strongly indicating that these three species are responsible for the observed activity. At $_s^s pH$ values below 9, the La$^{3+}_2$($^-$OCH$_3$)$_2$ complex accounts for essentially all the activity, while, at $_s^s pH$ 10 and above, the dominantly active form is La$^{3+}_2$($^-$OCH$_3$)$_3$.

Scheme 1 ^{a}
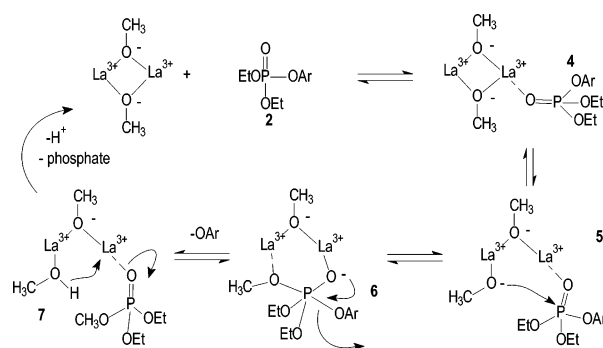
^{a} Methanols of solvation omitted for clarity.

A. Proposed Mechanism. We have shown above that La^{3+} in methanol is a remarkably effective catalyst for the decomposition of paraoxon and that there are three dimeric species which have maximal activities at different $_s^s pH$ values. Of these, the highest activity is attributed to La$^{3+}_2$($^-$OCH$_3$)$_2$ operating most effectively in the neutral $_s^s pH$ region between 7.7 and 9.2 (neutral $_s^s pH$ in methanol is 8.4). Given in Scheme 1 is a proposed mechanism by which La$^{3+}_2$($^-$OCH$_3$)$_2$, as a bis-methoxy bridged dimer, promotes the methanolysis of **2**. Although none of our k_{obs} versus [La^{3+}] kinetics profiles show saturation behavior indicative of formation of a strong complex between **2** and La^{3+}, given the well-known coordinating ability of trialkyl phosphates to lanthanides and actinides,[27] the first step probably involves transient formation of a **2**:La$^{3+}_2$($^-$OCH$_3$)$_2$ complex (**4**).

It is unlikely that a methoxy group bridged between two La^{3+} ions, as in **4**, is sufficiently nucleophilic to attack the coordinated phosphate,[28] so we propose that one of the La^{3+}−$^-$OCH$_3$−La^{3+} bridges opens to reveal a singly coordinated La^{3+}−$^-$OCH$_3$ adjacent to a Lewis acid-coordinated phosphate (**5**) which then undergoes intramolecular nucleophilic addition (**6**) followed by ejection of the *p*-nitrophenoxy leaving group to give **7**. La$^{3+}_2$($^-$OCH$_3$)$_2$ is regenerated from **7** by a simple deprotonation of one of the methanols of solvation and dissociation of the phosphate product, (EtO)$_2$P(O)OCH$_3$.

There are well-accepted stereochemical requirements for phosphoryl transfer that generally involve an apical attack of the nucleophile, a pseudorotation within the five-coordinate intermediate, and an apical departure of the leaving group.[29] These requirements may place constraints on the La^{3+}-catalyzed

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methanolysis of phosphate esters which are not specifically addressed in Scheme 1 at this time. Some light on this question may be shed by comparison of the La^{3+}-catalyzed methanolysis of carboxylic esters and phosphate triesters. It is particularly interesting to us that $La^{3+}_2(^-OCH_3)_2$ can catalyze the methanolysis of carboxylic esters with both good and poor leaving groups, as exemplified by its k_2 value for the methanolysis of *p*-nitrophenyl acetate (72 M^{-1} s^{-1}) and ethyl acetate (0.14 M^{-1} s^{-1}).[6] However, La^{3+} catalysis of the methanolysis of phosphate triesters shows a great discrimination between good and poor leaving groups. This is exemplified by the fact that the k_2 value for paraoxon is 50 M^{-1} s^{-1}, comparable to that for *p*-nitrophenyl acetate, but the k_2 value for trimethyl phosphate is 5×10^6 fold lower at 9.7×10^{-6} M^{-1} s^{-1}.[30] In the case of the methanolysis of carboxylic and phosphate triesters, good leaving groups can depart from the intermediates without additional assistance by the metal ion as a Lewis acid aiding departure. However, by microscopic reversibility, a La^{3+}-catalyzed delivery of methoxide via a putative $La^{3+}-OCH_3$ requires that the expulsion of a poor leaving group (ethoxide or methoxide) be catalyzed through coordination to La^{3+} which seems to be the case for carboxylic esters. Apparently, for the less sterically demanding intermediates involved in the transacylation of esters, the La^{3+} dimer can accommodate the tetrahedral geometries imposed. However, in the transesterification of phosphates, the La^{3+} dimer, although capable of delivering the nucleophile, may not be geometrically suitable to assist in the departure of a poor leaving group from the apical position of the more extended trigonal−bipyramidal intermediate.

Conclusions

In the above, we have demonstrated that a methanol solution containing 2×10^{-3} M La(OTf)$_3$, at ^s_spH values around

neutrality, can be used to promote the methanolysis of paraoxon with a 10^9-fold acceleration over the base reaction at that ^s_spH. As far as we know, this system provides the largest reported acceleration for any man-made catalyst capable of promoting the solvolysis of a phosphate triester. Through the joint consideration of the k_{obs} versus [La^{3+}] kinetics and a detailed analysis of the potentiometric titration data for La^{3+} in methanol, we have determined that the dominant species in solution are dimers of the general formula $La^{3+}_2(^-OCH_3)_n$ where $n = 1-5$, and three of these dimers, $La^{3+}_2(^-OCH_3)_1$, $La^{3+}_2(^-OCH_3)_2$, and $La^{3+}_2(^-OCH_3)_3$, account for all the catalytic activity with $La^{3+}_2(^-OCH_3)_2$ being the most important at ^s_spH < 9. Interestingly, one cannot come to this conclusion considering only the k_{obs} versus [La^{3+}] kinetic data. The ^s_spH profile of the second-order observed catalytic rate constant (k_2^{obs}) for the La^{3+}-promoted methanolysis of **2** has a slope close to unity in the low ^s_spH domain, as shown in Figure 2. Cursory consideration of those data leads to the erroneous conclusion that the activated complex of the catalyst and phosphate contains a single $^-OCH_3$, with a bell-shaped activity profile. In reality, the ^s_spH dependence of the metal ion is such that several complexes are present with their individual concentrations maximized at different ^s_spH values. It is only through complementary analyses of the kinetic and potentiometric titration data that one can satisfactorily explain the kinetic behavior of complex mixtures having several pH-dependent forms.

Supporting Information Available: Tables S1−S11. Observed pseudo-first-order rate constants for the La^{3+}-catalyzed methanolysis of **2** under various conditions of ^s_spH and varying [La^{3+}], (6 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Determined by ^{1}H NMR analysis of the reaction of d_4-methanol solvent containing 1.3×10^{-2} M NaOCH$_3$ and La(OTf)$_3$ and 8.18×10^{-2} M trimethyl phosphate, ^s_spH $\approx$ 8.5, ambient temperature, which generates 2% of CH$_3$OH product over the course of 90 h.