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# A Study of the Kinetics of $La^{3+}$-Promoted Methanolysis of *S*-Aryl Methylphosphonothioates: Possible Methodology for Decontamination of EA 2192, the Toxic Byproduct of VX Hydrolysis

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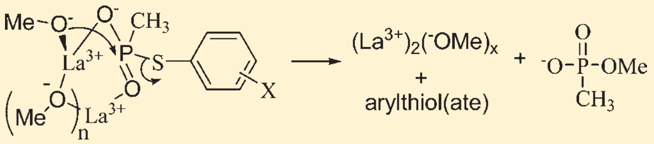
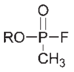
*Supporting Information*

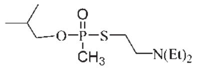
**ABSTRACT:** The kinetics of the $La^{3+}$-catalyzed methanolysis of a series of *S*-aryl methylphosphonothioates (**4a**−**e**, phenyl substituents = 3,5-dichloro, 4-chloro, 4-fluoro, 4-H, 4-methoxy) were studied at 25 °C with ${}^{s}_{s}pH$ control. The reaction involves saturation binding of the anionic substrates to dimeric $La^{3+}$/methoxide catalysts formulated as $La_2^{3+}(^{-}OCH_3)_x$, where $x$ = 2−5 depending on the solution ${}^{s}_{s}pH$. Cleavage of the $La^{3+}$-bound methylphosphonothioates is fast, ranging from $5 \times 10^{-3}\ s^{-1}$ to $5.5 \times 10^{-5}\ s^{-1}$ for substrates **4a**−**e** at a ${}^{s}_{s}pH$ of 8.4 and $1.6 \times 10^{-1}\ s^{-1}$ to $4 \times 10^{-3} s^{-1}$ at a ${}^{s}_{s}pH$ of 11.7. The rate accelerations for the methanolysis of substrates **4a**−**e**, relative to their background methoxide-promoted reactions, average $7 \times 10^{10}$ and $1.5 \times 10^{9}$, respectively, at ${}^{s}_{s}pH$'s of 8.4 and 11.7. The catalytic system is predicted to cleave EA 2192 (*S*-2(N,N-di-*iso*-propylaminoethyl) methylphosphonothioate), a toxic byproduct of the hydrolysis of VX, with a $t_{1/2}$ between 4 and 8 min at a ${}^{s}_{s}pH$ of 8.4, and 27 min at a ${}^{s}_{s}pH$ of 11.7.

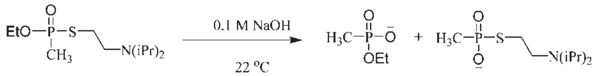


## 1. INTRODUCTION

The phosphonofluoridate G agents (**1**) and phosphonothioate V agents (**2**) are potent acetylcholine esterase inhibitors that have been widely employed as chemical warfare materials. Such G agents readily undergo hydrolysis of the P−F bond to yield a nontoxic *O*-alkyl methylphosphonic acid product. For example, Sarin (**1a**) is hydrolyzed with a halftime ($t_{1/2}$) of <6 min in water at a pH of 10 and at 25 °C to produce *O*-*iso*-propyl methylphosphonate.[1] By contrast, the base-promoted hydrolysis of V agents such as VX (**2a**) and Russian-VX (**2b**) is slower and more problematic, owing to their propensity to undergo a P−OR cleavage in competition with the desired P−SR cleavage reaction. For example, hydrolysis of VX with 0.1 M NaOH produces an 87% yield of the desired cleavage product **3a** (*O*-ethyl methylphosphonic acid, EMPA) and 13% **3b** *S*-(N,N-(diethylaminoethyl) methylphosphonic acid, commonly known as EA 2192) arising from P−OEt cleavage (eq 1).[2] Being some 3700 times less reactive to hydroxide nucleophilic attack than VX, EA 2192 is highly resistant to further degradation and yet retains a high level of oral and i.v. toxicity.[3] Alternative simple strategies for the decomposition of VX that avoid formation of EA 2192 are much sought after, and highly activated stoichiometric oxidants and nucleophiles such as $H_2O_2$, *O*-iodosylcarboxylates, oxone, and NaOCl have been investigated for their potential to degrade VX.[4] Other hydrolytic methodologies including the use of latex dispersions,[5] glycerophosphodiesterases,[6] and metallocene complexes[7] [e.g., $Cp_2Mo(OH)(OH_2)$] have also been disclosed.


**1**, **a** R = $(CH_3)_2CH$, (GB, Sarin)
**b** R = cyclohexyl (GF, cyclosarin)
**c** R = $CH(CH_3)C(CH_3)_3$, (GD, Soman)


**Russian-VX (2b)**



**VX (2a)** **3a** **3b** (EA 2192) (1

As part of an ongoing research program to develop methods to deactivate organophosphate CW agents and pesticides, we have investigated the potential of various metal ions to promote the alcoholysis of a variety of neutral carbon esters and organophosphorous (OP) esters. These metal-ion catalyzed alcoholysis (MICA) reactions, using lanthanides ($Ln^{3+}$) and complexes of certain transition metal ions such as $Zn^{2+}$ and $Cu^{2+}$, are very effective for cleaving neutral phosphate and phosphorothioate triesters,[8] *O*-ethyl-*O*-aryl methylphosphonate esters,[9] P=S-containing phosphorothioate triesters,[10] and carboxylate esters.[11] Changing from water to the light alcohols leads to increased solubility of the neutral OP substrates and metal ions (as their kinetically active alkoxide forms), and in general, metal-ion catalyzed alcoholysis in methanol and ethanol is far more rapid than the corresponding hydrolysis in water.[12] Importantly, the overall process is one of transesterification and not true hydrolysis. This is significant because the hydrolysis of neutral substrates leads to the production of acidic OP products that can bind, as their anions, to the metal ion and inhibit catalysis.

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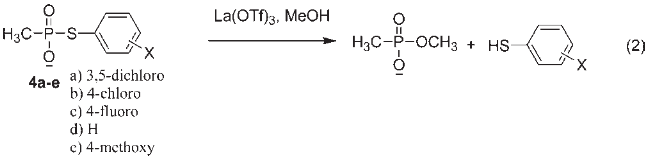
We recently reported[13] that the methanolysis of a series of VX simulants (*O*-ethyl *S*-aryl methylphosphonates) was strongly catalyzed by $[La^{3+}(^{-}OCH_3)]_2$ and $[Zn(II)(^{-}OCH_3)(1,5,9\text{-triazadodecane})]$, which allowed us to predict a 0.3 and 18 s half-time for the destruction of VX in the presence of 1 mM of each respective catalyst at near neutral pH. A major advantage of using a light alcohol such as methanol or ethanol for the decomposition of VX is that any competitive P—OEt cleavage that accompanies the desired P—SR displacement from **2a** or **2b** results in a neutral transesterification intermediate (MeOP(=O)(CH$_3$)(SR)) that is subject to further reaction to displace the P—SR group. The predicted rapid La$^{3+}$-promoted transformation of VX into its methanolysis product (*O*-ethyl *O*-methyl methylphosphonate, EMMP) was subsequently verified by tests with a live agent performed at the Edgewood Chemical and Biological Center (ECBC).[14]

Herein, we describe an extension of these studies[13,14] demonstrating that La(OTf)$_3$ in methanol cleaves anionic phosphonothioate models, namely, *S*-aryl methylphosphonothioates, **4a**—**4e**. The linear free energy study of the methanolysis of these allows us to predict a $t_{1/2}$ for the decomposition of EA 2192 of ∼4—8 min at 25 °C and essentially neutral pH in methanol.



(2)

## 2. EXPERIMENTAL SECTION

**a. Materials.** Kinetic reactions were carried out in commercially available EMD Drisolv Methanol (99.8%, anhydrous). All other solvents used in the study were anhydrous and subsequently treated with an Innovative Technology, Inc. Pure Solv solvent purification system comprising alumina packed columns. Reagents, sodium methoxide (0.50 M solution in methanol, titrated against N/2 certified standard aqueous HCl solution and found to be 0.50 M), La(CF$_3$SO$_3$)$_3$, CF$_3$SO$_3$H (titrated to be 167 mM in ethanol), thiophenol (97%), and triethylamine (99%) were purchased from Aldrich and used without further purification. The compounds 4-fluorothiophenol (98%) and 3,5-dichlorothiophenol (97%) were obtained from TCI America. 4-Chlorothiophenol (98%) was obtained from Acros Organics. 4-Methoxythiophenol (97%) was obtained from Alfa Aesar, and methylphosphonyl dichloride (97%+) was purchased from Fluka.

The phosphonothioates (**4**) were prepared from methylphosphonyl dichloride following a general route.[15] Thiophenol (5 mmol) was added to a solution of methylphosphonyl dichloride (2.5 mmol) in 10 mL of dry CH$_2$Cl$_2$, after which triethylamine (5 mmol) was slowly added to the mixture. The reaction mixture was stirred at 40 °C for 4 h, after which the crude reaction mixture was washed with water (6 × 15 mL) and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layers were washed with brine and then dried over anhydrous Na$_2$SO$_4$. The crude product, obtained after filtering away the drying agent and removing the solvent, was added to a well-stirred mixture of 3 mL of 5 M KOH in 16 mL of 1,4-dioxane; stirring was continued at 50 °C for 8 h. The solution was concentrated under reduced pressure to remove 1,4-dioxane, and the aqueous layer was acidified with 20 mL of 3 M aqueous HCl and subsequently extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined extracts were washed with brine and dried over Na$_2$SO$_4$. CH$_2$Cl$_2$ was removed under reduced pressure, and **4a**—**4e** were obtained in nonoptimized yields of 40—80%. The physical data for **4a**—**4e** are given in the Supporting Information.

**b. Methods.** The ${}^{s}_{s}pK_a$ values in methanol for the thiophenol leaving groups of **4a**—**4e** were obtained from previous work.[13] The ${}^{s}_{s}pH$ values in methanol reported here were determined by subtracting the correction constant of −2.24 from the electrode readings as described.[16] The ${}^{s}_{s}pH$ values (defined as in ref 16) in the kinetic experiments were measured at the end of the reactions to avoid the possibility of chloride leaching from the electrode (Cl$^-$ is an inhibitor of La$^{3+}$ catalysis in methanol). For the titrations of La(OTf)$_3$ and **4e**, the $[CH_3OH_2^+]$ was determined potentiometrically using a combination glass electrode (Fisher Scientific Accumet electrode model #13-620-183A) calibrated with certified standard aqueous buffers (pH = 4.00 and 10.00). The values of the species formation constants in methanol were calculated using the computer program Hyperquad 2000 (version 2.1 NT),[17] with the autoprotolysis constant of pure methanol taken to be $10^{-16.77}$ at 25.0 ± 0.1 °C .[18] The formation constants for the species $(La^{3+})_2$:**4e**:$(CH_3O^-)_n$ ($n$ = 1—5) were determined from the analysis of the potentiometric titration of a methanol solution containing 2 mM La(OTf)$_3$ and 1 mM **4e**. The results for these experiments can be found in the Supporting Information.

**c. Kinetics.** La$^{3+}$-catalyzed reactions were followed by UV/vis spectrophotometry under buffered conditions. Reaction progress at a ${}^{s}_{s}pH$ of 8.4 was monitored at 242 nm (**4a**), 246 nm (**4b**), 235 nm (**4c**), 242 (**4d**), and 240 nm (**4e**), while at a ${}^{s}_{s}pH$ of 11.7, reactions were monitored at 282 nm (**4a**), 282 (**4b**), 270 (**4c**), 280 (**4d**), and 262 nm (**4e**). Amine buffers, partially acidified with triflic acid, were employed to control ${}^{s}_{s}pH$: N-methylimidazole (${}^{s}_{s}pK_a$ = 7.60), N-ethylmorpholine (${}^{s}_{s}pK_a$ = 8.28), and triethylamine (${}^{s}_{s}pK_a$ = 10.78). Total [buffer] varied from (1—4) × $10^{-2}$ M.

**d. Identification of Reaction Products in the La$^{3+}$-Catalyzed Cleavage of 4b.** Substrate **4b** (1 × $10^{-4}$ M), La(OTf)$_3$ (1.5 × $10^{-3}$ M), and a NEt$_3$ buffer (40 mM, ${}^{s}_{s}pH$ 11.7) were combined in a 1-cm-path-length cell and the UV—vis spectrum obtained following complete conversion. The spectrum was identical to that of a methanol solution containing 4-chlorothiophenol (1 × $10^{-4}$ M), La(OTf)$_3$ (1.5 × $10^{-3}$ M), and NEt$_3$ (40 mM, ${}^{s}_{s}pH$ 11.7).

**e. Determination of Second Order Rate Constants for Base-Promoted Methanolysis of 4a—4e.** An aliquot of a 1 M solution of tetrabutylammonium hydroxide in methanol was added individually to substrates **4a**—**4e** in a standard 5 mm NMR tube. It is assumed that all hydroxide is converted to methoxide under these reaction conditions.[19] Substrate concentrations ranged from 7 to 16 mM, and in all cases, the base consumed during the course of the reaction was less than 5%, so standard pseudo-first-order reaction conditions are assumed. The NMR tubes were thermostatted at 25 °C, and the reaction progress was determined by $^{31}$P NMR. Fits of the integrated intensities of $^{31}$P signals corresponding to substrates **4a**—**e** and the product *O*-methyl methylphosphonate to a standard single exponential equation provided the observed pseudo-first-order rate constants ($k_{obs}{}^{-OMe}$) at a given [base]. The second order rate constant ($k_2{}^{-OMe}$) was assigned as the gradient of the plot of $k_{obs}{}^{-OMe}$ vs [NBu$_4$OMe].

## 3. RESULTS

**a. Identification of Reaction Products.** Substrate **4b** was subjected to methanolysis at 25 °C in the presence of 1.5 × $10^{-3}$ M La(OTf)$_3$ at a ${}^{s}_{s}pH$ of 11.7, maintained with a 40 mM triethylamine buffer partially acidified with triflic acid. Comparison of the UV—vis spectra obtained after complete reaction to that of an authentic sample of 4-chlorothiophenol ($\varepsilon^{275\text{ nm}}$ = 1.38 × $10^4$ M$^{-1}$ cm$^{-1}$) under experimental conditions confirmed methanolytic cleavage of the P—SAr bond as depicted in eq 2.

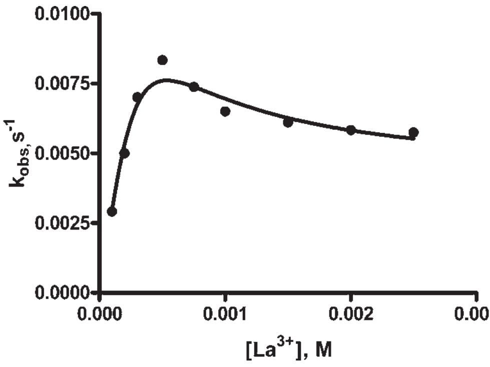


**Figure 1.** Plot of $k_{obs}$ versus [La(OTf)$_3$] for the methanolysis of **4a** ($1 \times 10^{-4}$ M) determined at 25.0 ± 0.1 °C; ${}_{s}^{s}$pH = 8.4 (0.04 M *N*-ethylmorpholine buffer). NLLSQ fit of the data to eq 3 provides $k_1$ = (28.0 ± 3.0) M$^{-1}$ s$^{-1}$ and $k_{cat}{}^{8.4}$ = (5.9 ± 0.2) × 10$^{-3}$ s$^{-1}$.

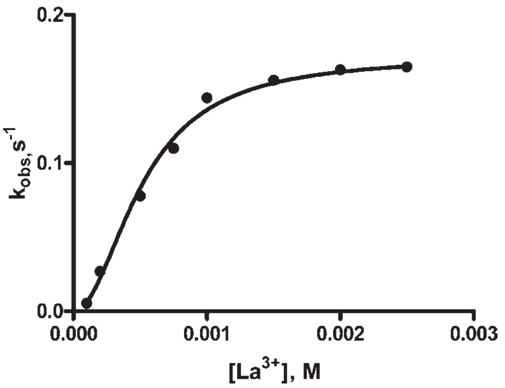
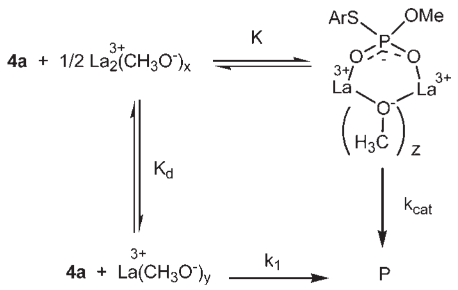


**Figure 2.** Plot of $k_{obs}$ versus [La(OTf)$_3$] for the methanolysis of **4a** ($1 \times 10^{-4}$ M) determined at 25.0 ± 0.1 °C; ${}_{s}^{s}$pH = 11.7 (0.04 M triethylamine buffer). NLLSQ fit of the data to eq 3 gives a $k_1$ indistinguishable from 0 M$^{-1}$ s$^{-1}$ and a $k_{cat}{}^{11.7}$ = (1.64 ± 0.01) × 10$^{-1}$ s$^{-1}$.

**Scheme 1. Simplified Scheme for the La$^{3+}$-Catalyzed Methanolysis of 4a from which eq 3 is Obtained**



### b. La$^{3+}$-Catalyzed Methanolysis of Phosphonothioate 4a.

Shown in Figures 1 and 2 are plots of $k_{obs}$ versus [La$^{3+}$] obtained for the decomposition of **4a** at a ${}_{s}^{s}$pH of 8.4 and 11.7, respectively. The rate data obtained as a function of [La$^{3+}$] were fit to eq 3, derived for the simplified reaction mechanism presented in Scheme 1. In this model, $k_1$ refers to a bimolecular reaction between the anionic substrate and metal ion, $k_{cat}$ represents the unimolecular rate constant for a substrate fully bound to a dimeric La$^{3+}$ -complex and the constants $K$ and $K_d$ are defined as indicated in Scheme 1 (the $k_{cat}{}^{pH}$ referred to later is defined as the $k_{cat}$ at specific ${}_{s}^{s}$pH values). The errors associated with the individual constants from the multiparameter nonlinear least-squares fits are quite large, owing to the fact that the four fitted constants are heavily correlated. A simpler method for determining the experimental $k_{cat}{}^{pH}$ values takes an average rate constant in the plateau regions seen in Figures 1 and 2 at high [La$^{3+}$]. The so-determined $k_{cat}{}^{pH}$ values for reaction of the metal bound **4a** are (5.9 ± 0.2) × 10$^{-3}$ s$^{-1}$ and (1.64 ± 0.01) × 10$^{-1}$ s$^{-1}$ at a ${}_{s}^{s}$pH of 8.4 and 11.7, respectively. This treatment of the rate data for the La$^{3+}$-catalyzed methanolysis of phosphonothioate **4a** is the same as was presented earlier for the La$^{3+}$-catalyzed cleavage of phosphate diesters containing aryloxy leaving groups where the rate constant vs [La$^{3+}$} profiles for catalyzed methanolysis of some phosphate diesters were strikingly similar to those presented here.[20]

$$\begin{aligned} k_{obs} = {} & (2k_1K((1+8[\mathrm{La}^{3+}]_t/K_d)^{0.5}-1)+k_{cat}(4[\mathrm{La}^{3+}]_t/K_d \\ & -(1+8[\mathrm{La}^{3+}]_t/K_d)^{0.5}+1))/(8K/K_d+4[\mathrm{La}^{3+}]_t/K_d \\ & -(1+8[\mathrm{La}^{3+}]_t/K_d)^{0.5}+1) \end{aligned} \tag{3}$$

### c. Brønsted Correlation of $k_{cat}{}^{pH}$ Values.

Phosphonothioates **4a**−**4e** ($1 \times 10^{-4}$ M) were subjected to La$^{3+}$-catalyzed methanolysis at 25 °C under buffered conditions at ${}_{s}^{s}$pH's of 8.4 (*N*-ethylmorpholine) and 11.7 (triethylamine). The [La(OTf)$_3$] was varied between 1 and 2.5 mM, and the observed pseudo-first-order rate constants ($k_{obs}$) were determined to be independent of the [La$^{3+}$]$_{total}$. This indicates that the substrate is fully bound to the La$^{3+}$ species at these concentrations, and so $k_{obs}$ is the first-order rate constant for cleavage of the *S*-aryl group from a complex comprising (La$^{3+}$)$_2$, (methoxide)$_x$, and a bound **4**. The averages of the various $k_{obs}$ values are given as the $k_{cat}{}^{8.4}$ and $k_{cat}{}^{11.7}$ values reported in Table 1. The data are presented graphically in Figure 3 as the Brønsted correlations that fit linear regressions of log($k_{cat}{}^{8.4}$) = (−0.67 ± 0.03)${}_{s}^{s}$p$K_a^{HSAr}$ + (3.89 ± 0.43) and log($k_{cat}{}^{11.7}$) = (−0.55 ± 0.04)${}_{s}^{s}$p$K_a^{HSAr}$ + (4.15 ± 0.45) at a ${}_{s}^{s}$pH of 8.4 and 11.7. Substrates **4a**−**4e** ($1 \times 10^{-4}$ M) were also subjected to reaction at 25 °C employing a commercially available La$^{3+}$-containing decontamination solution known as System 4[21] operating at a ${}_{s}^{s}$pH of 9.2. The observed first order rate constants, $k^{Syst4}$, for this series of experiments are presented in Table 1, and the experimental protocols are given in the Supporting Information. The Brønsted correlation for the System 4 reactions shown in Figure 3 is log($k^{Syst4}$) = (−0.72 ± 0.03)${}_{s}^{s}$p$K_a^{HSAr}$ + (4.22 ± 0.33).

### d. Potentiometric Titration of La(OTf)$_3$ in the Presence of Phosphonothioate 4e.

In Figure 18S (Supporting Information) are two titration curves (${}_{s}^{s}$pH vs added [$^-$OMe]) acquired from a 2 mM solution of La(OTf)$_3$ in methanol with and without 1 mM **4e**, while in Table 18S (Supporting Information) are compiled the computed stability constants and the associated microscopic ${}_{s}^{s}$p$K_a^{2:1x}$ data. The calculated speciation diagram illustrating the concentrations of the various [(La$^{3+}$)$_2$:**4e**:($^-$OCH$_3$)$_x$] complexes as a function of the ${}_{s}^{s}$pH determined at 2 mM La(OTf)$_3$ and 1 mM **4e** is shown in Figure 19S (Supporting Information).

The dependence of the rate of La$^{3+}$-catalyzed methanolysis of substrate **4b** on [$^-$OMe] was determined at 7.6 ≤ ${}_{s}^{s}$pH ≤ 11.7 at 25 °C under buffered conditions, and the $k_{cat}{}^{pH}$ values for cleavage of **4b** when bound to La$^{3+}{}_2$(CH$_3$O$^-$)$x$, determined

Table 1. Rate Constants $k_2^{-OMe}$ for Methoxide Reaction of Substrates 4, $k_{cat}^{8.4}$ and $k_{cat}^{11.7}$ (at a $^{s}_{s}$pH of 8.4 and 11.7), and $k^{Syst4}$ Determined for the $La^{3+}$-Catalyzed Methanolysis of Substrates 4, $T$ = 25 ± 0.1 °C

| sub | $^{s}_{s}pK_a^{HSAr}$ [a] | $k_2^{-OMe}$ ($M^{-1}$ $s^{-1}$)[b] | $k_{cat}^{8.4} \times 10^3$ ($s^{-1}$)[c] $^{s}_{s}$pH 8.4 | rate accel.[d] $^{s}_{s}$pH 8.4 | $k_{cat}^{11.7} \times 10^2$ ($s^{-1}$)[e] $^{s}_{s}$pH 11.7 | rate accel.[d] $^{s}_{s}$pH 11.7 | $k^{Syst4} \times 10^3$ ($s^{-1}$)[f] $^{s}_{s}$pH 9.2 |
|---|---|---|---|---|---|---|---|
| **4a** | 9.08 | $(4.7 \pm 0.1) \times 10^{-5}$ | $5.9 \pm 0.2$ | $2.9 \times 10^{10}$ | $16.4 \pm 0.1$ | $4.0 \times 10^{8}$ | $5.6 \pm 0.1$ |
| **4b** | 10.47 | $(2.7 \pm 0.1) \times 10^{-6}$ | $0.58 \pm 0.05$ | $5.1 \times 10^{10}$ | $1.79 \pm 0.08$ | $7.9 \times 10^{8}$ | $0.5 \pm 0.1$ |
| **4c** | 11.07 | $(9.8 \pm 0.2) \times 10^{-7}$ | $0.33 \pm 0.03$ | $8.0 \times 10^{10}$ | $1.22 \pm 0.01$ | $1.2 \times 10^{9}$ | |
| **4d** | 11.28 | $(6.1 \pm 0.4) \times 10^{-7}$ | $0.230 \pm 0.001$ | $8.9 \times 10^{10}$ | $0.8 \pm 0.1$ | $1.6 \times 10^{9}$ | |
| **4e** | 11.98 | $(1.5 \pm 0.4) \times 10^{-7}$ | $0.055 \pm 0.005$ | $8.6 \times 10^{10}$ | $0.40 \pm 0.09$ | $3.1 \times 10^{9}$ | $0.047 \pm 0.003$ |

[a] Data as reported in ref 13. [b] Second order rate constants, $k_2^{-OMe}$, determined from slopes of plots of $k_{obs}$ vs [$NBu_4OMe$], 25 °C. [c] $k_{cat}^{8.4}$ determined from the plateau region in the plots of $k_{obs}$ vs [$La^{3+}$] at a high metal ion concentration, a $^{s}_{s}$pH of 8.4 (0.04 M *N*-ethylmorpholine buffer), and $T$ = 25 °C. [d] The rate accelerations are computed from the $k_{cat}^{pH}/k^{-OMe}$ ratio, where $k^{-OMe}$ has units of $s^{-1}$ and is determined as $k_2^{-OMe} \times [^{-}OMe]$ at either $^{s}_{s}$pH 8.4 or 11.7 using the autoprotolysis constant $K_{auto} = 10^{-16.77}$ for methanol; $[^{-}OMe] = K_{auto}/[H^+]$. [e] $k_{cat}^{11.7}$ determined from the plateau region in the plots of $k_{obs}$ versus [$La^{3+}$] at a high metal ion concentration at a $^{s}_{s}$pH of 11.7 (0.04 M $NEt_3$ buffer) and 25 °C. [f] $k^{Syst4}$ determined from duplicate runs using System 4 decontamination system.[21]

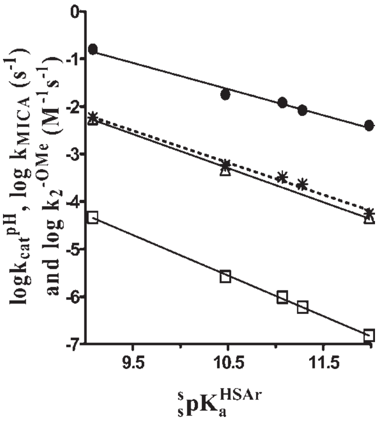


**Figure 3.** Brønsted plots for (a) $La^{3+}$-catalyzed methanolysis of **4a**−**4e** determined at a $^{s}_{s}$pH of 11.7, $T$ = 25.0 ± 0.1 °C, linear regression $\log(k_{cat}^{11.7}) = (-0.55 \pm 0.04)^{s}_{s}pK_a^{HSAr} + (4.15 \pm 0.45)$, $r^2 = 0.98$ (solid line, ●); (b) $La^{3+}$-catalyzed methanolysis of **4a**−**4e** determined at a $^{s}_{s}$pH of 8.4, $T$ = 25.0 ± 0.1 °C, linear regression $\log(k_{cat}^{8.4}) = (-0.67 \pm 0.04)^{s}_{s}pK_a^{HSAr} + (3.89 \pm 0.43)$, $r^2 = 0.99$ (dashed line, ∗); (c) reaction of **4a**, **4b**, and **4e** with the System 4 decontamination solution at $T$ = 25.0 ± 0.1 °C, linear regression $\log(k^{Syst4}) = (-0.72 \pm 0.03)^{s}_{s}pK_a^{HSAr} + (4.22 \pm 0.33)$, $r^2 = 0.99$ (solid line, Δ); and (d) methoxide promoted reaction of **4a**−**4e** linear regression $\log(k_2^{-OMe}) = (-0.85 \pm 0.02)^{s}_{s}pK_a^{HSAr} + (3.40 \pm 0.17)$, $r^2 = 0.9989$ (solid line, □).

Table 2. Table of Catalytic Rate Constants, $k_{cat}^{pH}$, for the $La^{3+}$-Catalyzed Methanolysis of 4b Determined under Buffered Conditions at 25.0 ± 0.1 °C from a $^{s}_{s}$pH of 7.6−11.7[a]

| $^{s}_{s}$pH | $k_{cat}^{pH} \times 10^3$ ($s^{-1}$) |
|---|---|
| 7.6 | $0.32 \pm 0.05$ |
| 8.4 | $0.58 \pm 0.01$ |
| 8.9 | $3.5 \pm 0.1$ |
| 9.9 | $7.3 \pm 0.2$ |
| 10.9 | $12.4 \pm 0.6$ |
| 11.7 | $17.9 \pm 0.8$ |

[a] Catalytic rate constants computed as described in the text as the average of the values in the plateau region seen at high [$La^{3+}$] in the plots of $k_{obs}$ vs [$La^{3+}$].

Table 3. Kinetic Constants ($k_{cat}^{2:1:x}$) for the Methanolysis of 4b Catalyzed by the Various $(La^{3+})_2$:4b:$(CH_3O^-)_x$ Species Present at [$La^{3+}$] = 2.0 mM and 25.0 ± 0.1 °C

| | $(La^{3+})_2$:**4b**:$(CH_3O^-)_x$ | | | | |
|---|---|---|---|---|---|
| | $x = 1$ | $x = 2$ | $x = 3$ | $x = 4$ | $x = 5$ |
| $k_{cat}^{2:1:x}$ [a] ($s^{-1}$) | 0[b] | (2.5 ± 1.0) | (19 ± 5) | (11 ± 3) | (27 ± 4) |

[a] $k_{cat}^{2:1:x}$ determined using a fit of the data to eq 4. [b] $k_{cat}^{2:1:1}$ constrained to a value of zero for fitting of the $^{s}_{s}$pH/rate data to eq 4. All attempts to carry out an unconstrained fit resulted in excessively large errors.

as described above, are presented in Table 2. A plot of $\log(k_{cat}^{pH})$ versus $^{s}_{s}$pH (not shown) provides a poor linear correlation with a slope of 0.44 ± 0.07 and $r^2 = 0.8997$. The $k_{cat}^{pH}$ values are shown overlaid on the speciation diagram of Figure 19S to give an indication of the pH dependence for the decomposition of the $(La^{3+})_2$:**4b**:$(^{-}OCH_3)_x$ complexes. The $k_{cat}^{pH}$ vs $^{s}_{s}$pH data were then analyzed as a linear combination of the individual rate constants by fitting to eq 4 to determine the first order rate constants ($k_{cat}^{2:1:1}$, $k_{cat}^{2:1:2}$, ...$k_{cat}^{2:1:x}$) for spontaneous decomposition of the specific metal ion complexes [$(La^{3+})_2$:**4b**:$(^{-}OCH_3)_x$]; where $x$ = 1−5. This analysis rests on a reasonable assumption that the complex stability constants with **4b** can be accurately modeled by those of the slower reacting material, **4e**. The first order rate constants, $k_{cat}^{2:1:x}$, appear in Table 3, and a plot of $\log(k_{cat}^{2:1:x})$ versus the microscopic $^{s}_{s}pK_a^{2:1:x}$ values from Table 2 is fit to $\log(k_{cat}^{2:1:x}) = (0.28 \pm 0.07)\ ^{s}_{s}pK_a^{2:1:x} - (1.9 \pm 0.8)$, $r^2 = 0.88$.

$$k_2^{cat} = \sum (k_{cat}^{2:1:x}[(La^{3+})_2 : Sub : (CH_3O^-)_x])/[La_2]_{total} \quad (4)$$

**e. Methoxide Promoted Cleavage of 4a−4e.** The methanolysis of substrates **4a**−**4e** was carried out at 25 °C under pseudo-first-order conditions of excess $NBu_4OMe$, and the rates were determined by integration of the $^{31}P$ NMR peaks corresponding to unreacted starting material and product. The intensity vs time data were fit to a standard first order exponential equation to obtain the $k_{obs}$ values, and the second order rate constants, $k_2^{-OMe}$, were obtained as the slopes of the linear plots of $k_{obs}$ vs [$NBu_4OMe$], the values of these being given in Table 1.

Included in Figure 3 is a Brønsted correlation of the $k_2^{-\mathrm{OMe}}$ values vs the corresponding ${}^{s}_{s}\mathrm{p}K_a^{\mathrm{HSAr}}$ values of the HSAr leaving groups: $\log(k_2^{-\mathrm{OMe}}) = (-0.85 \pm 0.02){}^{s}_{s}\mathrm{p}K_a^{\mathrm{HSAr}} + (3.40 \pm 0.17)$. When viewed as pseudo-first-order rate constants obtained at a standard state of 1 M, the methoxide data presented in Figure 3 can be easily compared with the metal-catalyzed reactions. The raw rate data and $^{31}$P NMR spectra are included in the Supporting Information.

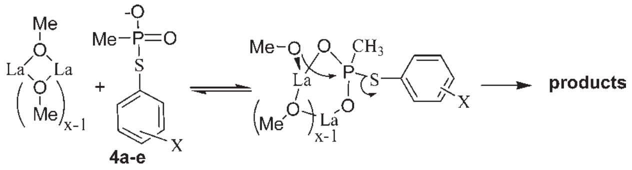
## 4. DISCUSSION

Plots of $k_{\mathrm{obs}}$ versus $[\mathrm{La}^{3+}]$ for the catalyzed methanolysis of **4a** at ${}^{s}_{s}$pH's of 8.4 and 11.7 are complex, albeit consistent with the simplified model shown in Scheme 1 derived previously for the related La$^{3+}$-catalyzed methanolysis of *O*-methyl *O*-aryl phosphodiesters.[20] Acceptable fits of the rate data to eq 3, derived for the simplified process given in Scheme 1, appear in Figures 1 and 2. However, the kinetic constants are heavily correlated, so a simpler treatment of the rate data is applied as described in the Results section, whereby the $k_{\mathrm{obs}}$ constants for the methanolysis of La$^{3+}{}_2$-bound **4** determined between 1 and 2.5 mM were obtained, and averaged, to give $k_{\mathrm{cat}}^{\mathrm{pH}}$ (the rate constant for cleavage of **4** by the La$^{3+}$dimer at a desired ${}^{s}_{s}$pH), which was used for all further analyses.[20]

The methanolytic cleavage of anionic phosphonothioates promoted by La$^{3+}$ is relatively insensitive to lyoxide concentration, as exemplified by the reaction of **4b**, which displays less than a 60-fold rate difference ($3.2 \times 10^{-4}$ to $1.8 \times 10^{-2}$ s$^{-1}$) over a four ${}^{s}_{s}$pH unit increase. The plot of $\log(k_{\mathrm{cat}})$ vs ${}^{s}_{s}$pH has a nonunit slope of 0.44. This result is consistent with the spontaneous decompositions of a set of ${}^{s}_{s}$pH dependent complexes formulated simply as $(\mathrm{La}^{3+})_2$:**4**:$(\mathrm{CH_3O^-})_x$; where $x = 1-5$. The computed kinetic constants given in Table 2 pertaining to the decomposition of each of the individual complexes, $k_{\mathrm{cat}}{}^{2:1:x}$ indicate that the $(\mathrm{La}^{3+})_2$:**4**:$(\mathrm{CH_3O^-})_x$ complexes with 3, 4, and 5 associated methoxides (or their kinetic equivalents where an external methoxide strikes the La$^{3+}$-complex having 2, 3, or 4 associated methoxides) are the most active, although modest activity is also attributed to the $x = 2$ species. From the speciation diagram of Figure 19S (Supporting Information) and the catalytic constants $k_{\mathrm{cat}}{}^{2:1:x}$, we compute that 96% of the reaction occurs by the decomposition of $(\mathrm{La}^{3+})_2$:**4b**:$(\mathrm{CH_3O^-})_2$ with about 4% coming from $(\mathrm{La}^{3+})_2$:**4b**:$(\mathrm{CH_3O^-})_3$ at a ${}^{s}_{s}$pH of 8.4. At a ${}^{s}_{s}$pH of 11.7, the complexes $(\mathrm{La}^{3+})_2$:**4b**:$(\mathrm{CH_3O^-})_4$ and $(\mathrm{La}^{3+})_2$:**4b**:$(\mathrm{CH_3O^-})_5$ account for 41 and 54% of the reaction with <5% coming from the decomposition of $(\mathrm{La}^{3+})_2$:**4b**:$(\mathrm{CH_3O^-})_3$.

The Brønsted plot of $\log(k_2{}^{2:1:x})$ vs ${}^{s}_{s}\mathrm{p}K_a^{2:1:x}$ for the cleavage of substrate **4b** is linear with a small positive slope of $\beta^{\mathrm{Nu}} = +0.28$. A comparison can be made to the methanolytic cleavage of phosphate triesters catalyzed by the series of metal alkoxides $(\mathrm{La}^{3+})_2$:$(\mathrm{CH_3O^-})_x$ where the $\beta^{\mathrm{Nu}}$ was determined to be +0.02.[22] The low value of the $\beta^{\mathrm{Nu}}$ found in that study was proposed to result from a competing combination of increased nucleophilicity for the CH$_3$O$^-$ attached to the species with the highest ${}^{s}_{s}\mathrm{p}K_a$ values, coupled with a concomitant decreased Lewis acidity/electrophilic activation of the coordinated substrate due to the reduced net positive charge on the La$^{3+}$ ions in the complex. Slightly positive, or even negative, values of $\beta^{\mathrm{Nu}}$ are reported for reactions promoted by metal coordinated lyoxides, including the dinuclear Zn(II)-complex-promoted hydrolysis of *bis*-4-nitrophenyl phosphate,[23] the mononuclear Zn(II) triamine-complex-catalyzed hydrolysis of diethyl 2,4-dinitrophenyl phosphate,[24] the Ln(OH)$^{2+}$-promoted hydrolysis of *bis*-4-nitrophenyl phosphate,[25] and the metal-hydroxo attack on C═O-containing compounds.[26] In the present case, the $\beta^{\mathrm{Nu}}$ of +0.28 for the La$^{3+}$-catalyzed methanolysis of **4b** is in the range expected for a bifunctional process involving delivery of a metal-coordinated nucleophile and Lewis acid activation of the coordinated phosphorothioate.

**Scheme 2. Proposed Mechanism for the La$^{3+}$-Catalyzed Methanolysis of 4a−4e Where the Charges and Associated Counter Ions Have Been Omitted for Visual Clarity**



In Scheme 2 is a mechanism originally proposed for the La$^{3+}$-catalyzed cleavage of monoanionic phosphate diesters,[20] which is consistent with the present results for the catalyzed methanolysis of monoanionic phosphonothioate substrates. The common feature is the *bis*-coordination of the two phosphate or phosphonothioate oxygens to the dimeric La$^{3+}$-complex to provide double Lewis acid activation toward nucleophilic attack by a metal-coordinated methoxide. A bridging methoxide bound by two La$^{3+}$ ions likely does not possess sufficient nucleophilicity to displace the −SAr leaving group, and accordingly we propose that the nucleophilic CH$_3$O$^-$ is coordinated to a single metal ion.

The Brønsted plots for the La$^{3+}$-catalyzed methanolysis of **4a**−**4e** at a ${}^{s}_{s}$pH of 11.7 and 8.4 have very similar gradients ($\beta^{\mathrm{LG}}$ coefficients) of $-0.55 \pm 0.04$ and $-0.67 \pm 0.04$, respectively, but given the bifunctional nature of the catalysis and lack of $\beta^{\mathrm{Equilibrium}}$ values for phosphonyl transfer between oxyanion and thiolate nucleophiles, a detailed analysis of the transition state charges or extent of cleavage of the P−SAr bond cannot be made. Phosphonothioates **4a**, **4b**, and **4e** are also readily cleaved by the System 4 decontamination solution,[21] and the limited plot of $\log(k^{\mathrm{Syst4}})$ vs ${}^{s}_{s}\mathrm{p}K_a^{\mathrm{HSAr}}$ gives a $\beta^{\mathrm{LG}}$ of −0.72 that can essentially be overlaid on the plot constructed for reactions carried out at a ${}^{s}_{s}$pH of 8.4 (see Figure 3). The Brønsted coefficients determined here are similar to that observed for the La$^{3+}$-catalyzed methanolysis of the neutral OP V-agent simulants EtO(CH$_3$)P(═O)SAr (${}^{s}_{s}$pH 9.1, $\beta^{\mathrm{LG}} = -0.75$)[13] and suggest a similar level of charge development on the leaving groups is occurring in the TS for all of these reactions. The $\beta^{\mathrm{LG}}$ of −0.85 determined for methoxide-promoted cleavage of **4a**−**4e** indicates a slightly greater dependence of the reaction rate on the ${}^{s}_{s}\mathrm{p}K_a^{\mathrm{HSAr}}$ of the leaving groups as compared to the metal-catalyzed reactions. Comparison of the latter value and those obtained for the La$^{3+}$-promoted processes suggests that the metal-containing complexes exhibit a catalytic preference for less activated substrates with poorer leaving groups.

The methoxide promoted reactions of **4a**−**4e** have computed second-order rate constants falling in the range of $1.5 \times 10^{-7}$ to $4.7 \times 10^{-5}$ M$^{-1}$ s$^{-1}$. A visual comparison of the rates of methoxide reactions to those of the La$^{3+}$-catalyzed processes is seen in Figure 3, if the methoxide second order rate constants are brought to first order ones at the standard state of 1 M, $T$ = 25 °C. The vertical separation of the various plots is indicative of the level of catalysis achieved by coordinating the methoxide and substrate to a $(\mathrm{La}^{3+})_2$:$(^{-}\mathrm{OCH_3})_{x-1}$ metal ion complex in the transition state to form $[(\mathrm{La}^{3+})_2{:}\mathbf{4}{:}(^{-}\mathrm{OCH_3})_x]^{\ddagger}$. An alternative assessment of catalytic efficiency comes from the $k_{\mathrm{cat}}/(k_2{}^{-\mathrm{OMe}}[^{-}\mathrm{OMe}])$ value at the same ${}^{s}_{s}$pH, where $[^{-}\mathrm{OMe}]$ is given as $K^{\mathrm{Auto}}/[\mathrm{H}^+]$ or alternatively $10^{-16.77}/10^{-\mathrm{pH}}$. The computed rate accelerations range from (2.9−8.6) × $10^{10}$ at a ${}^{s}_{s}$pH of 8.4 to (0.4−3.1) × $10^{9}$ at a ${}^{s}_{s}$pH of 11.7. Somewhat higher catalytic efficiencies are calculated for the less activated substrates with higher ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}^{\mathrm{HSAr}}$ values as a direct result of the observed slopes in the Brønsted plots of Figure 3.

**a. Predicted Rate of Decomposition of EA 2192.** A predicted rate acceleration for decomposition of this substrate can be calculated if one assumes that the Brønsted correlations described for cleavage of thioaryl leaving groups from **4** are applicable to the reaction of EA 2192 and that the conditions for cleavage have the $\mathrm{La}^{3+}$-containing catalyst in excess of the EA 2192 as it is in this study. The leaving group of EA 2192 at a ${}^{s}_{s}$pH of 8.4 is the N-protonated zwitterion $^{-}\mathrm{SCH_2CH_2N^+H(^{\mathit{i}}Pr)_2}$, and the ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ of $\mathrm{HSCH_2CH_2N^+H(^{\mathit{i}}Pr)_2}$ dissociating to form the zwitterion in methanol is estimated to be 9.54.[13] Inserting this ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ value into the Brønsted relationship, $\log(k_{\mathrm{cat}}{}^{8.4}) = (-0.67 \pm 0.04){}^{s}_{s}\mathrm{p}K_{\mathrm{a}}^{\mathrm{HSAr}} + (3.89 \pm 0.43)$ gives a predicted rate constant ($t_{1/2}$) of 3.15 × $10^{-3}$ $\mathrm{s}^{-1}$ (corresponding to a $t_{1/2}$ of 4 min) for the cleavage of EA 2192 at a ${}^{s}_{s}$pH of 8.4. Unfortunately, since we do not know the ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ value for acid dissociation of the thiol group of $\mathrm{HSCH_2CH_2N(^{\mathit{i}}Pr)_2}$, we cannot calculate the anticipated rate constant for the cleavage of EA 2192 at a ${}^{s}_{s}$pH of 11.7.[27]

The large structural disparity between the thioaryl and (di-*iso*-propylaminoethyl)thio- leaving groups makes it unclear as to whether the same Brønsted relationship can be used for aryl thiols and aliphatic thiols, so we consider an alternative estimate. The methoxide-promoted cleavage reaction of EA 2192 is reported[4a] to have a $t_{1/2}$ of 140 h in 0.3 M methoxide, corresponding to a second order rate constant of 4.6 × $10^{-6}$ $\mathrm{M^{-1}s^{-1}}$ from which one can calculate $k_{\mathrm{obs}}$ values of 2 × $10^{-14}$ and 4 × $10^{-11}$ $\mathrm{s}^{-1}$ at ${}^{s}_{s}$pH's of 8.4 and 11.7. The average rate accelerations for cleavage of **4** by saturating $\mathrm{La}^{3+}$ catalysis relative to the background methoxide promoted reactions provided at ${}^{s}_{s}$pH values of 8.4 and 11.7 are 7 × $10^{10}$ and 1.5 × $10^{9}$, respectively. Assuming that a similar level of catalysis is obtained with EA 2192, we predict that at saturating $[\mathrm{La}^{3+}]$ the $t_{1/2}$ for cleavage of EA 2192 at these ${}^{s}_{s}$pH values is 8 and 27 min. The predicted $t_{1/2}$ for the reaction of EA 2192 is likely an underestimate at the lower ${}^{s}_{s}$pH since it is expected to be N-protonated at a ${}^{s}_{s}$pH of 8.4 and so may result in a substantially more activated phosphonothioate owing to a combination of nucleophilic attack on a formally neutral substrate.

## 5. CONCLUSION

$\mathrm{La}^{3+}$ ions in methanol are shown to be highly effective for cleaving anionic *S*-aryl methylphosphonates (**4**). The reaction proceeds via a pre-equilibrium binding of the substrate to a dimeric $\mathrm{La}^{3+}$ complex formulated as $\mathrm{La^{3+}}_2{:}(^{-}\mathrm{OCH_3})_x$ to form $\mathrm{La^{3+}}_2{:}\mathbf{4}{:}(^{-}\mathrm{OCH_3})_x$, where $x$ can assume values of 2−5 depending on the ${}^{s}_{s}$pH of the solution. Methanolytic cleavages of the phosphorothioate bound to the catalyst relative to cleavage by the background methoxide reactions at ${}^{s}_{s}$pH values of 8.4 and 11.7 are 7 × $10^{10}$ and 1.5 × $10^{9}$. The $\mathrm{La^{3+}}_2{:}(^{-}\mathrm{OCH_3})_x$ system is also predicted to be active for the decontamination of EA 2192. The $t_{1/2}$ values for the methanolysis cleavage reaction of EA 2192 in the presence of saturating $\mathrm{La}^{3+}$ are estimated to be 4−8 and 27 min at a ${}^{s}_{s}$pH of 8.4 and 11.7, respectively. The commercially available System 4 decontamination solution[21] operating at a ${}^{s}_{s}$pH of 9.2 performed comparably to the simple $\mathrm{La}^{3+}$-contaning solution at a ${}^{s}_{s}$pH of 8.4. This represents a significant advantage of metal ion catalyzed alcoholysis for the decomposition of the CW agent VX,[13] particularly munitions grade material or that which has been exposed to adventitious hydrolysis during storage.[14]

## ■ ASSOCIATED CONTENT

**Ⓢ Supporting Information.** Descriptions of syntheses and physical data of **4a**−**4e**; $^{31}$P NMR spectra for determining the rate constants for methoxide catalyzed cleavage of **4a**−**4e**; procedures for UV/vis kinetics and potentiometric titration of $\mathrm{La}^{3+}$ in the presence of **4e**; and speciation diagrams and the computed stability constants for the $\mathrm{La^{3+}}_2{:}\mathbf{4e}{:}(^{-}\mathrm{OCH_3})_x$ complexes (24 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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