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Dissociative Solvolytic Cleavage of Methyl (*ortho*-Carboxymethyl)Aryl Phosphate Diesters Mediated by Yb^{3+} in Methanol Gives a 10^{12}-Fold Rate Acceleration Attributable to Leaving Group Assistance

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Abstract: The Yb^{3+}-catalyzed cleavage of a series of eight methyl aryl phosphates (**2a**−**h**) where the aryl groups all contain an *ortho*-methoxycarbonyl group was studied in acidic methanol from $1.34 \leq {}^s_s\mathrm{pH} \leq 3.34$ at 25 °C. All substrates show saturation binding of the metal ion that is analyzed to provide a conditional binding constant (K_b) for a 1:1 substrate/Yb^{3+} complex and catalytic rate constant (k_{cat}) that varies between about 2×10^{-3} and 50×10^{-3} s^{-1} over the range of substrates. Detailed analysis indicates that at very low concentration of Yb^{3+}, 3 equiv of substrate are bound, and with increasing [Yb^{3+}], the binding changes to a 1:1 complex which decomposes by a pathway independent of ${}^s_s$pH over the range investigated. Control studies show that substrates without the *o*-methoxycarbonyl group still bind to the Yb^{3+} with approximately the same strength as do the *o*-methoxycarbonyl containing substrates but have no observable reaction when bound. A Jaffé plot of the k_{cat} vs substituent σ-values indicates that, during the catalyzed reactions of **2a**−**h**, the phenoxy-O and $C(O)OCH_3$ groups accommodate negative and positive charge respectively, the $\rho_{phosphate}$ and $\rho_{C(O)OMe}$ values being (1.84 ± 0.11) and (-0.85 ± 0.14). For all these substrates, the final reaction products are dimethyl phosphate and the Yb^{3+} complex of the phenoxide. A study of the binding of the parent phenols to Yb^{3+} indicates that $\log(K_{bind}) = (0.84 \pm 0.06){}^s_s\mathrm{p}K_a + (3.4 \pm 0.9)$, $r^2 = 0.9664$ for phenols containing the *o*-methoxycarbonyl group; for those lacking that substituent $\log(K_{bind}) = (0.96 \pm 0.04){}^s_s\mathrm{p}K_a - (1.73 \pm 0.4)$, ($r^2 = 0.99$). For the catalyzed reaction the $\beta_{lg} = -0.48$, while the $\beta_{eq} = -0.95$, leading to a Leffler parameter of $\alpha = 0.51$. A mechanism is presented for the catalyzed reaction which is highly dissociative, having a transition state where the Yb^{3+} translocates during the cleavage reaction to assist the leaving group's departure with weak nucleophilic assistance by the solvent methanol. A comparison of the catalyzed rate of reaction with a computed rate of reaction attributable to solvent alone indicates that Yb^{3+} provides leaving group assistance on the order of 10^{12}-fold, stabilizing the transition state for cleavage by some 16 kcal/mol.

Introduction

The 3′-P−O−ribose bond in the phosphate diester backbone of RNA and DNA is among the most robust of chemical linkages employed by nature in biological systems. The half-life for hydrolysis of RNA has been estimated at 110 years, while that of DNA might well approach 10^8-10^{11} years,[1] so that in order to carry out cleavage of these highly stable entities, extensive enzymatic catalysis is required. Numerous enzymes that catalyze the cleavage of phosphate esters contain within their active sites metal ions such as Mn^{2+}, Ni^{2+}, Mg^{2+}, Zn^{2+}, and Ca^{2+},[2] and enzymatic rate accelerations on the order of $10^{12}-10^{17}$-fold[3] have been reported. Given the importance of the biological processes and the rapidity of the enzymatic cleavage, it is not surprising that the mechanisms by which metallo-phosphodiesterases achieve transition state stabilization of this magnitude remain topics of current interest.[4]

Previous work from this laboratory showed that the cleavage of carboxylate and phosphate esters is greatly accelerated by metal ions in the light alcohols, methanol and ethanol, relative to comparable catalyzed reactions under aqueous conditions.[5] The general theme emerging is that the reduced dielectric constant/polarity medium effect in methanol and ethanol relative to water intensifies the binding interactions between the oppositely charged substrate and the metal catalyst, both in their preliminary cat−substrate binding and the subsequent catalytic transformations. A recent study employing the dinuclear Zn(II) catalyst **1** demonstrated rate accelerations of $10^{11}-10^{13}$-fold over the uncatalyzed methanolysis on a series of aryl methyl phosphodiesters, eq 1.[6] The highest rate accelerations were achieved with substrates bearing *ortho*-NO_2 and *ortho*-meth-

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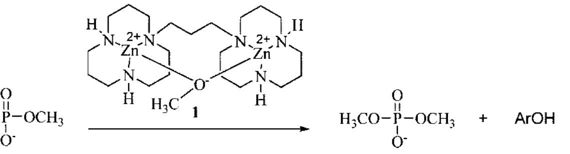
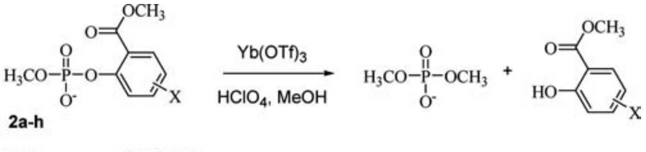
oxycarbonyl substituents on the aryloxide leaving groups. Notable were the β_{lg} values of -0.34 and -0.57 for the **1**-catalyzed methanolysis of substrates containing the *ortho*-NO_2 or C(=O)OCH_3 groups, and substrates that do not, while the β_{lg} value for the methoxide promoted reaction for all substrates was -0.57.[6] This was interpreted as resulting from leaving group assistance whereby the positively charged core of the catalyst bound more strongly to the reaction TS when these ortho functional groups were present.



(1)

The cleavage of phosphate diesters promoted by such enzymes as DNA polymerase I, hammerhead ribozyme, RNase H, human topoisomerase IIα, and others is commonly proposed to involve leaving group assistance via metal ion coordination,[7] although due to the complexity of the enzyme promoted cleavage, this is difficult to demonstrate unambiguously.[1a] There are several examples in small molecule chemistry demonstrating general *acid* assistance of leaving group departure from phosphate esters, including phosphate diesters.[8] There is also a limited number of small molecule catalysts proposed to facilitate leaving group departure via metal ion coordination. For example, the cleavage of *bis*(8-hydroxyquinoline) phosphate is catalyzed by Ni^{2+}, Co^{2+}, and Zn^{2+},[9] and it was proposed that the nitrogen atom of one of the 8-hydroxyquinoline substituents acts as an intramolecular nucleophile while the other coordinates to the metal ion. Rate accelerations on the order of 10^4 were attributed to assistance of leaving group departure by metal ion coordination to the aromatic nitrogen. In another example, the cleavage of adenosine 3′-alkyl phosphate esters was observed in the presence of certain metal ions from which it was determined that up to $\sim10^5$ rate acceleration was imparted by La^{3+}-coordination to the leaving group.[10] More efficient catalysis was achieved with phosphate *monoesters* bearing pendent anionic or nitrogen containing groups in the presence of metal ions. For example, the dianions of 8-quinolyl phosphate[11] and salicyl phosphate[12] undergo Cu(II)-catalyzed hydrolysis with rate accelerations of 10^6 and 10^8 over the uncatalyzed reactions of the dianions. The large rate accelerations obtained in these studies were reasonably attributed to assistance of the leaving group departure, which is entirely consistent with predicted effects of metal ions on the highly dissociative reactions of phosphate monoesters where there is extensive departure of the leaving group in the transition state.[13]

In order to access the potential for leaving group assistance in the catalysis of phosphate *diester* cleavage, it is desirable to study a highly dissociative system where other modes of catalysis, such as nucleophilic activation of solvent and/or electrophilic activation of the phosphorus moiety, are minimized. Disclosed herein are the results of a study of the $Yb(OTf)_3$ catalyzed cleavage of phosphate diesters **2a–h** at low ${}^{s}_{s}$pH in methanol. The data show that the combination of an *ortho*-methoxycarbonyl substituent, a highly Lewis acidic metal ion and the medium effect brought about by methanol accelerate the P–O bond cleavage by 10^{12}-fold as a direct result of metal ion coordination to the leaving group in a highly dissociative TS. Although leaving group assistance has been widely proposed as a mode of catalysis likely to be employed by enzymes to achieve their remarkable acceleration of phosphate diester cleavage,[1,7] as far as we are aware, this is the first unambiguous kinetic demonstration of such catalysis acting alone in the simple cleavage of a phosphate diester.



2a-h

a) H e) 5-fluoro
b) 5-nitro f) 4-methoxy
c) 5-chloro g) 5-methoxy
d) 4-iodo h) 4-methyl

Experimental Section

Materials. Methanol (99.8% anhydrous), $Yb(CF_3SO_3)_3$, sodium methoxide (0.50 M solution in methanol, titrated against N/50 certified standard aqueous HCl solution and found to be 0.49 M), methyl salicylate (ReagentPlus >99%), methyl 5-chlorosalicylate (97%), methyl 4-iodosalicylate (97%), methyl 5-fluoro-2-benzoate (97%), methyl 5-methoxysalicylate (98%), pentafluorophenol (99+%), 2-chloro-4-nitrophenol (97%), 2,4,5-trichlorophenol (99%), Amberlite IR-120H ion-exchange resin (functionalized as sulfonic acid), dimethyl chlorophosphate (96%), and sodium hydride (60% dipersion in mineral oil) were purchased from Aldrich and used without further purification. $HClO_4$ (70% aqueous solution, titrated to be 11.40 M) and methyl 4-methoxysalicylate (98%) were purchased from Acros Organics and used as supplied. Tetrabutylammonium perchlorate (>98%) was purchased from Fluka and used as supplied. Methyl 4-methylsalicylate (98%) was purchased from TCI America. Methyl 2-hydroxy-5-nitrobenzoate (98%) was obtained from Alfa Aesar and was used as supplied. The lithium salts of all phosphate diesters (**2a–h**), as well as the *para*-methoxycarbonyl analogue of **2a,** were synthesized according to the general method described;[14] see Supporting Information. The lithium salts of the phosphate diesters were converted into their acids by ion exchange chromatography over 30 g of Amberlite IR-120H ion-exchange resin. Each of **2a–h** had ^{1}H NMR, ^{31}P NMR, and exact MS spectra consistent with the structure (see Supporting Information).

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Methods. The ${}^{s}_{s}pK_a$ values in methanol for the phenol leaving group of **2a** and **2b** were obtained from previous work.[6] The ${}^{s}_{s}pK_a$ values for the phenols of **2c, 2d**, and **2e** were determined by half-neutralization with NaOMe in methanol and the $CH_3OH_2^+$ concentrations were determined potentiometrically as described previously.[15] The ${}^{s}_{s}pK_a$ of phenols **2f**, **2g**, and **2h** were determined by half-neutralization in water and these values were plotted according to the relationship, ${}^{s}_{s}pK_a^{MeOH} = (1.08 \pm 0.03)pK_a^{HOH} + (3.50 \pm 0.20)$ as described previously,[6] and all ${}^{s}_{s}pK_a$ values are listed in Table 2. For reactions run at high acid concentration in the absence of buffers, the ${}^{s}_{s}pH$ values reported in this study refer to $-\log[HClO_4]$. For experiments where buffers were employed, the reported ${}^{s}_{s}pH$ refers to that determined potentiometrically following complete reaction. ^{31}P NMR chemical shifts were referenced to a 70% phosphoric acid standard.

UV−Visible Kinetics in Methanol. The rates of the $Yb(OTf)_3$-catalyzed reactions of phosphates **2a−h** were monitored by UV−vis spectrophotometry at 25.0 ± 0.1 °C. Varying $[Yb(OTf)_3]$ and $HClO_4$ were added to a standard 1 cm path length UV cell to a final concentration of acid of 2.2 mM in a total volume of 2.5 mL methanol. Reactions were initiated by the addition of substrates **2a−h** such that the final concentration of phosphate diester was $\sim 10^{-5}$ M. Reaction progress was monitored for product formation at 343 (**2a**,**c**,**d**,**g**), 340 (**2e**,**f**,**h**), and 330 nm (**2b**) which were determined to be the λ_{max} of the Yb^{3+}-bound phenoxides. The procedure used to determine the kinetics at variable ${}^{s}_{s}pH$ for **2a** was modified in order to obtain sufficient absorbance changes (ΔAbs) at high acid concentrations. Reactions were monitored for the formation of free phenol from **2a** at 305 nm and the concentration of substrate was increased to 5×10^{-5} M. The ionic strength was controlled during this portion of the study by the addition of tetrabutylammonium perchlorate such that the total $[ClO_4^-]$ remained constant at 45.6 mM. Other modifications of the standard procedure listed above are described in the main body of the text and in footnotes to the various figures presented in the Results and Discussion section.

Temperature Studies. Duplicate solutions of $HClO_4$ (2.2 mM) and $Yb(OTf)_3$ (0.674 mM) were prepared in methanol (total volume 2.5 mL) by the addition of the reagents to the UV−vis cells. The cells were capped with fitted Teflon stoppers and placed in the thermostatted cell compartment of the UV−vis spectrophotometer at the appropriate temperature for 10 min. Following thermal equilibration, a 10 μL aliquot of phosphodiester **2a** (10^{-5} M) was added via syringe to initiate the reaction which was monitored for product formation at 343 nm. This procedure was carried out on **2a** at five different temperatures spanning 7−45 °C. Activation parameters were evaluated by fitting the data to the Eyring equation.

Binding Constants. A general procedure was used to determine the conditional binding constant, K_{cond}, for phenol **2a** with $Yb(OTf)_3$ whereby a UV−vis cell was charged with $HClO_4$ (2.2 mM) and phenol **2a** (5.2×10^{-5} M) in 2.5 mL total volume of methanol, and the spectrum was obtained from 250 to 400 nm. A 10 μL aliquot from a 32.3 mM $Yb(OTf)_3$ stock solution was added to the cell and another scan obtained. This procedure was repeated until the observed absorbance change at 343 nm became negligible indicating saturation binding. The change in total volume during titration of **2a** was ~2%. The conditional binding constant, K_{cond}, was obtained by fitting of the ΔAbs_{343} vs $[Yb(OTf)_3]$ data to eq 2, see text.

Results and Discussion

a. Identification of Products. The products from reaction of 22 mM **2a** and 30 mM $Yb(OTf)_3$ were determined to be the corresponding phenol and $(CD_3O)(CH_3O)PO_2^-$, termed here as dimethylphosphate (DMP), by ^1H NMR following complete reaction in CD_3OD (see Supporting Information).

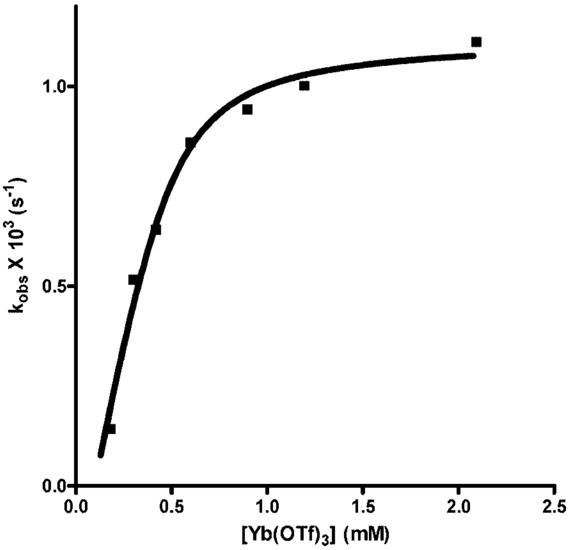

Figure 1. Plot of k_{obs} vs $[Yb(OTf)_3]$ for the catalyzed methanolysis of **2a** (3.9×10^{-4} M) determined from the rate of appearance of product phenol at 305 nm, ${}^{s}_{s}pH$ 2.0 and $T = 25.0 \pm 0.1$ °C. Fitting the data to the expression given in eq 2 gives $K_b = (1.52 \pm 0.76) \times 10^4$ M^{-1}, $k_{cat} = (1.12 \pm 0.06) \times 10^{-3}$ s^{-1}.

Table 1. Kinetic Constants (Maximum Rate Constant (k_{cat}), Binding Constant (K_b)) for the Methanolysis of **2a** Catalyzed by $Yb(OTf)_3$ at $T = 25.0 \pm 0.1$°C

entry	${}^{s}_{s}pH$	$k_{cat} \times 10^3$ (s^{-1})[a]	K_b (M^{-1})[a]
1	1.34	1.79 ± 0.03	$(6.7 \pm 0.8) \times 10^3$
2	1.86	2.45 ± 0.06	$(8.9 \pm 2) \times 10^3$
3	2.34	3.04 ± 0.04	$(9.4 \pm 3) \times 10^3$
4	2.86	2.46 ± 0.07	$(2.8 \pm 0.7) \times 10^4$
5	3.34	2.25 ± 0.07	$(2.0 \pm 0.4) \times 10^4$

[a] k_{cat} and K_b determined by fits of the k_{obs} vs $[Yb(OTf)_3]$ data to eq 2 as described in the text.

b. pH/Rate Profile of Phosphate Diester 2a. The effect of $[H^+]$ on the $Yb(OTf)_3$-catalyzed solvolysis of **2a** was determined between $1.35 \leq {}^{s}_{s}pH \leq 8.84$, but above ${}^{s}_{s}pH \approx 6$ the plots of k_{obs} versus $[Yb(OTf)_3]$ became complex with an apparent inhibition of catalysis at higher metal ion concentrations. This behavior is similar to what was previously reported for other lanthanides in methanol and is attributable to the formation of $Ln^{3+}(^-OCH_3)_x$ species and higher-order dimers thereof.[5,16] No further characterization of the system was sought in the ${}^{s}_{s}pH$ region above 4, which is about 1.3 units less than the ${}^{s}_{s}pK_{a1}$ of 5.3 for $Yb^{3+}(HOCH_3)_n$.[15] In Figure 1 is presented a plot determined at ${}^{s}_{s}pH$ 2.0 for the Yb^{3+}-catalyzed cleavage reaction of substrate **2a** that shows the saturation behavior typical of the overall appearance in the range of $1.34 \leq {}^{s}_{s}pH \leq 3.34$. The plots that displayed saturation binding were fit to a universal binding eq 2, described previously,[17] that gives the maximal catalytic rate constant, k_{cat}, and binding constant, K_b, see Table 1. Note that the K_b referred to here is not a true 1:1 binding constant but a more complex unitless equilibrium constant discussed later in Section c.

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$$k_{obs} = k_{cat}(1 + K_B * [S] + [Cat] * K_B - X)/(2K_B)/[S] \quad (2)$$

where

$$X = (1 + 2K_B * [S] + 2 * [Cat] * K_B + K_B^2 * [S]^2 - 2 * K_B^2 * [Cat][S] + [Cat]^2 * K_B^2)^{0.5}$$

Normally one expects that binding of a metal ion to an acidic substrate will increase with $^{s}_{s}$pH up to the point where the substrate is fully ionized, although this is not the case for the current reaction with **2a** since entries 1−5 in Table 1 show the k_{cat} and K_b constants for **2a** are essentially $^{s}_{s}$pH independent. The data are most consistent with **2a** being completely ionized and strongly bound at very low concentrations as Yb(**2a**)$_3$ (see Supporting Information) with the saturation behavior at increasing [**2a**] attributed to formation of a catalytically competent **2a**−Yb^{3+} complex. Evidence for such a process is presented in the following section.

c. Metal Ion Speciation. The plot displayed in Figure 1 has an observable x-intercept calculated to be 0.10 ± 0.02 mM. Analogous experiments performed under various reaction conditions always led to x-intercepts in the plots of k_{obs} vs [Yb(OTf)$_3$] that were determined to be approximately equal to one-third of the initial concentration of **2a** within the error limits of fit to the data.[18] In a subsequent set of experiments the [**2a**] was varied from 1.3×10^{-5} to 1.25×10^{-3} M and the Yb(OTf)$_3$ concentration was held constant at 2.1 mM. At these concentrations it can be shown that the substrate is fully bound, so one can treat the observed reaction as a first-order process providing a rate constant, k_{cat}. Shown in Figure 2 is a plot of k_{cat} vs [**2a**] where it is seen that k_{cat} decreases with increasing concentrations of phosphate diester. As described in the legend, the line through the data is derived from a fit to a model for the formation of inhibitory dimeric complexes of negligible catalytic activity.

A ^{31}P NMR study was conducted in order to characterize the stoichiometry of the ground-state complex formed between the phosphate diester and Yb^{3+}. Phosphodiester **2a** undergoes reaction too rapidly to be used for this study and so was replaced by a far less reactive substrate, dimethyl phosphate (DMP). A 13.2 mM solution of DMP in CH$_3$OH was prepared in an NMR tube at a $^{s}_{s}$pH of 1.64: this was fitted with a sealed capillary containing K$_3$PO$_{4(aq)}$ as an internal standard. The ^{1}H-decoupled ^{31}P NMR spectrum obtained at 298 K contained two sharp singlets at 3.83 and 1.15 ppm in a 1.0:0.65 ratio corresponding to the inorganic phosphate and DMP, respectively. In Figure 3 is shown the titration plot showing that each addition of Yb(OTf)$_3$ leads to the consumption of at least three equivalents of DMP. This is consistent with what is calculated theoretically for the most stable form of a Yb^{3+}(DMP)$_x$ complex, namely Yb^{3+}(DMP$^-$)$_3$, where each phosphate is bidentate bound in an overall six-coordinate species.[19] Interestingly, there is no observed signal for the DMP associated with the Yb^{3+}, perhaps indicative of an intramolecular dynamic site exchange phenomenon along with a metal-induced ^{31}P chemical shift. The complex formed between DMP and Yb^{3+} cannot undergo rapid site exchange with *free* DMP on the NMR time scale since there is no significant broadening or shift in the position of the free DMP peak at 1.15 ppm. At [Yb(OTf)$_3$] = 2.11 mM (0.16 equiv) a precipitate formed. Upon the addition of one full equivalent of Yb(OTf)$_3$, complete dissolution of the precipitate had occurred and the signal at 1.15 ppm was replaced by a new broad resonance detected at −16.05 ppm, the origins of which are uncertain at present but are probably representative of a dynamic mixture of higher-order (Yb^{3+}:DMP)$_n$ oligomers, (n = 2, 3,...n).

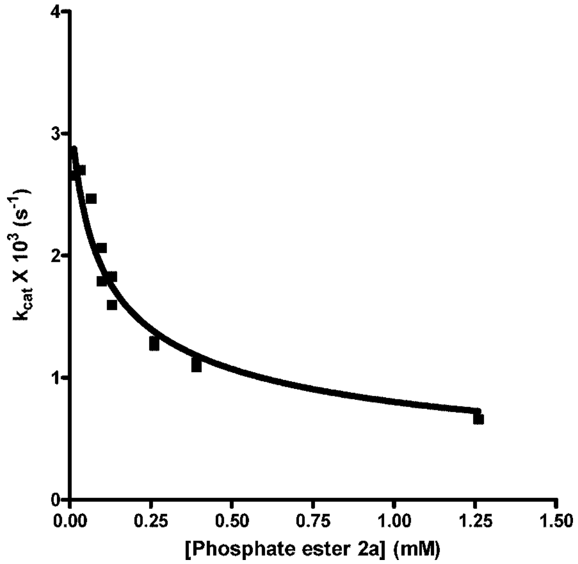

Figure 2. Plot of k_{cat} vs [**2a**] for the Yb(OTf)$_3$ (2.1 mM) catalyzed methanolysis reaction determined from the rate of appearance of product phenol at 305 nm, $^{s}_{s}$pH 2.0 and T = 25.0 ± 0.1 °C. Fitting the data to the expression $k_{obs} = k_{cat} = k_{max}*(0.25*K_d*((1 + 8*[\mathbf{2a}]/K_d)^{1/2} - 1))/[\mathbf{2a}] + k_{inf}$ gives $k_{max} = (3.30 \pm 0.30) \times 10^{-3}$ s^{-1}, $K_d = (1.6 \pm 0.1) \times 10^{-4}$ M and $k_{inf} = 0$ where k_{max} is the theoretical rate constant at infinite dilution and K_d is the dissociation constant for the dimeric complex and k_{inf} defines the plateau at infinite [**2a**]. (For the derivation of the above equation, see Desloges, W.; Neverov, A. A.; Brown, R. S. *Inorg Chem.* **2004**, *43*, 6752).

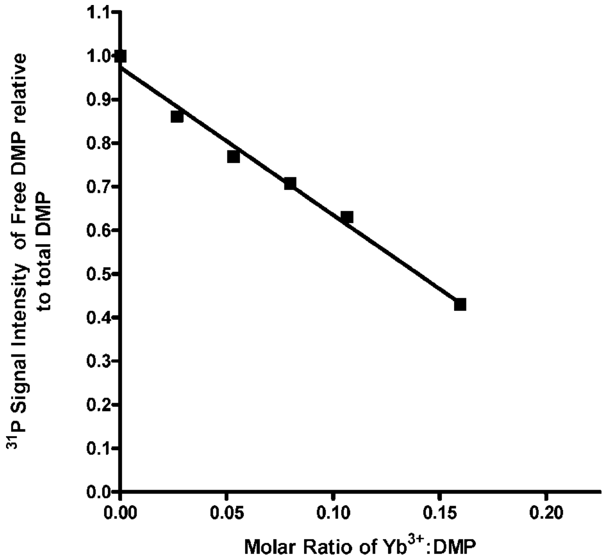

Figure 3. Titration plot of [DMP]$_{free}$/[DMP]$_{total}$ vs the molar ratio of [Yb(OTf)$_3$]/[DMP]$_{total}$ determined by the ^{31}P NMR signal intensity for [DMP]$_{free}$ as a function of added Yb(OTf)$_3$ at T = 25 °C. Spectra were recorded on a 600 MHz spectrometer operating at a frequency of 243.06 MHz. Fitting the data to a standard linear regression gives [DMP]$_{free}$/[DMP]$_{total}$ = (−3.39 ± 0.18) × [Yb(OTf)$_3$]/[DMP]$_{total}$ + (0.97 ± 0.02) with an r^2 = 0.989.

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[18] An x intercept is also apparent in the plot of k_{obs} versus [Yb(OTf)$_3$] shown in Figure 1. Although the relatively low concentration of substrate used to generate this plot leads to an x intercept that is close to zero at the 95% confidence interval. Increasing [**2a**] to 3.9×10^{-4} M removes this ambiguity.

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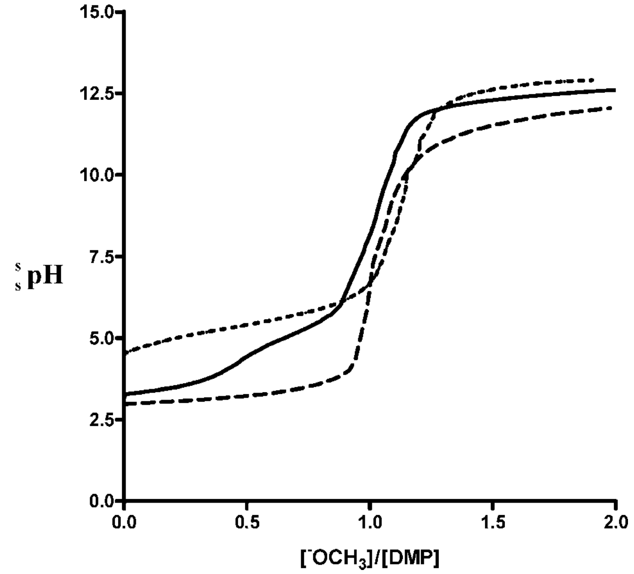
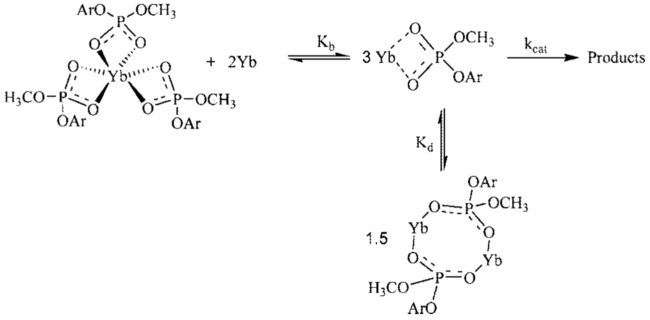


Figure 4. Potentiometric titration of DMP (1.65 mM) in CH_3OH at T = 25 °C in the presence of (a) 1/3 equiv of added $Yb(OTf)_3$ (broken line); (b) 1/6 equiv of added $Yb(OTf)_3$ (solid line, second ${}^{s}_{s}pK_a = 5.33$ at the equivalence point for the second ionization); (c) no added $Yb(OTf)_3$ (dotted line, ${}^{s}_{s}pK_a = 5.42$ at the equivalence point).

Scheme 1. Proposed Reaction Scheme Showing the Complexes Involved in the $Yb(OTf)_3$ Catalyzed Cleavage of **2a**[a]



[a] Charges omitted for clarity.

Further evidence for the formation of a tight $Yb^{3+}(DMP^{-})_3$ complex was obtained from the potentiometric titration data of Figure 4 where DMP was titrated in the presence of 1/3 equiv of $Yb(OTf)_3$ from which it was determined that the phosphate ester titrates as a strong acid liberating all its associated H^+ in a single ionization event. In a subsequent experiment, DMP was titrated in the presence of 1/6 equiv of $Yb(OTf)_3$. Under these experimental conditions, one-half of the added DMP titrates as a strong acid, which is followed by a second ionization event at slightly higher ${}^{s}_{s}$pH with a ${}^{s}_{s}pK_a$ of 5.33, consistent with ionization of free DMP (${}^{s}_{s}pK_a = 5.42$; ${}^{s}_{s}pK_a$ of diphenyl phosphate is 3.95[20]). Each of these ionization events accounts for one-half of the total amount proton added in the form of DMP. Also included in Figure 4 is the titration curve for DMP without added $Yb(OTf)_3$.

Scheme 1 shows a simplified process showing the species involved in the cleavage reaction promoted by Yb^{3+} that is consistent with all the data presented so far. In accord with the data of Figures 3 and 4, the ground-state complex is formulated as a 3:1 phosphate/Yb^{3+} species. The three phosphate diesters coordinated to the metal ion are shown as fully ionized, in agreement with the observed ${}^{s}_{s}$pH independent binding constant K_b, and bidentate bound, which is suggested by the calculated structure.[19]

The reactive species is formulated as the 1:1 phosphate/Yb^{3+} complex, which is in equilibrium with the inactive, or far less reactive, 2:2 dimeric complex. The structure of the 2:2 complex is not known but probably has the phosphates bridging between the two Yb^{3+} ions, with the residual coordination sites occupied by up to six solvent molecules. The dissociation constant, K_d, for the dimerization process is calculated to be $(1.6 \pm 0.1) \times 10^{-4}$ M from the fit of the data in Figure 2. The broadened ^{31}P NMR signal observed at −16.05 ppm is consistent with a dynamic exchange process of this type but does not rule out the existence of higher-order complexes, $(Yb^{3+}(DMP^{-}))_n$. For clarity, the charges and associated counterions, perchlorate and triflate, have been omitted from the scheme.

It is evident from the mechanistic scheme presented above that the binding constants (K_b) shown in Table 1, which were calculated from a fit of the k_{obs} vs [$Yb(OTf)_3$] data to eq 2, do not represent a typical binding process where single molecules of substrate and catalyst mutually associate to form the reactive 1:1 complex. The process shown in Scheme 1 actually involves the 3:1 phosphate/Yb^{3+} complex and 2 equiv of metal ion in an equilibrium with what is proposed as three reactive 1:1 phosphate/Yb^{3+} complexes. An exact analytical solution for this binding process is too complicated to be used for NLLSQ fitting of the data. Accordingly, the k_{obs} vs [$Yb(OTf)_3$] data have been fit to eq 2 which provides a reasonable approximation for the preference of the phosphate to be in the 1:1 relative to the 3:1 state. This approximation, while crude, is justified given that we do not attempt to analyze the binding constants of Table 1 beyond verifying that they are all numerically equivalent within error limits, and do not show a ${}^{s}_{s}$pH dependence over the [H^+] investigated.

d. Temperature Effects. The temperature dependence of k_{cat} was investigated for **2a** by determining the observed first-order rate constants (in duplicate) for the methanolysis of **2a** at saturating [$Yb(OTf)_3$] at ${}^{s}_{s}$pH 2.66 from 7 to 45 °C. Fitting of the k_{cat} vs $1/T$ data to a standard Eyring equation gave $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of 16.1 ± 0.5 kcal/mol and −15 ± 2 cal/mol·K (see Supporting Information).

e. Quantifying the Leaving Group Assistance by Bound Yb^{3+}. The position of the methoxycarbonyl substituent on the aryl ring is an essential component for effective Yb^{3+}-catalysis. While **2a** is highly reactive, its *para*-methoxycarbonyl isomer gives no observable reaction over 24 h in the presence of excess $Yb(OTf)_3$. The difference in reactivity is suggested to arise from a strong binding of Yb^{3+} to the TS for departure of the phenoxide leaving group from **2a**, which cannot occur with the para isomer. Evidence that the additional binding interaction occurs only in the TS for reaction of **2a** and is not realized in the ground state 1:1 complex comes from a comparison of the kinetically determined binding constant, K_b, for **2a** (Table 1) and that determined by spectrophotometric titration of its para isomer, $(3.2 \pm 0.8) \times 10^4$ M^{-1} (see Supporting Information). Since the average value for K_b of **2a** given in Table 1 is $(1.5 \pm 0.8) \times 10^4$ M^{-1}, it is apparent that the *ortho*-methoxycarbonyl group does not substantially enhance binding in the 1:1 complex prior to reaction, meaning that the binding in both cases is

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(20) Neverov, A. A.; Brown, R. S. *Inorg. Chem.* **2001**, *40*, 3588.

(21) Liu, T.; Neverov, A. A.; Tsang, J. S. W.; Brown, R. S. *Org. Biomol. Chem.* **2005**, *3*, 1525.

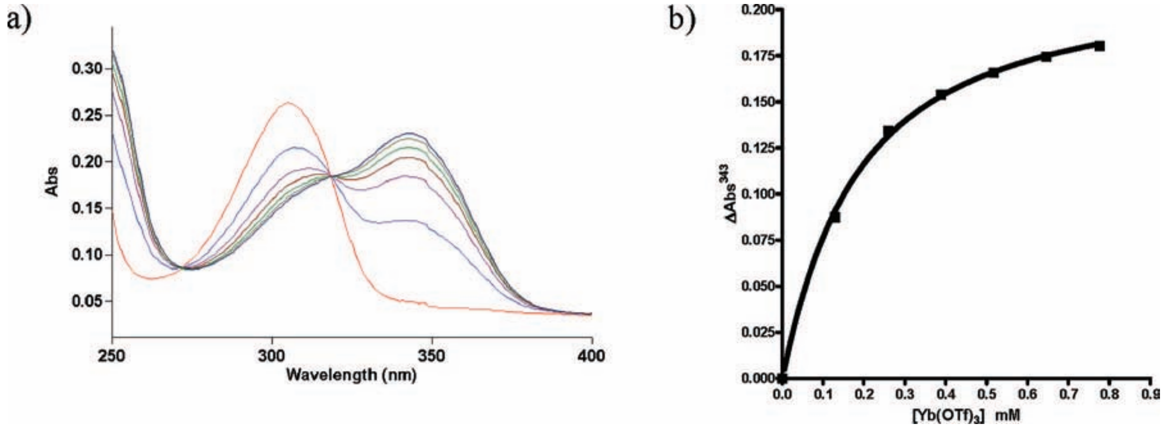


Figure 5. (a) UV−vis spectra corresponding to titration of 2-carbomethoxyphenol (5.2×10^{-5} M) with $Yb(OTf)_3$ at ${}^{s}_{s}\mathrm{pH}$ 2.66 and 25.0 ± 0.1 °C and (b) plot of $\Delta\mathrm{Abs}^{343\mathrm{nm}}$ vs $[Yb(OTf)_3]$; fit of the data to eq 2 gives $K_{\mathrm{cond}} = (6.6 \pm 0.5) \times 10^3\ \mathrm{M}^{-1}$.

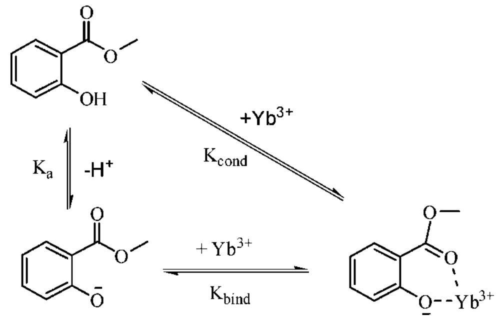
dominated by the interaction between the Yb^{3+} and the PO_2^- portion of the substrate.

The product of the kinetic reaction, which is only observed when there is an *ortho*- methoxycarbonyl group, is clearly tightly bound to the Yb^{3+}. To give an estimate of the enhancement of binding of provided by the *ortho*-methoxycarbonyl group, the binding constants of the series of phenols corresponding to phosphates **2a**−**h** with $Yb(OTf)_3$ were determined by spectrophotometric titrations at constant ${}^{s}_{s}\mathrm{pH}$. Lanthanides are known to undergo changes in speciation with the formation of $Ln_x(RO^-)_y(ROH)_z$ complexes at ${}^{s}_{s}\mathrm{pH}$ values above the ${}^{s}_{s}\mathrm{p}K_a$ of bound solvent.[5] Therefore titrations were all performed at least one ${}^{s}_{s}\mathrm{pH}$ unit below the reported ${}^{s}_{s}\mathrm{p}K_a$ of 5.3[15] for $Yb^{3+}(HOCH_3)_n \leftrightarrow Yb^{3+}(^-OCH_3)(HOCH_3)_m + H^+$ to ensure constant metal ion speciation throughout the binding studies. This limits the number of phenols we can study to those that exhibit significant binding at these low ${}^{s}_{s}\mathrm{pH}$ values. Shown in Figure 5a is a series of UV−visible spectra at ${}^{s}_{s}\mathrm{pH}$ 2.66 corresponding to the titration of 2-(methoxycarbonyl)phenol ($\lambda_{\max} = 305$ nm; $\varepsilon_{305} = 4326$ Abs/cm·M) with increasing $[Yb(OTf)_3]$ giving the Yb^{3+}/phenoxide complex ($\lambda_{\max} = 343$ nm; $\varepsilon_{343} = 5353$ Abs/cm·M). In Figure 5b is a plot of the $\Delta\mathrm{Abs}^{343\mathrm{nm}}$ vs $[Yb(OTf)_3]$ where the line through the data is obtained by fitting the data to eq 2, generating a conditional binding constant, $K_{\mathrm{cond}} = (6.6 \pm 0.5) \times 10^3\ \mathrm{M}^{-1}$ that corresponds to the process shown in Scheme 2. From K_{cond}, the ${}^{s}_{s}\mathrm{p}K_a$ of the phenol and ${}^{s}_{s}\mathrm{pH}$ of 2.66 at which the spectroscopic titration was performed, one calculates the binding constant, K_{bind}, using eq 3.

$$K_{\mathrm{bind}} = \frac{[\mathrm{H}^+]K_{\mathrm{cond}}}{K_a} \tag{3}$$

Shown in Table 2 are the calculated K_{cond} and K_{bind} values determined for the various parent phenols of phosphates **2a**−**h**. A Brønsted plot (Figure 6) of log K_{bind} vs the ${}^{s}_{s}\mathrm{p}K_a$ values of the corresponding phenols fits a standard linear regression of log $K_{\mathrm{bind}} = (0.84 \pm 0.06)\ {}^{s}_{s}\mathrm{p}K_a + (3.4 \pm 0.9)$; $r^2 = 0.9664$, 8 data. Binding constants were also determined for phenols not possessing the *ortho*-methoxycarbonyl substituent in order to quantify the stabilization afforded by this group to the binding of Yb^{3+}, see Table 2, last three entries. These data were fit to a standard linear regression of log $K_{\mathrm{bind}} = (0.96 \pm 0.04)\ {}^{s}_{s}\mathrm{p}K_a - (1.73 \pm 0.40)$. The two linear regressions are essentially parallel but offset along the *y* axis. Extrapolation of the lower line to ${}^{s}_{s}\mathrm{p}K_a$ 14.20 gives a computed binding constant of $8 \times 10^{11}\ \mathrm{M}^{-1}$ for a substrate of identical ${}^{s}_{s}\mathrm{p}K_a$ to 2-(methoxycarbonyl)phenol but lacking the *ortho*-substitution, demonstrating that the *o*-C(=O)OCH$_3$ provides an additional stabilization of ~3000-fold, or about 4.7 kcal/mol.

Scheme 2. Thermodynamic Cycle for the $Yb(OTf)_3$ Binding of the Phenol Corresponding to **2a**



f. Catalytic Rate and Binding Constants for Cleavage of Substrates 2a−h Promoted by Yb^{3+}. Phosphodiesters **2b**−**h**, having substituents at the 4- and 5-positions of the aryloxy leaving group were prepared in order to access their electronic effects in the Yb^{3+}-catalyzed cleavage reaction. All reactions were run at a constant low concentration of substrate, 10^{-5} M, in order to limit the effect of $[(Yb^{3+})(\mathbf{2a{-}h})]_2$ inhibition on k_{cat}. In any event, the K_d for formation of the inactive dimer responsible for the inhibition process demonstrated in Figure 2 is expected to be nearly invariant over the series of substrates **2a**−**h**. Plots of k_{obs} vs $[Yb(OTf)_3]$ (see Supporting Information) displayed saturation binding and the kinetic data were fit to eq 2 from which the catalytic rate constants k_{cat} and K_b presented in Table 3 were calculated.

Attempts to correlate log k_{cat} with the ${}^{s}_{s}\mathrm{p}K_a^{\mathrm{phenol}}$ in a single linear Brønsted plot resulted in extensive scatter of the data ($r^2 = 0.31$). Poor results were also obtained with the standard Hammett equation ($r^2 = 0.77$, using σ). Jaffé's extension of the Hammett equation to correlate substituent perturbations that influence more than one reactive center, shown in eq 4, has previously been employed to correlate rate data obtained for the hydrolysis of salicylic acid analogues of phosphate and sulfate esters, as

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(22) (a) Jaffé, H. H. *J. Am. Chem. Soc.* **1954**, *76*, 4261. (b) Greig, I. R.; Kirby, A. J. *J. Phys. Org. Chem.* **2004**, *17*, 498. (c) Bromilow, R. H.; Kirby, A. J. *J. Chem. Soc. Perkin Trans. 2* **1972**, 149. (d) Hopkins, A. R.; Green, A. L.; Williams, A. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1279. (e) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc. Perkin Trans. 2* **1974**, 61. (f) Barber, S. E.; Dean, K. E. S.; Kirby, A. J. *Can. J. Chem.* **1999**, *77*, 792.

Table 2. K_{cond} and K_{bind} Binding Constants of Yb^{3+} with Phenols Corresponding to Phosphates **2a**−**h**

phenol corresponding to parent phosphate	$^{s}_{s}\mathrm{p}K_a$ [a]	$[H^+]$ [b] × 10^3M	K_{cond} [c] × 10^3 M^{-1}	K_{bind} [d] M^{-1}
2a	14.20	2.2	6.6 ± 0.5	$(2.3 \pm 0.2) \times 10^{15}$
2b	11.18	21.9	2.3 ± 0.1	$(7.7 \pm 0.3) \times 10^{12}$
2c	12.57	3.7	4.1 ± 0.2	$(5.5 \pm 0.4) \times 10^{13}$
2d	12.79	7.3	4.9 ± 0.6	$(2.2 \pm 0.3) \times 10^{14}$
2e	13.20	3.7	2.6 ± 0.2	$(1.5 \pm 0.1) \times 10^{14}$
2f	14.50	2.2	10.0 ± 1.2	$(6.9 \pm 0.9) \times 10^{15}$
2g	14.65	2.2	3.8 ± 0.4	$(3.7 \pm 0.4) \times 10^{15}$
2h	14.82	2.2	4.8 ± 0.9	$(7.0 \pm 1.3) \times 10^{15}$
pentafluorophenol	8.84 [e]	(9.3×10^{-2}) [g]	$(8.0 \pm 3) \times 10^{-2}$	$(5.2 \pm 1.8) \times 10^{6}$
2-Cl-4-NO_2-phenol	9.35 [f]	6.8×10^{-2}	$(1.2 \pm 0.1) \times 10^{-1}$	$(1.9 \pm 0.1) \times 10^{7}$
2,4,5-trichlorophenol	10.73 [f]	(6.9×10^{-2}) [g]	$(1.0 \pm 0.3) \times 10^{-1}$	$(3.9 \pm 0.9) \times 10^{8}$

[a] Protocols for the determination of $^{s}_{s}\mathrm{p}K_a$ in methanol described in the Experimental Section. [b] Corresponds to $[HClO_4]$. [c] Determined by fitting ΔAbs vs $[Yb(OTf)_3]$ data to eq 2. [d] Calculated with eq 3 as described in text. [e] From ref 21. [f] From ref 6. [g] 12.9 mM 3-Br-pyridine partially ionized with 1.4 mM $HClO_4$ added as buffer and the reported $[H^+]$ refers to that measured potentiometrically.

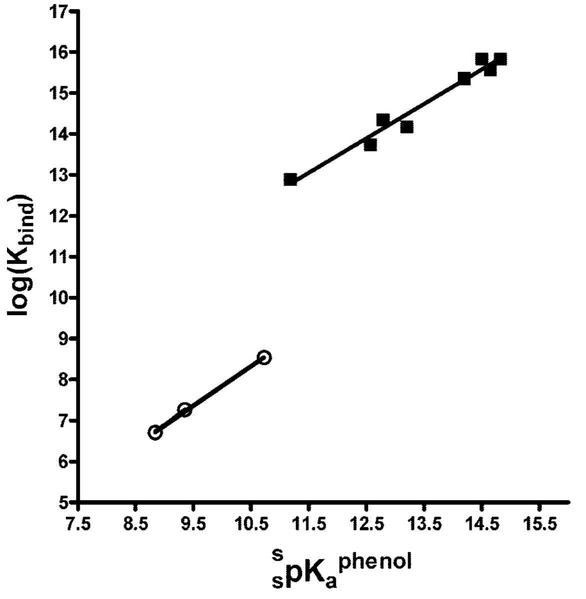


Figure 6. Plot of log K_{bind} vs $^{s}_{s}\mathrm{p}K_a$ for phenols corresponding to phosphates **2a**−**h** (filled squares ■) which fit a standard linear regression of log $K_{\mathrm{bind}} = (0.84 \pm 0.06)\ ^{s}_{s}\mathrm{p}K_a + (3.4 \pm 0.9)$, $r^2 = 0.9664$, and for phenols lacking an *ortho*-methoxycarbonyl substituent (open circles ○) which fit a standard linear regression of log $K_{\mathrm{bind}} = (0.96 \pm 0.04)\ ^{s}_{s}\mathrm{p}K_a - (1.73 \pm 0.4)$, $r^2 = 0.9984$.

Table 3. Kinetic Constants (Maximum Rate Constant (k_{cat}) and Binding Constant (K_b)) for the Methanolysis of 1× 10^{-5} M **2a**−**h** Catalyzed by $Yb(OTf)_3$ at $^{s}_{s}$pH 2.7 and $T = 25.0 \pm 0.1$°C

phosphate diester	$^{s}_{s}\mathrm{p}K_a^{\mathrm{MeOH}}$	$k_{\mathrm{cat}} \times 10^3$ (s^{-1}) [a]	K_b (M^{-1}) [a]
2a	14.20	5.3 ± 0.2	$(2.3 \pm 1.1) \times 10^{5}$
2b	11.18	51.2 ± 0.8	$(2.8 \pm 0.3) \times 10^{5}$
2c	12.57	7.6 ± 0.2	$(5.9 \pm 1.5) \times 10^{4}$
2d	12.79	18.5 ± 0.2	$(1.4 \pm 0.3) \times 10^{5}$
2e	13.20	2.3 ± 0.04	$(9.1 \pm 2.3) \times 10^{4}$
2f	14.50	19.1 ± 0.6	$(3.5 \pm 1.1) \times 10^{4}$
2g	14.65	1.5 ± 0.06	$(1.5 \pm 0.3) \times 10^{4}$
2h	14.82	5.6 ± 0.1	$(3.6 \pm 0.8) \times 10^{4}$

[a] $k_{\mathrm{cat}}^{\mathrm{max}}$ and K_b determined by fits of the k_{obs} vs $[Yb(OTf)_3]$ data to eq 2 as described in text.

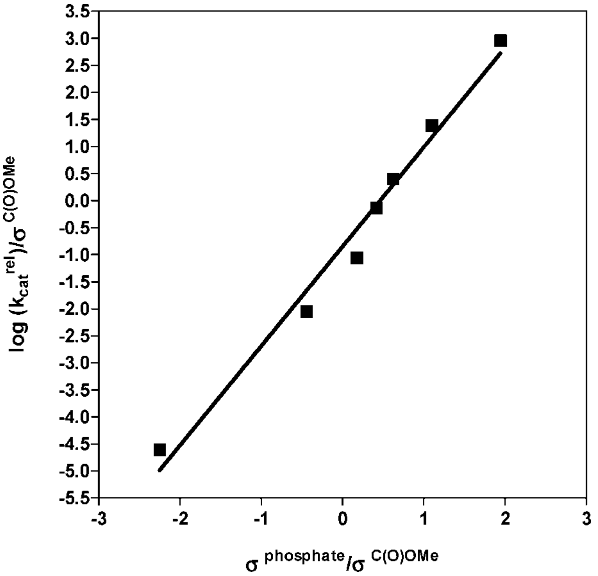


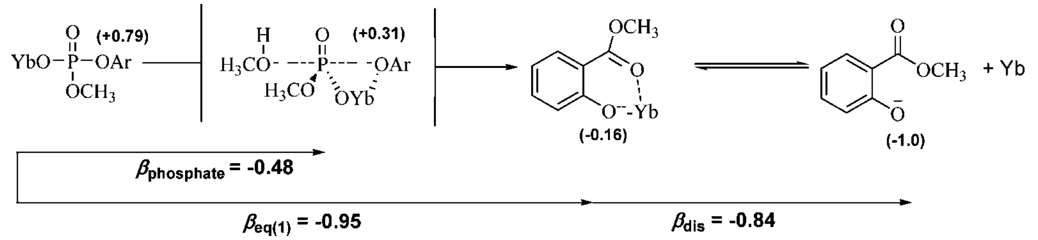
Figure 7. Jaffé plot for the $Yb(OTf)_3$-catalyzed methanolysis of phosphate diesters **2a**−**h** (1 × 10^{-5} M) determined at $^{s}_{s}$pH 2.66 and 25.0 ± 0.1 °C. The data are fit to eq 4 ($r^2 = 0.981$) as described in the text from which $\rho_{\mathrm{phosphate}}$ and $\rho_{\mathrm{C(O)OMe}}$ were determined to be (1.84 ± 0.11) and (−0.85 ± 0.14).

well as for numerous other reactions where an ortho substituent is thought to play a direct role in transition state stabilization through general acid/base catalysis or by other means.[22] Shown in Figure 7 is the Jaffé plot obtained for the $Yb(OTf)_3$-catalyzed solvolysis of phosphate diesters **2a**−**h**, from which the sensitivities at the phosphate and $C(O)OCH_3$ groups to substituents, $\rho_{\mathrm{phosphate}}$ and $\rho_{\mathrm{C(O)OMe}}$, were determined to be (1.84 ± 0.11) and (−0.85 ± 0.14), respectively. The relatively large and positive value of $\rho_{\mathrm{phosphate}}$ indicates that aryl substituents that withdraw electron density from the phenolic oxygen render the system more reactive. On the other hand, $\rho_{\mathrm{C(O)OMe}}$ is found to have a significantly negative value which indicates that electron donation to the methoxycarbonyl substituent accelerates the catalytic reaction. The opposing effect substituents can have on reactivity depending on the aryl substitution pattern is most dramatically illustrated with substrates **2f** and **2g**, which have 4-OMe and 5-OMe substituents, respectively. Despite the fact that the corresponding phenols have nearly identical $^{s}_{s}\mathrm{p}K_a^{\mathrm{phenol}}$ values, the Table 3 data indicate that these two substrates have k_{cat} values that are an order of magnitude different.

$$\frac{\log(k_{\mathrm{cat}}^{\mathrm{x}}/k_{\mathrm{cat}}^{\mathrm{H}})}{\sigma^{\mathrm{C(O)OMe}}} = \rho_{\mathrm{phosphate}} \frac{\sigma_{\mathrm{phosphate}}}{\sigma^{\mathrm{C(O)OMe}}} + \rho_{\mathrm{C(O)OMe}} \qquad (4)$$

g. Charge Map and Transition State Analysis. The $\rho_{\mathrm{phosphate}}$ determined for solvolysis of **2a**−**h** can be converted to a

Scheme 3. Charge Map for the Yb(OTf)$_3$ Catalyzed Methanolysis of Phosphate Diesters **2a**−**h**



Brønsted slope of −0.48.[23] This value qualitatively indicates a build-up of negative charge on the phenolic oxygen of substrates **2a**−**h** on going from the ground-state to the transition state of the reaction. However, in order to quantify the extent of bond rupture at the transition state, an estimation of effective charge residing at this site in the ground-state and product must first be determined and from this the β_{eq} calculated.

The effective charge residing on the phenolic oxygen in a phosphate diester has been calculated at +0.74 in aqueous solution.[24] In a similar manner the effective charge on a phenolic oxygen of a phosphate triester is calculated to be +0.83. The starting state of the current Yb^{3+}-catalyzed reaction in methanol, however, involves neither a fully ionized phosphate diester nor the neutral protonated species resembling a phosphate triester, but rather a fully ionized phosphate diester tightly bound to Yb^{3+} as a 1:1 complex. Accordingly, the effective charge on the phenolic oxygen of the metal bound phosphate diesters in Yb^{3+}/(**2a**−**h**) is assigned an intermediate value of +0.79 under the assumption that the solvent effect of methanol is comparable to that of water insofar as the net charges on the aryloxy O are concerned.[25,26] By definition, the effective charges residing on the phenol and phenolic oxygens are 0 and −1, but if the aryloxy group in the transition state of the Yb^{3+}-promoted cleavage reaction is being transformed into a metal-bound phenoxide, the effective charge on the phenolic oxygen should be less negative than −1 in the product state. Several lines of evidence suggest that the nascent product of the reaction is the metal-bound phenoxide. First, the UV−vis observable product under standard reaction conditions is observed to be the Yb^{3+}-bound phenoxide (λ_{max} = 343 nm) rather than the free phenol (λ_{max} = 305 nm). Additionally, the $\rho_{C(O)OMe}$ of −0.85 ± 0.14 indicates that the methoxycarbonyl substituent acquires positive charge in the transition state of the reaction, consistent with its proposed role in binding the Yb^{3+}. Finally, only substrates possessing an *ortho*-methoxycarbonyl substituent, which is shown to substantially stabilize the Yb^{3+}-bound phenoxide complexes, undergo any measurable cleavage under the conditions of this study, suggesting that this group acts as a template to orient the Yb^{3+} into position where it can physically bind to the *ortho*-phenoxy oxygen to provide leaving group assistance.

In accord with the preceding arguments the effective charge residing on the metal-bound phenoxide is calculated as $EC_{ArOYb} = EC_{ArO^-} + \beta_{bind} = -1.0 + (0.84) = -0.16$, where EC = effective charge and the numerical value of 0.84 comes from the slope of the relationship shown in Figure 6 for Yb^{3+}-binding to phenols where $\log K_{bind} = (0.84 \pm 0.06){}^{s}_{s}pK_a + (3.4 \pm 0.9)$. The total charge change on the phenoxy oxygen for the equilibrium reaction from Yb^{3+}/**2** ↔ Yb^{3+}/phenoxide is calculated to be $\beta_{eq} = (-0.16 + (-0.79)) = -0.95$ which should represent the magnitude of the Brønsted slope expected for complete cleavage of the phosphorus−OAr bond in the Yb^{3+}-catalyzed reaction. The extent of bond cleavage can be estimated through the Leffler parameter,[27] $\alpha = \beta_{phosphate}/\beta_{eq} = (-0.48/-0.95) = 0.51$, suggesting that the P−OAr bond cleavage has progressed about halfway from bound substrate to bound phenoxide. The complete charge map is shown in Scheme 3.

Cleavage reactions of phosphate diesters and triesters with departing OAr groups are typically interpreted in terms of concerted A_nD_n mechanisms where bond formation and rupture occur simultaneously.[13] The "tightness" of the diester transition state is generally thought to be intermediate between those of phosphate triesters and monoesters, which react by associative and highly dissociative processes, respectively.[28] Stepwise ($A_n + D_n$) mechanisms have also been reported for several metal-catalyzed reactions of phosphate diesters.[29] In these cases the rate-limiting step can be either nucleophilic addition or departure of the leaving group and both mechanisms have been proposed. The extensive bond cleavage in the transition state of the current reaction (~50%) requires that if the stepwise ($A_n + D_n$) mechanism is in operation then nucleophilic attack at this point along the reaction coordinate must also be well advanced. Demonstration that this criterion is not met provides evidence that the cleavage reaction may proceed by a concerted A_nD_n mechanism.

The nucleophile in the present reaction cannot be external or free methoxide for two reasons. First, inspection of the data in Table 1 indicates that the k_{cat} term is independent of ${}^{s}_{s}$pH over at least 2 units. Also, from Table 1, entry 2, k_{cat} is $(2.45 \pm 0.06) \times 10^{-3}$ s^{-1} at ${}^{s}_{s}$pH 1.86, and since the autoprotolysis constant of methanol is $10^{-16.77}$,[15] the second-order rate constant for any free methoxide-catalyzed solvolysis of phosphodiester **2a** would need to be 2.0×10^{12} M^{-1} s^{-1}, exceeding the reported diffusion limit[30] of 5.2×10^{10} M^{-1} s^{-1} in methanol by almost 2 orders of magnitude. The fact that the k_{cat} term is independent

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(23) The fact that there is more than one aryl substituent involved in the catalysis of phosphate esters **2a**−**h** necessitates the use of the Jaffé equation as opposed to the more common Brønsted relationship. The reaction constants obtained from the Jaffé plot can be converted to a Brønsted slope using the relationship $\beta = \rho \times \Delta\sigma/\Delta{}^{s}_{s}pK_a$.

(24) Bourne, N.; Williams, A. *J. Org. Chem.* **1984**, *49*, 1200.

(25) On the basis of the changes in the first and second acid dissociation constants of $H_2PO_4^-$ bound between two Co(III) centers, it appears that two metal ions have the effect of a single proton. By extension, a single metal ion is predicted to have the effect of 1/2 a proton: (a) Edwards, J. D.; Foong, S.-W.; Sykes, A. G. *J. Chem. Soc., Dalton Trans.* **1973**, 829.

(26) Williams, N. H.; Cheung, W.; Chin, J. *J. Am. Chem. Soc.* **1998**, *120*, 8079.

(27) (a) Leffler, J. E.; Grunwald, E. *Rates and equilibria of organic reactions*; Wiley: New York, 1963. (b) Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425.

(28) Hengge, A. C. *Curr. Org. Chem.* **2005**, *9*, 61.

(29) (a) Linjalahti, H.; Feng, G.; Mareque-Rivas, J. C.; Mikkola, S.; Williams, N. H. *J. Am. Chem. Soc.* **2008**, *130*, 4232. (b) Humphry, T.; Forconi, M.; Williams, N. H.; Hengge, A. C. *J. Am. Chem. Soc.* **2002**, *124*, 14860. (c) Humphry, T.; Forconi, M.; Williams, N. H.; Hengge, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 11864.

(30) Chen, R.; Freeman, G. R. *J. Phys. Chem.* **1995**, *99*, 4970.

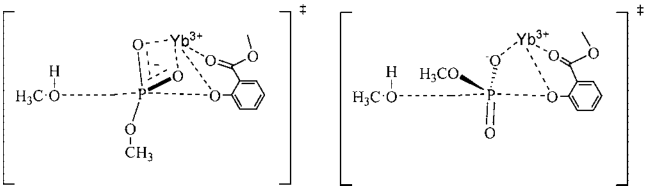

Figure 8. Two proposed transition structures for the Yb(OTf)$_3$-catalyzed concerted methanolysis of phosphate diesters **2a**−**h**. Associated counterions have been omitted for clarity.

of $^{s}_{s}$pH effectively rules out the delivery of a Yb^{3+}-coordinated methoxide since the $^{s}_{s}$pK_a reported for a Yb^{3+}(CH$_3$OH) $\leftrightarrow$ Yb^{3+}($^{-}$OCH$_3$) ionization is 5.3,[15] and a $^{s}_{s}$pK_a for a similar system in which a negatively charged phosphate is also bound to the Yb^{3+} should be at least this value or greater. Accordingly, either Yb^{3+}-coordinated methanol or solvent methanol appear to be the only reasonable nucleophiles in the reaction medium.

The extent to which nucleophilic attack by methanol has progressed at the transition state can be gauged from the solvent deuterium kinetic isotope effect. An average k^H/k^D of 1.10 ± 0.15 was determined at the four $^{s}_{s}$pH values examined, see Supporting Information. This value is within experimental error of unity and far less than the normal primary kinetic isotope effect that would signify a proton in flight between an attacking methanol and the most likely base, the solvent. The observed isotope effect is consistent with a minimal amount of nucleophilic participation in the transition state. This is not an unexpected result since free methanol or a metal-coordinated one is a poor nucleophile so it would be improbable that the Yb^{3+}-assisted leaving group departure would lag behind bond formation to phosphorus. The reaction is therefore classified as a concerted A$_n$D$_n$ mechanism with a transition state formulated as having extensive departure of the leaving group assisted by Yb^{3+}-coordination to the methoxycarbonyl group, phenolic oxygen, and at least one of the phosphoryl oxygens and little association of the incoming nucleophile as illustrated in Figure 8. This would be consistent with the activation parameters showing a low enthalpy and slightly negative entropy suggestive of dissociative process with some restriction of solvent and nucleophile in the TS. The degree of advancement of leaving group departure relative to nucleophile association falls short of formation of a neutral meta-phosphate-like (CH$_3$OPO$_2$) intermediate. Such species have been shown by a variety of techniques to be too unstable to exist as freely diffusible entities.[31]

h. Catalytic Rate Acceleration. The level of transition state stabilization realized during the Yb^{3+}-promoted reaction of **2a** can be gauged by determining the rate acceleration obtained in the current reaction relative to a suitable comparison rate in the absence of metal ion. However, the spontaneous decomposition of phosphate diesters **2a**−**h** is exceedingly slow and in fact no discernible reaction of **2a** is seen over a several month period at $^{s}_{s}$pH 1.5. For this reason we resort to a correlation analysis from literature data.

The spontaneous hydrolysis of bis-aryl phosphate diesters is reported to be highly dependent on the basicity of the leaving group and conforms to the linear regression $\log k_{hyd} = 1.57 - 0.97\mathrm{p}K_a^{lg}$ at 100 °C, where k_{hyd} is in min^{-1}.[32] From the Brønsted correlation one can calculate a k_{hyd} of 1.48×10^{-10} s^{-1} for cleavage of a hypothetical *bis*-**2a** phosphate diester of pK_a^{H2O} 9.92.[33] To correct this rate constant at 100 °C to one predicted in methanol at room temperature requires knowledge of the aqueous activation parameters. The entropy of activation ($\Delta S^{\ddagger}$) for the neutral hydrolysis of *bis*-2,4-dinitrophenylphosphate is reported to be −25.5 eu, and we assume that this value obtains for the series of bis-aryl phosphates in question. Employing the Eyring equation and the $\Delta S^{\ddagger}$ determined for *bis*-2,4-dinitrophenylphosphate, one computes a $\Delta H^{\ddagger}$ for hydrolysis of *bis*-**2a** phosphate diester of 29.3 kcal/mol from the calculated k_{hyd} at 100 °C. The hydrolysis rate constant for **2a** determined at 25 °C is computed to be 5.4×10^{-15} s^{-1}, which we assume is roughly the same as the spontaneous methanolysis rate constant. Comparing this value to the average k_{cat} for the Yb^{3+}-catalyzed reaction in methanol provides a rate acceleration on the order of 1×10^{12}, which corresponds to 16.4 kcal/mol of transition state stabilization.[34]

Conclusions

Dissection of the roles that metal ions play in catalysis and evaluation of their individual contributions to the overall rate enhancement has been markedly advanced by the study of highly efficient small-molecule catalysts.[1,5,6,26,35−37] For example, double Lewis acid activation of some methyl aryl phosphate diesters (as DNA models) by a ligand exchange inert dicobalt(III) system is reported to enhance the rate of cyclization by a factor of ~10^{11} over the uncatalyzed reaction through a combination of Lewis acid activation and provision of an intramolecular oxide nucleophile.[38,39,26] In a related system, a TrpnCo(III)-complex-promoted cleavage of aryl methyl phosphates[14] indicates the catalyst accelerates the hydrolysis of methyl *p*-nitrophenyl phosphate by ~4 × 10^5 relative to the hydroxide promoted hydrolysis at 37 °C.[40] Cleavage of aryl methyl phosphate diesters[6] and 2-hydroxypropyl aryl phosphate diesters[37a] mediated by **1** in *methanol* affords very high rate enhancements for cleavage of a relatively large range of these

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(34) A comparison of the neutral hydrolysis rate constants obtained over the $^{s}_{s}$pH range 2−9 for bis-aryl phosphate diesters and aryl methyl phosphate diesters reveals that the former react on the order of 3 times faster and accordingly the calculation of the catalytic rate acceleration for the Yb(OTf)$_3$-catalyzed methanolysis of **2a** can be corrected upwards by this amount Kirby, A. J.; Younas, M. *J. Chem. Soc. B* **1970**, 1165.

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phosphates ($10^{11}-10^{13}$) via a combination of Lewis acid activation, provision of an internal nucleophile, and in a few cases with methyl aryl phosphates having *o*-NO_2 *or* $C(=O)OCH_3$ substituents,[6] what appears to be leaving group assistance.

It has been proposed, but only sparsely demonstrated in the case of simple phosphate diester reactions, that metal ions can assist the departure of the leaving group as is often suggested to be the case within the active site of metalloenzymes.[7] It seems odd that, if leaving group departure assisted by metal ions confers such an energetic advantage to the biological systems that are said[7] to employ it, this is not a widely, nor easily, demonstrated effect in small molecule catalytic chemistry. It is probable that the aqueous or, in some cases, largely aqueous media in which most of the studies of small molecule, enzyme-mimicking, catalysts have been studied, solvate the anionic substrates and positively charged metal ion containing catalysts to an extent that dampens the interactions between the transforming substrate, its leaving group and the catalyst that are required to realize significant levels of catalysis.

The reaction of phosphates **2a**−**h** catalyzed by Yb^{3+} does not appear to involve modes of catalysis other than leaving group assistance by the metal ion. The available data indicates that the unreactive *p*-isomer of **2a** binds to Yb^{3+} as well as does the ortho isomer **2a**, so the *o*-methoxycarbonyl group does not provide a significant enhancement of substrate binding to the Yb^{3+}. However, the kinetic data indicate that its presence is absolutely required for any Yb^{3+}-mediated cleavage which suggests that, somehow in the TS of the reaction, the *o*-methoxycarbonyl provides assistance to the departure of the leaving group. Coordination of the diester−PO_2^- unit to Yb^{3+} without translocation of the metal ion to accept binding to the *o*-methoxycarbonyl in the TS is only expected to inhibit the ability of the phosphoryl oxyanion to provide the electron push to initiate OAr cleavage via a highly dissociative transition state. There is some question as to the nature of the nucleophile in the reaction, for which we favor free methanol, since coordination of a methanol to the metal ion for an intramolecular attack would only render a poor nucleophile worse and seems unlikely on geometric grounds in any event.

The effect we note here is not small. It is remarkable that the combination of a weakly coordinating *ortho*-methoxycarbonyl substituent on a departing aryloxy anion, a strongly Lewis acidic Yb^{3+} ion that binds the phosphoryl group in the ground-state and the leaving group in the transition state and perhaps, most importantly, a methanolic reaction medium of reduced dielectric constant, serve to stabilize the transition state for cleavage of this class of phosphate diester by 16 kcal/mol, thereby imparting rate accelerations on the order of 10^{12}-fold.

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Supporting Information Available: Tables of pseudo-first-order rate constant for reactions of **2a** with Yb^{3+} from 7−45 °C and tables of pseudo-first-order rate constants for reaction of **2a** in CD_3OD. Plots of the pseudo-first-order rate constants vs $[Yb(OTf)_3]$ for reactions of substrates **2a**−**h**. Plots of the pseudo-first-order rate constants vs $[Yb(OTf)_3]$ for reactions of substrate **2a** at the various ${}^{s}_{s}pH$ values listed in Table 1. Supporting text describing the NMR experiment for product study for Yb^{3+} promoted cleavage of **2a** and NMR and mass spectroscopic data for all substrates used in this study; (10 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) The reported second-order rate constant for the hydrolysis of methyl *p*-nitrophenyl phosphate promoted by TrpnCo(II) is 0.69 $M^{-1}\ s^{-1}$ at 37 °C, while the second-order rate constant for the hydroxide reaction is $\sim 1.9\times 10^{-6}\ M^{-1}\ s^{-1}$ at 45 °C (ref 39).