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Mononuclear Co(III)-complex promoted phosphate diester hydrolysis: dependence of reactivity on the leaving group[†]

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ABSTRACT: The TrpnCo(III)(OH)(OH_2)-promoted hydrolysis of a range of methyl aryl phosphate diesters was investigated at 37 °C and $I = 0.1\,\text{M}$ ($NaClO_4$). The pH–rate profile confirms that the aqua-hydroxy form of the complex is the only kinetically significant ionic form. At pH 6.9, all the reactions are first order in both diester and Co(III) complex. Plotting the second-order rate constant for Co(III) complex-promoted hydrolysis against the pK_a of the leaving aryloxy group revealed a bent LFER indicating a change in rate-limiting step. This is discussed in terms of either a change from rate-limiting hydrolysis to rate-limiting binding or the presence of a phosphorane intermediate. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: phosphate diester; metal ion catalysis; hydrolysis; linear free energy relationship; phosphorane

INTRODUCTION

Phosphate esters are extremely kinetically stable to hydrolysis under physiological conditions.[1] This means that the enzymes that catalyse these processes are the most proficient established to date.[2] Many of these enzymes require metal ion cofactors,[3] which are often in intimate contact with the substrate at the active site. Hence extensive efforts over the years have been directed at understanding the link between these interactions and efficient catalysis.[4] A central question is whether the same transition state as in solution is stabilized by the contact with the ions, or whether they significantly change the nature of the transition state.[5] Model complexes provide the most accessible route to investigating this question in detail for defined interactions between metal ions and substrates.

Metal ion complexes also form the basis of the most effective artificial systems that have been created in efforts to reproduce enzyme-like reactivity. Since the structure of the ligands coordinating the metal ions are the only means to control the modes of action and activity of a particular ion, rational improvement will depend on understanding how activity and ligand structure are related. Owing to its defined coordination geometry and relatively slow rates of ligand exchange, Co(III) has been used extensively to explore metal ion-promoted phosphate hydrolysis.[6]

A key example is the systematic investigation by Chin *et al*.[7] on the effect of ligand structure on the reactivity of mononuclear Co(III) complexes with *cis* binding sites in promoting hydrolysis of bis-4-nitrophenyl phosphate. Despite the similarities in structure, the complexes **1**, **2** and **3** showed relative reactivities of 1:50:300. These data were rationalized by considering the increase in strain at the metal ion centre as it becomes part of a four-membered ring including the reacting phosphate diester (as shown schematically in Fig. 1). The angle ϕ becomes more acute as the transition state is formed, and this is facilitated if the ligand can accommodate an obtuse complementary bite angle θ.

However, to understand better whether the metal ion-promoted pathway involves any change in transition state at the phosphate and to be able to extend these data to different substrates, systematic study of the effect of changing the substrate structure is required. To show that the differences correspond to rate-limiting diester cleavage for diester substrates, it was demonstrated that bis-2,4-dinitrophenyl phosphate reacted more rapidly in each case.[7] However, the effect of varying the leaving group on the transition state structure of the phosphate diester was not investigated in detail. In this paper, we describe the TrpnCo (**3**)-promoted hydrolysis of the methyl aryl phosphates (**4**).

EXPERIMENTAL

Materials

Acetone and *tert*-butyl alcohol were dried over activated 4 Å molecular sieves and distilled prior to use. Dichloromethane was distilled from calcium hydride prior to use.

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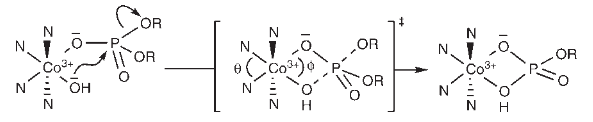
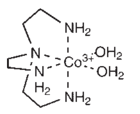
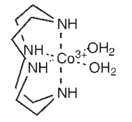


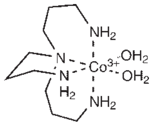
Figure 1. As the transition state for metal hydroxide attack at the phosphate is reached, the angle ϕ has to become acute. This is facilitated if the complementary angle θ can become obtuse



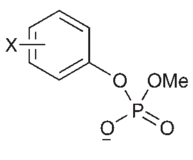
TrenCo
1



CyclenCo
2



TrpnCo
3



4a X = 3-chloro
4b X = 3-nitro
4c X = 4-nitro
4d X = 3,5-dinitro
4e X = 3-fluoro,4-nitro
4f X = 3,4-dinitro
4g X = 2,4-dinitro

cis-Diaqua-Co(III)-tris(3-aminopropyl)amine was synthesized according to previously published methods.[8]

Methyl aryl phosphate diesters were synthesized according to the following general procedure. Dry imidazole (0.26 g, 3.7 mmol) was dissolved in dichloromethane (5 ml) and added slowly to a solution of phenol (3.7 mmol) in dichloromethane (5 ml). Dimethyl chlorophosphate (0.4 ml, 3.7 mmol) in dichloromethane (2 ml) was added slowly with stirring and the solution was stirred at room temperature for 16 h. The resulting precipitate was removed by filtration, washed with dichloromethane and the filtrate concentrated *in vacuo*. The crude triester was purified by flash chromatography on silica if necessary, then dissolved in dry acetone (5 ml) and added dropwise to a stirred solution of lithium chloride (0.16 g, 3.7 mmol) in dry acetone (~25 ml). The solution was heated at reflux for 30 min and allowed to stand overnight. The precipitate was filtered off, washed with dry acetone (3 × 10 ml) and air dried to yield the lithium salt of the methyl aryl phosphate diester. **4a**: δ_H (250 MHz, D_2O) 3.70 (3H, d, $J = 11$ Hz), 7.01–7.12 (2H, m), 7.15–7.22 (1H, m), 7.29–7.35 (1H, m); δ_P (101 MHz, D_2O) -2.38. **4b**: δ_H (250 MHz, D_2O) 3.68 (3H, d, $J = 11.3$ Hz), 7.65–7.58 (2H, m), 8.11–8.09 (2H, m); δ_P (101 MHz, D_2O) -2.47. **4c**: δ_H (250 MHz, D_2O) 3.68 (3H, d, $J = 11.3$ Hz), 7.50 (2H, d, $J = 8.5$ Hz), 8.17 (2H, d, $J = 8.5$ Hz), δ_P (101 MHz, D_2O) -2.90. **4d**: δ_H (250 MHz, D_2O) 3.65 (3H, d, $J = 11.3$ Hz), 8.40 (2H, dd, $J = 2.2, 1.2$ Hz), 8.90 (1H, t, $J = 2.1$ Hz); δ_P (101 MHz, D_2O) -3.01. **4e**: δ_H (250 MHz, D_2O) 3.65 (6H, d, $J = 11.3$ Hz), 6.78–6.64 (1H, m), 7.27–7.17 (1H, m), 8.17–8.06 (1H, m); δ_P (101 MHz, D_2O) -3.42. **4f**: δ_H (250 MHz, D_2O) 3.70 (3H, d, $J = 11.3$ Hz), 7.50 (1H, ddd, $J = 9.2, 2.5, 0.9$ Hz), 7.71 (1H, dd, $J = 2.5, 0.6$ Hz), 8.09 (1H, d, $J = 9.2$); δ_P (101 MHz, D_2O) -3.62. **4g**: δ_H (250 MHz, D_2O) 3.66 (3H, d, $J = 11.6$ Hz), 7.69 (1H, dd, $J = 9.1, 0.6$ Hz), 8.50 (1H, dd, $J = 9.1, 0.6$ Hz), 8.91 (1H, dd, $J = 2.7, 0.6$ Hz); δ_P (101 MHz, D_2O) -3.81.

To prepare isotopically labelled dimethyl phosphate, ^{18}O-enriched water (97% ^{18}O) (0.075 ml, 4.16 mmol) was added to potassium *tert*-butoxide (0.8 g, 8.33 mmol) in 10 ml of *tert*-butyl alcohol. Dimethyl chlorophosphate (0.38 ml, 3.75 mmol) was added and the solution stirred overnight. The solution was then lyophilized and the resulting white solid was crystallized from ethanol to yield dimethyl [^{18}O] phosphate (0.2 g, 32%). δ_H (250 MHz, D_2O) 3.63 (6H, d, $J = 10.7$ Hz, CH_3); δ_P (101 MHz, D_2O) 3.56. MS (ES): 126.9 (%TIC: 68.18, ^{18}O-enriched dimethyl phosphate), 124.9 (%TIC: 28.26, dimethyl [^{16}O]phosphate).

Kinetic methods

All solutions were made up with doubly distilled, deionized water and AnalaR-grade reagents. Alkaline and acidic solutions were made up from BDH ConvoL ampoules. The buffers used in determining the pH–rate constant profile were MES, MOPS, EPPS, CHES and CAPS and were freshly prepared for each experiment. The experiments at pH 6.9 used MOPS buffer. The stock TrpnCo (**3**) solution was titrated to the relevant buffer pH before mixing with the buffer prior to each experiment. The pH was measured at 37 °C before and after each run and did not vary in the course of the experiment. All UV–visible readings were taken on a Varian Cary 1 Bio UV–visible spectrophotometer and first-order rate constants obtained by fitting the observed changes in absorbance to a first-order exponential curve with Cary WinUV software. In all experiments, TrpnCo (**3**) was in $\geq$10-fold excess over the phosphate substrate. For the slower reactions (**4a** and **4b**), the reaction progress was monitored by quenching aliquots using an equal volume of pH 12.5 phosphate buffer (2 M), analysing them by HPLC and using an initial rate analysis of the data. Solvents for HPLC were of HPLC grade, filtered through Sartolon polyamide 0.2 μm filters and degassed with helium; the column used was a Phenomenex Luna C18(2) 5 μm, 250 × 4.6 mm i.d. reversed-phase column and the eluent was a 60:40 methanol–20 mM ammonium phosphate buffer (pH 5.5). Both the UV–visible and HPLC methods were used with **4c** and gave excellent agreement.

RESULTS

The pH dependence of the hydrolysis reaction was measured at 37 °C using **4f** as the substrate and a TrpnCo (**3**) concentration of 1 mM, 10 mM buffer and 0.1 M $NaClO_4$ (Fig. 2). These data were fitted to a single

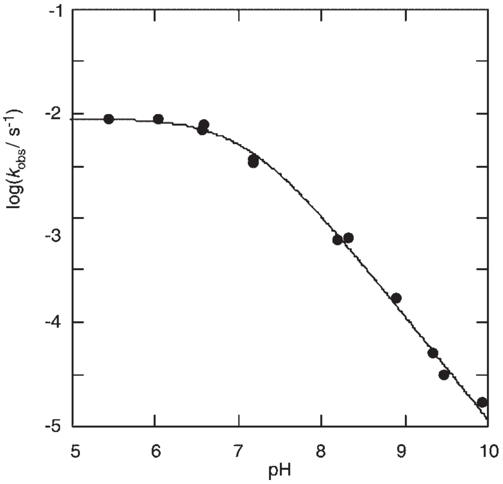


Figure 2. pH–rate constant profile for the hydrolysis of 0.05 mM **4d** promoted by 1 mM **3** (37 °C, 10 mM buffer and 0.1 M $NaClO_4$). The line shown is a non-linear least-squares fit to a scheme where a single ionisation controls the pH dependence, and gives a kinetic pK_a of 7.11 ± 0.06 and a maximal rate of $(9.0 \pm 0.9) \times 10^{-3}\ s^{-1}$

ionization event with $pK_a = 7.11 \pm 0.06$. None of the substrates have ionizable groups within the pH range measured, and all subsequent reactions were followed at pH 6.9. Using **4c** as substrate, the rate of hydrolysis promoted by 1.2 mM TrpnCo (**3**) was measured with and without 10 mM MOPS at pH 6.9 in the presence of 0.1 M $NaClO_4$ and showed a 10% increase in the observed rate constant; however, in the absence of added $NaClO_4$, the rate constants decreased by a similar proportion with the same change in buffer concentration. Thus, at the buffer concentrations used, buffer catalysis was ignored as a significant contribution to the observed reaction rate. All the subsequent reactions were buffered at pH 6.9 using 10 mM MOPS buffer and the buffering action of the complex itself, in the presence of 0.1 M $NaClO_4$.

To establish the order of reaction in complex, the TrpnCo (**3**) concentration was varied over the range 0.8–3.2 mM for each of substrates **4a–g** (maintaining at least a 10-fold excess of complex over substrate). In each case, a first-order curve gave an excellent fit to the data, showing the reaction to be first order in diester. Plotting these pseudo-first-order-rate constants against TrpnCo (**3**) concentration gave good linear plots, confirming that the reaction is also first order in metal ion complex, and linear least-squares fitting provided the second-order rate constants for complex promoted hydrolysis of the diester (Table 1).

The pK_a of each of the phenol leaving groups was measured by spectrophotometric titration under the experimental conditions (37 °C, 10 mM buffer and 0.1 M $NaClO_4$); these are recorded in Table 1. The second-order rate constants were plotted against these pK_as to generate a linear free energy relationship (LFER) (Fig. 3).

Table 1. Second-order rate constants k_2 for the TrpnCo (**3**)-promoted hydrolysis of diesters (**4**) and pK_a values of the aryloxy leaving groups at 37 °C, in the presence of 10 mM buffer and 0.1 M $NaClO_4$

Substrate	k_2 ($M^{-1}\ s^{-1}$)	Leaving group pK_a
4a	$(9.9 \pm 0.3) \times 10^{-6}$	8.73 ± 0.03
4b	$(6.3 \pm 0.3) \times 10^{-5}$	8.13 ± 0.02
4c	0.69 ± 0.01	6.83 ± 0.01
4d	2.96 ± 0.03	6.36 ± 0.01
4e	4.31 ± 0.05	5.92 ± 0.01
4f	8.0 ± 0.1	5.11 ± 0.03
4g	15.4 ± 0.5	3.89 ± 0.01

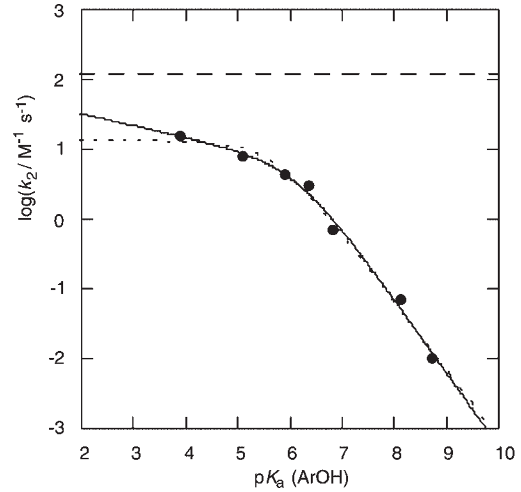
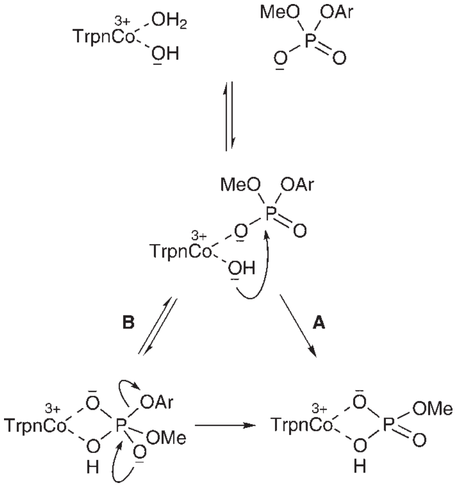


Figure 3. Linear free energy relationship between the second-order rate constant for hydrolysis of esters **4** promoted by **3** and the pK_a of the aryl leaving group at 37 °C in the presence of 10 mM buffer and 0.1 M $NaClO_4$. The solid and dotted lines are the non-linear least-squares fits to the reaction schemes described in the text. The dashed line represents the rate of binding of inorganic phosphate with **3** at 25 °C and pH 7 as reported by Chin *et al.*[7]

When dimethyl phosphate was used as substrate (6 mM in the presence of 2 mM complex), no hydrolysis could be detected over a period of 3 days at 37 °C, as expected. Similarly, no change in the isotopic ratio of ^{18}O-enriched dimethyl phosphate could be detected by ESMS. The complex does not appear to catalyse exchange of solvent oxygen into the non-bridging phosphoryl positions.

DISCUSSION

The pH–rate profile is consistent with the assumption that the only active ionic form of the complex is the aqua-hydroxy form, as previously described by Chin *et al.*,[7] and has been fitted to this scheme, revealing a kinetic pK_a of 7.1; this is consistent with the previously reported values for the second pK_a of TrpnCo (**3**). As the association constant has been measured as $\sim 1\ M^{-1}$,[9] the proportion of the substrate that is complexed with the TrpnCo **3**



Scheme 1

is not significant under our experimental conditions, and the first-order dependence on both complex and substrate reflect the presence of only one of each in the rate-limiting transition state. This is also consistent with Chin *et al.*'s[7] earlier report and shows that there is no contribution from an active dimer as observed for **2** at high concentrations.[10]

However, the LFER is clearly non-linear, indicating a change in rate-limiting step when the leaving group has $\mathrm{p}K_\mathrm{a} \approx 6$; the solid line shown is a non-linear least-squares fit to this scheme, and indicates that β_lg changes from -0.17 to -1.05 as the leaving group becomes poorer.

The likely mechanisms are shown in Scheme 1. Under the conditions used, there is initially a complexation step, followed by intramolecular attack of the metal-bound hydroxide which displaces the aryloxy leaving group either in a single step (pathway A) or via a pentacoordinate intermediate (pathway B).

As Co(III) undergoes ligand exchange slowly, it is plausible that the substrate binding step will become rate limiting for highly reactive substrates.[11] If this is the case, then it is known that binding at Co(III) complexes is very insensitive to the nature of the incoming anion,[11] and since the effect of varying the aryl moiety on the binding properties of the diester will be small in any case, the rate of the binding step will be constant for all the compounds **4**. Hence, to apply this interpretation, the rate-limiting binding regime needs to be constrained to a β_binding value of zero. The resulting non-linear least-squares fit is shown by the dotted lines on the graph, and still leads to an acceptable fit to the data (with the break now occurring at leaving groups with $\mathrm{p}K_\mathrm{a} \approx 5.7$), a similar β_lg for the poorer leaving groups of -0.98 and a limiting rate constant of $13\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$.

These data can be compared with the rate of complexation of TrpnCo (**3**) by inorganic phosphate measured by Chin *et al.*[7] at 25 °C and pH 7, which leads to a second-order rate constant for binding of $120\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, which is ~10-fold faster than the limiting rate shown by the LFER (Fig. 3, dashed line); this difference is a lower limit due to the 12 °C temperature difference. This appears to suggest that the change in rate-limiting step is unlikely to be due to rate-limiting binding.

If this is not the rate-limiting step, then the reaction of the bound diester would have to involve an intermediate (pathway B). The likelihood of such an intermediate is open to debate; in the course of studying many Co(III)-promoted reactions, Sargeson and colleagues have frequently invoked pentacoordinate intermediates even for monoester hydrolysis.[13] Recent heavy atom kinetic isotope studies have led to the suggestion that in dinuclear complexes, diesters with such good aryl oxy leaving groups could form a phosphorane-like intermediate.[14] However, related evidence for the reaction between similar phosphate diester substrates and hydroxide is in favour of a concerted mechanism.[15] Similarly, investigations of Co(III)-promoted hydrolysis of phosphate diesters using heavy atom kinetic isotope effects have been interpreted in terms of a single step concerted reaction (pathway A).[10] If such a phosphorane intermediate exists on the reaction pathway, rate-limiting attack at phosphorus would be expected to be relatively insensitive to the nature of the leaving group (assuming binding is independent of leaving group $\mathrm{p}K_\mathrm{a}$). As bond fission to the leaving group becomes rate limiting, β_lg increases in magnitude as expected, reflecting the expected increase in effective charge development on the O atom in the rate-limiting transition state.

If a phosphorane intermediate is reversibly formed (i.e. for diesters with relatively poor leaving groups), then it opens up the possibility of observing exchange of oxygen between the solvent and the non-bridging phosphoryl oxygens of the diester. To explore this, dimethyl phosphate enriched in the non-bridging positions with ^{18}O was incubated with TrpnCo (**3**) for 3 days. No hydrolysis was observed over this time-scale, as would be expected by extrapolating the LFER to a leaving group of $\mathrm{p}K_\mathrm{a} = 15.5$. However, no measurable change in the isotopic composition of the dimethyl phosphate is observed. This is perhaps unsurprising, as the exchange process would require both a proton transfer and pseudo-rotation step to occur to allow the nucleophilic hydroxide become incorporated into the diester. Furthermore, the TrpnCo (**3**) complex is not stable for long periods in aqueous solution, and so a decrease in catalyst concentration may also be occurring on these time-scales. Hence the absence of exchange does not preclude the presence of such an intermediate.

The above data do not lead to a definitive distinction between the two pathways, and need to be examined more closely. First, there may be a difference between (monoanionic) diester binding and (dianionic) inorganic phosphate binding if preliminary ion pair formation is a key step in the binding event. Assuming that this is the case, Haim suggested that dianionic ligands may bind approximately an order of magnitude more rapidly than monovalent anions.[16] At the pH of Chin *et al.*'s[7] binding experiment, inorganic phosphate is 60% monoanion and 40% dianion. Thus, if the dianion does bind ~10-fold more rapidly owing to its higher charge, partitioning the observed rate constant between the two species leads to an estimate of $26\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ for binding by monoanionic phosphate at 25 °C. This is close to the limit indicated by the LFER, but anation at Co(III) has a high enthalpy of activation[17] and so the temperature difference will be a significant factor. Assuming the same entropy of activation as reported for anation of the aqua-hydroxy form of bis (diethylenediamine)-Co(III) by phosphate[17] leads to an estimated temperature factor of ~4-fold for the 12 °C temperature increase, leaving the overall estimate for binding at around $120\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ as shown in Fig. 2. Second, Banaszczyk *et al.*[18] have reported the second-order rate constant for the binding of sulfate to TrpnCo (**3**) at pH 2.9 and 25 °C. Assuming that the hydroxy-aqua species is the only active form for binding leads to a second-order rate constant of $\sim 11\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, in contrast with the data reported by Chin *et al.*[7] for inorganic phosphate binding. Nevertheless, the binding of monoanionic phosphate is clearly the most relevant data, although the difference in binding rates (expected to be independent of anion) is surprising. It is not clear from the data reported by Banaszczyk *et al.*[18] whether the rates correspond to rate limiting binding or the rate of chelation of the Co(III) centre by initially monodentate sulfate, which may explain the discrepancy.

On the other hand, when considering the expected β_{lg} for rate-limiting attack at the phosphate, it is noteworthy that even the nucleophilic substitution of phenols by oxygen nucleophiles with high $\mathrm{p}K_\mathrm{a}$ (which is most likely to involve a mechanism of rate limiting phosphorane formation), shows a greater sensitivity to the leaving group ($\beta_{\mathrm{lg}} \approx -0.35$)[19] than the very shallow β_{lg} (-0.17) obtained in the LFER reported here. In a similar vein, the hydroxide-catalysed cyclization of both UpOAr[20] and UpOR[21] esters has been studied at 25 °C with a range of aryloxy and alkoxy leaving groups, respectively. Interestingly, constructing an LFER from these two data sets (Fig. 4) also yields a bent plot (with the break occurring for leaving groups with $\mathrm{p}K_\mathrm{a} \approx 12.5$), but in comparison with Fig. 3, the shallower β_{lg} is substantially larger in magnitude at -0.52. The steeper β_{lg} is also greater in magnitude than in Fig. 3 (-1.33). In this case, there is no binding step to consider and the simplest explanation is in terms of a pentacoordinate intermediate (although the data may also be explained in terms of a Hammond effect on a concerted pathway[20]).

Regardless of the mechanisms, the LFER does provide information about the transition state for the poorer leaving groups. Following the effective charge analysis of Williams,[22] the effective charge on the O-Ar atom in the starting diester is $+0.74$ and becomes -1.0 in the product aryloxy anion. As the β_{lg} for leaving groups where the bond breaking step is clearly rate limiting is -1.0, this leads to an estimate of -0.26 for the effective charge on the leaving oxygen in the transition state. Assuming that the charge reflects bond cleavage, bond cleavage in the transition state would be ~0.57 along the reaction coordinate. This is further advanced than the hydroxide promoted cleavage of the uncomplexed diester (~0.37),[23] and suggests more substantial bond formation to the nucleophile in the transition state than for the intermolecular reaction.

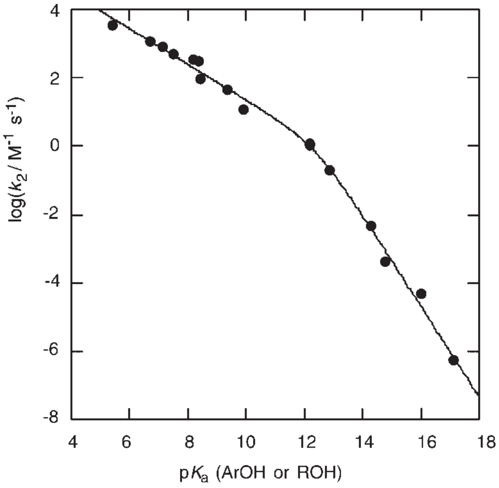


Figure 4. Linear free energy relationship between the second-order rate constant for hydroxide catalysed hydrolysis of UpOAr and UpOR esters and the $\mathrm{p}K_\mathrm{a}$ of the aryloxy or alkoxy leaving group at 25 °C; data taken from Refs. 20 and 21, respectively. The solid line is a non-linear least-squares fit to a two-step reaction mechanism, giving β_{lg} values of -0.52 and -1.33 for good and poor leaving groups, respectively

CONCLUSION

Overall, we have to conclude that these data and analyses cannot unambiguously exclude rate-limiting binding for the most reactive diesters; this is a conservative interpretation of the data, but is not wholly convincing. If it can be shown that binding is significantly faster than the observed rate of hydrolysis for all phosphate diesters under the conditions of our experiments, then it would appear that the metal ion diverts the reaction into an addition–elimination reaction from the concerted process observed in the intermolecular attack of hydroxide. In considering the phosphorane intermediate interpretation, we note that the bound diester will have its negative charge partially quenched by the metal ion, and so will be somewhere between a diester and triester in character, so the proposal of a pentacoordinate intermediate is not unreasonable. Furthermore, the break in LFER occurs close to the $\mathrm{p}K_\mathrm{a}$ of the incoming nucleophile, which is where such a break is expected. At this point, the rate of return to starting material and breakdown to products will be in balance, and in a symmetrical system will occur when the nucleophile and leaving group have matching pK_as. In this system, the nucleophile is part of a small ring, and so its departure might be slightly enhanced relative to its pK_a. The same observation is made for the transesterification uridyl esters, where the break is observed at around 12.5, close to the pK_a of the 2′-hydroxyl nucleophile.

In any case, the metal ion-promoted reaction leads to a transition state where the leaving oxygen develops more effective charge (-0.26) than the corresponding intermolecular hydroxide-promoted hydrolysis ($+0.10$),[23] suggesting that the transition state is changed and that the way to more effective catalysts may be focus on interactions at the leaving group.

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