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Mechanistic studies of La^{3+} and Zn^{2+}-catalyzed methanolysis of *O*-ethyl *O*-aryl methylphosphonate esters. An effective solvolytic method for the catalytic destruction of phosphonate CW simulants†

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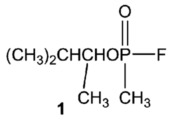
The kinetics of methanolysis of six *O*-ethyl *O*-aryl methylphosphonates (**6a**–**f**) promoted by methoxide, La^{3+} and 1,5,9-triazacyclododecane complex of Zn^{2+}($^{-}$OCH$_3$) (**5**:Zn^{2+}($^{-}$OCH$_3$)) were studied as simulants for chemical warfare (CW) agents, and analyzed through the use of Brønsted plots. The β_{lg} values are, respectively, −0.76, −1.26 and −1.06, pointing to significant weakening of the P–OAr bond in the transition state. For the metal-catalyzed reactions the data are consistent with a concerted process where the P–OAr bond rupture has progressed to the extent of 84% in the La^{3+} reaction and *ca.* 70% in the Zn^{2+} catalyzed reaction. The catalysis afforded by the metal ions is remarkable, being about 10^{6}-fold and 10^{8}-fold for poor and good leaving groups, respectively, relative to the background reactions at $^{s}_{s}$pH 9.1. Solvent deuterium kinetic isotope studies for two of the substrates promoted by **5**:Zn^{2+}($^{-}$OCH$_3$) give $k_H/k_D = 1.0 \pm 0.1$, consistent with a nucleophilic mechanism. A unified mechanism for the metal-catalyzed reactions is presented which involves pre-equilibrium coordination of the substrate to the metal ion followed by intramolecular delivery of a coordinated methoxide.

Introduction

Phosphonoflouridate esters such as soman and sarin (**1** (GD), **2** (GB)) as well as phosphonothioate esters such as VX and Russian VX (**3**, **4**) are extremely effective acetylcholinesterase inhibitors and have nefarious notoriety as chemical warfare (CW) agents.[1] Due to their toxicity, and the 1992 Chemical Weapons Convention Treaty[2] that requires destruction of CW stockpiles by the signatory nations by 2007, considerable effort has been directed at developing methods for destruction of these and related organophosphorus (OP) materials.[1,3] In addition to the required large-scale destruction of these (estimated to be several tens of thousands of tons), recent geopolitical events have hastened military and civilian initiatives to develop effective decontamination methods for the removal of smaller amounts of materials from surfaces and equipment.[4] Although some effective methods are available, none is applicable to all situations or classes of compounds thus spurring research into alternative methods for their destruction.



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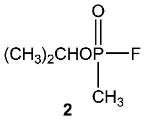

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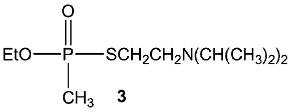

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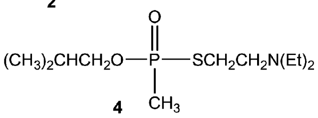

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Numerous reports have appeared concerning the metal-catalyzed *hydrolyses* of neutral phosphate triesters[5] and a lesser number concerning phosphonate diesters.[6] While it may be considered by some that hydrolytic media are convenient for the reactions of noxious substrates, any acceptable process considered for large scale application requires cleaning of the hydrolysate before returning it to the biosphere, a non-trivial task that spurs research into alternative methodologies. Previous work from our laboratories showed that metal-catalyzed alcoholysis is very effective for the catalytic decomposition of phosphate and phosphorothioate triesters, converting these into non-toxic methoxy esters.[7] The most effective metal ions are La^{3+} and the Zn^{2+} and Cu^{2+} complexes of 1,5,9-triazacyclododecane (**5**), all of which are active when bound with one eq. of methoxide per metal.[8] More recently we have shown that a dimethylbenzyl amine palladacycle is very effective in promoting the methanolytic decomposition of some P=S-containing pesticides although the palladium based catalysts are not effective for promoting the methanolysis of P=O based OP materials.[9]

The alcoholysis process offers some advantages over hydrolysis of these particularly noxious materials. We have found that the metal-catalyzed reactions are very much faster in methanol than they are in water, presumably due to a medium effect which we speculate to involve better pre-equilibrium binding of the substrate and metal ion and an enhanced rate of intramolecular delivery of the methoxide nucleophile.[7] Second, the OP materials are far more soluble in the lower polarity alcohol medium than in water which obviates the use of cosolvents or micellar conditions as is often required for OP decomposition in aqueous media. Third, the reactions occur in mild conditions of essentially neutral $^{s}_{s}$pH[10,11] and ambient temperature. Fourth, the products of the reactions are relatively innocuous phosphate triesters which, if necessary for large scale, can be safely disposed of by conventional burning along with the solvent. Finally, the P-containing products of alcoholysis are neutral phosphorus esters which are non-inhibitory to the reaction,[7,9] while those from hydrolysis are phosphoric acids which can dissociate to form anionic materials which bind to the metal ion and thereby inhibit the catalysis.[12]

In this report we extend the methanolysis study to La^{3+} and **5**:Zn^{2+}($^{-}$OCH$_3$) promoted methanolysis of a series of *O*-ethyl *O*-aryl methylphosphonates **6a**–**f**, these being of the same general class as the phosphonofluoridate CW agents. Both catalysts are shown to be very effective for this type of OP material, such that a solution containing 1 mmol dm^{-3} of the La^{3+}-catalyst provides about 10^{8}-fold acceleration of the methanolysis of **6a** relative to the background reaction at essentially neutral $^{s}_{s}$pH and ambient temperature.

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† Electronic supplementary information (ESI) available: physical characterisation data. See http://dx.doi.org/10.1039/b511550g

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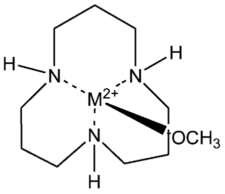
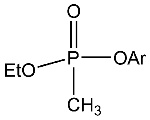


5:$M^{2+}(^{-}OCH_3)$



6 a Ar = (4-Cl-2-NO_2)phenyl
b Ar = (4-NO_2)phenyl
c Ar = (3-NO_2)phenyl
d Ar = (4-Cl)phenyl
e Ar = phenyl
f Ar = (4-OCH_3)phenyl

Experimental

(a) Materials

3-Nitrophenol (99%), 4-chlorophenol (99+%), 4-chloro-2-nitrophenol (98%), 4-methoxyphenol (99%), sodium 4-nitrophenoxide (~90%), phenol (99+%), methylphosphonic dichloride (98%) and triethylamine (99.5%) were obtained from Aldrich and used without further purification.

Caution: phosphonates **6** *are all acetylcholinesterase inhibitors. These, and the methyl phosphonic dichloride precursor, should be synthesized and used with due attention to safety protocols.*

Ethyl methylphosphonochloridoate ($C_3H_8ClO_2P$)[13]

To a 500 mL three-necked round-bottom flask equipped with a magnetic stirring bar and a condenser was added 5.62 g of methylphosphonic dichloride. With use of an addition funnel, 100 mL of toluene (dried over Na) was added under argon, followed by a solution comprising 2.5 mL of absolute ethanol, 7.0 mL of triethyl amine and 30 mL of dry toluene while the contents of the flask were stirred in an ice bath. This reaction was left to stir for 1 h under the described conditions after which the temperature was raised to 40 °C and the contents were allowed to stir for 2 h. After 2 h, the salt ($HNEt_3Cl$) was filtered away and the filtrate was evaporated to give a crude yield of 43.7%. This material was immediately used for the subsequent preparations.

General route for the preparation of *O*-ethyl *O*-aryl methylphosphonates (6)[13]

To 100 mg of the sodium salt of the desired phenol suspended in 5 mL of toluene (dried over Na) was added 1 eq. of ethyl methylphosphonochloridate (from above) dissolved in 2 mL of dry toluene. The mixture was heated to reflux under an argon atmosphere for 1 h, cooled to room temperature and then filtered through glass wool packed into a Pasteur pipette. The filtrate was stripped of solvent *via* rotary evaporation and the residue was dissolved in 1 mL of dichloromethane and mixed with silica for dry loading for flash column chromatography. The dichloromethane was evaporated and the silica coated with product was loaded onto a Biotage flash silica column (12 + M, KP–SIL, 12 × 150 mm, 40–63 μm, 60 Å) and purified with a Biotage SP1 HPFC Purification System with an elution profile based on a TLC separation using 50 : 50 hexanes–ethyl acetate.

The solvent from the final product was evaporated using rotary evaporation and then the compound was placed under vacuum pump aspiration for several hours prior to use. All materials were characterized by ^{1}H and ^{31}P NMR and exact mass. The analytical data are given in the electronic supplementary information.

(b) General UV-vis kinetics

The following materials were used to make stock solutions: sodium methoxide (0.5 mol dm^{-3}), 1, 5, 9-triazacyclododecane (97%), tetrabutylammonium hydroxide (1.0 mol dm^{-3}), $La(OTf)_3$ (99.999%), anhydrous methanol (99.8%) and *N*-ethylmorpholine (99%), all being obtained from Aldrich and used as received. $Zn(OTf)_2$ (98%) was purchased from Strem Chemical and $Cu(OTf)_2$ (98%) was obtained from Acros Organics. Methanol-d_1 was purchased from Aldrich (99 atom%) and used as received.

Stock solutions of phosphonates **6** were formulated between 5 and 10 mmol dm^{-3} in anhydrous methanol. $La(OTf)_3$, tetrabutylammonium hydroxide, $Zn(OTf)_2$, 1,5,9-triazacyclododecane and $Cu(OTf)_2$ stock solutions were made to a concentration of 50 mmol dm^{-3} in anhydrous methanol.

Kinetic determinations were done by UV-vis spectrophotometry as reported in our earlier publications, as were $^{s}_{s}$pH measurements.[7] Each kinetic run using Zn^{2+} consisted of formulating the **5**:$Zn^{2+}(^{-}OCH_3)$ catalyst *in situ* by adding measured amounts of the $Zn(OTf)_2$, 1,5,9-triazacyclododecane and tetrabutylammonium hydroxide stock solutions to anhydrous methanol to form a final volume of 2.5 mL. The ratios of the components of the catalyst were 1 : 1 : 0.5, respectively, to self-buffer the mixtures at $^{s}_{s}$pH 9.1. Kinetic runs using Cu^{2+} were prepared in the same manner and self-buffered at $^{s}_{s}$pH 8.75. Final **5**:M^{2+} concentrations in the kinetic runs ranged from 0.2 to 1.2 mmol dm^{-3}, while the *O*-ethyl *O*-aryl methylphosphonate concentrations ranged from 0.5 to 2 × 10^{-4} mol dm^{-3}. The water content in the methanol resulting from the stock solutions was not more than 0.1%.

For the solvent deuterium kinetic isotope effect studies, the solutions were made exactly as for the protiated methanol kinetics, except that the medium was 99% d_1-methanol and to preserve consistency the stock solutions were the same ones used for the protiated methanol determinations. For these kinetics, the maximum amount of protium is 8% depending on the [**5**:M^{2+}]. Although we did not measure the $^{s}_{s}$pH of the solutions, the medium is self-buffered at the $^{s}_{s}pK_a$ in methanol-d_1 through the addition of 0.5 eq. of tetrabutylammonium hydroxide.

The kinetics of disappearance of **6a**–**f** or appearance of the phenol/phenoxide products were monitored at 25 °C in duplicate under pseudo-first order conditions of excess catalyst at 428, 312, 340, 290, 277 and 300 nm. Pseudo-first-order rate constants, k_{obs}, were obtained by fitting the absorbance *vs.* time data to a standard first-order exponential model and the second order rate constants, k_2, were obtained as the gradients of the k_{obs} *vs.* [active catalyst] plots. Reactions were also carried out using buffered La^{3+} solutions at $^{s}_{s}$pH 9.14 and monitored by both UV-vis spectrometry and stopped-flow spectrometry using an Applied Photophysics SX-17MV Sequential Stopped-Flow ASVD Spectrophotometer. The buffer was prepared using 17 mmol dm^{-3} *N*-ethylmorpholine and perchloric acid in a 4 : 1 ratio.

Background reactions with methoxide as the active species were carried out in duplicate using three methoxide concentrations between 0.02 and 0.1 mol dm^{-3}.

(c) Turnover experiment

To an NMR tube charged with 600 μl of d_4-methanol containing 5 mmol dm^{-3} of 4-chloro-2-nitrophenyl methylphosphonate (**6a**) as well as 17 mmol dm^{-3} *N*-ethylmorpholine and perchloric acid in a 4 : 1 ratio was added 6 μl of a 50 mmol dm^{-3} stock solution of $La(OTf)_3$ such that the final concentration of La^{3+} was 0.5 mmol dm^{-3}. The ^{31}P NMR spectrum was recorded periodically at 25 °C and the disappearance of the starting material signal at 28.20 ppm monitored as a function of time. After 20 min the starting material signal was completely replaced by a peak at 30.69 ppm corresponding to the product *O*-ethyl *O*-methyl methylphosphonate.

Table 1 Acid dissociation constants and second order rate constants for the various methanolysis reactions of phosphonates **6a**–**e** promoted by methoxide, La^{3+}, **5**:$Zn^{2+}(^{-}OCH_3)$ and **5**:$Cu^{2+}(^{-}OCH_3)$

Phosphonate	pK_a	${}_{s}^{s}pK_a$	k_2^{OMe}/mol dm^{-3} s^{-1}	k_2^{La}/mol dm^{-3} s^{-1}	$k_2^{\mathbf{5}:Zn(OMe)}$/mol dm^{-3} s^{-1}	$k_2^{\mathbf{5}:Cu(OMe)}$/mol dm^{-3} s^{-1}
6a	6.32	10.64	14.3 ± 0.1 (21 ± 1)^{a}	$(2.60 \pm 0.20) \times 10^{4}$	517 ± 3 (510 ± 20)^{a}	2100 ± 300
6b	7.14	11.30	2.70 ± 0.02	$(1.45 \pm 0.03) \times 10^{3}$	46.8 ± 0.5	243 ± 10
6c	8.39	12.41	1.44 ± 0.02	$(2.60 \pm 0.20) \times 10^{2}$	22 ± 1	20.8 ± 0.1
6d	9.38	13.59	0.118 ± 0.001	3.97 ± 0.03	0.45 ± 0.01	N.a.
6e	10.00	14.33	0.0217 ± 0.0003	$(4.0 \pm 0.1) \times 10^{-1}$	0.072 ± 0.002	N.a.
6f	10.20	14.70	0.008 4 ± 0.0001	$(1.4\,0 \pm 0.02) \times 10^{-1}$	0.014 ± 0.002	N.a.

^{a} In $DOCH_3$, determined at a **5** : Zn^{2+} : $^{-}OCH_3$ ratio of 1 : 1 : 0.5.

Results

Given in Table 1 are the second order rate constants for the methanolysis of **6a**–**f** promoted by $^{-}OCH_3$, La^{3+}, **5**:$Zn^{2+}(^{-}OCH_3)$ and, for three examples, **5**:$Cu^{2+}(^{-}OCH_3)$. The limited number of data with the Cu^{2+} complex was a consequence of its being highly absorbing such that only those substrates with nitrophenoxy leaving groups (**6a**–**c**) could be monitored by UV-vis kinetics. The second order kinetic terms were determined from the gradients of the plots of k_{obs} *vs.* [methoxide] or $[\text{metal}^{x+}]_{total}$. For **5**:$Zn^{2+}$ and **5**:Cu^{2+} the solutions were self buffered at ${}_{s}^{s}pH$ 9.1 and 8.75 through half neutralization of the catalyst ($[\mathbf{5}:M^{2+}(^{-}OCH_3)]/[\mathbf{5}:M^{2+}(HOCH_3)] = 1$). Since earlier work showed that the catalytic activity was entirely due to the methoxide form, **5**:$Zn^{2+}(^{-}OCH_3)$,[7b,d] or **5**:$Cu^{2+}(^{-}OCH_3)$,[7e] the $k_2^{\mathbf{5}:Zn(OMe)}$ and $k_2^{\mathbf{5}:Cu(OMe)}$ values reported in Table 1 were calculated based on half the added metal ion being in the active form. La^{3+}catalysis for all substrates was determined by observing the k_{obs} *vs.* $[La^{3+}]_{total}$ in a 17 mmol dm^{-3} *N*-ethylmorpholine buffer at an ${}_{s}^{s}pH$ value of 9.14 which is the value where the rate maximum for La^{3+} catalysis of phosphate esters occurs.[7a,b] Also given in Table 1 are the ${}_{s}^{s}pK_a$ values for the phenols which are experimentally determined[11b,14] or can be calculated from their water values by the linear regression given in reference 11*b* ($pK_a^{MeOH} = 1.12pK_a^{H2O} + 3.56$).

In Fig. 1 are presented Brønsted plots of the second order rate constants for methoxide, La^{3+} and **5**:$M^{2+}(^{-}OCH_3)$ catalyzed methanolysis of the phosphonates with the linear regressions presented in eqn (1) to (4).

$$\log k_2^{OMe} = (9.24 \pm 0.81) - (0.76 \pm 0.06)\, {}_{s}^{s}pK_a^{HOAr};\quad r^2 = 0.9896,\ 6\ \text{data} \tag{1}$$

$$\log k_2^{La} = (17.78 \pm 0.84) - (1.26 \pm 0.06)\, {}_{s}^{s}pK_a^{HOAr};\quad r^2 = 0.9716,\ 6\ \text{data} \tag{2}$$

$$\log k_2^{\mathbf{5}:Zn(OMe)} = (14.04 \pm 1.17) - (1.06 \pm 0.09)\, {}_{s}^{s}pK_a^{HOAr};\quad r^2 = 0.9734,\ 6\ \text{data} \tag{3}$$

$$\log k_2^{\mathbf{5}:Cu(OMe)} = (15.10 \pm 1.39) - (1.12 \pm 0.12)\, {}_{s}^{s}pK_a^{HOAr} \tag{4}$$

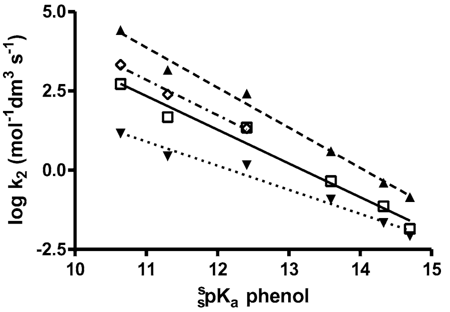


Fig. 1 Brønsted plots of the second order rate constants for methoxide and metal ion catalyzed methanolysis of **6a**–**e** at 25 °C. ($(La^{3+}(^{-}OCH_3))_2$ (▲), **5**:$Cu^{2+}(^{-}OCH_3)$ (◇), **5**:$Zn^{2+}(^{-}OCH_3)$ (□), $^{-}OCH_3$ (▼).

In Fig. 2 are alternative presentations of the data where the La^{3+} or **5**:$M^{2+}(^{-}OCH_3)$ rate constants for methanolysis of **6a**–**f** are plotted *vs.* the methoxide rate constants. The linear regressions for these are given in eqn (5), (6) and (7) with the latter line having rather large error limits due to it being defined only by three points.

$$\log k_2^{La} = (1.65 \pm 0.07) \log k_2^{OMe} + (2.36 \pm 0.06);\quad r^2 = 0.9923,\ 6\ \text{data} \tag{5}$$

$$\log k_2^{\mathbf{5}:Zn(OMe)} = (1.40 \pm 0.03) \log k_2^{OMe} + (1.08 \pm 0.04);\quad r^2 = 0.9981,\ 6\ \text{data} \tag{6}$$

$$\log k_2^{\mathbf{5}:Cu(OMe)} = (1.86 \pm 0.56) \log k_2^{OMe} + (1.26 \pm 0.40) \tag{7}$$

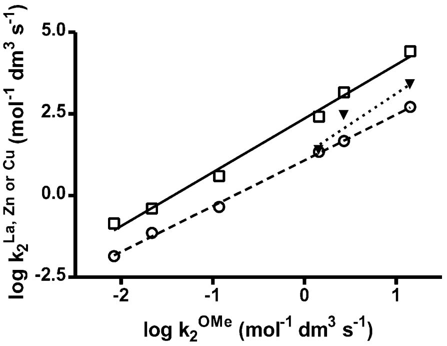


Fig. 2 Plots of log k_2^{Mx+} *vs.* log k_2^{OMe}, $(La^{3+}(^{-}OCH_3))_2$ (□), **5**:$Zn^{2+}(^{-}OCH_3)$ (○), **5**:$Cu^{2+}(^{-}OCH_3)$ (▼).

In order to confirm that the system was truly catalytic, a ^{31}P NMR experiment in d_4-methanol containing 5 mmol dm^{-3} of **6a** along with 0.5 mmol dm^{-3} La^{3+} buffered with 17 mmol dm^{-3} NEM was performed. After the first five minutes of data acquisition (128 scans), the reaction had progressed to the extent of at least 10 turnovers per catalyst based on the ^{31}P signals for starting material at 28.20 ppm and *O*-ethyl-*O*-methylmethylphosphonate product at 30.69 ppm.[15]

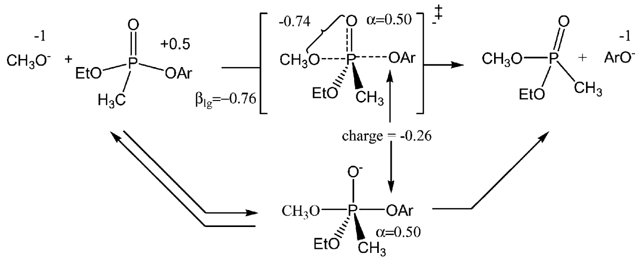
Discussion

In constructing the various Brønsted plots for the La^{3+}-catalyzed processes, we used the second order rate constants obtained as the gradients of plots of $\Delta k_{obs}/\Delta[La^{3+}]$ under buffered conditions with 17 mmol dm^{-3} NEM buffered at ${}_{s}^{s}pH$ 9.14, where the maximal activity occurs, so the k_2^{La} values in Table 1 are presented per La^{3+} ion even though we have determined that the actual catalytic species are dimers $(La^{3+})_2(^{-}OCH_3)_{2,3,4}$ the relative catalytic importance of which depend on the ${}_{s}^{s}pH$.[16,17] At this ${}_{s}^{s}pH > 90\%$ of the catalysis occurs through $La^{3+}{}_2(^{-}OCH_3)_2$. The phosphonate esters encompass a range of 10^4 in leaving group acidity and about 10^5 in k_2^{La} but only about 10^3 in k_2^{OMe}. For the same series of phosphonates, the $k_2^{\mathbf{5}:Zn(OMe)}$ at ${}_{s}^{s}pH$ 9.1 span a range of 3×10^4 fold.

(a) Reaction of methoxide

The Brønsted plot for methoxide shown in Fig. 1 provides a linear correlation with a β_{lg} value of −0.76 ± 0.06 ($n = 6$, $r^2 = 0.9734$). This β_{lg} value can be compared with the −0.70 found for the attack of methoxide on *O*,*O*-diethyl *O*-aryl phosphate triesters,[7b] values of −0.43 and −0.44 for hydroxide attack on the same species,[18,19] as well as −0.66 and −0.79 for the attack of phenoxide and *p*-nitrophenoxide respectively on *O*-aryl diphenylphosphinates.[20] In general, low β_{lg} values observed with strong nucleophiles on phosphates imply relatively little cleavage of the aryloxy bond in the transition state and suggest a two step reaction, where the rate limiting step is attack. However, as the nucleophile becomes weaker, the β_{lg} values become increasingly negative, signalling a shift in the reaction mechanism so, if it is two steps, the second (involving the departure of the leaving group) is rate limiting, or alternatively the reaction is concerted.[19,21,22,23] Buncel and co-workers have presented evidence that the mechanism can change from concerted to stepwise depending on the solvent, citing ethoxide promoted ethanolysis of $(CH_3)_2P(O)$–OAr and $Ph_2P(O)$–OAr[24] as stepwise in pure ethanol but respectively concerted[25] or stepwise[26] in 90% water–dioxane. Apparently, the increased basicity of the nucleophile in the less polar solvent has the effect of enhancing the bond formation relative to the leaving group departure.

Following the 'effective charge treatment' described by Jencks[27] and Williams,[28] the Brønsted β_{lg} value of −0.76 for nucleophilic attack of methoxide on the aryl phosphonates **6** implies a process where the rate-limiting transition state has appreciable changes in the P–OAr bond. This could be viewed as resulting from either a two step process with the attack step largely rate limiting because methoxide is a poorer leaving group than any of the aryloxy anions[29] or with a concerted process, both of which are shown in Scheme 1. The progress of P–OAr bond breaking in the TS is measured by the Leffler parameter (α) that relates the Brønsted β_{lg} to the β_{eq} for equilibrium transfers of acyl or phosphoryl groups between oxyanion nucleophiles. For transfer of the $(EtO)_2P{=}O$ group the β_{eq} value is 1.87[19] with the *O*–Ar oxygen in the starting material having a net effective charge of +0.87. For transfer of the diphenylphosphinoyl group ($(C_6H_5)_2P{=}O$), between oxyanion nucleophilies the β_{eq} value is 1.25[20] with the *O*–Ar oxygen in the starting phosphinate having a net charge of +0.25. The net charge difference on the *O*–Ar of phosphates relative to phosphinates is due to the high net electronegativity of the $(EtO)_2P{=}O$ group relative to the $Ph_2P{=}O$ group. Although the β_{lg} is not known for the $EtO(CH_3)P{=}O$, we predict that its value would be roughly midway between that of the phosphoryl and phosphinoyl groups, *ca.* 1.5.[30] The Leffler parameter of $-\beta_{lg}/\beta_{eq} = 0.50$ suggests that for the methoxide reaction on **6**, the P–OAr cleavage is *ca.*50% of the way from starting material to product with the departing aryloxy group having a net charge of −0.26. The other mechanism for the strongly nucleophilic methoxide shown in Scheme 1 involves rate-limiting formation of a highly unstable five-coordinate intermediate and cannot be distinguished from the concerted process.[20]



Scheme 1

(b) La³⁺ and 5:Zn²⁺(⁻OCH₃) catalyzed methanolysis

Also given in Fig. 1 are Brønsted plots for the metal-catalyzed methanolysis of the phosphonates, the β_{lg} values for La^{3+} and **5**:$Zn^{2+}(^-OCH_3)$ being −1.26 ± 0.06 and −1.06 ± 0.09. The value for **5**:$Cu^{2+}(^-OCH_3)$ is −1.12 ± 0.12, but is less well-defined since it is based only on the three NO_2-containing derivatives. These large negative β_{lg} values suggest a metal catalyzed process where there is more cleavage of the leaving group in the transition state than is the case for the methoxide reaction. For La^{3+} and **5**:$Zn^{2+}(^-OCH_3)$ promoted methanolysis of *O*,*O*-diethyl *O*-aryl phosphates[7b] the β_{lg} values for the La^{3+} and Zn^{2+} catalysts are also large and negative at −1.43 ± 0.08 and −1.12 ± 0.13 which we interpreted as indicative of an associative process with concerted displacement of the leaving group: the phosphonate Brønsted data are also consistent with a concerted displacement. The solvent deuterium kinetic isotope effect (dkie) for the methanolysis of **6a** promoted by methoxide and **5**:$Zn^{2+}(^-OCH_3)$ in methanol or $DOCH_3$ are, respectively, $k_D/k_H = 1.47 \pm 0.08$ and 0.99 ± 0.05, both cases supporting a nucleophilic mechanism rather than a general base one. Although a complete analysis of the dkie values for methanolysis of phosphate, phosphorothioate, phosphonate, phosphonothioate and carboxylate esters promoted by **5**:$Zn^{2+}(^-OCH_3)$ will be presented elsewhere,[31] our available phosphonate data are consistent with either of two kinetically equivalent nucleophilic processes, termed internal methoxide (IM) or external methoxide (EM)[32] which are presented in eqn (8), (9), (10) and (11). However, the observed second order rate constants for the metal-catalyzed reactions, along with a reasonable value for the equilibrium binding constant, rules out the EM mechanism since the computed rate constants (k'_1) for methoxide attack on the La^{3+} and **5**:Cu^{2+}-bound substrates for at least one phosphonate (**6a**) exceeds the diffusion limit of 5 × 10^9 mol^{-1} dm^3 s^{-1}.[33,34]

$$5:M^{2+}(^-OCH_3) + EtO(CH_3)P(=O)\text{-}XAr \xrightleftharpoons{K_b} 5:M^{2+}(^-OCH_3):EtO(CH_3)P(=O)XAr \quad (8)$$

$$5:M^{2+}(^-OCH_3):EtO(CH_3)P(=O)XAr \xrightarrow{k_1} P \quad (9)$$

$$5:M^{2+} + EtO(CH_3)P(=O)\text{-}XAr \xrightleftharpoons{K'_b} 5:M^{2+}:EtO(CH_3)P(=O)XAr \quad (10)$$

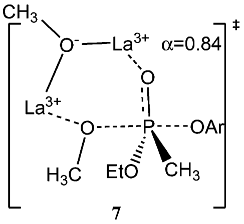
$$5:M^{2+}:EtO(CH_3)P(=O)XAr + {}^-OCH_3 \xrightarrow{k'_1} P \quad (11)$$

The favoured mechanism is thus the IM process of eqn (8) and (9), for which the derived kinetic expressions are given in eqn (12) and (13) where β_b and β_1 refer to the Brønsted β_{lg} values for the binding and kinetic steps, and ${}^s_s\mathrm{p}K_a$ refers to the acid dissociation constant for the conjugate acid of the leaving groups. The experimental Brønsted β_{lg} values

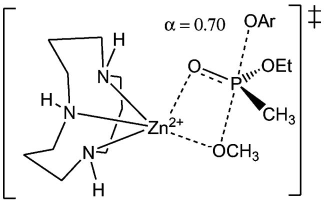
$$k_2^{obs} = K_b k_1 = C_b C_1 10^{(\beta_b + \beta 1){}^s_s\mathrm{p}K_a} \quad (12)$$

$$\log k_2^{obs} = \{\log C_b + \log C_1\} + (\beta_b + \beta_1){}^s_s\mathrm{p}K_a \quad (13)$$

comprise the influence of the leaving group on the pre-equilibrium binding step and on the intramolecular kinetic step ($\beta_b + \beta_1$). The available literature data[35] suggest that β_b should be slightly positive, so the observed negative β_{lg} should be dominated by β_1. The proposed transition states for the $(La^{3+}(^-OCH_3))_2$ and **5**:$Zn^{2+}(OCH_3)$ catalyzed methanolysis of the phosphonates are shown in **7** and **8**. The Leffler parameter for the La^{3+}-catalyzed process is $-\beta_{lg}/\beta_{eq} = 1.26/1.5^{30} = 0.84$, so transition state **7** has extensive cleavage of the P–OAr bond. In the case of the **5**:$Zn^{2+}(^{-}OCH_3)$ catalyzed reaction, a similar mechanism is envisioned but this time transition structure **8** will involve five-coordinate Zn^{2+} with a Leffler *α* of 0.7.



7



8

(c) Comparision of k_2^{OMe} and $k_2^{5:\mathrm{Zn(OMe)}}$ or k_2^{La}

As in the case of phosphate and phosphorothioate ester methanolysis,[7b] we assume here that the mechanism of CH_3O^--promoted methanolysis is similar enough for all the phosphonate esters with nucleophilic addition being either rate limiting or concerted with leaving group departure so that the rate constant, k_2^{OMe}, can be used as an empirical measure of the composite effects of structural changes that incorporate both electronic and steric effects. Comparison of the La^{3+} and **5**:$M^{2+}(^{-}OCH_3)$ kinetic data in Table 1 with the corresponding k_2^{OMe} kinetic data indicates that the metal ion systems are more effective than methoxide for promoting the methanolysis of this series of phosphonates, a phenomenon observed before for the methanolysis of phosphates and phosphorothioates.[7b,d] The $k_2^{\mathrm{La}}/k_2^{\mathrm{OMe}}$ ratio varies from 1800-fold for the most reactive phosphonate **6a** to16-fold the least reactive derivative **6f**. Over the same series, the $k_2^{5:\mathrm{Zn(OMe)}}/k_2^{\mathrm{OMe}}$ ratio varies only by 36-fold to *ca.* 1.6-fold. Shown in Fig. 2 is a graphical representation the data plotting log k_2^{La}, log $k_2^{5:\mathrm{Zn(OMe)}}$, and log $k_2^{5:\mathrm{Cu(OMe)}}$ *vs.* log k_2^{OMe}, the respective gradients of the lines being 1.65 ± 0.07, 1.40 ± 0.03 and a less defined 1.86 ± 0.56 for the copper complex. The fact that all of the plots adhere to respectable linearity suggests that the changes in the leaving group influence both the methoxide and metal-catalyzed reactions in much the same way, supporting the idea that both reactions could be concerted, and that neither process involves a change in mechanism nor rate limiting step over the series investigated.

It is interesting to speculate as to why these catalysts are more effective (relative to methoxide) toward substrates with better leaving groups. Based on the widely held notion that catalysis in general must result from better stabilization of the TS than ground state,[36] the metal containing systems must preferentially bind to the 'dissociated' or exploded five-coordinate TS as shown in **7** or **8** relative to the corresponding four-coordinate P=O substrate. Shown in Fig. 3 is a reaction coordinate diagram[37] for the M^{x+}–$^{-}OCH_3$ catalyzed reaction where the lower left and upper right corners represent the starting and final states, and the upper left and lower right corners represent the M^{x+}-complexed five-coordinate phosphorane intermediate and the M^{x+}:O=P⁺ < + $^{-}$OAr separated state respectively. The left/right axes represent the nucleophile–P distance as defined by $\beta_{\mathrm{nuc}}/\beta_{\mathrm{eq}}$ while the upper/lower axes represent the P-leaving group separation as defined by $-\beta_{\mathrm{lg}}/\beta_{\mathrm{eq}}$, the value of which is 0.7–0.84 in the present work. Also shown on Fig. 3 is a hypothetical methoxide concerted reaction (structures with the encircled M^{x+} removed) for which the Leffler index is $-\beta_{\mathrm{lg}}/\beta_{\mathrm{eq}} = 0.5$ in the present case.

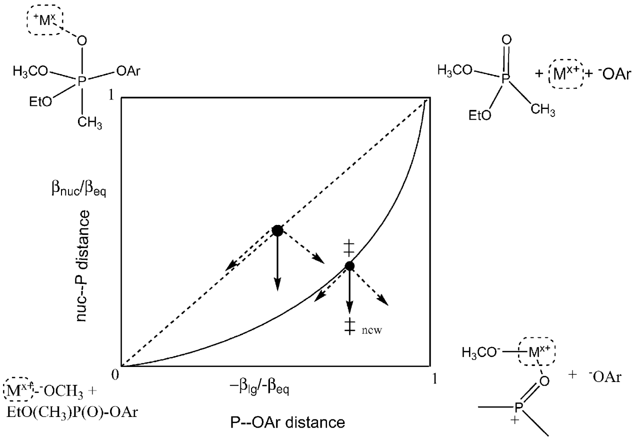


Fig. 3 A reaction coordinate diagram for the metal-methoxide catalyzed methanolysis of phosphonates **6**.

Under the assumption that both the reactions are concerted and thus have the same rate limiting step in the forward and reverse direction, we can locate the respective transition states for the methoxide reaction as $\beta_{\mathrm{eq}} = \beta_{\mathrm{nuc}} - \beta_{\mathrm{lg}} = -1.5$; $\beta_{\mathrm{nuc}} = 0.75$, $\beta_{\mathrm{lg}} = -0.76$, and for the metal-catalyzed ones as $\beta_{\mathrm{nuc}} = 0.24$–$0.44$ and $\beta_{\mathrm{lg}} = -1.26$ to -1.06 for the La^{3+} and **5**:$Zn^{2+}(^{-}OCH_3)$ reactions. Making the leaving group better depresses the right side of the diagram, forcing the TS in both cases toward starting materials along the reaction coordinate, and toward the lower right side perpendicular to the reaction coordinate. The result that the new TS in both cases is more charge separated with the methoxide–P distance being less and the P–OAr distance little changed. The current data do not allow a detailed charge analysis, but the emerging picture is that the metal ion must stabilize the exploded, charge separated transition structures, perhaps through an electrostatic stabilization as has been suggested in related cases involving metal ion catalysis of the hydrolyses of anionic phosphorus materials.[38]

Conclusion

The above study indicates that La^{3+} and **5**:$M^{2+}(^{-}OCH_3)$ catalyzed methanolysis is an effective strategy for the solvolytic destruction of phosphonates. As far as we are aware, the data obtained in this study provides the most complete mechanistic picture of the metal-catalyzed solvolysis reactions of phosphonates, which may in turn provide mechanistic information of relevance to the metal promoted solvolyses of CW G-agents and spur development of effective methods for destroying these materials.[12] The phosphonates are about 100-fold more reactive than the corresponding phosphate triesters with the same leaving groups[7b] toward methanolysis promoted by methoxide, La^{3+} and the **5**:$Zn^{2+}(^{-}OCH_3)$ systems. Nevertheless, the catalysis we observe is quite impressive considering that the catalysts are maximally operative at $^{s}_{s}$pH values near neutrality (8.34) in methanol. For the most reactive substrate **6a** a solution containing 1 mmol dm^{-3} of catalyst $(La^{3+}(^{-}OCH_3))_2$, **5**:$Zn^{2+}(^{-}OCH_3)$ and **5**:$Cu^{2+}(^{-}OCH_3)$ accelerates the methanolysis relative to the background methoxide reaction at $^{s}_{s}$pH optimum values of 9.1 and 8.75 by 8.5 × 10^7-fold, 1.7 × 10^6-fold and 1.4 × 10^7-fold respectively, leading to $t_{1/2}$ values of 0.026, 1.33 and 0.33 s, respectively. For the least reactive substrate, **6f**, under the same conditions, a 1 mmol dm^{-3} solution of $(La^{3+}(^{-}OCH_3))_2$ or **5**:$Zn^{2+}(^{-}OCH_3)$ promote the methanolysis reaction by 7.8 × 10^5-fold and 7.8 × 10^4-fold relative to the background reaction at $^{s}_{s}$pH 9.1, giving $t_{1/2}$ values of 1.37 and 13.7 h respectively.

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12 It has been pointed out by a referee that, for methanolysis of the G-agents, the fluoride product may bind to the metal ion and be inhibitory and so the reactions could be stoichiometric. This is a distinct possibility that further research will have to confirm and, if present, circumvent. On the other hand, since our previous work has shown that the La^{3+} catalysts promote phosphorothioate methanolysis reactions for at least 100 turnovers,[7c] thiolate inhibition of that system does not appear to present a problem.

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15 The overall rate constant for the ^{31}P NMR experiment is somewhat slower than observed in the UV-vis kinetics and probably stems from a non-optimal ${}^{s}_{s}pH$ setting in d_1-methanol and a low initial concentration of catalyst, neither of which favours complete conversion to the $(La^{3+}(^{-}OCH_3)_2)$ dimer.[16b].

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29 Given that the autoprotolysis constant of methanol is $10^{-16.77}$ $(mol\ dm^{-3})^2$ (ref. 11) one can compute a ${}^{s}_{s}pK_a$ for methanol itself of 18.13 on the mol dm^{-3} scale.

30 Buncel[24] analyzes the Douglas and Williams[25] data for the transfer of $(CH_3)_2P(O)$ group between oxyanion nucleophiles as giving a β_{eq} of 0.88, suggesting that the *O*Ar has a net starting charge of −0.12. If one makes a correlation between the net *O*Ar oxygen charge and the $\Sigma\sigma_I$ values of the EtO, Ph and CH_3 groups on the P, *i.e.* charge $O = n(\Sigma\sigma_I)$, then $n = 1.43 \pm 0.13$, and the net positive charge for the OAr group attached to a $EtO(CH_3)P(O)$ moiety is predicted to be 0.5 ± 0.05.

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