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Solvent deuterium kinetic isotope effects for the methanolyses of neutral C=O, P=O and P=S esters catalyzed by a triazacyclododecane : Zn^{2+}-methoxide complex

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Received 2nd September 2005, Accepted 17th October 2005
First published as an Advance Article on the web 7th November 2005

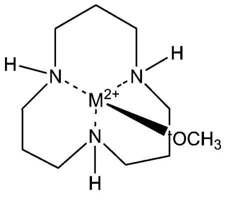
The methanolyses of several organophosphate/phosphonate/phosphorothioate esters (*O*,*O*-diethyl *O*-(4-nitrophenyl) phosphate, paraoxon, **3**; *O*,*O*-diethyl *S*-(3,5-dichlorophenyl) phosphorothioate, **4**; *O*-ethyl *O*-(2-nitro-4-chlorophenyl) methylphosphonate, **5**; *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate, fenitrothion, **6**; *O*-ethyl *S*-(3,5-dichlorophenyl) methylphosphonothioate **7**) and a carboxylate ester (*p*-nitrophenyl acetate, **2**) catalyzed by methoxide and the $Zn^{2+}(^{-}OCH_3)$ complex of 1,5,9-triazacyclododecane (**1** : $Zn^{2+}(^{-}OCH_3)$) were studied in methanol and d_1-methanol at 25 °C. In the case of the methoxide reactions inverse skie's were observed for the series with values ranging from 2 to 1.1, except for **7** where the $k_D/k_H = 0.90 \pm 0.02$. The inverse k_D/k_H values are consistent with a direct nucleophilic methoxide attack involving desolvation of the nucleophile with varying extents of resolvation of the TS. With the **1** : $Zn^{2+}(^{-}OCH_3)$ complex all the skie values are $k_D/k_H = 1.0 \pm 0.1$ except for **7** where the value is 0.79 ± 0.06. Arguments are presented that the fractionation factors associated with complex **1** : $Zn^{2+}(^{-}OCH_3)$ are indistinguishable from unity. The skie's for all the complex-catalyzed methanolyses are interpreted as being consistent with an intramolecular nucleophilic attack of the Zn^{2+}-coordinated methoxide within a pre-equilibrium metal : substrate complex.

Introduction

Metal ion catalyses of the hydrolyses of carboxylate esters, amides[1] and phosphate mono-, di- and triesters[2] have been extensively studied to ascertain the practical applications and as an aid to understanding the mechanism of action of hydrolytic metalloenzymes.[3] Many reports have appeared concerning the metal catalyzed hydrolyses of neutral phosphate triesters[4] and a lesser number on neutral phosphonate diesters[4q,v,w,x,y] due to their importance as acetylcholinesterase inhibitors. In the bulk of these studies the most active catalytic species were identified as the M^{x+}–^{-}OH forms generated at high pH through ionization of a metal-bound water. The general consensus for the hydrolytic mechanism of all these esters is that the M^{x+}–^{-}OH acts as a nucleophile, either directly on the C=O[4b] or P=O unit without coordination, or more probably through a pre-equilibrium metal–ester binding[4] or a hybrid mechanism.[5] Alternative mechanisms have been proposed where an external ^{-}OH nucleophilically attacks a M^{x+}-coordinated substrate[6] or where a metal-coordinated ^{-}OH or external hydroxide acts as a general base.[7]

In ideal cases experimental evidence for the nucleophilic or general base mechanisms should be provided through the use of solvent deuterium kinetic isotope effects (skie) but to our knowledge there is a paucity[7] of these reported for the metal catalyzed hydrolysis of neutral carboxylate and phosphate, phosphorothioate, phosphonate or phosphonothioate esters. There are a few skie studies reported for metal catalyzed hydrolyses of phosphate diesters[8] and ribozyme-catalyzed cleavage of phosphate diesters[9] where the binding of the anionic phosphate substrates to the metal centres is far stronger than is the case with neutral substrates. For simpler cases where metal ions were involved in the cleavage of phosphate diesters[8] skie values of 1.0 ± 0.1 were interpreted as indicating a nucleophilic rather than a general base mechanism because there was no strong primary effect as is expected for a 'proton in flight' or one being transferred between a base and nucleophilic water during the reaction. The situation with the Mg^{2+}-dependent ribozyme-catalyzed phosphoryl transfer reactions is more complicated due to the fact that there are likely two or more catalytic functional groups that act in a base/acid role to promote the phosphate cleavage. Roles for the Mg^{2+}–^{-}OH as a general base,[9b] or Mg^{2+} acting as a Lewis acid to assist the departure of the oxyanion leaving group[9a,c] have been suggested. Interpretation of skie experiments dealing with enzymatic systems is fraught with difficulties, as Kresge[10] has pointed out, since there are numerous exchangeable-proton and solvation sites on the enzyme which could contribute to the observed effect but are not directly associated with the catalytic machinery.

Recently we reported examples of the methanolyses of carboxylate esters,[11] phosphate and phosphorothioate triesters[12] and some phosphonates[13] promoted by La^{3+}, **1** : Cu^{2+} and **1** : Zn^{2+}, in methanol solution under buffered conditions to control $^{s}_{s}$pH.[14,15] The 1,5,9-triazacyclododecane complexes of Zn^{2+} and Cu^{2+}, as their mono-methoxy forms (**1**), are monomeric throughout the $^{s}_{s}$pH regions of interest for catalysis. The $^{s}_{s}pK_a$ for ionization of the **1** : Zn^{2+}–$HOCH_3$ complex is 9.1[12d] while that for the **1** : $Cu^{2+}HOCH_3$ complex is 8.75.[12e] The stoichiometric simplicity of the **1** : $M^{2+}(^{-}OCH_3)$ system as well as being able to use it to set the $^{s}_{s}$pH or $^{s}_{s}$pD of the solution at values corresponding to the $^{s}_{s}pK_a$ when the [**1** : $M^{2+}(^{-}OCH_3)$]/[**1** : $M^{2+}(LOCH_3)$] ratio is unity (L = H, D) makes it a good candidate for skie studies[16,17] As recognized earlier by Gold[18] and Schowen,[19] the choice of methanolysis also removes the problem of an internal fractionation factor for the *H*O$^-$ that is associated with hydroxide-promoted hydrolyses and introduces additional complications when assessing skie processes in water. In what follows we report the skie for $^{-}OCH_3$



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

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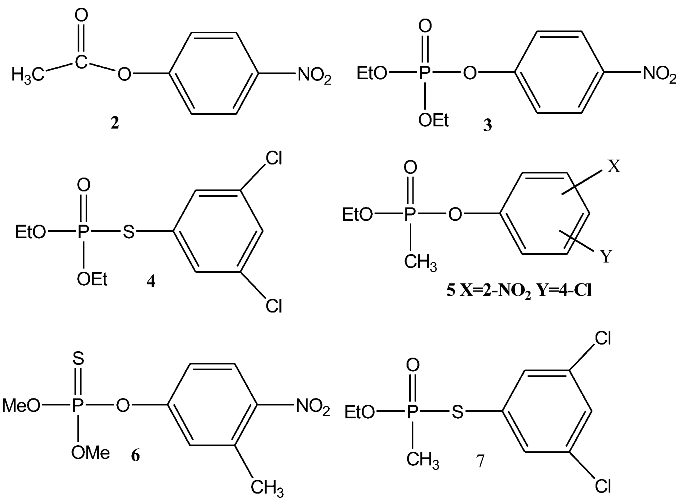


and **1** : $Zn^{2+}(^{-}OCH_3)$-catalyzed methanolysis of some neutral carboxylate and phosphorus esters **2–7**.

Experimental

i) Materials

Anhydrous methanol (99.8%), methanol-d_1 (99 atom%), NaOMe (0.5 M), NBu_4OH (1.0 M) were from Aldrich. $Zn(OTf)_2$ (98%) was from Acros Organics. Paraoxon (98.4%) was from Chem Service Ltd. *p*-Nitrophenyl acetate (**2**, Aldrich) was recrystallized from ethyl acetate and acetic anhydride. Fenitrothion (**6**, 96.7%) was from Sumitomo Chemicals and used as received. *O*,*O*-Diethyl *S*-(3,5-dichlorophenyl) phosphorothioate (**4**) was supplied by Mr Tony Liu from an earlier study.[12b] *O*-Ethyl *O*-(2-nitro-4-chlorophenyl) methylphosphonate (**5**) was prepared by and its kinetics of methanolysis determined by Ms Roxanne Lewis[13] and 1,5,9-triazacyclododecane was supplied by Mr Graham Gibson. *O*-Ethyl *S*-(3,5-dichlorophenyl) methylphosphonothioate (**7**) was synthesized and its kinetics of methanolysis determined by Ms Stephanie Melnychuk.[20]

ii) Methods

UV/vis kinetic determinations and $^{s}_{s}pH$ measurements were done using instruments and methods described earlier.[11–13] Stock solutions of the substrates (5 mmol dm^{-3}), NaOMe (25 mmol dm^{-3}), NBu_4OH (25 mmol dm^{-3}), $Zn(OTf)_2$ (50 mmol dm^{-3}) and 1,5,9-triazacyclododecane (50 mmol dm^{-3}) were made in anhydrous methanol. The catalyst for kinetic runs was formed *in situ* by addition of known aliquots of $Zn(OTf)_2$, 1,5,9-triazacyclododecane and NaOMe or NBu_4OH to anhydrous methanol or methanol-d such that the final volume in each UV cell was 2.5 ml. $^{s}_{s}pH$ was controlled in methanol at 9.14 by maintaining a constant ratio of $Zn(OTf)_2$: 1,5,9-triazacyclododecane : base = 1 : 1 : 0.5. The kinetics were measured by monitoring the change in absorbance corresponding to the destruction of starting material (paraoxon; λ = 268 nm) or the formation of products (*O*,*O*-diethyl *S*-(3,5-dichlorophenyl)phosphorothioate; λ = 281 nm, fenitrothion; λ = 335 nm, 4-nitrophenyl acetate; λ = 339 nm) with a Cary 100 Bio UV-Vis spectrophotometer thermostated at 25 °C. The absorbance *vs.* time data were fit to a standard first order exponential equation to obtain the pseudo-first order rate constants, k_{obs}. The rates of reaction were measured in duplicate at different catalyst concentrations from 0.2–3 mmol dm^{-3} for **1** : Zn^{2+} and from 3–30 mmol dm^{-3} for the methoxide reactions. The second order rate constants for catalysis of methanolysis of **2–7** were determined as the gradients of the k_{obs} *vs.* [active catalyst]. After each kinetic run in non-deuterated solvent, $^{s}_{s}pH$ was measured with an Accumet Ag/AgCl electrode.

For consistency, kinetic runs in d_1-methanol utilized the same stock solutions that were used in protiated methanol. This introduces some protium into the solution but it is never more than 9.6% and has at most a 5% effect on the skie for the most inverse case (methoxide + **2**) and very little effect on the results with **1** : $Zn^{2+}(^{-}OCH_3)$ since all the examples have k_D/k_H values near unity.

Results

Given in Table 1 are the second order rate constants determined for the methoxide and **1** : $Zn^{2+}(^{-}OCH_3)$ promoted methanolyses of **2–7** determined in methanol and d_1-methanol. The constants were determined from the gradients of plots of the pseudo-first order rate constant (k_{obs}) for methanolysis of each substrate as a function of $[^{-}OCH_3]$ or $[\mathbf{1} : Zn^{2+}(^{-}OCH_3)]$ using at least three concentrations of reactant in duplicate. The skie is given as k_D/k_H which is generally inverse for all the methoxide reactions except with **7** and indistinguishable from unity for all the metal ion catalyzed reactions except with **7** where the value is $k_D/k_H = 0.79 \pm 0.05$.

Discussion

i. General considerations for fractionation factor analysis.

The solvent kie can be predicted[21] as:

$$k_D/k_H = \Pi_i(1 - x + x\phi_i^{TS})/\Pi_j(1 - x + x\phi_j^{GS}) \quad (1)$$

where $\Pi_i\phi^{TS}$ and $\Pi_j\phi^{GS}$ are the products of the fractionation factors (ϕ) for all exchangeable *i* and *j* protons (L = H, D) in the transition (TS) and ground states, and *x* is the mole fraction of deuterium in the solvent mixture. The fractionation factors for hydrogens refer to the tendency of H or D to accumulate at a given site relative to bulk solvent. In less precise terms they refer to the 'tightness of bonding' and the general rule is that the heavier isotope accumulates in the stronger bond. Fractionation factors are significantly less than unity for L's being transferred or "in flight" between O and N, or O and O as part of the rate-limiting step. In these cases normal primary dkie's of $k_H/k_D > 1$ (generally from 2–4) are expected unless other

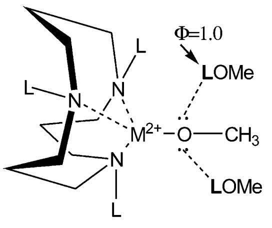
Table 1 Solvent deuterium kinetic isotope effects for the reactions of methoxide and **1** : $Zn^{2+}(^{-}OCH_3)$ with esters **2–6**

	$k_2^{OMe}/mol^{-1}\ dm^3\ s^{-1}$			$k_2^{1:Zn(OMe)}/mol^{-1}\ dm^3\ s^{-1\ a}$		
Subst.	CH_3OH	CH_3OD^b	k_D/k_H	CH_3OH	CH_3OD^b	k_D/k_H
2	216 ± 6	430 ± 9	2.0 ± 0.1	8.4 ± 0.3	9.4 ± 0.3	1.1 ± 0.1
3	0.016 ± 0.0002	0.018 ± 0.0002	1.10 ± 0.02	0.48 ± 0.007	0.47 ± 0.007	0.98 ± 0.02
4	0.155 ± 0.003	0.244 ± 0.003	1.5 ± 0.04	0.83 ± 0.07	0.83 ± 0.04	1.0 ± 0.1
5^c	14.3 ± 0.1	21 ± 1	1.47 ± 0.08	517 ± 3	510 ± 20	0.98 ± 0.04
6	$(5.9 \pm 0.02) \times 10^{-4}$	$(7.5 \pm 0.2) \times 10^{-4}$	1.3 ± 0.03	6.3 ± 0.2	6.9 ± 0.3	1.1 ± 0.1
7^d	2.17 ± 0.03	1.96 ± 0.02	0.90 ± 0.02	95.2 ± 1.4	75.7 ± 4.6	0.79 ± 0.06

^{a} Determined at **1** : Zn^{2+} : $(^{-}OCH_3)$ = 1 : 1 : 0.5. ^{b} Computed as gradient of k_{obs} *vs.* [catalyst] without correction for amount of protium which can be as high as 9.6%; see ref. 42. ^{c} From ref. 13. ^{d} From ref. 20.

compensating factors, such as changes in solvation, are at play. In hydrogen bonding situations where the overall bonding is loose, the ϕ values are also less than unity and these can contribute secondary effects of solvation which may significantly alter the overall dkie.[22]

Gold and Grist[18a] and More O'Ferrall[23] determined that the methanolic methoxide ion exists as $MeO^-(\mathbf{L}OMe)_3$ where each of the three solvating hydrogen bonding **L** has a fractionation factor value of $\phi = 0.74$; this value will be used for the ground state for discussing the methoxide dependent reactions below. There are a few fractionation factors available for water solvated metal ions such as Fe^{3+}, Mn^{2+} and Cr^{3+}[24] as well as the alkali metal cations, Ag^{2+} and Cd^{2+}[25] and these are close to unity indicating that the associated solvent does not behave very differently from bulk water. As far as we are aware no fractionation factors have been published for $M^{x+}(^-OR)$ systems, although a value of 0.72 was interpreted from NMR T_2 measurements[26] for the high pH forms of Co^{II} carbonic anhydrase isozymes I and II in water where the active site comprises a His$_3$-bound Co^{II}-($^-$OL). In **1** : $Zn^{2+}(^-OCH_3)$ the Zn^{2+} electrostatically stabilizes the coordinated methoxide which accounts for the fact that the $^{s}_{s}pK_a$ of methanol is reduced from 18.13[12b] to 9.14 when coordinated to the Zn^{2+}. Due to the reduced need for H-bonding stabilization of the complex we suggest the working model **8**, where the fractionation factors associated with the N–L groups are unity and that for the two possible solvating **L**OMe groups is 1.0 or slightly less, but nowhere as low as for free methoxide. In support of the near unit fractionation factor we have been able to confirm the ϕ of 0.74 for the solvating methanols of methoxide using the ^{1}H NMR methodology of Gold[18a] but have not been able to detect any effect of added **1** : $Zn^{2+}(^-OCH_3)$ up to 10 mmol dm^{-3} on the exchangeable proton peak position relative to the ^{13}C satellite of CH_3OL. The inability to observe a detectable effect with **1** : $Zn^{2+}(^-OCH_3)$ suggests that the solvation of the $Zn^{2+}(^-OCH_3)$ in **8** is sufficiently weak that the hydrogen bonds to the coordinated methoxide cannot be distinguished from those in bulk water.[27] This lack of solvation might be one of the reasons that **1** : $Zn^{2+}(^-OCH_3)$ is such an effective catalyst since it does not take much energy to remove a H-bond to liberate a free electron pair for the catalytic step.



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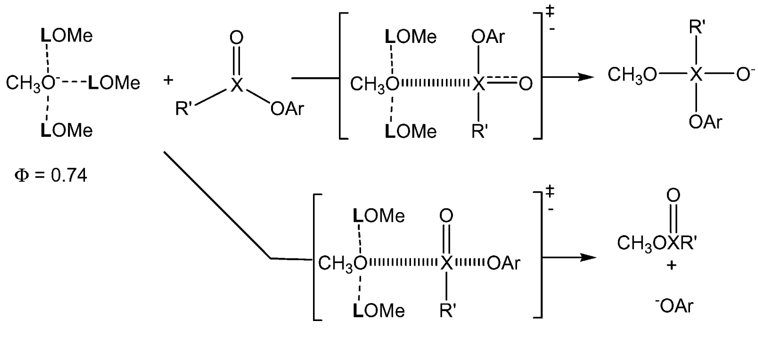
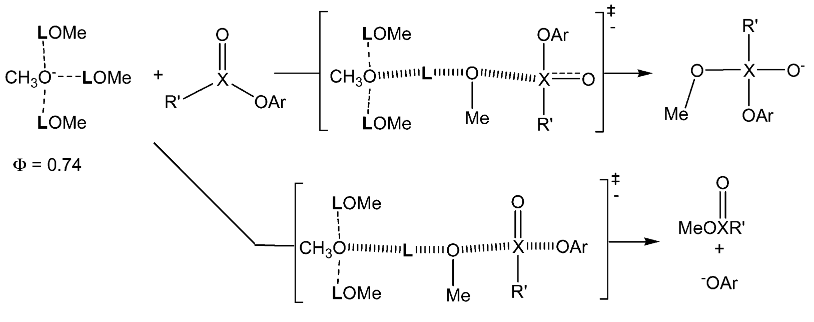
ii. General mechanistic possibilities for lyoxide reactions with carboxylate and phosphate esters

To interpret the skie one needs first to ascertain the rate-limiting step for the reactions in question. Schemes 1 and 2 illustrate the two general nucleophilic (Nuc) and general base (GB) mechanisms where the bold **L** represents the exchangeable H or D in the ground and transition states. Although most of HO^-- promoted hydrolyses of carboxylate esters are interpreted as nucleophilic,[28] Marlier has proposed a GB mechanism for the alkaline hydrolysis of methyl formate based on heavy atom kinetic isotope effects[29] A more recent analysis of a proton inventory study of the alkaline hydrolysis of ethyl acetate also was interpreted[30] in support of the GB mechanism, although not uniquely so in our opinion.[31] As far as we know, the main role for lyoxide reaction with phosphate triesters is deemed to be Nuc[32] although weakly nucleophilic additives can function in GB roles as was demonstrated by a key study of the acetate promoted methanolysis of some phosphate triesters[33]

Possible variants of the Nuc and GB mechanisms for carboxylate and phosphate esters involve concerted or stepwise reactions. Transfer of an acetyl group from *p*-nitrophenyl acetate to phenolate and oxyanion acceptors is probably a concerted one step reaction[34a] with little imbalance between bond formation and cleavage. Shames and Byers[34b] suggest that oxyanions which are more basic than the leaving group react with *p*-nitrophenyl acetate through a transition state which is nearly tetrahedral and with very little barrier to breakdown which is not necessarily at variance with a concerted process. Finally, Hengge and Hess conclude from heavy atom kinetic isotope effects that hydroxide



Scheme 1 Nucleophilic mechanisms for attack of methoxide. (Carboxylate esters, X = C, R′ = CH_3. Phosphorus esters, R′ = ethoxy, X = P(alkyl), P(ethoxy)).



Scheme 2 General base mechanisms for methoxide reaction. (Carboxylate esters, R′ = CH_3; X=C. Phosphorus esters, R′ = ethoxy, X= P(alkyl), P(ethoxy)).

and hexafluoroisopropanolate react with **2** *via* a concerted mechanism.[34c]

By contrast, the lyoxide reactions of 2-aryloxy-2-oxo-1,3-dioxaphosphorinanes[35,36] have been discussed in terms of two step processes that proceed *via* rate limiting formation of a 5-coordinate intermediate. The relatively low Brønsted β_{lg} values of −0.4 obtained for the HO^- or CH_3O^- nucleophiles with these substrates are consistent with little cleavage of the P–OAr bond in the TS. Hydroxide promoted hydrolyses of *O*,*O*-diethyl *O*-aryl phosphate triesters[37,38] and *O*,*O*-diethyl *S*-aryl phosphorothiolates[37] give relatively low β_{lg} values of −0.4 and was discussed in terms of a common mechanism involving nucleophilic attack of HO^-, although it was not specified in the latter study whether the reaction of these substrates is a two step one or concerted. Williams and co-workers provided evidence for a concerted transfer of the diphenylphosphoryl group between phenoxide anions in water[39] and considered that HO^- reacting with diethyl aryloxy phosphates was probably concerted but with little cleavage of the ArO–P bond. This is consistent with the ^{18}O-phenoxy kinetic isotope effect of 1.006 for HO^--promoted cleavage of paraoxon **3** that was interpreted[40] as having a P–OAr bond order of 0.75 within an "S_N2-like transition state of an associative mechanism with concerted, asynchronous departure of the leaving group."

iii. Skie for the methoxide reactions of carboxylate and neutral phosphate esters

a. Carboxylate esters. Inverse k_D/k_H values of 1.9 for methanolysis of phenyl benzoate at 25 C and 2.6 for the methanolysis of *p*-nitrophenyl acetate at −78 C[41] are consistent with a Nuc but not GB mechanism. The k_D/k_H = 1.84 for methoxide reacting with phenyl acetate at 25 C was rationalized[19b] in terms of the Nuc mechanism of Scheme 1. One of the three solvating **L**OMe groups on methoxide is removed to liberate a nucleophilic lone pair with the two remaining solvating **L**OMe molecules loosening their association in the transition state to have $\phi = 0.88$; the computed skie for this process is $k_D/k_H = (0.88)^2/(0.74)^3 = 1.91$.

The skie for methanolysis of *p*-nitrophenyl acetate (**2**) found here is $k_D/k_H = 2.0 \pm 0.1$ at 25 °C which, when interpreted as above, gives a fractionation factor for the two TS solvating protons of 0.9 : $k_D/k_H = (0.9)^2/(0.74)^3 = 2.0$.[42] That all skie values for methanolysis of aryl esters are substantially inverse effectively rules out the GB mechanism shown in Scheme 2. That mechanism, with the proton in flight having a predicted ϕ value between 0.4–0.25 (for a primary k_H/k_D contribution of 2.5–4) and with ϕ values of 0.9 for the two residual solvating **L**OMe molecules, would have a computed normal skie of k_H/k_D = 1.25–2.0.

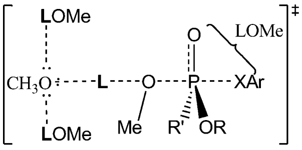
The methoxide reaction of a series of aryloxy acetates generates a Brønsted β_{lg} value of −0.66[11b] which is consistent with either a concerted reaction[34] or a two step process with rate-limiting methoxide addition to create and unstable tetrahedral intermediate with essentially no charge on the departing group. The skie data do not add to the two step/concerted case other than to imply that resolvation of either TS must lag far behind desolvation of the nucleophile, a conclusion similar to one we reached for the alkaline hydrolysis of formamide and ethyl acetate on the basis of proton inventory data.[31] Such resolvation of the TS, if significant, would introduce additional ϕ contributions of <1 into the numerator of eqn (1) leading to k_D/k_H values which are closer to unity than observed.

b. Phosphorus esters

Given in Table 1 are respective values of k_D/k_H = 1.1, 1.5, 1.47, 1.3 and 0.90 for the methoxide promoted methanolysis of phosphorus esters **3** (paraoxon), **4** (*O*,*O*-diethyl-*S*-(3,5-dichlorophenyl) phosphorothioate), **5** (*O*-ethyl-*O*-(2-nitro-4-chlorophenyl) methylphosphonate), **6** (fenitrothion) and **7** (*O*-ethyl *S*-(3,5-dichlorophenyl) methylphosphonothioate). The value we obtained for paraoxon is experimentally identical to the $k_D/k_H = 1.2$ provided by Schowen[33] for the methanolysis of *O*,*O*-dimethyl-*O*-(*p*-nitrophenyl) phosphate (methyl paraoxon) implying a negligible steric effect on the inverse nature of the skie. That none of the skie values for the phosphorus esters is as inverse as found for the carboxylate ester **2** suggests there is some additional solvation of the transition states for phosphate methanolysis which is not present in the solvolysis of **2**. Resolvation of the TS offsets the desolvation of the nucleophile bringing the observed skie closer to unity as observed, but the skie experiments do not indicate where such resolvation occurs. Schowen[33] suggests, on the basis of proton inventory data and a comparison with an observed acetate promoted general base methanolysis reaction[43,44] of methyl paraoxon, that methoxide promoted methanolysis probably occurs through a transition state characterized by a "one proton bridge plus solvation model". Although the position of the proton bridge is not known, if it occurs between the methoxide and a second attacking methanol this would be almost equivalent to a general base mechanism, but one with little removal of the bridging proton in the TS since its fractionation factor is never less than 0.67.

Recent studies[12b,13] found Brønsted β_{lg} dependencies of −0.70, −0.76 and −0.76 respectively for the methoxide promoted methanolysis of three series of *O*,*O*-diethyl *O*-aryl phosphates, *O*,*O*-diethyl *S*-aryl phosphorothioates and *O*-ethyl *O*-aryl methylphosphonates at 25 °C. These are consistent with two step or concerted reactions where the charge on the aryloxy or arylthio groups in the TS of the three series is +0.17, −0.2, and −0.26 respectively. The skie's for these phosphorus esters do not provide additional information to distinguish stepwise from concerted mechanisms, but combining the skie, proton inventory[33] and the Brønsted β_{lg} data suggest possible TS structures **9** or **10** with the P–XAr bond being intact or partially cleaved and with one specific stronger H-bonding (proton bridging) interaction along with additional numbers of non-specific hydrogen bonds. The transition state contribution of these (TSC) in either **9** or **10** can be computed from eqn (2) for **3**–**7** as 0.45, 0.61, 0.60, 0.53 and 0.36 respectively when ϕ_{gs} = 0.74.

$$k_D/k_H = \mathrm{TSC}/(1 - n + n\phi_{gs})^3 \qquad (2)$$



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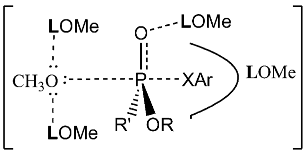

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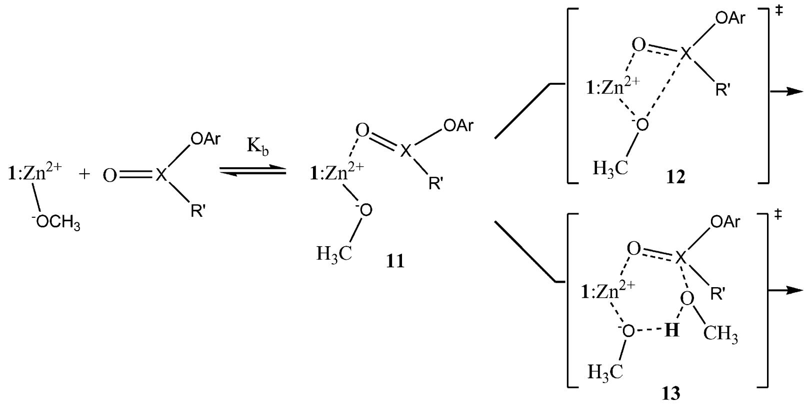
iv. 1 : Zn²⁺(⁻OCH₃) promoted methanolysis of 2–7

Numerous authors have considered that invoking a dual role for the metal ion (as a Lewis acid and deliverer of metal-bound lyoxide) requires that the metal promoted: lyoxide reaction is faster than lyoxide alone.[4b,h,m,p,5,11,12,13] Since the **1** : $Zn^{2+}(^-OCH_3)$-catalyzed reactions of all the phosphorus esters[11,12,13,20] presented in Table 1 are faster than the methoxide reactions, we envision a common mechanism with a rapid pre-equilibrium binding of the metal complex to the P=O or P=S unit with subsequent intracomplex metal-bound methoxide attack although there are some kinetically equivalent alternatives that can be ruled out later.

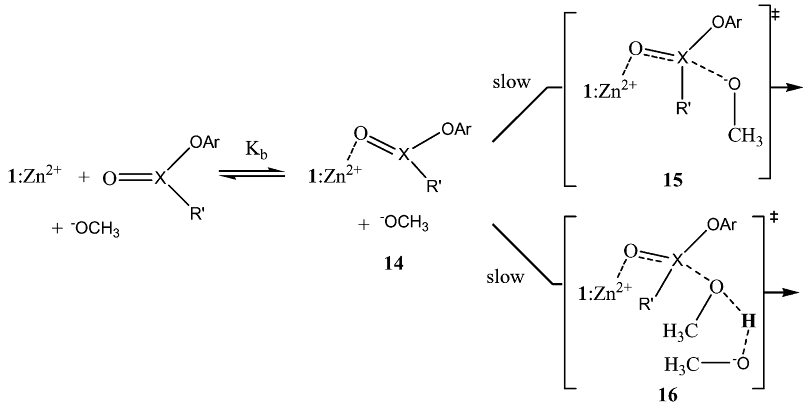
The situation with carboxylate esters is more difficult to analyze and the interpretation depends on whether the leaving group is good or bad. Since the reported reaction of hydroxide[45] with the carboxylate ester **2** was 230 times faster than that of **1** : Zn^{2+}($^-$OH), Kimura and Koike[4b] concluded that a simple bimolecular mechanism was predominant for the latter where the "Zn^{2+}- bound hydroxide (less basic than free $^-$OH ion) acts merely as a nucleophile (or general base to generate $^-$OH) to the carbonyl group". Suh, Son and Suh[6] subsequently suggested that this mechanism is incorrect and that a kinetically equivalent process occurs where a metal–ester complex suffers rate limiting attack of external $^-$OH to form a M^{2+}-bound tetrahedral intermediate. Our own study of the **1** : Zn^{2+}($^-$OCH$_3$) promoted methanolysis of an extensive series of carboxylate esters with good and poor leaving groups[11b] revealed a downward break in the Brønsted plot, consistent with a two step mechanism with a change in rate-limiting step (RDS) due to partitioning of a metal-coordinated tetrahedral intermediate, the formation and breakdown of which is rate limiting for good and poor leaving groups respectively. Importantly, for all the cases with poorer aryloxy leaving groups than 4-nitrophenoxy such as 4-Cl-, 4-OCH$_3$-, 4-H-, 2,4-dimethyl- and 2,3,5-trimethylphenoxy, methoxide is significantly less reactive than is **1** : Zn^{2+}($^-$OCH$_3$). However with 4-nitrophenoxy and all leaving groups better than that, methoxide is the better nucleophile. This reinforces the caveat that proposing a catalytic mechanism based on the results with a limited number of substrates, particularly those containing examples limited to the good leaving group *p*-nitrophenoxy,[46] is often incorrect.

If we accept the reasonable premise that there is a common pre-equilibrium binding of the Zn^{2+}-complex to both the phosphorus and carboxylate esters, there are at least eight mechanisms for the metal-catalyzed reactions of the ensuing complexes which are divided into two kinetically equivalent main classes: 1) an intramolecular process where a metal-bound methoxide acts on a transiently M^{2+}-bound substrate (the IM process); or 2) an external methoxide reacting with a transient M^{2+}-bound substrate (the EM process). Each of these could involve Nuc or GB processes and each could be concerted or two steps. Schemes 3 and 4 show the possibilities where the slow step of the reactions involves the IM and EM attack on the complex either directly or as a GB *via* the concerted or stepwise processes.

Some of the possibilities can be ruled out. As described above, the reactions of a series of acetate esters are two step ones[11b] with **2** falling in a domain where the RDS is attack on a transiently coordinated substrate. All the phosphate esters, including **7**[20] have large negative Brønsted β_{lg} values signifying extensive cleavage of the P–OAr or P–SAr bonds in the transition state which is consistent with a concerted reaction.[12b,13,20] The near unity skie values for all the species allow us to rule out the IM mechanism where there is a GB role for the methoxide. Large normal kie's of $k_H/k_D > 2$ are commonly found for general base catalyzed processes whereas direct nucleophilic addition usually involves little or no isotopic distinction[47] unless large secondary effects associated with solvation changes are at play which is not the case here. Since the fractionation factors associated with the initial complex **8** are unity (*vide supra*), the TSC in eqn (2) for the metal catalyzed reactions of **2–6** must be essentially unity as well, so there cannot be any proton in flight or extensive H-bonding resolvation of the TS having a $\phi < 1.0$, otherwise the skie would be normal and substantially >1. With **7** the skie is normal but slightly so at $k_D/k_H = 0.79$ which is not large enough to strongly support a GB process but may indicate some extra transition state solvation relative to the starting materials. The preferred IM process consistent with all the results is shown in Scheme 3



Scheme 3 Intramolecular nucleophilic and general base mechanisms for catalysis by **1** : Zn^{2+}($^-$OCH$_3$). (Carboxylate esters, R′ = CH$_3$; X = C. Phosphorus esters, R′ = ethoxy, X = P(alkyl), P(ethoxy)).



Scheme 4 External methoxide nucleophilic and general base catalyzed methanolysis of **1** : Zn^{2+} + substrate complex. (Carboxylate esters, R′ = CH$_3$; X = C. Phosphorus esters, R′ = ethoxy, X = P(alkyl), P(ethoxy)).

and proceeds by the equilibrium formation of a metal–substrate complex **11** followed by the rate limiting nucleophilic TS **12** in which the C–XAr bond is intact for carboxylate esters and the P–XAr bond is partially cleaved for phosphate esters.

In Scheme 4 is the kinetically equivalent EM process for the nucleophilic and general base possibilities. The ground state contributions to the fractionation factors are ~1.0 for the **1** : Zn^{2+} ($HOCH_3$) complex[24,25] and 0.74 for each of the solvating methanols on the methoxide. The predicted k_D/k_H = TSC/(1.0)(0.74)^3, so the TSC would have to be 0.36–0.44 in order to accommodate the essentially unity skie observed for all species. Given the above skie results for $^-OCH_3$ promoted methanolysis of **2–7** and methylparaoxon,[33] a direct nucleophilic role for external methoxide does not seem possible unless there is considerable resolvation of TS **15**. The GB process proceeding through TS **16** with a proton in flight is possible mathematically although we can rule this out, at least for the phosphorus esters, with other evidence. Simple consideration of the observed second order rate constants for the metal catalyzed reaction of **5** and reasonable values for the equilibrium binding constants allows us to rule out the external methoxide Nuc or GB processes since the computed rate constants for external attack on a **1** : Zn^{2+}-bound substrate exceeds the diffusion limit of 5×10^9 mol^{-1} dm^3 s^{-1}.[48] It is customarily assumed[6] that the equilibrium binding constant for various metal ion complexes with neutral C=O or P=O substrates is ~1 $mol^{-1}dm^3$. We also assume this number to be appropriate for methanol noting that there is no saturation behaviour of the reaction kinetics at concentrations of catalyst up to 10 mmol dm^{-3}. In the case of 1 mmol dm^{-3} of [**1** : Zn^{2+}] at $^{s}_{s}$pH 9.14, the [$^-OCH_3$] = $10^{-7.65}$ mol dm^{-3} and the computed second order rate constant for methoxide attack on **5** would be 2.1×10^{10} mol^{-1} dm^3 s^{-1}, a value that exceeds the diffusion limit by roughly 4-fold.[49]

Conclusion

The reaction of **1** : $Zn^{2+}(^-OCH_3)$ with the entire series of neutral OP derivatives appears to adhere to a common mechanism that involves pre-equilibrium binding of the substrate, followed by intramolecular attack of the coordinated methoxide concerted with OAr or SAr leaving group departure. The present skie and rate data do not support an external methoxide mechanism as at least one of the OP substrates would have to react at a rate exceeding the diffusion limit. Since the OP derivatives all appear to react by a common concerted mechanism there is no justification for an EM process for some, but not other, members of this series. Further, the combination of the skie and rate data are not consistent with GB mechanisms for the metal catalyzed reactions that involve protons in flight having low fractionation factors as these would give normal skie values substantially in excess of 1, contrasting the observed skie values which are all essentially unity.

For the carboxylate esters the mechanism of the **1** : Zn^{2+} catalyzed reaction still has some ambiguities. Unfortunately the available skie data cannot distinguish a direct nucleophilic IM process from an external methoxide acting as a GB toward a metal coordinated C=O. Chemical intuition and precedence suggests that GB mechanisms are most likely for weaker nucleophiles displacing poorer leaving groups, and not likely for good nucleophiles displacing good leaving groups as is the case for the EM mechanism. For carboxylate esters with good leaving groups our preferred mechanism thus involves pre-equilibrium binding of the substrate to the **1** : $Zn^{2+}(^-OCH_3)$ complex, followed by rate-limiting intramolecular attack of the coordinated methoxide to form a tetrahedral intermediate stabilized *via* coordination to the Zn^{2+}. The mechanism for carboxylate esters with poor leaving groups is essentially the same IM process, but this time the breakdown of the tetrahedral intermediate must be rate-limiting. For a symmetrical reaction, involving Zn^{2+}-delivery of the coordinated methoxide, microscopic reversibility requires that the loss of the leaving group also involves Zn^{2+} coordination but this is not required for good leaving groups.

The preferred intramolecular mechanism involving *cis* binding of a substrate and internal nucleophilic attack through a four-membered TS has been suggested many times before, but usually without detailed skie, Brønsted or other studies with an extensive series of substrates. Its attractiveness is simplicity, and its acceptance probably inspired by the earlier mechanisms elucidated for the hydrolysis of several exchange inert *cis*-$Co^{III}(^{-18}OH)$: (amide), : (ester) and : (phosphate) complexes which are convincingly shown by ^{18}O-isotope labeling and other techniques to involve intramolecular^{18}O-transfer to the substrate.[50]

Acknowledgements

The authors gratefully acknowledge the financial assistance of the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, Queen's University and the United States Department of the Army, Army Research Office, Grant No. W911NF-04-1-0057 and the Defence Threat Reduction Agency, Joint Science and Technology Office (06012384BP).[51] Chris Maxwell thanks Queen's University for a Summer Work Experience Program grant and Natural Sciences and Engineering Council of Canada for additional financial support. We are also indebted to Ms Stephanie Melnychuk, Ms Roxanne Lewis and Ms Josephine Tsang for technical assistance in performing some of the experiments. Finally they are grateful to Professor David Evans (Harvard University) and Professor Jerry Kresge (University of Toronto) for helpful discussions.

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51 The content of the information does not necessarily reflect the position or the policy of the federal government, and no official endorsement should be inferred.