REVIEW

Acyl and phosphoryl transfer to methanol promoted by metal ions

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1 Introduction

Metal ion catalyses of acyl[1] and phosphoryl[2] transfers have been extensively studied in aqueous media both for their fundamental importance and as simplified models for hydrolytic processes mediated by metalloenzymes,[3] and great strides have been made in our understanding of these. A deleterious aspect of studying metal ion catalysis of any hydrolytic process is that, above the pK_a values of the $M^{x+}(H_2O)_n$ species, formation of metal–hydroxo gels and precipitates occurs,[4] thus complicating mechanistic evaluation. This is indeed unfortunate since most studies indicate that the catalytically interesting species are the metal–hydroxo forms. Understandably, a great deal of attention has been paid to stabilization of the M^{x+}-$(HO^{-})_z$ through complexation to ligands of varying complexity,[1,2] but even so precipitation becomes a problem at high pH due to the very low solubility of $M^{x+}(HO^{-})_z$.

Less studied mechanistically, but none-the-less important from fundamental and socioeconomic standpoints, is metal ion catalysis of transesterifications,[5] where acyl or phosphoryl transfer to alcoholic solvents occurs. Alcohols have different solvent characteristics from water which include lower relative permittivities, better solubility of organic functionality and an increased propensity to favour ion pair formation, but for detailed mechanistic studies there is always the problem of defining and measuring pH in such media.[6] Among organic solvents methanol is closest to water in terms of its structure and solvent properties and its reduced relative permittivity (31.5 *vs.* 78.5 at 25 °C)[7] may be relevant to the reduced polarity extant in an enzyme's interior.[8] Furthermore, one might take advantage of the enhanced ion-pairing tendency in methanol to encourage association of anionic substrates with the metal ion in ways that could be relevant to enzymatic processes. In the following we deal with our recent but fledgling studies of metal ion catalysis of the methanolysis of esters, reactive amides and phosphate diesters. Particularly important for mechanistic studies is the finding that a variety of metal ions that we have tested, such as Zn^{2+}, Co^{2+}, Ti^{4+} and lanthanides such as La^{3+} and Eu^{3+}, usually introduced as trifluoromethanesulfonate (OTf^{-}) or ClO_4^{-} salts, are completely soluble throughout the entire pH domain where ionization of the $M^{x+}(CH_3OH)_y$ occurs to give metal-bound methoxides. Furthermore, the practical problem of pH determination and control in methanol has now been essentially solved by the recent research of Bosch and coworkers[9] who have shown that the pH in methanol ($^{s}_{s}$pH)† can be measured simply using a glass electrode.

2 Metal titrations in methanol

It is important for kinetic studies to determine the state of ionization of the various species in solution, and the ionization constants for $M^{x+}(CH_3OH)_y$ can now be easily determined in methanol by applying the simple potentiometric titration methods recently described[9] for non-metallic systems. Following Bosch,[9] an electrode standardized with aqueous buffers is used to determine the experimental meter reading in methanol ($^{w}_{s}$pH), to which a correction parameter of 2.24 is added to obtain the $^{s}_{s}$pH. The values of the dissociation constants, ($^{s}_{s}$pK_a), determined from the usual volume of titrant *vs.* $^{s}_{s}$pH plots, were calculated using the computer program PKAS[10] in which the $^{s}_{s}$pK_w in the program was replaced by the autoprotolysis constant for methanol at 25 °C ($^{s}_{s}$pK_{MeOH} = 16.77).[9]

Shown in Table 1 is a partial list of conditional $^{s}_{s}$pK_a values for various metal ions that we have investigated.‡ These are determined using 10^{-3} mol dm^{-3} solutions of the metal triflate or perchlorate in anhydrous methanol, titrated with a standardized $NaOCH_3$ solution, the details of which are described in our publications referenced in subsequent sections. It is important to note that values of the metal ion dissociation constants are dependent on the experimental conditions such as concentration of the metal salt, the overall ionic strength, and also specific interactions with counterions. The ($^{s}_{s}$pK_a)$_1$ and ($^{s}_{s}$pK_a)$_2$ values given in Table 1 refer to the first and second consumptions of methoxide or macroscopic $^{s}_{s}$pK_a values for ionization of methanols bound to the metal. Certain metal ions, notably Zn^{2+}

† For the designation of pH in non-aqueous solvents we use the forms described by Bosch and co-workers[9] based on the recommendations of the IUPAC, *Compendium of Analytical Nomenclature. Definitive Rules 1997,* 3rd edn., Blackwell, Oxford, UK, 1998. If one calibrates the measuring electrode with aqueous buffers and then measures the pH of an aqueous buffer solution, the term $^{w}_{w}$pH is used; if the electrode is calibrated in water and the 'pH' of the neat buffered methanol solution then measured, the term $^{w}_{s}$pH is used; if the electrode is calibrated in the same solvent and the 'pH' reading is made, then the term $^{s}_{s}$pH is used.

‡ Full experimental details, methods and analyses will be presented in a forthcoming publication, A. A. Neverov, G. Gibson and R. S. Brown, manuscript in preparation.

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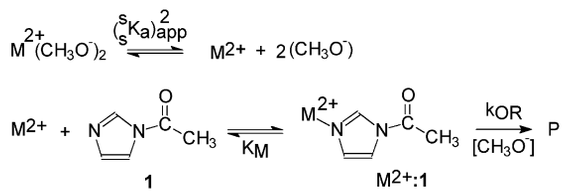
Table 1 Conditional values for ${}^{s}_{s}pK_a$ values for $M^{x+}(CH_3O)_x$ in methanol at ambient temperature

Metal ion	$({}^{s}_{s}pK_a)_1$	$({}^{s}_{s}pK_a)_2$	$({}^{s}_{s}pK_a)_{app}$ [d]
Zn^{2+} [a]	10.34 ± 0.14	9.25 ± 0.18	9.79 ± 0.16
Co^{2+} [a]	12.84 ± 0.03	9.96 ± 0.06	11.4 ± 0.06
La^{3+} [b]	7.30 ± 0.05	10.36 ± 0.06	
Eu^{3+} [b]	6.61 ± 0.06	8.17 ± 0.04	
Ti^{4+} [a]	<3.0 [c]	5.17 ± 0.07 [c]	

[a] Introduced as perchlorate salt. [b] Introduced as triflate salt, concentration of $La^{3+}(^{-}OTf)_3 = 8 \times 10^{-4}$ mol dm^{-3}. [c] For Ti^{4+}, the first ${}^{s}_{s}pK_a$ incorporates the dissociation of three protons from the $Ti^{4+}(CH_3OH)_x$, all occurring below ${}^{s}_{s}pH$ 3. The second ${}^{s}_{s}pK_a$ describes the fourth dissociation constant to form $Ti^{4+}(CH_3O^{-})_4$. [d] Defined as $[({}^{s}_{s}pK_a)_1 + ({}^{s}_{s}pK_a)_2]/2$.

and Co^{2+}, exhibit a titration profile showing steep consumption of two equivalents of CH_3O^{-} per metal indicating a cooperative effect between the first and second ionizations, reflected by $({}^{s}_{s}pK_a)_2$ being lower than $({}^{s}_{s}pK_a)_1$, see Table 1. For this reason, we refer to the value, $({}^{s}_{s}pK_a)_{app}$, the apparent midpoint of the titration curve, defined as $[({}^{s}_{s}pK_a)_1 + ({}^{s}_{s}pK_a)_2]/2$ in Scheme 1.



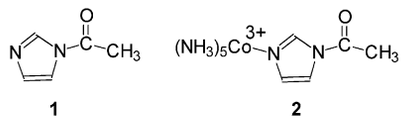
Scheme 1

However, Eu^{3+} exhibits a normal titration profile with stepwise consumption of two equiv. of CH_3O^{-} per metal ion. For La^{3+} the titration at first reveals consumption of one equiv. of CH_3O^{-} per metal having an apparent ${}^{s}_{s}pK_a$ of 7.30, followed by a second event leading to the consumption of 1.5 equiv. of CH_3O^{-} per La^{3+}, the non-integral number of methoxides suggesting that dimeric La^{3+} species are present. In this case the $({}^{s}_{s}pK_a)_2$ shown in Table 1 represents the macroscopic ${}^{s}_{s}pK_a$ corresponding to the midpoint of the non-integral titration step. $Ti^{4+}(CH_3OH)_x$, a tetrabasic acid, shows the consumption of three equivalents of methoxide before ${}^{s}_{s}pH$ 3 and a fourth having a ${}^{s}_{s}pK_a$ of 5.17, illustrating the unusually strong acidifying nature of this metal ion.

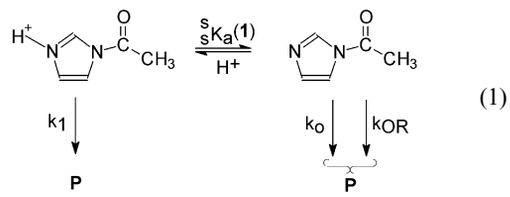
3 Methanolysis of activated amides

3.1 Acetylimidazole and *N*-acetylimidazolepentammine-Co^{III}

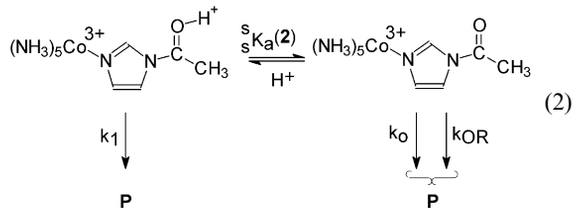
Our initial studies [11] concentrated on the effect of Zn^{2+}, Co^{2+} and La^{3+} in promoting the methanolysis of acetylimidazole (**1**) [12] and its ligand-exchange inert complex *N*-acetylimidazolepentammine-Co(III) perchlorate, $[(NH_3)_5CoImCOCH_3](ClO_4)_3$ (**2**).[13] These two activated amides were chosen because: 1) their hydrolyses are relatively well understood but, to our knowledge, their methanolyses have not been studied although this can be done easily by UV kinetics; 2) the Co^{III} complex, **2**, prevents further metal ion complexation to the distal N thus removing one possible site of catalysis; and 3) despite extensive investigation, it has yet to be shown that metal ions can catalyze the hydrolysis of **1**. Fife and co-workers have shown [1a,k,l] that *N*-acylimidazoles and *N*-acylbenzimidazoles incorporating proximal metal binding sites often do undergo M^{2+}-catalyzed hydrolyses but without these, or when metal binding occurs away from the scissile (N)C=O unit, catalysis is not observed. Indeed a proximal binding site is a general requirement for strong metal ion catalysis of the hydrolysis of more normal amides as well [1f-j,m-q] since without this, metal ion catalysis of their hydrolysis is not observed.



In the absence of metal ions the methanolysis of **1** and **2** follows the general processes outlined in eqn. (1) and (2) for which a generalized rate expression is given in eqn. (3),



(1)



(2)

$$k_{obs} = \frac{k_1[H^+] + (k_O + k_{OR}\,{}^{s}_{s}K_{MeOH}/[H^+])\,{}^{s}_{s}K_a^{(n)}}{({}^{s}_{s}K_a^{(n)} + [H^+])} \qquad (3)$$

where ${}^{s}_{s}K_{MeOH}$ refers to the autoprotolysis constant of methanol ($10^{-16.77}$ M^2) and ${}^{s}_{s}K_a^{(n)}$ is the dissociation constant of protonated **1** or **2** in MeOH. In the case of **2**, the kinetics are determined at $[H^+] \ll {}^{s}_{s}K_a^{(2)}$, so the equation simplifies to the form given in eqn. (4) where $k_{H^+} = k_1/{}^{s}_{s}K_a^{(2)}$.

$$k_{obs} = k_{H^+}[H^+] + k_o + k_{OR}{}^{s}_{s}K_{MeOH}/[H^+] \qquad (4)$$

The pH–rate profiles for methanolysis of **1** and **2** [11b] bear a striking resemblance to those determined in water,[12a,13] suggesting similar mechanisms having acid, neutral and base domains for both reactions. From NLLSQ fitting, the kinetic ${}^{s}_{s}pK_a$ of 4.2 determined for **1**-H$^+$ in methanol is slightly above its water ${}^{w}_{w}pK_a$ (3.6),[12a] generally agreeing with the relative trends in ${}^{s}_{s}pK_a$ for nitrogen-protonated bases in methanol [9b] that show slight increases (0.2–0.6) compared to their ${}^{w}_{w}pK_a$ values in water. The rate constants for the acid and neutral reactions of **1** and **2** (k_1, k_o) are within factors for four and 10 respectively for hydrolysis [12a] and methanolysis [11b] and only the lyoxide terms (k_{OR}) are substantially different. In the case of **1** the methoxide reaction is 25-fold faster (7900 dm^3 mol^{-1} s^{-1} (methanol) and 320 dm^3 mol^{-1} s^{-1} (water, I = 0.2 mol dm^{-3}) [12a]), presumably a consequence of the greater nucleophilicity of methoxide in methanol. In the case of **2** the methoxide reaction is very much faster than the hydroxide one (4.7×10^7 dm^3 mol^{-1} s^{-1} in methanol [11b] *vs.* 6.86×10^3 dm^3 mol^{-1} s^{-1} in water),[13] and the 7000-fold acceleration of the former can be accommodated by the reduced relative permittivity of methanol enhancing the reaction of oppositely charged reactants.

The promotion of the methanolysis of **1** by metal ions falls into two distinct classes depending on whether the catalytic ions are Zn^{2+} and Co^{2+} or La^{3+}. For the former two metals, the dependence of the observed pseudo-first order rate constant for methanolysis (k_{obs}) *vs.* $[M^{2+}]$ as a function of ${}^{s}_{s}pH$ shows that the reactions depend upon $[M^{2+}]$ and $[CH_3O^{-}]$. A proposed mechanism is given in Scheme 1 [11b] which is based on the following three observations. First, neither M^{2+} catalyzes the methanolysis of **2**, suggesting that the ligation of Co^{III} to acetylimidazole, while catalytically important, blocks further access of the

divalent metal ions and thus interferes with any additional catalysis. This suggests that all catalysis afforded by these metal ions involves coordination to the distal N of **1**. Second, with neither M^{2+} is there evidence of saturation binding to **1** since the plots of k_{obs} *vs.* $[M^{2+}]$ at all values are linear up to concentrations of 8×10^{-3} mol dm^{-3}, suggesting that the M^{2+}–**1** dissociation constants (K_M) are ≥ 0.1 mol dm^{-3}. Third, the slopes of the k_{obs} *vs.* $[M^{2+}]$ plots at each $^{s}_{s}$pH provide the second order rate constants (k_2) for metal ion catalysis. When these are plotted in the usual way against $^{s}_{s}$pH they exhibit bell-shaped profiles maximizing at $^{s}_{s}$pH 10 and 11 respectively, giving kinetic $(^{s}_{s}pK_a)_{app}$ values of 9.67 and 10.82, which correlate acceptably well with the titrimetic values presented in Table 1. The linear decrease of catalytic activity at high $^{s}_{s}$pH suggests that the $M^{2+}(CH_3O^-)_2$, which forms above the $(^{s}_{s}pK_a)_{app}$, is inactive, probably due to its decreased electrophilicity.

The preferred mechanism involves a pre-equilibrium binding of the divalent metal ion to the distal N of **1**, followed by nucleophilic attack of external CH_3O^- on the complex. The rate constants for methoxide attack on the complex (k_{OR}), using a lower limit of 0.1 mol dm^{-3} for K_M, are 5.6×10^7 and 2.5×10^7 dm^3 mol^{-1} s^{-1} for Zn^{2+} and Co^{2+} respectively. These values compare favourably with the rate constant for attack of CH_3O^- on the Co^{III} complex **2**, (4.7×10^7 dm^3 mol^{-1} s^{-1}), suggesting that the ligand exchange inert Co^{III} complex can be taken as a model for M^{2+}–**1**.

La^{3+} catalyzes the methanolysis of both **1** and **2** by a mechanism which is fundamentally different from that exhibited by Zn^{2+} and Co^{2+} and there are trends that bear scrutiny here since they will reappear when we discuss the La^{3+}-catalysis of esters in Section 4. First is the fact that, for both substrates, the plots of k_{obs} *vs.* $[La^{3+}]_t$ at all $^{s}_{s}$pH values are curved upward between $0 \leq [La^{3+}]_t \leq 5 \times 10^{-4}$ mol dm^{-3} as shown in Fig. 1a, followed by a linear dependence at higher $[La^{3+}]_t$ as shown in Fig. 1b for the

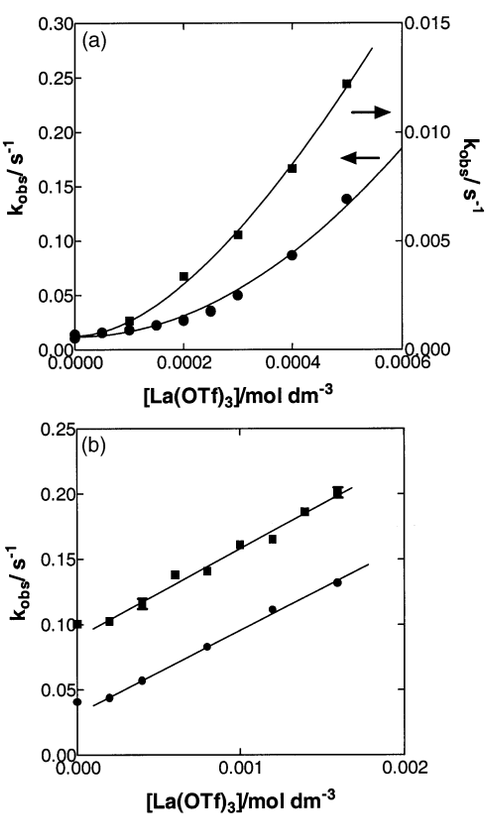


Fig. 1 (a) Plots of pseudo-first order rate constants for the methanolysis of **1** ($^{s}_{s}$pH = 6.7 (■), right axis) and **2** ($^{s}_{s}$pH = 7.6 (●), I = 0.2 mol dm^{-3} ($NaClO_4$), left axis) *vs.* [La(OTf)$_3$] (low concentration) at 25 °C. Redrawn from ref. 11*b*. (b) Plots of pseudo-first order rate constants for the methanolysis of **2** *vs.* [La(OTf)$_3$] (high concentration) at 25 °C; $^{s}_{s}$pH = 7.95 (■) and $^{s}_{s}$pH = 7.6 (●). Redrawn from ref. 11*b*.

methanolysis of **2**.[11b] The plots suggest the active form of the catalyst has more than a single La^{3+}, the preferred form being a dimer which mathematical modeling shows has a dissociation constant of (0.5–1.0) × 10^{-4} mol dm^{-3}. The slope of the linear part of the k_{obs} *vs.* $[La^{3+}]_t$ plots represents the second order rate constant (k_2) for dimer promoted methanolysis of **1** or **2**. Shown in Fig. 2 are plots of log k_2 *vs.* $^{s}_{s}$pH for the dimer catalyzed

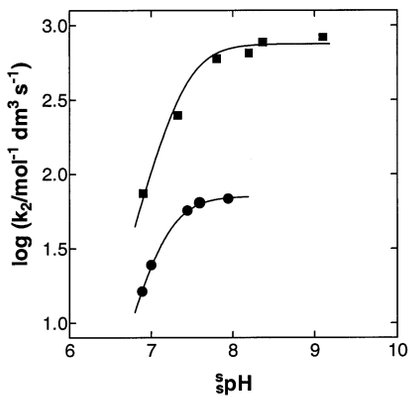
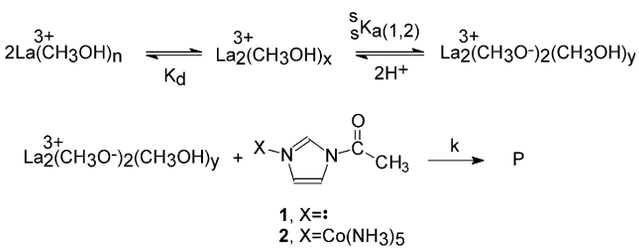


Fig. 2 Plots of second order rate constant (k_2) *vs.* pH for La(OTf)$_3$ catalyzed methanolysis of AcIm (■) and $AcImCo(NH_3)_5^{3+}$ (●). Redrawn from ref. 11*b*.

methanolysis of these which each exhibit a linear section of slope 2, requiring that the transition structure incorporates two methoxides. This is followed by a plateau above $^{s}_{s}$pH 8.

Taken together the above data can be accommodated by the mechanism shown in Scheme 2 for which a complex kinetic



Scheme 2

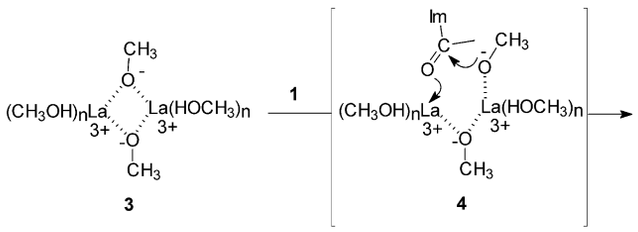
expression describing k_{obs} as a function of both $[La^{3+}]_t$ and $^{s}_{s}$pH can be derived.[11b] In Scheme 2 $^{s}_{s}K_{a(1,2)}$ represents the apparent dissociation constant for two protons from the dimer to generate the active form. Restricting ourselves to the analysis of the linear part of the k_{obs} *vs.* $[La^{3+}]_t$ plots (as shown in Fig. 1b) we obtain the simplified kinetic expression given in eqn. (5) to which NLLSQ fitting of the data provides the parameters:

$$k_2 = \frac{k^{s}_{s} K_{a(1,2)}}{2(^{s}_{s}K_{a(1,2)} + [H^+]^2)} \quad (5)$$

$k = (1.50 \pm 0.1) \times 10^3$ dm^3 mol^{-1} s^{-1}; $^{s}_{s}K_{a(1,2)} = 10^{(-14.8 \pm 0.1)}$ (mol dm^{-3})^2 (kinetic $^{s}_{s}pK_a = 7.40$) for **1**; and $k = (1.42 \pm 0.02) \times 10^2$ dm^3 mol^{-1} s^{-1}; $^{s}_{s}K_{a(1,2)} = 10^{(-14.30 \pm 0.02)}$ (mol dm^{-3})^2 (kinetic $^{s}_{s}pK_a = 7.15$) for **2**. The kinetic $^{s}_{s}pK_a$ values compare well with the titrimetric value given in Table 1 thus supporting our hypothesis that the active species is a bis methoxy bridged dimer as proposed in Scheme 2.

Evidence for these dimers also comes from mass spectral data.[14] The electrospray MS of La(OTf)$_3$ in methanol shows a pattern of peaks separated by 32 units attributable to $[La_2(CH_3OH)_x]$ associated with five triflate counterions where x varies from 1 to 6. With one equivalent of CH_3O^- per La^{3+} added, the mass spectrum shows the presence of $[La_2(CH_3O^-)_2(CH_3OH)_y]$ with three additional triflates and $y = 0$, 1. While the

mass spectrum provides no evidence as to structure, it is consistent with a bis methoxy-bridged dimer (**3**) which we propose is the catalytically active form. Shown in Scheme 3 is a proposed bifunctional mechanism where an open form, **4**, created by transient cleavage of one La–OCH_3 bond, bimolecularly delivers a metal-bound CH_3O^- to the acylimidazole C=O group aided by Lewis acid stabilization by the second La^{3+}. This mechanism must involve a transient tetrahedral addition intermediate which rapidly breaks down to expel imidazole and reform **3**.



Scheme 3

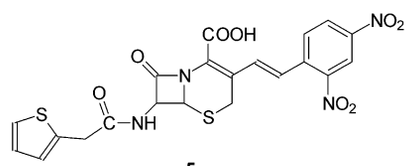
3.2 Metal ion catalysis of the methanolysis of the β-lactam, nitrocefin (5)

The β-lactam antibiotics comprising the penicillin, cephalosporin and carbapenem families are widely used to combat bacterial infections.[15] Bacterial resistance to these antibiotics[16] through the evolution of β-lactamases presents a serious threat to human health. The recently discovered class B Zn^{2+}-β-lactamases[17] hydrolyze a broad spectrum of β-lactam antibiotics but unlike the serine β-lactamases, have no clinically useful inhibitors. Crystal structures are available for several members of the Zn^{2+}-β-lactamases[3a,17,18] that reveal active sites containing one or two Zn^{2+}-ions bound to various peptide ligands and a coordinated HO^- which, in the cases of the dinuclear enzymes, either bridges the two Zn^{2+} ions, or is singly coordinated. This Zn^{2+}-coordinated HO^- is thought to be the active nucleophile that attacks the C=O unit of the β-lactam.

Despite the fact that several members of the mononuclear[19] and dinuclear[20] Zn^{2+}-β-lactamases are under active investigation, a detailed picture of the mechanism, and particularly the role of the second Zn^{2+} in the mechanism of enzyme-promoted hydrolysis of β-lactams, has yet to emerge. For the mononuclear β-lactamase from *B. cereus*, the rate-limiting step is said to be cleavage of the tetrahedral intermediate[19] formed from rapid attack of the sole active site Zn^{2+}–HO^-. A recent suggestion for the mechanism operative in the dinuclear enzyme from *B. fragilis*,[20] where the rate limiting step appears to be protonation of the product formed after breakdown of the tetrahedral intermediate, involves one Zn^{2+} coordinating to the substrate COO^- (required for binding all good substrates[21]) and possibly to the lactam N, thus enhancing its leaving ability as an anionic N^-–Zn^{2+} form. There is, however, uncertainty with respect to the universality of COO^- binding to the metal since a crystal structure available for an IMP-1 metallo-β-lactamase from a *Pseudomonas aeruginosa* enzyme–inhibitor complex indicates the COO^- of the inhibitor interacts with lysine-161.[22] It has been suggested that the two-metal ion mechanism is similar to that proposed for other dinuclear hydrolases[3c] wherein one metal ion provides the bound HO^- nucleophile and serves as a counterpart for the oxyanion hole in stabilizing the tetrahedral intermediate, while the other possibly helps to: a) position the substrate for proper nucleophilic attack; b) polarize further the (N)C=O scissile bond; and c) stabilize the (−)-charge developed on the leaving group.

There is important early work showing very marked catalysis by divalent metal ions of the aqueous hydrolysis of benzyl penicillin[23a–c] and cephaloridine.[23c] The observed saturation behaviour of the k_{obs} *vs.* $[M^{2+}]$ plots for these requires metal ion binding to the carboxylate of the penicillin or cephalosporin, neutralizing the charge on the substrate and promoting attack of external hydroxide on the β-lactam C=O with possible binding to the lactam N facilitating breakdown of the tetrahedral intermediate. More recently, β-lactam degradation in methanol has been reported[24] to be promoted by Cd^{2+} under non-pH controlled conditions, although a detailed mechanism was not reported. A limited number of simple mono- and dinuclear Zn^{2+} models for the Zn^{2+}-β-lactamases has been presented,[25] but the catalysis afforded to hydrolysis of nitrocefin (**5**) was modest, and importantly, no kinetic benefit of the second Zn^{2+} could be demonstrated.

Our own work concerning the methanolysis of **5** promoted by Zn^{2+} clearly indicates the kinetic involvement of mechanisms having one, and two metal ions.[26] There is both kinetic and titrimetric evidence that binding of the **5**-COO^- by Zn^{2+} is important in methanol. Potentiometric titration of a 2×10^{-3} mol dm^{-3} solution of $Zn(ClO_4)_2$ in methanol containing equimolar CH_3CO_2H reveals three ionizations. The first has a ${}^{s}_{s}pK_a$ of 7.70 ± 0.19 corresponding to the ionization of acetic acid which is reduced from its ${}^{s}_{s}pK_a$ of 9.37 ± 0.14 without metal ion but in the presence of 0.01 M $N(n\text{-}Bu)_4ClO_4$ (9.71 ± 0.22 in MeOH without $N(n\text{-}Bu)_4ClO_4$, lit. 9.63[9a]). This is followed by two other ionizations having ${}^{s}_{s}pK_a{}^{1}$ and ${}^{s}_{s}pK_a{}^{2}$ values of 10.94 ± 0.02 and 11.08 ± 0.25 corresponding to stepwise association of two methoxides to the $Zn^{2+}(^-O_2CCH_3)$ (midpoint of the titration, ${}^{s}_{s}pK'_{app}$ 11.01) as in eqn. (6). The dissociation constant of $CH_3CO_2^-$–Zn^{2+}, determined from the titration data, is ~2×10^{-5} mol dm^{-3} pointing to the strong affinity of $RCOO^-$ for Zn^{2+} in methanol.



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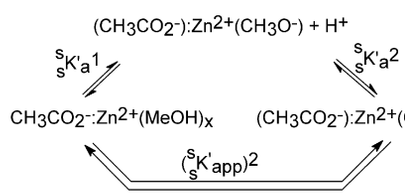
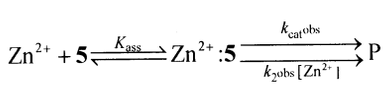


(6)

Binding of the carboxylate of **5** is kinetically productive and there are two general observations revealed in the k_{obs} *vs.*$[Zn^{2+}]_t$ data as a function of ${}^{s}_{s}$pH that must be explained. First, at a given ${}^{s}_{s}$pH, plots of k_{obs} *vs.* $[Zn^{2+}]_t$ are curved, revealing a Zn^{2+} + **5** ⇌ **5**–Zn^{2+} saturation binding. However, as revealed by the two representative plots at ${}^{s}_{s}$pH 8.55 and 8.91 given in Fig. 3, these do not plateau, but rather exhibit a linear portion at high $[Zn^{2+}]_t$. Notably, none of these plots shows the characteristic upward curvature which would suggest the involvement of catalytically active Zn^{2+}-dimers. The linear portion of the plot, occurring at a $[Zn^{2+}]_t$ greater than required for saturation, must then arise from a second Zn^{2+} interacting with the Zn^{2+}–**5** complex as schematized in eqn. (7). From the slopes and intercepts of these plots at various ${}^{s}_{s}$pH values can be determined $k_2{}^{obs}$ and $k_{cat}{}^{obs}$ respectively.[26]



(7)

Shown in Fig. 4 are the plots of log $k_{cat}{}^{obs}$ and log $k_2{}^{obs}$ *vs.* ${}^{s}_{s}$pH that provide information concerning the kinetic dependence of these rate constants on $[CH_3O^-]$. The $k_{cat}{}^{obs}$ plot shows a bell-

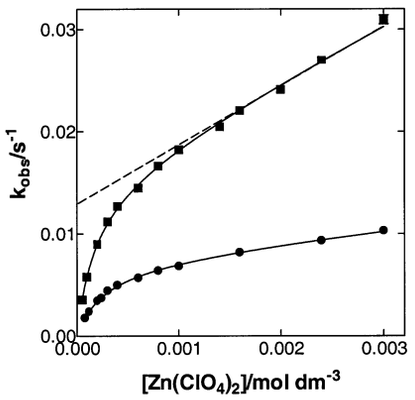


Fig. 3 Plots of pseudo-first order rate constants for the methanolysis of nitrocefin (**5**) *vs.* $[Zn(ClO_4)_2]$ at 25 °C; ${}^{s}_{s}$pH = 8.55 (●) and ${}^{s}_{s}$pH = 8.91 (■). Redrawn from ref. 26.

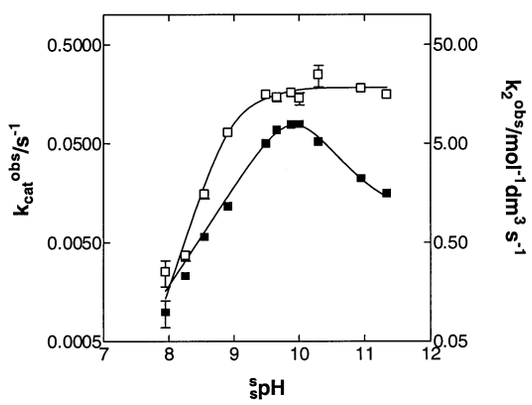
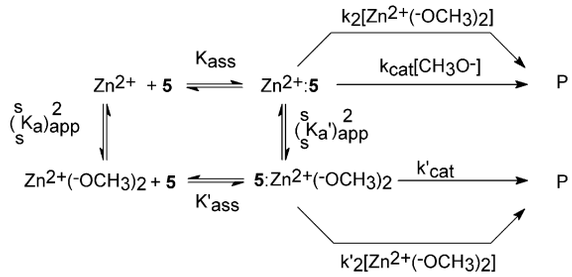


Fig. 4 Plot of log k_{cat}^{obs} (■) and log k_2^{obs} (□) *vs.* ${}^{s}_{s}$pH for $Zn(ClO_4)_2$ catalyzed methanolysis of nitrocefin (**5**), T = 25 °C. Individual data points determined as described in text. Lines through the data computed from fits to eqns. (8) and (9) respectively. Redrawn from ref. 26.

shaped ${}^{s}_{s}$pH dependence of the reaction of the Zn^{2+}–**5** complex, maximizing at ~${}^{s}_{s}$pH 10, with ascending and descending domains each first order in $[CH_3O^-]$. The ${}^{s}_{s}$pH dependence of the reaction involving the second Zn^{2+} (k_2^{obs}) gives an ascending domain second order in $[CH_3O^-]$, followed by a plateau at ${}^{s}_{s}$pH > 9.5, suggesting that the active species is $Zn^{2+}(CH_3O^-)_2$. Given in Scheme 4 is a set of processes which is an expanded variant of eqn. (7) consistent with the kinetic data. The expressions given in eqns. (8) and (9) can be derived to describe the ${}^{s}_{s}$pH behavior of k_{cat}^{obs} and k_2^{obs} where ${}^{s}_{s}K_{app}$ and ${}^{s}_{s}K'_{app}$ refer to the deprotonation constants for the $Zn^{2+}(CH_3OH)_x$ and $(CH_3OH)_2Zn^{2+}$–**5**



Scheme 4

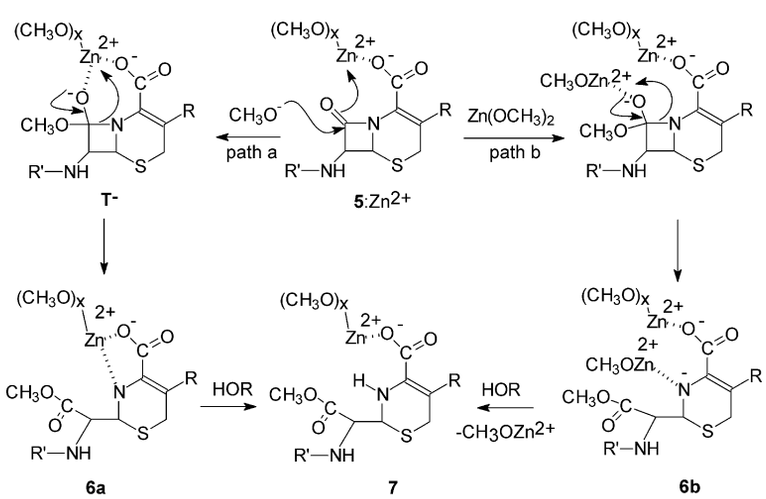
complexes and ${}^{s}_{s}K_{MeOH}$ refers to the autoprotolysis constant of MeOH. NLLSQ fitting of each set of data to the appropriate expression, setting K_{app} at the constant value of $10^{-9.79}$ based on the $Zn^{2+}(CH_3OH)_x$ titration results, generates the lines through the data shown in Fig. 4.

$$k_{cat}^{obs} = \frac{k_{cat}{}_{s}^{s}K_{MeOH}[H^+] + k'_{cat}({}^{s}_{s}K'_{app})^2}{[H^+]^2 + ({}^{s}_{s}K'_{app})^2} \quad (8)$$

$$k_2^{obs} = \frac{k_2({}^{s}_{s}K_{app})^2[H^+]^2 + k'_2({}^{s}_{s}K_{app})^2({}^{s}_{s}K'_{app})^2}{([H^+]^2 + ({}^{s}_{s}K_{app})^2)(H^+]^2 + ({}^{s}_{s}K'_{app})^2)} \quad (9)$$

3.2.1 One-Zn^{2+} mechanisms: the reactions of Zn^{2+}–5

The saturation behavior exhibited in the k_{obs} *vs.* $[Zn^{2+}]$ plots for methanolysis of **5** (*e.g.* Fig. 3) and the linear dependence of the log k_{cat}^{obs} *vs.* ${}^{s}_{s}$pH plot up to ~${}^{s}_{s}$pH 10 (Fig. 4) suggest that external methoxide attacks a Zn^{2+}–**5** complex, a process similar to what is reported for the Zn^{2+}- and Cu^{2+}-promoted hydrolysis of benzyl penicillin[23c] and to what we have observed before for the Zn^{2+}-promoted methanolysis of acetylimidazole.[11] Shown in Scheme 5 (path a) are the one-Zn^{2+} mechanisms in which the coordinated Zn^{2+} has zero or two attached methoxides, ignoring for the sake of simplicity possible forms with a single methoxide. The form with no attached methoxides is the dominant species below ${}^{s}_{s}$pH 10, while the two-methoxy Zn form dominates above ${}^{s}_{s}$pH 10. The maximal second order rate constant for methoxide attack on the Zn^{2+}–**5** complex (k_{cat} = 1.1 × 10^6 dm^3 mol^{-1} s^{-1}) is roughly 9 × 10^5-fold larger than for uncatalyzed methoxide attack on **5** (k_{OCH_3} = 1.18 dm^3 mol^{-1} s^{-1}),[26] pointing to the strong Lewis acid role for the bound Zn^{2+} shown in Scheme 5 as **5**–Zn^{2+} ⟶ $\mathbf{T}^-$, forming intermediate **6a** with the postulated complexation of the anionic N to the Zn^{2+}, and finally the methanolyzed product **7**. By way of comparison, the Zn^{2+}-bound form of benzyl penicillin is activated toward HO^-



Scheme 5

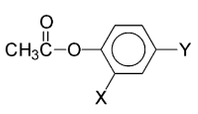
attack by 4×10^5-fold (6.0×10^4 *vs.* 0.15 dm^3 mol^{-1} s^{-1} respectively).[23b,c] At ^s_spH values higher than 10, the log k_{cat}^{obs} *vs.* ^s_spH plot turns downward which is explained by formation of **5**–$Zn^{2+}(CH_3O^-)_2$, decreasing the metal ion's Lewis acidity and concomitantly the rate constant for attack of external methoxide on the latter.

3.2.2 Two-Zn^{2+} mechanisms: the reactions of Zn^{2+}–5 with $Zn^{2+}(^-OCH_3)_2$

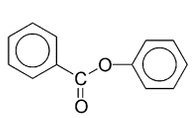
The involvement of a second Zn^{2+} in the methanolysis of Zn^{2+}–**5** is readily apparent from the k_{obs} *vs.* $[Zn^{2+}]_t$ plots at all ^s_spH values as a linear section (the slope being k_2) following the saturation attributable to the formation of Zn^{2+}–**5**, see Fig. 3. The ascending portion of the log k_2^{obs} *vs.* ^s_spH profile shown in Fig. 4 is second order in $[CH_3O^-]$ and so requires the second Zn^{2+} to have two methoxides associated with it, undoubtedly as $Zn^{2+}(^-OCH_3)_2$ which is fully formed above ^s_spH 10. The most likely process consistent with all the above involves Zn^{2+}-$(CH_3O^-)_2$ nucleophilically reacting with both Zn^{2+}–**5** and Zn^{2+}–**5**–$(CH_3O^-)_2$ as in Scheme 5, (path b). The rate constants for attack of $Zn^{2+}(^-OCH_3)_2$ and CH_3O^- on **5**–Zn^{2+} are k_2 = 440 dm^3 mol^{-1} s^{-1} *vs.* $k_{cat} = 1.1 \times 10^6$ dm^3 mol^{-1} s^{-1}. The far greater reactivity of methoxide relative to $Zn^{2+}(^-OCH_3)_2$ can be understood by considering that the direct attack of methoxide on **5**–Zn^{2+} benefits greatly from electrostatic attraction of oppositely charged reactants (see Section 3.1 above) which is not the case for neutral $Zn^{2+}(CH_3O^-)_2$ reacting with **5**–Zn^{2+}.

4 Methanolysis of esters promoted by La^{3+}

Considerable attention has been devoted to esterification reactions, including the acid (Fischer esterification) and base promoted pathways.[27] Due to the industrial applications of this process, substantial information is available concerning the mechanisms of action of catalysts developed to promote transesterification,[28] and examples of metal catalyzed transesterification have appeared.[5,29] Based on the success of the La^{3+} catalysis of the methanolysis of activated amides **1** and **2**, and the proposed mechanistic involvement of a dimer of stoichiometry $(La^{3+})_2(CH_3O^-)_2$ reacting bimolecularly with the C=O unit without the requirement for a proximal binding site, it seemed likely that species would also catalyze transesterifications. However, an early report[5b] described rather modest catalysis of the transesterifications of $PhCO_2R$ (R = Me, Et, iso-Pr, *tert*-Bu) with various alcohols, including MeOH, using lanthanide triisopropoxides, these requiring some hours at elevated temperatures. Our subsequent work[14] on the La^{3+}-catalyzed methanolysis of esters **8**–**14** indicated that very strong



8 X=Y=NO_2
9 X=H, Y=NO_2
10 X=Y=H



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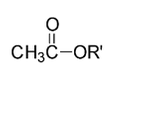


12 R'=Et
13a,**b** R'=*i*-Pr, C_6H_{11}
14 R'=*t*-Bu

catalysis was in operation at 25 °C for all esters except **14** and that the catalytic mechanism was essentially identical to what we reported for the methanolysis of the reactive amides **1** and **2**.[11] Detailed kinetic studies with ester **9** confirmed two general features: a) an upward curvature of the plots of k_{obs} *vs.* $[La^{3+}]_t$ at low concentration at all ^s_spH values, yielding linear plots above $[La^{3+}]_t \sim 3$–4×10^{-4} mol dm^{-3}; and b) that plots of log k_2 (determined from the linear portions of the k_{obs} *vs.* $[La^{3+}]_t$ plots) *vs.* ^s_spH increase with slope = 2 and plateau above ^s_spH 8. In effect, this behaviour is almost identical to that we observed earlier[11] for La^{3+} catalysis of methanolysis of **1** and **2**, and a similar kinetic analysis can be employed. However, due to the expanded ^s_spH range for the ester study an additional feature is observed. The plot[14] of the log k_2 *vs.* ^s_spH data for catalyzed methanolysis of **9** shown in Fig. 5 exhibits a drop in activity at

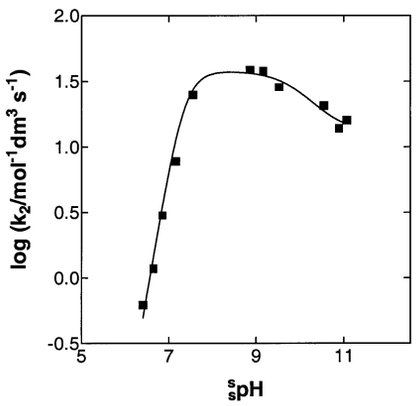


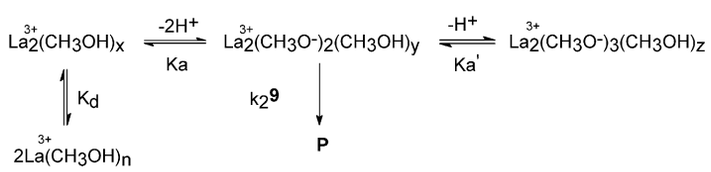
Fig. 5 Plot of second order rate constant (k_2) *vs.* ^s_spH for $(La^{3+})_2$ dimer promoted methanolysis of *p*-nitrophenyl acetate (**9**), T = 25 °C. Line through data from NLLSQ fits to eqn. (10).

^s_spH > 9.5 due to addition of CH_3O^- to $(La^{3+})_2(CH_3O^-)_2$ which decreases the activity, presumably from a reduced Lewis acidity of the $(La^{3+})_2(CH_3O^-)_{3-5}$ forms. The data are accommodated by the mechanism given in Scheme 6 for which the eqn. (10) rate

$$k_2 = \frac{k_2^{\,9}\,{}^s_sK_a[H^+]}{2({}^s_sK_a + [H^+]^2)({}^s_sK_a' + [H^+])} + \frac{k_2'^{9}\,{}^s_sK_a'}{2({}^s_sK_a' + [H^+])} \quad (10)$$

expression is derived with a computed $k_2^{\,9}$ of 72 dm^3 mol^{-1} s^{-1} and a kinetic ^s_spK_a of 7.35, nicely consistent with the ^s_spK_a titrimetric and previously determined kinetic ^s_spK_a for methanolysis of **1** and **2**. The fit also provides a kinetic ^s_spK_a' of 10.0 ± 0.4 corresponding to the association of the additional deactivating methoxides to the metal complex and a $k_2'^{9}$ of 12.7 dm^3 mol^{-1} s^{-1} reflecting the decreased catalytic activity of that complex.

Given in Table 2 are kinetic data for methoxide and La^{3+}-catalyzed methanolysis of esters **8** to **14**. Of particular note are columns 5 and 6 which give the $k_2^{ester}/k_{OMe}^{ester}$ for the series, and the acceleration afforded relative to the background reaction of a ^s_spH 8.5 solution containing 5×10^{-3} mol dm^{-3} of the active dimer $(La^{3+})_2(CH_3O^-)_2$. Notable is the fact that CH_3O^- attack on the activated esters drops 200-fold in passing from **8** to **10** as expected for a process involving rate limiting addition to the ester influenced by electron withdrawing substituents. However there is little effect on the La catalyst's ability to promote the methanolysis of **8** to **10**. This points to a balance of electrophilic and nucleophilic catalytic effects as expected if the mechanism proceeds through a transition structure similar to **4**



Scheme 6

Table 2 Maximal second order rate constants for $(La^{3+})_2(CH_3O^-)_2$ catalyzed methanolysis of esters **8**–**14**, and second order rate constants for methoxide attack on esters, $T = 25$ °C

Substrate	${}^{s}_{s}pH_{max}$	k_2^{ester}/dm^3 mol^{-1} s^{-1} [a]	$k_{MeO^-}{}^{ester}$/dm^3 mol^{-1} s^{-1} [c]	$k_2^{ester}/k_{MeO^-}{}^{ester}$	Acceleration [g] at ${}^{s}_{s}$pH 8.5
8	9.8	29 ± 2	410 [d]	0.07	42,000
9	8–9	72	220 ± 100 [c]	0.6–0.225	243,000
10	8.8	58 ± 3	2.66 [e]	21	18,750,000
11	8.7	3.0 ± 0.06	0.338 ± 0.006 [f]	8.9	5,300,000 [h]
12	8.5 [b]	0.143	$(5.7 \pm 0.2) \times 10^{-2}$ [f]	2.5	2,300,000
13a	8.5 [b]	0.0083	$(7.0 \pm 0.1) \times 10^{-3}$ [f]	1.2	1,120,000
14	8.5 [b]	$\ll 5.7 \times 10^{-6}$	$(2.0 \pm 0.1) \times 10^{-4}$ [f]	$\ll 0.03$	

[a] Esters **8**–**11** determined by UV kinetics in CH_3OH; **12**–**14** by ^{1}H NMR in d_4-methanol. [b] ${}^{s}_{s}$pH estimated from titration curve of La^{3+} and set by 1 : 1 $La^{3+}/^-OCH_3$ stoichiometry. [c] 27.4 °C; R. L. Schowen and C. G. Behn, *J. Am. Chem. Soc.*, 1968, **90**, 5839. [d] V. Machacek, S. Mareckova and S. Vojeslav, *Collect. Czech. Chem. Commun.*, 1979, **44**, 1779. [e] C. G. Milto, M. Gresser and R. L. Schowen, *J. Am. Chem. Soc.*, 1969, **91**, 2047. [f] Ref. 14. [g] Catalytic value at ${}^{s}_{s}$pH 8.5, in the presence of 5×10^{-3} mol dm^{-3} $(La^{3+})_2(CH_3O^-)_2$. Background rate computed from $k_{MeO^-}{}^{ester}$ assuming value for solvent reaction at ${}^{s}_{s}$pH 8.5 is entirely attributed to CH_3O^- + ester; the autoprotolysis constant of methanol is $10^{-16.77}$ (ref. 9). [h] Acceleration computed at ${}^{s}_{s}$pH 8.7.

where there is both a Lewis acid and nucleophilic role for the catalyst. Correspondingly the data reveal an unusual situation where the catalyst is more reactive toward less-activated esters than it is toward activated esters. For the series of esters given in Table 2 the acceleration afforded by a 5 mmol dm^{-3} solution of catalyst ranges from 42,000-fold for the most activated ester **8**, to 18,000,000-fold for phenyl benzoate **11**. Notably alkyl esters are also susceptible to strong catalysis except for *tert*-butyl acetate (**14**).

The question arises as to why the previous study [5b] of lanthanide-promoted transesterification failed to detect the strong accelerations we observe.[14] In our opinion this is a consequence of the amount of alkoxide in that study being much greater than the optimal 1 : 1 [alkoxide] : [La^{3+}] ratio we found necessary to make a highly active catalyst. Interestingly, titanium alkoxides, which are widely used to promote transesterifications industrially, failed to show significant catalysis under our conditions. This is probably due to the very high acidifying nature of that metal, where even at neutrality the dominant species is $Ti(OMe)_4$ (see Table 1). Our experience shows that a high number of associated methoxides leads to poor catalytic activity, probably due to decreased Lewis acidity.

Our studies [14] also show how one can generate preparatively useful conditions using large excesses of the ester relative to catalyst. Thus a solution of 10^{-2} mol dm^{-3} $La(OTf)_3$ or $La(ClO_4)_3$, to which is added one equivalent of $NaOCH_3$, generates a $(La^{3+})_2(CH_3O^-)_2$ catalyst concentration of 5 mmol dm^{-3} which is synthetically useful and several applications can be envisioned such as the removal of acyl protecting groups from alcohols. It must be borne in mind that the overall reaction involves the RC(O)OR′ + $CH_3OH \rightleftharpoons$ RC(O)OCH$_3$ + R′OH equilibrium so under synthetic conditions both esters will be present in amounts reflecting the initial ([CH_3OH] : [ester]) ratio.

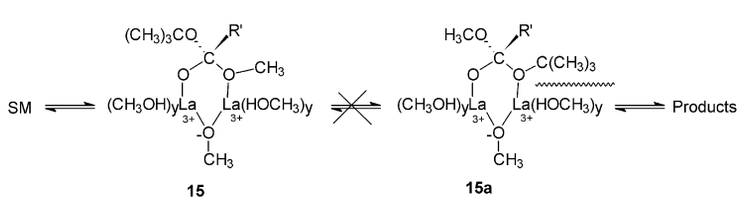
There are, however, two classes of esters for which we are currently unable to provide good catalysts. The first class comprises *tert*-alkyl esters which show no susceptibility to transesterification promoted by La^{3+}. We speculate that this is due to a steric effect which inhibits a necessary step in the catalytic cycle as shown in eqn. (11). If metal ion delivery of methoxide is the important step in forming the addition intermediate **15**, then, by microscopic reversibility, the departure of a metal associated *tert*-butoxy as in **15a** is required for product formation. This species is likely to be too sterically crowded to be formed in any appreciable concentration, accounting for the lack of reactivity of *tert*-esters.

The second class for which La^{3+} promoted methanolysis is problematic, involves the esters of polyols such as ethylene glycol or glycerol. In these cases, at a [catalyst] of 5 mmol dm^{-3} with at least 10-fold greater [substrate], the reaction proceeds smoothly to the extent of 20–30%, and then terminates due to inhibition by the glycol or glycerol product which binds the La^{3+} in a catalytically unproductive way.[14] Indeed glycerol or ethylene glycol can inhibit the catalysis of the methanolysis of other esters. For example, 5×10^{-2} mol dm^{-3} of glycerol gives a 600-fold rate reduction for methanolysis of ethyl acetate catalyzed by 5×10^{-3} mol dm^{-3} $(La^{3+})_2(CH_3O^-)_2$.[14] A similar experiment in the presence of 5×10^{-2} mol dm^{-3} ethylene glycol gave a seven-fold rate reduction, meaning that glycerol is about 100-fold better an inhibitor of catalysis than is ethylene glycol. Further work utilizing different Ln^{3+} ions will be necessary to overcome these problems.

5 Methanolysis of phosphate diesters catalyzed by La^{3+}

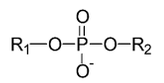
In Nature many enzymes that promote the hydrolysis of phosphate esters have active sites containing two or more metal ions.[3a,c,d] These include enzymes cleaving phosphate mono esters [3e] (such as alkaline phosphatase, inositol phosphatase and purple acid phosphatase), and those cleaving phosphate diesters [30] (such as the RNAse from HIV reverse transcriptase,[30a] 3′–5′ exonuclease from DNA polymerase I,[30b] and P1 nuclease [30c]). Due to its obvious biological relevance pertaining to the storage of genetic information in DNA and RNA, much attention has been focused on hydrolysis of phosphodiesters mediated by metal ions.[2,31] Among the metal ions lanthanides exhibit the most dramatic accelerations, particularly under basic conditions as their metal-hydroxo forms, but above the pK_a's of metal-aquo complexes formation of precipitates or gels of poor definition often complicates mechanistic evaluation.

Our own studies in this important field concentrated on the catalysis of the methanolysis of phosphate diesters **16**–**18** mediated by La^{3+}-ion.[32] Although this is not a hydrolytic process and involves no net change in charge on the phosphoryl moiety accompanying the ester exchange, the catalysis bears

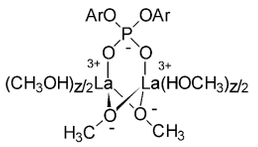


(11)

a strong resemblance to hydrolysis and clearly involves both one and two La^{3+}-mechanisms wherein the phosphate diester is complexed to the metal ion(s).



16 R_1=R_2 = *p*-nitrophenyl
17 R_1=R_2=phenyl
18 R_1=*p*-nitrophenyl, R_2=CH_3

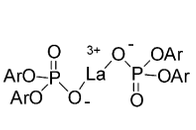


19

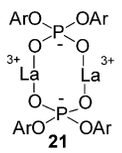
5.1 Phosphate binding to La^{3+}

Clear evidence for complex formations of these anionic phosphates to one and two metal ions comes from titrimetric, ^{31}P NMR and kinetic studies. The titration curve for a solution of 4 mmol dm^{-3} $La(OTf)_3$ in methanol containing 2 mmol dm^{-3} diphenyl phosphate (**17**)[32] is similar to that of $La(OTf)_3$ alone (described above in Section 2) but with two notable differences. Diphenyl phosphate (**17**) has a single $^{s}_{s}pK_a$ of 3.95 in methanol without added metal ion which is lowered to 3.0 ± 0.1 in the presence of $La(OTf)_3$ suggesting strong complexation of the phosphate monoanion to La^{3+}. Continued titration leads to the consumption of one CH_3O^- per La^{3+} having an apparent $^{s}_{s}pK_a$ of 7.8, indicating that the presence of phosphate slightly perturbs the first $^{s}_{s}pK_a$ of the dimeric lanthanide-bound methanol from its value of $^{s}_{s}pK_a$ 7.2–7.4 determined previously as described in Section 2. Further titration leads to the consumption of an additional 1.5 equivalents of CH_3O^- per La^{3+} with an apparent $^{s}_{s}pK_a$ of 11.1, perturbed upward by ~0.7 units by the presence of the phosphate.

The room temperature ^{31}P NMR spectrum of 5 mmol dm^{-3} **17** in methanol, buffered at $^{s}_{s}$pH 6.7 by 10 mol dm^{-3} *N*-methylimidazole, shows a single peak at δ −9.175 ppm which, after the addition of 2 equivalents of $La^{3+}(^-OTf)_3$, disappears due to exchange phenomena. By reducing the temperature to −80 °C we have been able to observe signals at δ −13.140, −19.359 and −21.490 ppm in an approximate 5 : 1 : 3 ratio which suggests the presence of three distinct **17**–La^{3+} complexes of different stoichiometry in slow exchange. The relative intensities of these change as the [La^{3+}] : [**17**] ratio increases, allowing us to propose that the respective peaks are due to a 2 : 1 La^{3+} : **17** complex, a 1 : 2 La^{3+} : **17** complex, and a 1 : 1 (or possibly 2 : 2) La^{3+} : **17** complex. At the highest [La^{3+}]/[**3**] = 3, only peaks attributable to the 2 : 1, and 1 : 1 (2 : 2) complexes are observed, the ratio being 11 : 4. From the NMR experiments it is not possible to ascertain the structures of these complexes or how many associated methoxides are present. However combination of the NMR and titration data supports structure **19** for the 2 : 1 complex. Possible structures **20** and **21** are suggested for the 1 : 2 and 2 : 2 complexes, the number of associated solvent and methoxide molecules being omitted for lack of data. Similar phosphate bridged dimers have been identified;[33] for example a $La^{3+}{}_2(^-OH)_5$–RNA analogue,[34] two (Co^{III}–macrocycle)$_2(^-OH)_2$–phosphate diester systems,[35] and two dinuclear Cu^{2+}–phosphate systems.[36,37] A bridged dimer has also been proposed for a (BisTris-La^{3+})$_2(^-OH)_4$–diphenyl phosphate complex as the active species in the hydrolysis of **16**.[38]



20



21

5.2 Kinetics of methanolysis of phosphates 16–18

In order to determine a background rate with which the catalytic rates can be compared, we have looked at methoxide reactions. Initial rate measurements at high [CH_3O^-] provide second order rate constants for its attack on **16** and **18** of 2.5 × 10^{-6} and (7.9 ± 0.6) × 10^{-7} dm^3 mol^{-1} s^{-1} at 25 °C, values which are close to those for the respective hydroxide reactions in water, 5.8 × 10^{-6} and 4.7 × 10^{-7} dm^3 mol^{-1} s^{-1}.[39,40] While it is exceedingly difficult to determine a rate constant for hydrolysis or methanolysis in the neutral pH or $^{s}_{s}$pH regions because of the slowness of the reactions, evidence exists that hydrolyses of diphosphates with monosubstituted aryl leaving groups are controlled throughout the entire pH domain by the acid and base terms.[41] Thus the anticipated rates of hydrolysis or methanolysis of these can be extrapolated to the required pH region from the lyoxide terms. The computed values for **16** and **18** at neutral $^{s}_{s}$pH of 8.5 in methanol would be ~1.25 × 10^{-14} and 4 × 10^{-15} s^{-1}, corresponding to respective half-times of about 1.7 and 5.5 million years! As expected on the basis of leaving group ability, diphenyl phosphate (**17**) is less susceptible to nucleophilic attack by methoxide than is **16** and due to the extreme slowness of this reaction, we cannot experimentally determine a $k_{CH_3O^-}$[17]. However, based on literature data for the reaction of HO^- with **17**[2k,m,41] one can infer that methoxide would react ~10^4 slower with **17** than with **16**, leading to an estimated rate constant of $k_{CH_3O^-}$[17] ~2 × 10^{-10} dm^3 mol^{-1} s^{-1} which leads to a half time for methanolysis at $^{s}_{s}$pH 8.5 of ~17 billion years!

Plots of the k_{obs} *vs.* [La^{3+}] data for methanolysis of **18** are highly unusual. For example in Fig. 6 one sees a linear catalytic

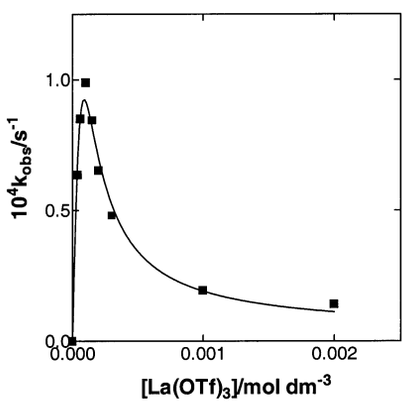


Fig. 6 Plot of pseudo-first order rate constant for the methanolysis of 2 × 10^{-5} mol dm^{-3} **18** *vs.* [$La(OTf)_3$] at 25 °C; $^{s}_{s}$pH = 9.5 (0.04 mol dm^{-3} *N*-ethylmorpholine buffer). Redrawn from ref. 32: lines through the data computed by fits to eqn. (5) in ref. 32.

effect of [La^{3+}]$_t$ at $^{s}_{s}$pH 9.5 changing suddenly to an inhibitory effect with further increases in concentration, suggestive of changes in speciation of La^{3+}. Typically all these plots between 7.5 ≤ $^{s}_{s}$pH ≤ 12 show three domains of interest which are $^{s}_{s}$pH dependent as illustrated in Figs. 6 ($^{s}_{s}$pH 9.5) and 7 ($^{s}_{s}$pH 11.1). Generally there is a linear acceleration of k_{obs} from 1 × 10^{-5} mol dm^{-3} < [La^{3+}] < 1 × 10^{-4} mol dm^{-3}, giving rise to a non-linear dependence on further increases in [La^{3+}]$_t$ suggestive of the intervention of La^{3+} dimers. At low $^{s}_{s}$pH (Fig. 6) there is a dramatic decrease in observed rate constant with [La^{3+}]$_t$ increasing above 10^{-4} mol dm^{-3}, while at higher $^{s}_{s}$pH (Fig. 7) the rate constant increases in that same concentration range. In all cases the plots plateau at high [La^{3+}]$_t$ indicating saturation phenomena where **18** is completely bound to a La^{3+} dimer as a kinetically competent species. The highly simplified process shown in Scheme 7 minimally accommodates the data, and the values for k_1[18] (the second-order rate constant for La^{3+} promoted methanolysis of **18**) and k_2[18] (the first-order rate constant for spontaneous methanolysis of the putative **18**–(La^{3+})(OCH_3)$_2$ dimer) can independently be evaluated at each $^{s}_{s}$pH as the slopes of the initial portion of the k_{obs} *vs.* [La^{3+}]$_t$ plots and the plateau value at high [La^{3+}]$_t$. The overall shape of

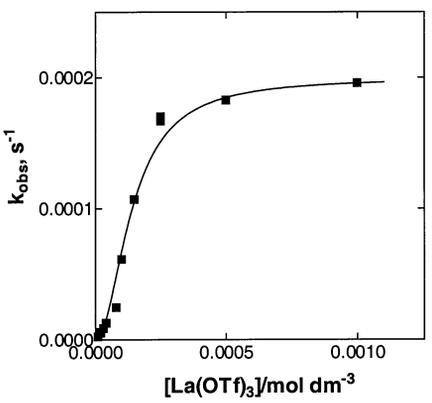
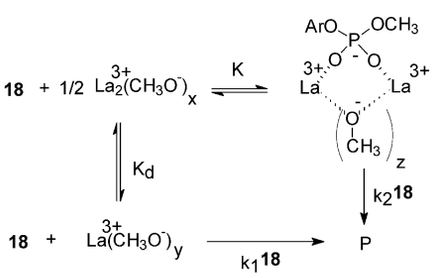


Fig. 7 Plot of pseudo-first order rate constant for the methanolysis of 2×10^{-5} mol dm^{-3} **18** *vs.* [La(OTf)$_3$] at 25 °C; $^{s}_{s}$pH = 11.1 (0.02 mol dm^{-3} triethylamine buffer). Redrawn from ref. 32: lines through the data computed by fits to eqn. (5) in ref. 32.

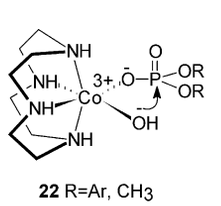


Scheme 7

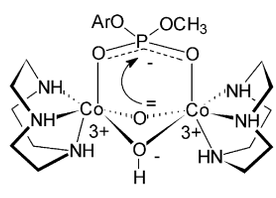
the kinetic profile at a given $^{s}_{s}$pH is determined by the relative activity of the monomeric and dimeric La^{3+}-bound species. While we refer the reader to the original paper[32] for the complete compendium of kinetic data and its analysis, the values of the constants at neutral $^{s}_{s}$pH of 8.5 are $k_1^{18} = 0.26$ dm^3 mol^{-1} s^{-1} and $k_2^{18} = 7.5 \times 10^{-6}$ s^{-1}. The acceleration of methanolysis of **18** promoted by one La^{3+} can be determined from the $k_1^{18} : k_{OCH_3}^{18}$ ratio which, at $^{s}_{s}$pH 8.5, is 329,000. The effect of associating **18** with two La^{3+} ions is given as $k_2^{18} : k_{background}^{18}$, which at $^{s}_{s}$pH 8.5, is an impressive 1.7×10^9-fold relative to the background reaction.

Equally impressive rate accelerations are observed for methanolysis of phosphates **16** and **17**. For example, an initial rate experiment conducted with 4×10^{-5} mol dm^{-3} **16** and 5×10^{-4} mol dm^{-3} $La^{3+}(^{-}OTf)_3$ at $^{s}_{s}$pH 8.9 yielded a pseudo-first order rate constant for release of *p*-nitrophenoxide of $k_{obs} = 4.8 \times 10^{-4}$ s^{-1}, which can be compared with a computed background reaction of 3.4×10^{-14} s^{-1}, an acceleration of 1.4×10^{10}-fold assuming that the background reaction is entirely attributable to CH_3O^- attack on **16**. In non-buffered 80 : 20 CD_3OD–CH_3OH at 25 °C containing 4.0×10^{-2} mol dm^{-3} La(OTf)$_3$, 2×10^{-2} mol dm^{-3} **17** and 0.1 mol dm^{-3} $NaOCH_3$, $^{s}_{s}$pH 11.6 (controlled by the $La^{3+}(^{-}OCH_3)_x$), monitoring of the aromatic protons by ^{1}H NMR as a function of time yields a k_{obs} for methanolysis of $(6.6 \pm 0.1) \times 10^{-5}$ s^{-1}, an acceleration of 5×10^{10}-fold relative to the CH_3O^- reaction at that $^{s}_{s}$pH!

As is the case with most metal ion mediated acyl and phosphoryl transfer reactions, it is difficult to ascertain whether base promoted methanolysis of the monomeric or dimeric La^{3+}–**16**–**18** complexes involves attack of external CH_3O^- or a La^{3+}-coordinated CH_3O^-. Williams, Takasaki, Wall and Chin, in an authoritative analysis of the possible roles of metal ion catalysis,[2b] point out that the metal coordinated hydroxide in **22**[42] can be a very effective nucleophile in promoting hydrolysis of a bound phosphate containing good or poor leaving groups. They also point out[2b] that ^{-}OH bridged between two metal centers as in **23**[43] is a much poorer nucleophile than when associated with only one metal center, and intramolecular attack involving a bridged hydroxide can only occur when it is further deprotonated as a bridging oxide which is not possible for bridging methoxide. Extending these findings to the case of La^{3+}-promoted methanolysis of **16**–**18**, it is possible that the monomeric forms could act as a bifunctional catalyst delivering coordinated methoxide to a bound phosphate as in **24**, thus explaining the 329,000-fold acceleration compared to the reaction of the much more basic methoxide alone. In the case of La^{3+} dimers, the doubly-bridged methoxide cannot be considered an effective nucleophile which may account for the limited reactivity of $(La^{3+})_2(CH_3O^-)_2$–**16** (structure **19**) in the neutral $^{s}_{s}$pH region. For the latter, methanolysis can only occur by attack of external methoxide or if **19** undergoes equilibrium opening of a methoxy bridge to expose a singly coordinated and now nucleophilic methoxide.



22 R=Ar, CH$_3$



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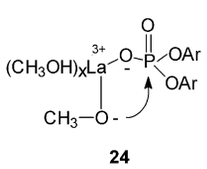

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6 Conclusions

The finding that metal ions like Zn^{2+}, Co^{2+} and La^{3+} are soluble in methanol throughout the entire $^{s}_{s}$pH region where ionization of the metal-bound methanols occurs opens up studies of the catalysis of methanolysis under homogeneous conditions without the requirement of having additional ligands to induce metal ion solubility. This, and the fact that it is now possible to undertake detailed kinetic studies in methanol under conditions where the $^{s}_{s}$pH can be measured and controlled as easily as in aqueous media, should spur further work in determining the mechanisms by which metal ions exert their catalysis. The preliminary results we present above for the methanolysis of activated amides, esters without proximal binding sites, and phosphate diesters are encouraging in that impressive catalysis can be demonstrated. Particularly interesting is the observation that La^{3+} ions in methanol self assemble into catalytically active dimers without the need for sophisticated ligands that hold the two metal ions in proximity. To be sure there are still uncertainties in the exact mechanism by which certain reactions occur, notably those of phosphoryl transfer where speciation is a problem. Recently Martell[44] and Yatsimirsky[45] have demonstrated, through the application of a complex fitting routine, successful analysis of Ln^{3+} speciation in water solutions. Current work in our laboratories shows this approach to be viable for complex speciation in methanol as will be reported in our forthcoming publications.

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