

Metal ion promoted transesterifications of carboxylate esters. A structure/activity study of the efficacy of Zn^{2+} and La^{3+} to catalyze the methanolysis of some aryl and aliphatic esters

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The methanolysis of various aryl and aliphatic carboxylate esters promoted by methoxide, 1,5,9-triazacyclododecane : $\text{Zn}^{2+}(-\text{OCH}_3)$ and $\text{La}^{3+}(-\text{OCH}_3)$, were studied and the derived rate constants (k_{OCH_3} , $k_{\text{cat}}^{3\text{Zn}(\text{OCH}_3)}$ and $k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$) correlated in various ways. The metal ion catalyzed reactions are very much faster than the background reactions in some cases reaching up to 7×10^6 -fold acceleration when present at concentrations of 5 mmol dm^{-3} . The data for both metals exhibit non-linear Brønsted correlations with the $\text{p}K_{\text{a}}$ of the leaving group which are analyzed in terms of a change in rate limiting step from formation to breakdown of a metal-coordinated tetrahedral intermediate as the $\text{p}K_{\text{a}}$ increases above values of ~ 14.7 . Plots of the $\log k_{\text{OCH}_3}$ reaction vs. the $\log k_{\text{cat}}$ values for each metal ion indicate low sensitivity for aryl esters and a higher sensitivity for the aliphatic esters. A mechanistic rationale for the observations is presented.

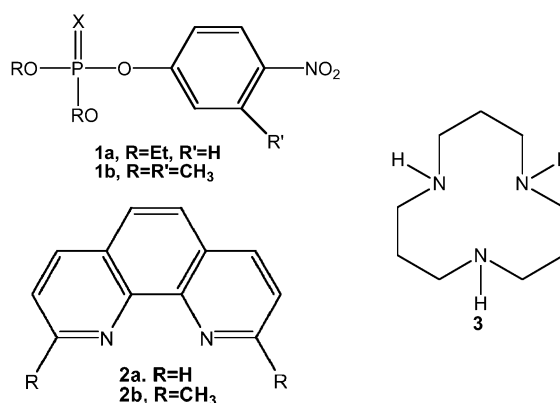
Introduction

Considering their importance to industrial processes and synthetic chemistry it is not surprising that considerable attention has been devoted to the synthesis of carboxylate esters *via* acid and base promoted pathways.¹ Limited information is available concerning the mechanisms of action of catalysts developed to promote transesterification,² although several examples of metal catalyzed transesterification have been reported³ and some important industrial applications are compiled in Parshall and Ittel's authoritative treatise.⁴

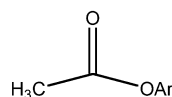
In earlier studies we demonstrated that La^{3+} ^{5a} and Eu^{3+} ^{5b} introduced into methanol solution as their triflate or perchlorate salts along with one equivalent of NaOCH_3 , greatly accelerated the transesterification of both activated and non-activated esters. These metal ions have greatest activity as their monomethoxides, $\text{Ln}^{3+}(-\text{OCH}_3)_1$, and general mechanisms were proposed consistent with the fact that the La^{3+} system reacts through dimeric forms ($\text{La}^{3+}_2(-\text{OCH}_3)_{2,3,4}$), while the Eu^{3+} system apparently reacts as a monomer ($\text{Eu}^{3+}(-\text{OCH}_3)$). One important general aspect of these reactions is revealed through comparison of the second order rate constants for Ln^{3+} -catalyzed methanolysis with those for methoxide attack on a given ester ($k_{\text{cat}}^{\text{ester}}/k_{\text{OMe}^{\text{ester}}}$) which shows that the less activated esters are more susceptible to Ln^{3+} catalysis than the activated esters. For example, for the La^{3+} -methoxide system the $k_{\text{cat}}^{\text{ester}}/k_{\text{OMe}^{\text{ester}}}$ ratios for phenyl acetate, phenyl benzoate and ethyl acetate are 21, 8.9 and 2.5 respectively, while that ratio for 2,4-dinitrophenyl acetate is 0.07.^{5a} In the case of Eu^{3+} , the ratio is 4.3 for phenyl acetate, and 0.2 for *p*-nitrophenyl acetate.^{5b} A second general aspect of the Ln^{3+} -catalyzed systems is the rather spectacular rate enhancements seen for the methanolysis of esters in general, where the catalysis is 1–100million-fold relative to the background reaction in the presence of as little as $5 \times 10^{-3} \text{ mol dm}^{-3}$ of metal ion at near neutral pH^6 and ambient temperature. This belies the situation in water where intermolecular metal ion catalysis of hydrolysis of esters, particularly non-activated ones, is generally poor or non-existent, as opposed to intramolecular hydrolysis where the metal ion is held through binding to some group, close to the scissile $\text{C}=\text{O}$ bond. The origins of the rate enhancements we see in methanol are uncertain but could include stronger pre-equilibrium binding of the ester to the metal ion in the reduced polarity medium and greater

nucleophilicity of the metal-coordinated methoxide to attack the transiently associated $\text{C}=\text{O}$ unit. Clearly more work is needed to understand the origins, scope and limitations of M^{n+} -catalysis of transesterification.

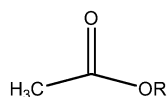
The metal catalyzed phosphoryl and acyl transfer reactions are not limited to lanthanides since we have shown that Zn^{2+} and Cu^{2+} , either alone or preferably as complexes with various ligands, can promote both methanolysis of phosphate and carboxylate esters.^{7,8} In a recent study⁸ we investigated the methanolysis of some phosphate triesters such as paraoxon (**1a**) and fenitrothion (**1b**) promoted by $\text{Zn}^{2+}(-\text{OCH}_3)$ and three of its complexes formed by association with phenanthroline (**2a**), 2,9-dimethylphenanthroline (**2b**, DMP) and 1,5,9-triazacyclododecane (**3**). Each of these complexes is capable also of accelerating the methanolysis of *p*-nitrophenyl acetate (PNPA) although the phenanthroline complexes form equilibrium distributions of inactive dimers ($\text{Phen} : \text{Zn}^{2+} : -\text{OCH}_3)_2$ which reduce the overall catalytic efficacy relative to the most active catalyst **3** : $\text{Zn}^{2+} : -\text{OCH}_3$. A subsequent report⁹ has noted the problematic dimerization and suggested that Cu^{2+} , complexed to 2,9-dimethylphenanthroline (DMP) which sterically suppresses the dimerization, is also capable of modestly promoting the methanolysis of some carboxylate esters. The Cu^{2+} /DMP combination appears to be an unfortunate choice for metal promoted methanolysis given the known preference of that ligand for Cu^+ and destabilization of the square-planar Cu^{2+} .¹⁰ DMP does favour binding to the tetrahedral Zn^{2+} and



gives good catalysis as the monomethoxide, but dimerization is still a problem.⁸ Building on our previous work on the methanolysis of phosphate esters promoted by transition metal ions^{7,8} we have chosen **3**: $\text{Zn}^{2+}(\text{OCH}_3)^+$ as a superior catalyst for the methanolysis of a series of carboxylate esters (**4–15**) having alcohol portions of varying leaving group ability. Herein we report the kinetic studies with the zinc complex **3**: $\text{Zn}^{2+}(\text{OCH}_3)$ and for comparison purposes those with $(\text{La}^{3+}(\text{OCH}_3)_2)$.



- 4 Ar = 2,4-dinitrophenyl
 5 Ar = pentafluorophenyl
 6 Ar = 3-nitrophenyl
 7 Ar = 4-nitrophenyl
 8 Ar = 4-chlorophenyl
 9 Ar = 4-methoxyphenyl
 10 Ar = phenyl
 11 Ar = 2,4-dimethylphenyl
 12 Ar = 2,3,5-trimethylphenyl



- 13 R = CH_2CF_3
 14 R = CH_2CH_3
 15 R = $\text{CH}(\text{CH}_3)_2$

Experimental

a. Materials

4-Chlorophenol (99+%), 3-nitrophenol (99%), 4-methoxyphenol (99%), 2,3,5-trimethylphenol, pentafluorophenol (99+%), 2,4-dimethylphenol (98%) and 2,6-dimethylphenol, 4-nitrophenol and 2,4-dinitrophenol were all acquired from Aldrich and used as received for syntheses of the corresponding esters. Acetic anhydride (98%) from Aldrich and NaOH pellets (98.8%, Fisher Scientific) were also used as received for the syntheses. Trifluoroethyl acetate, 97% (Lancaster), phenyl acetate (Aldrich) and isopropyl acetate, 99% (Aldrich) were used as received as substrates. Syntheses of the aryl esters followed the general procedure detailed in the literature,¹² and in all cases gave products having ¹H NMR and mass spectra consistent with the structures. Sodium methoxide, 0.5 mol dm⁻³ (Aldrich), as well as HCl, 0.02 mol dm⁻³ solution (standardized, Fisher Scientific), 1,5,9-triazacyclododecane, 97% (Aldrich) (12-3N), zinc triflate ($\text{Zn}(\text{OTf})_2$), 98%, Strem Chemicals) and $\text{La}(\text{OTf})_3$, 99.999% (Aldrich) were used as supplied.

b. General UV/vis kinetics

Stock solutions (5 mmol dm⁻³) of each of the aryl esters were prepared in 99.8% anhydrous acetonitrile (Aldrich). For the Zn^{2+} -catalyzed reactions, stock solutions of $\text{Zn}(\text{OTf})_2$ and ligand **3** were made in anhydrous methanol to 0.05 mol dm⁻³ and tetrabutylammonium hydroxide was diluted from 1.0 mol dm⁻³ (as supplied) to 0.05 mol dm⁻³ with dry MeOH. For each kinetic run, the catalyst was formulated *in situ* by adding known aliquots of $\text{Zn}(\text{OTf})_2$, ligand **3** and $\text{NBu}_4(\text{OH})$, to methanol solvent such that the final volume was 2.5 ml. Since the final ratios of ligand, Zn^{2+} and OCH_3^- were 1 : 1 : 0.5 the solution is self buffered at $\text{pH} = 9.1$ corresponding to the pK_a of **3**: $\text{Zn}^{2+}(\text{HOCH}_3)$.^{7,13} The kinetics were followed by monitoring the change in absorbance of 2 to 10×10^{-5} mol dm⁻³ of esters **4–11** at 276.9, 309, 330, 310, 283, 291, 274.6, 280 and 275.9 nm respectively. The Abs. 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 the reaction were monitored at four to six different catalyst concentrations in duplicate ranging from 2.5×10^{-4} to 5.0×10^{-3} mol dm⁻³, and the gradients of the plots of k_{obs} vs. [**3**: $\text{Zn}^{2+}(\text{OCH}_3)$] were taken as the second order rate constants (k_2^{obs}) for the catalyzed reaction, these rate constants being given in Table 1.

The La^{3+} -catalyzed reactions were monitored by UV/vis spectrophotometry under buffered (*N*-ethylmorpholine, 12 mmol dm⁻³) conditions at $\text{pH} = 8.74$ in the presence of 0.2 to 2.0×10^{-3} mol dm⁻³ $\text{La}(\text{OTf})_3$ as described in our earlier publications.⁵ The rates of methanolysis of 2 to 10×10^{-5} mol dm⁻³ solutions of esters **5**, **6**, **8**, and **9** were monitored at 274.9, 335, 283 and 294 nm respectively to obtain the k_{obs} pseudo-first order rate constants at each [La^{3+}], and the gradients for the k_{obs} vs. [La^{3+}] plots were calculated to give the overall k_2^{obs} for La^{3+} -catalyzed methanolysis which are given in Table 1. Also included in Table 1 are the reported rate constants for methanolysis of esters **4**, **7** and **10** computed from k_{obs} vs. [La^{3+}] total data given in our previous paper.^{5a}

The rates of methanolysis of 20 mmol dm⁻³ solutions of esters **13** and **14** in CD_3OD were monitored at 25 °C by ¹H NMR in the presence of **3**: $\text{Zn}^{2+}(\text{OCH}_3)$ (for ester **13**) or La^{3+} plus one equivalent of NaOCH_3 (for esters **13** and **14**). The rates were determined through observation of both the rate of disappearance of the starting materials and rate of appearance of products, the pseudo-first order rate constant being evaluated from the exponential fits. The second order rate constants for catalysis were calculated as $k_{\text{obs}}/[\text{catalyst}]$ and are given in Table 1.

The rates of methanolysis promoted by OCH_3^- in the absence of any metal ion were determined by UV/vis or ¹H NMR as

Table 1 Second order rate constants for the methanolysis of esters **4–15** promoted by methoxide, **3**: $\text{Zn}^{2+}(\text{OCH}_3)$ and $\text{La}^{3+}(\text{OCH}_3)$ at 25 °C

Ester	pK_a of ArOH in MeOH	$k_{\text{OCH}_3^-}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{\text{cat}}^{\text{Zn}(\text{OCH}_3)}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{\text{cat}}^{\text{La}(\text{OCH}_3)}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
4	7.83 ^b	484.8	43.6	31
5	8.84 ^c	73.3	23.8	14.6
6	12.41 ^b	49.7	39.8	21.9
7	11.30 ^b	190 ^c	19.2	38.6 ^e
8	13.59 ^b	7.04	16.7	27.7
9	14.7 ^c	1.58	8.6	18.0
10	14.33 ^b	2.01(2.66) ^f	13.9	29.33 ^e
11	15.04 ^b	0.63	4.28	—
12	15.36 ^b	0.49	4.30	4.33
13	15.78 ^d	12.64	3.00	10.0
14	18.42 ^d	0.057 ^g	0.042	0.071 ^g
15	19.79 ^d	0.007 ^g	0.006	0.004 ^g
Methyl acetate	18.13	0.17 ^e		

^a Determined as the pH at half neutralization, this work. ^b From refs. 15,16,14. pK_a for **12** calculated according to the method provided in ref. 14; $\text{pK}_a^{\text{MeOH}} = 1.12\text{pK}_a^{\text{H}_2\text{O}} + 3.56$. ^c R. L. Schowen and K. S. Lathan, *J. Am. Chem. Soc.*, 1967, **89**, 4677. ^d Computed from $\text{pK}_a^{\text{MeOH}} = 0.748\text{pK}_a^{\text{H}_2\text{O}} + 6.53$, see text. ^e From ref. 9. ^f From C. G. Milton, M. Gresser and R. L. Schowen, *J. Am. Chem. Soc.*, 1969, **91**, 2047. ^g Data from ref. 5a for methoxide and lanthanum reactions; lanthanum reactions determined at $\text{pH} = 8.86$ for **7** and **10**; values are computed from the gradient of the plot of k_{obs} vs. [La^{3+}]. ^h Computed from the gradient of k_{obs} vs. [**3**: $\text{Zn}^{2+}(\text{OCH}_3)$] plots at $\text{pH} = 9.1$ under self buffered conditions. ⁱ Computed from the gradient of k_{obs} vs. [La^{3+}] plots at $\text{pH} = 8.74$ under buffered conditions.

appropriate for a given ester: for the aryl esters the pseudo-first order rate constant for methanolysis were determined in duplicate at four different $[\text{OCH}_3]$ ranging from 2.5×10^{-4} to $3.0 \times 10^{-2} \text{ mol dm}^{-3}$, lower $[\text{OCH}_3]$ being used for the more reactive esters and higher $[\text{OCH}_3]$ being used for the less reactive esters. The second order rate constants for these (k_{OCH_3}) were computed as the gradients of the k_{obs} vs. $[\text{OCH}_3]$ plots and are given in Table 1.

Results

Given in Table 1 are the second order rate constants for the transesterification reactions of esters **4–15** promoted by methoxide, **3** : $\text{Zn}^{2+}(\text{OCH}_3)$ and $\text{La}^{3+}(\text{OCH}_3)$. In all cases these were determined from the gradients of the plots of the pseudo-first order rate constants for methanolysis as a function of $[\text{methoxide}]$ or $[\text{metal containing catalyst}]$. In the case of catalysis by **3** : $\text{Zn}^{2+}(\text{OCH}_3)$ the solutions were self-buffered at pH 9.1 by adding half as much methoxide as the total added $[\text{3} : \text{Zn}^{2+}]$, converting half of the latter to the active species. The $\text{La}^{3+}(\text{OCH}_3)$ reactions were buffered with 12 mmol dm^{-3} *N*-ethyl morpholine at pH 8.74. Also included in Table 1 are the $\text{p}K_{\text{a}}$ values for the phenols from the literature or from measurements of the pH at half neutralization. While $\text{p}K_{\text{a}}$ values for most of the phenols are available^{14,15} or can be calculated from the methods given in references 14 and 16, the $\text{p}K_{\text{a}}$ values for the aliphatic alcohols corresponding to esters **13–15** are not available, to our knowledge. We may calculate the values based on a linear regression approach similar to that used by Bosch *et al.* for correlating the acidities of carboxylic acids, phenols and ammonium ions in water and methanol.¹⁴ From the autoprotolysis constant of methanol ($10^{-16.77} (\text{mol dm}^{-3})^2$)^{14,16} its $\text{p}K_{\text{a}}$ can be computed as 18.13 on the mol dm^{-3} scale. As far as we know, the only other aliphatic alcohol for which a $\text{p}K_{\text{a}}$ in methanol is available is hexafluoroisopropanol ($\text{p}K_{\text{a}} = 13.49$ ¹⁷ vs. $\text{p}K_{\text{a}}^{\text{H}_2\text{O}} = 9.3$ ¹⁸), so that a linear regression (admittedly only on two data points) gives $\text{p}K_{\text{a}}(\text{MeOH}) = 0.75\text{p}K_{\text{a}}(\text{H}_2\text{O}) + 6.53$. The $\text{p}K_{\text{a}}$ values for the aliphatic alcohols corresponding to **13–15** were computed from this regression line.

In order to aid in visualizing trends in the data, Brønsted plots of the $\text{p}K_{\text{a}}$ of phenols in methanol vs. the log second order rate constants for the methoxide, **3** : $\text{Zn}^{2+}(\text{OCH}_3)$ and $\text{La}^{3+}(\text{OCH}_3)$ catalyzed methanolysis of the esters are shown in Figs. 1, 2 and 3 respectively.

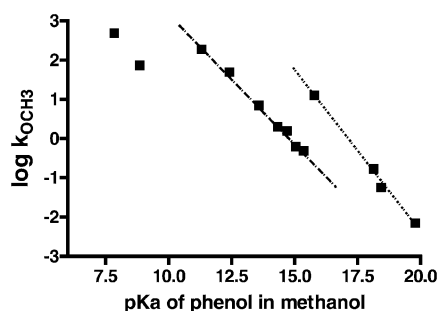


Fig. 1 Brønsted plots of $\text{p}K_{\text{a}}$ for phenol in methanol vs. $\log k_{\text{OCH}_3}$ for the methoxide promoted methanolysis of aryl and aliphatic acetates, $T = 25^\circ\text{C}$. Dashed line of slope $\beta = -0.656 \pm 0.021$ encompasses esters **6–12**, while excluded data points (from the left) correspond to esters **4** and **5** respectively. Dotted line of slope $\beta = -0.821 \pm 0.044$ corresponds to the three aliphatic esters **13–15** and methyl acetate.

The center part of the methoxide plot in Fig. 1 comprises seven phenols with $\text{p}K_{\text{a}}$ values ranging from 11.17 to 15.04 providing a very good linear correlation with $\beta = -0.656 \pm 0.021$, while the two left points for the pentafluoro and 2,4-dinitrophenyl acetates deviate markedly. The data for the aliphatic esters including methyl acetate for which the k_{OCH_3} is reported elsewhere,⁹ appear to define a different line, the gradient of which is $\beta_{\text{aliphatic}} =$

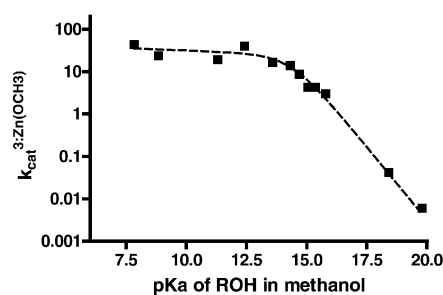


Fig. 2 A Brønsted plot of $\log \text{p}K_{\text{a}}$ phenol in methanol vs. $\log k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ for methanolysis of aryl acetates promoted by **3** : $\text{Zn}^{2+}(\text{OCH}_3)$, $T = 25^\circ\text{C}$. Dashed line corresponds to NLLSQ fit of data to eqn. (3) encompassing all esters with $\beta_1 = -0.023 \pm 0.03$ and $\beta_2 = -0.690 \pm 0.005$ with a breakpoint of $\text{p}K_{\text{a}}^{\text{ROH}} = 14.8$ (see text).

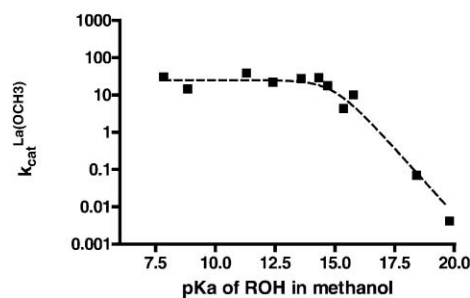
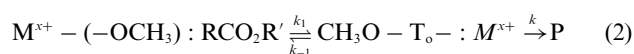
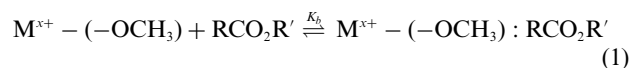


Fig. 3 A Brønsted plot of $\log \text{p}K_{\text{a}}$ phenol in methanol vs. $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ for methanolysis of aryl acetates promoted by $\text{La}^{3+}(\text{OCH}_3)$, $T = 25^\circ\text{C}$. Dashed line corresponds to NLLSQ fit of data to eqn. (3) encompasses all esters with values of $\beta_1 = 0.03 \pm 0.005$ and $\beta_2 = -0.715 \pm 0.005$ with a breakpoint of $\text{p}K_{\text{a}} = 14.7$ (see text).

-0.821 ± 0.044 . Admittedly this correlation is somewhat contrived since it is based on $\text{p}K_{\text{a}}$ values calculated from a linear regression of only two experimental data points. Nevertheless, it is consistent with the observation that the Brønsted plot for alkaline hydrolysis for aryl acetates vs. other acetate esters fits a similar two-line profile.¹⁹ The plots of the metal catalyzed reactions shown in Figs. 2 and 3 show definite evidence of a break where the rate constants are quite sensitive to phenols or alcohols with high $\text{p}K_{\text{a}}$ values, but far less sensitive to the nature of the ROH groups with low $\text{p}K_{\text{a}}$ values. In these cases there is no obvious discrepancy between aliphatic and aryl esters, so all esters are used for the subsequent treatment.

To compute the Brønsted dependences we assume that the overall metal-catalyzed processes follow eqns. (1) and (2) describing a fast pre-equilibrium binding followed by reversible creation of an intermediate, the formation and breakdown of which can be rate limiting depending on the nature of the leaving group. Steady state treatment gives the general relationship in eqn. (3) where the exponent $\text{p}K_{\text{a}}$ refers to the $\text{p}K_{\text{a}}$ of the ROH or ArOH leaving group in methanol and the β terms correspond to the various binding and kinetic steps. Eqns. (4) and (5) correspond to limiting cases where formation and breakdown of the tetrahedral addition intermediate ($\text{CH}_3\text{O-T}_\text{o}^- : \text{M}^{x+}$) is rate limiting.



$$k_2^{\text{obs}} = K_b k_1 k_2 / (k_{-1} + k_2) = C_b C_1 C_2 10^{(\beta b + \beta_1 + \beta_2)\text{p}K_{\text{a}}} / (C_{-1} 10^\beta - I \text{p}K_{\text{a}} + C_2 10^\beta 2\text{p}K_{\text{a}}) \quad (3)$$

$$k_2^{\text{obs}} = K_b k_1 = C_b C_1 10^{(\beta b + \beta_1)\text{p}K_{\text{a}}} \quad (4)$$

$$k_2^{\text{obs}} = K_b k_1 k_2 / k_{-1} = (C_b C_1 C_2 / C_{-1}) 10^{(\beta b + \beta_1 - \beta - 1 + \beta_2)\text{p}K_{\text{a}}} \quad (5)$$

The dashed lines in Figs. 2 and 3 are computed from the NLLSQ fits of all the data to eqn. (3): in Fig. 2, $(\beta_b + \beta_1) = -0.023$ and $(\beta_b + \beta_1 - \beta_{-1} + \beta_2) = -0.710$ with a breakpoint at $\text{p}K_a = 14.8$; in Fig. 3 $(\beta_b + \beta_1) = -0.02$ and $(\beta_b + \beta_1 - \beta_{-1} + \beta_2) = -0.710$ with a breakpoint at $\text{p}K_a = 14.7$.

Alternative presentations of the kinetic data are given in Figs. 4 and 5 which comprise two plots of $\log k_{\text{OCH}_3}$ vs. $\log k_{\text{cat}}^{3, \text{Zn}(\text{OCH}_3)}$ and $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ respectively. Following Kirsch and Jencks¹⁹ we assume that the mechanism of methoxide promoted methanolysis is similar enough for all the esters that the rate constant, k_{OCH_3} , can be used as an empirical measure of the composite effects of structural changes that incorporate both electronic and steric effects rather than using Hammett parameters or $\text{p}K_a$ values. This allows us to make a more common comparison of the effects of structural changes on the rates of methoxide and metal-promoted methoxide attack. For Zn^{2+} , the Fig. 4 plot comprising all data fits a rather poor linear dependence (not shown) with slope = 0.73 ± 0.13 ($r^2 = 0.7865$). Better linear relationships are drawn through the data representing the subset of aliphatic esters and aryl esters, and although there are only three aliphatic esters (**13–15**), the line for these is steeper than for the aryl esters (0.82 vs. 0.31). The $\text{La}^{3+}(\text{OCH}_3)$ vs. methoxide plot shown in Fig. 5 has a general appearance similar to that of the **3** : $\text{Zn}^{2+}(\text{OCH}_3)$ vs. methoxide data in Fig. 4, with an overall slope of 0.706 ± 0.117 ($r^2 = 0.820$). While the overall correlation is not good, breaking the data into the aliphatic (esters **13–15**) and aryl (esters **4–12**) subsets gives two lines of quite different slopes, the aliphatic slope being greater than the aryl one by a factor of ~ 5 – 6 .

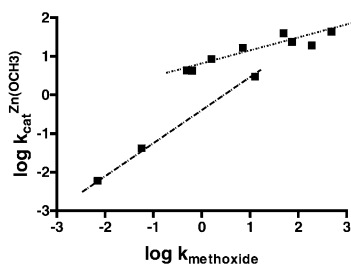


Fig. 4 Plot of $\log k_{\text{OCH}_3}$ vs. $\log k_{\text{cat}}^{3, \text{Zn}(\text{OCH}_3)}$ for the methoxide and **3** : $\text{Zn}^{2+}(\text{OCH}_3)$ catalyzed methanolysis of all acetyl esters, $T = 25^\circ\text{C}$. Lower dotted line comprises the aliphatic esters **13–15** with slope = 0.821 ± 0.030 ($r^2 = 0.9987$), and upper dotted line comprises aryl esters **4–12**, slope = 0.314 ± 0.055 ($r^2 = 0.8447$).

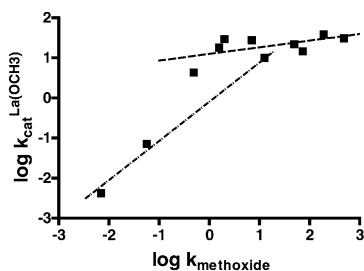


Fig. 5 Plot of $\log k_{\text{OCH}_3}$ vs. $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ for the methanolysis of all esters promoted by methoxide and $\text{La}^{3+}(\text{OCH}_3)$. Lower dashed line comprises aliphatic esters **13–15**, slope = 0.914 ± 0.125 ($r^2 = 0.9817$), while upper dotted line comprises aryl esters **4–12**, slope = 0.16 ± 0.09 ($r^2 = 0.3607$).

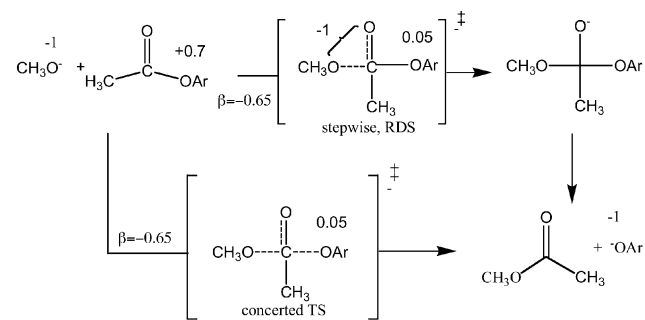
Discussion

The various rate constants are presented in Table 1 along with their alcohol $\text{p}K_a$ values in methanol where these are available or can be computed by literature methods from correlations with the aqueous $\text{p}K_a$ values.¹⁴ For the lanthanum methoxide promoted methanolysis the second order rate constant is determined as $\Delta k_{\text{obs}}/\Delta[\text{La}^{3+}]$ under buffered conditions at pH 8.74 and is thus presented per La^{3+} ion, even though we

have determined that the actual catalytic species are dimers $(\text{La}^{3+})_2(\text{OCH}_3)_{2,3,4}$ the relative importance of which depend on the pH and the [dimer].²⁰ The data in Table 1 reveal some interesting trends in the reactivities of the metal methoxides relative to methoxide itself. Within the aryl or aliphatic series the most activated esters toward methoxide attack, as expected, contain leaving groups with the lowest $\text{p}K_a$ values for their corresponding alcohols, and in these cases (esters **4–7** of the aryl series and **13** of the aliphatic series) the $k_{\text{cat}}^{3, \text{Zn}(\text{OCH}_3)}/k_{\text{OCH}_3}$ and $k_{\text{cat}}^{\text{La}(\text{OCH}_3)}/k_{\text{OCH}_3}$ ratios are generally less than 1. However, for the less activated esters one sees that the $k_{\text{cat}}^{3, \text{Zn}(\text{OCH}_3)}/k_{\text{OCH}_3}$ and $k_{\text{cat}}^{\text{La}(\text{OCH}_3)}/k_{\text{OCH}_3}$ ratios are generally greater than unity. Although one normally anticipates that simple Brønsted considerations would make a metal-coordinated methoxide less nucleophilic than methoxide itself, in analogous hydrolyses catalyzed by metal ions this is generally interpreted to arise from a dual role for the metal ion in providing Lewis acid catalysis and delivering the M^{x+} -coordinated OH or OR nucleophile.²¹

a. Uncatalyzed attack of methoxide

The plot of the $\log k_{\text{OCH}_3}$ for methoxide-promoted methanolysis of the esters vs. the $\text{p}K_a$ values shown in Fig. 1 provides a good linear correlation for the aryl esters except for the strongly electron withdrawing 2,4-dinitrophenyl and pentafluorophenyl derivatives which are less reactive than predicted on the basis of the $\text{p}K_a$ data. Non-linear Hammett and Brønsted behaviours have been observed for the hydroxide-catalyzed hydrolysis of substituted aryl benzoates²² and acetates.²³ Schowen²⁴ has observed that the “ ΔG^\ddagger for methoxide promoted methanolysis of aryl acetates and carbonates in methanol are not linearly related to the ΔG° values for ionization of the corresponding phenols,” noting that “the rate process becomes less sensitive to the substituent as the electron-withdrawing power of the substituent increases”. The fall-off in the rate results from a greater importance of the resonance interaction in the equilibrium ionization processes (on which the Hammett and $\text{p}K_a$ values are based) than in the kinetic processes where decidedly less charge development may have occurred in the rate-limiting TS.^{22–25} In the present study linear Brønsted behaviour ($\beta = -0.66 \pm 0.02$)²⁶ is observed for aryl esters with corresponding phenol $\text{p}K_a$ values between 11 and 15 and for these it is probable that if the reaction is a two step one, the rate limiting step involves methoxide attack since expulsion of the leaving aryloxy group from the anionic tetrahedral intermediate should be favoured over expulsion of the methoxide. Utilizing the ‘effective charge treatment’ described by Jencks *et al.*²⁷ and Thea and Williams,²⁸ the Brønsted β value suggests the process shown in Scheme 1 where the rate-limiting transition state has a nearly neutral aryloxy oxygen. The data are also consistent with a concerted mechanism with little cleavage of the OAr bond in the transition state, such as has been shown by Ba-Saif *et al.*²⁹ for the displacement of the *p*-nitrophenoxy group from ester **7** by phenoxy nucleophiles.



Scheme 1

In the case of the aliphatic esters the Brønsted plot (including the literature rate constant for the k_{OCH_3} of methyl acetate⁷) forms

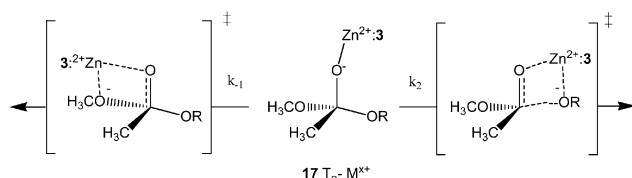
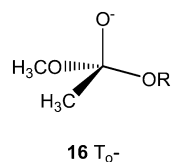
a reasonably straight line (slope = -0.821 ± 0.044) apparently separate from that for the aryl esters. Since there is only one experimental ${}^s\text{p}K_a$ value available for a member of these four esters (methanol), we estimate the ${}^s\text{p}K_a$ values from a linear regression relating $\text{p}K_a(\text{MeOH})$ and $\text{p}K_a(\text{H}_2\text{O})$ which is based on the only two experimental aliphatic alcohol ${}^s\text{p}K_a$ values in methanol of which we are aware. The ${}^s\text{p}K_a$ values presented in Table 1 are based on this calculation and must be viewed only as estimates. Although the slope of the Brønsted line for the aliphatic esters is within experimental error of that for the aryl esters, it lies an order of magnitude higher suggesting a steric¹⁹ and perhaps electronic retardation for the aryl esters.

Methoxide attack on the aliphatic esters must go through anionic tetrahedral addition intermediates which, with equally good or poorer leaving groups than methoxide, must revert to starting materials in competition with breakdown to product, the relative amounts of which are controlled by the ${}^s\text{p}K_a$ values of the ROH and the Brønsted β value for the k_{-1} and k_2 steps. The Brønsted line for the four aliphatic esters shown in Fig. 1 appears to be a straight line with a slightly greater gradient than for the aryl esters, which might arise from that fact that the series encompasses cases where the rate limiting steps is k_1 (**13**), a symmetrical case (methyl acetate) where the k_{obs} is $k_1/2$, and the case of isopropyl acetate where $k_{\text{obs}} = k_1k_2/(k_{-1} + k_2)$ which, in addition to any steric hindrance to the attack of methoxide on **15**, also might steepen the best fit line.

b. Catalysis by **3**: $\text{Zn}^{2+}(-\text{OCH}_3)$ and $\text{La}^{3+}(-\text{OCH}_3)$

Shown in Figs. 2 and 3 are the $\log k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ and $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ vs. ${}^s\text{p}K_a$ data for the methanolysis of the esters promoted by the two metal-methoxide complexes. Overall the leaving group acidity covers a range of $>10^{11}$ -fold while the kinetic data span a range of ~ 5000 -fold and 9000 -fold respectively for the two metal ions. Each plot exhibits a pronounced break suggestive of at least a two-step process where formation and breakdown of some intermediate is rate-limiting. In both the cases, the descending and plateau β values are experimentally the same at -0.71 and ~ 0 respectively with the breakpoint occurring at ${}^s\text{p}K_a = 14.7$ such that the plateau region covers roughly 10^6 -fold change in acidity of the leaving group with virtually no change in catalyzed rate constant.

The Fig. 2 and 3 data are analyzed according to the processes given in eqns. (1) and (2) which give rise to the steady state expression in eqn. (3) which contains both the M^{x+} + ester equilibrium binding constant (K_b) and the various rate constants for intramolecular formation and breakdown of the tetrahedral intermediate. Unlike the case where simple methoxide addition to the esters forms a highly unstable, and perhaps kinetically unstable (in the case of aryl esters)²⁹ anionic intermediate (**16**), the $\text{M}^{x+}-\text{OCH}_3$ catalyzed process forms a M^{x+} -stabilized tetrahedral intermediate with a significant lifetime (**17-T_o-M^{x+}**) which can partition to starting materials and products depending on the relative transition state energies corresponding to k_{-1} and k_2 (Scheme 2).



Scheme 2

Since addition of methoxide to the ester is metal-ion assisted, microscopic reversibility considerations require that the departure of poor leaving groups (with high ${}^s\text{p}K_a$ values for the corresponding alcohols) such as ethoxy or isopropoxy must also be metal ion assisted suggesting that the k_2 step must be partially or entirely rate-limiting and eqn. (5) applies. As the ${}^s\text{p}K_a$ decreases, eventually the leaving group is sufficiently good that it departs without metal-ion assistance and the rate-limiting step for the reaction must change from breakdown to formation of the intermediate, in both these cases when the ${}^s\text{p}K_a$ is about 14.7.

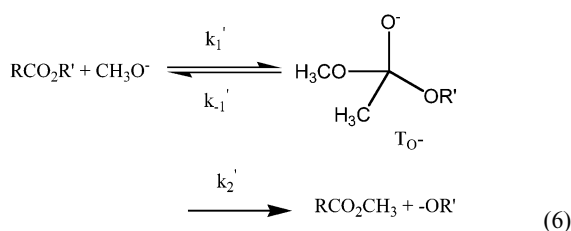
It is curious that in the plateau region, where the leaving groups are good and formation of the intermediate is rate-limiting, that the computed Brønsted β is ~ 0 , signifying little or no dependence on the nature of the leaving group. We rationalize this observation within the framework of the limiting case of eqn. (4) where formation of the intermediate depends on the counterbalancing effects of changes in the leaving group on both the K_b and k_1 steps, *i.e.* $(\beta_b + \beta_1) \rightarrow 0$. This situation is strongly reminiscent of the known insensitivity of the rates of acid-catalyzed hydrolysis of esters to changes in the nature of the leaving group ($\rho = 0$) which Taft³⁰ interpreted as resulting from a counterbalancing of the alkoxy/aryloxy substituent's electronic effect on protonation equilibrium and subsequent nucleophilic step of attack of water on the protonated C=O.

The descending wings of Figs. 2 and 3 have strong dependence on the nature of the leaving group $\beta = -0.71$ which, when analyzed within the framework of eqn. (5), is consistent with a significant cleavage of the C-OR bond in the TS. Since the net effect of the substituent ion K_b and k_1 steps cancel, this leads to the conclusion that the sum of $(-\beta_{-1} + \beta_2)$ is significantly negative.

c. Comparison of k_{OCH_3} and $k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ or $k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$

Presentation of the rate constant data as in Figs. 4 and 5 has some advantages over the customary Brønsted or Hammett plots since the latter rely on substituent induced changes to equilibrium $\text{p}K_a$ processes which may not be appropriate for how a substituent influences a particular reaction where the rate-limiting step(s) have little charge development on the departing OR. Comparison of $\log k_{\text{OCH}_3}$ vs. $\log k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ or $\log k_{\text{OCH}_3}$ vs. $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ allows one to assess how the rates for two reactions depend both on steric and electronic influences of the substituents and a break in such a plot requires that the substituents influence the two reactions in different ways. An additional benefit is that this treatment does not rely on experimental or estimated ${}^s\text{p}K_a$ values for a given substituent which, if in error, may influence the conclusions based on the slopes of Brønsted plots.

The plots in Figs. 4 and 5 are visually similar suggesting that both La and Zn catalysis respond to structural variations in a similar way relative to the methoxide reaction. Both plots show a break surrounded by an ascending domain encompassing the aliphatic alcohols **14** and **15**, followed by a less sensitive domain encompassing the aryl esters. While one could analyze the entire series within a common relationship, another approach is to consider that there are two families encompassing the aryl and aliphatic esters. The dashed lines drawn on the figures are linear fits for the two classes and for both metal ions indicate that the aliphatic esters have a greater sensitivity for the metal-methoxide reactions than do the aryl esters, probably because the aliphatic line includes two members with poor leaving groups. The methoxide and metal-methoxide reactions are related mechanistically in that esters containing poor leaving groups such as methoxide, ethoxide and isopropoxide must go through two step processes in each case with reversibly-formed tetrahedral intermediates (T_o^-) as shown in eqns. (6) and (1), (2) respectively.



Comparison of the steady state analyses of the process in eqns. (1), (2) and that in eqn. (6) gives eqn. (7),

$$\frac{\log k_{\text{cat}}^{\text{M}(\text{OCH}_3)}}{\log k_{\text{OCH}_3}} = \frac{\log \left(\frac{K_b k_1 k_2}{k_{-1} + k_2} \right)}{\log \left(\frac{k_1' k_2'}{k_{-1}' + k_2'} \right)} \quad (7)$$

for which the two limiting cases of $k_{-1} > k_2$ and $k_2 > k_{-1}$ can be derived. The gradients (S) of the extremes in plots in Figs. 4 and 5 are given as eqns. (8) and (9),

$$\frac{\Delta \log k_{\text{cat}}^{\text{M}(\text{OCH}_3)}}{\Delta \log k_{\text{OCH}_3}} = \frac{\Delta \log \left(\frac{K_b k_1 k_2}{k_{-1}} \right)}{\Delta \log \left(\frac{k_1' k_2'}{k_{-1}'} \right)} = S \quad (8)$$

$$\frac{\Delta \log k_{\text{cat}}^{\text{M}(\text{OCH}_3)}}{\Delta \log k_{\text{OCH}_3}} = \frac{\Delta \log (K_b k_1)}{\Delta \log (k_1')} = S \quad (9)$$

which are seen to differ only by the presence of the partitioning ratios (k_2/k_{-1} and k_2'/k_{-1}') of the tetrahedral intermediates. This must be factored into the gradient in the cases of the poor leaving groups becoming important when the ${}^{\text{s}}\text{p}K_a$ is $> \sim 14$ and thus within the domain described by the ascending wing in each plot. Although we cannot put quantitative values to any of these constants, it seems reasonable to suggest that the larger gradient observed with poorer leaving groups arises from the substituent changes influencing both the methoxide and the metal-catalyzed reactions in a similar way, *i.e.* a gradient closer to 1. Since methoxide is a strong base/nucleophile (${}^{\text{s}}\text{p}K_a = 18.13$) it is reasonable to conclude that the rate limiting step for its reaction with most of the esters (with the probable exception of the isopropyl ester) is attack with breakdown of the intermediate being fast.³¹ However the data with the metal catalyzed reactions, where the ${}^{\text{s}}\text{p}K_a$ of the attacking metal associated methoxide is lowered to ~ 9 , indicate that there is a change in rate-limiting step throughout the series. When the leaving groups are good, apparently as is the case with those having a ${}^{\text{s}}\text{p}K_a$ of < 14.7 , the rate limiting step for the metal catalyzed reactions becomes formation of the tetrahedral intermediate. We propose that the shallow gradient relating to eqn. (9) results from the fact that substituent changes tend to counterbalance K_b and k_1 such that their product is relatively constant over the aryl (and probably trifluoroethyl) series.

A third way of correlating the data is presented in Fig. 6 as a plot of $\log k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ vs. $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$. In this case, the data form a straight line with a slope of nearly unity ($0.997 \pm$

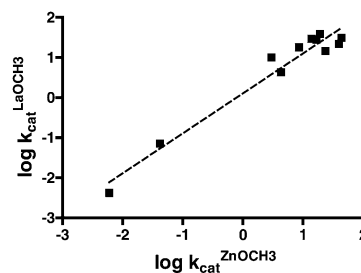


Fig. 6 A plot of the $\log k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}$ vs. $\log k_{\text{cat}}^{\text{La}(\text{OCH}_3)}$ values for methanolysis of all esters promoted by **3**: $\text{Zn}^{2+}(\text{-OCH}_3)$ and $\text{La}^{3+}(\text{-OCH}_3)$, $T = 25^\circ\text{C}$. Dashed line represents linear regression for all data, slope = 0.997 ± 0.071 ($r^2 = 0.9529$).

0.071 ; $r^2 = 0.9529$). The unit slope, with no break, indicates that the substituents influence both metal-methoxide reactions in the same way.

9 Conclusions

The above study shows that the methanolysis of both aryl and aliphatic esters is greatly accelerated by the two catalytic systems described above. In the case of La^{3+} , we have found that the catalytic entities are dimers with 2, 3 or 4 associated methoxides which are spontaneously formed in solution at the concentrations employed without the requirement of added ligands. However, transition metal ions such as Zn^{2+} or Cu^{2+} require added ligands to prevent the deleterious formation of dimers and oligomers, the latter being inactive relative to the monomeric forms. Our studies show that 1,5,9-triazacyclododecane is an optimal ligand for use with Zn^{2+} although phenanthroline and 2,9-dimethyl phenanthroline (DMP) can also provide catalytically active complexes despite the partial formation of dimers under these conditions.⁷ As little as 5 mmol dm^{-3} added La^{3+} with equimolar methoxide accelerates the methanolysis of phenyl acetate (**10**) by 7.8×10^6 -fold relative to the background methoxide reaction at the near neutral of 8.7. The **3**: $\text{Zn}^{2+}(\text{-OCH}_3)$ catalyst, when present at 5 mmol dm^{-3} , accelerates the methanolysis of phenyl acetate by 1.6×10^6 -fold relative to the background methoxide reaction at ${}^{\text{s}}\text{pH}$ 9.1. We observe that the best accelerations relative to the background reactions occur with less activated esters, and in many of these cases, the $k_{\text{cat}}^{3:\text{Zn}(\text{OCH}_3)}/k_{\text{OCH}_3}$ or $k_{\text{cat}}^{\text{La}(\text{OCH}_3)}/k_{\text{OCH}_3}$ ratios are greater than unity.

It is important to compare the efficacy of our catalytic systems to those of the Cu^{2+} : DMP methanolysis system⁹ and the **3**: $\text{Zn}^{2+}(\text{-OH})$ hydrolytic system.¹³ The relevant data are presented in Table 2 in which it is seen that the rate constants exhibited by the lanthanum and zinc systems for the methanolysis of phenyl acetate (**10**) and *p*-nitrophenyl acetate (**7**) are between 660 and 1400-fold larger than for the Cu^{2+} : DMP system and that their catalysis of ethyl acetate methanolysis is at least 100-fold larger (bearing in mind that for the latter the available comparison data are for reaction with a more reactive methyl

Table 2 Comparison of the second order rate constants for methanolysis and hydrolysis processes of given substrates, $T = 25^\circ\text{C}$

Catalyst	Substrate		
	Phenyl acetate $k_2/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	<i>p</i> -Nitrophenyl acetate $k_2/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	ROC=OCH ₃ $k_2/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
$\text{La}^{3+}(\text{-OCH}_3)^a$	29.3	38.6	7.1×10^{-2} (R = Et)
3 : $\text{Zn}^{2+}(\text{-OCH}_3)^a$	13.9	19.2	4.2×10^{-2} (R = Et)
-OCH_3 (in methanol) ^a	2.01	190 ^b	5.7×10^{-2} (R = Et)
Cu^{2+} : DMP ^b	1.6×10^{-2}	2.9×10^{-2}	4.2×10^{-4} (R = Me)
3 : $\text{Zn}^{2+}(\text{-OH})$ (in water)	1.5×10^{-2c}	4.9×10^{-2d}	$\sim 4 \times 10^{-4}$ (R = Me)
-OH (in water)	1.26 ^e	9.5 ^e	1.1×10^{-1} (R = Et) ^e

^a This work. ^b Ref. 9. ^c Computed from data given in ref. 11. ^d Computed from data given in Ref. 13 for reaction at pH 8.1. ^e From ref. 19.

acetate while the La^{3+} and Zn^{2+} catalysts refer to the methanolysis of ethyl acetate). A second point of note is that the La^{3+} and Zn^{2+} catalysts have second order rate constants comparable to the rate constant of methoxide attack in methanol, while the $\text{Cu}^{2+} : \text{DMP}$ and $\mathbf{3} : \text{Zn}^{2+}(-\text{OH})$ systems are at least 100-fold (and several thousand-fold in the case of methanolysis of *p*-nitrophenyl acetate) less reactive than methoxide or hydroxide respectively for a given ester. Interestingly, where a comparison can be made between the second order rate constants for hydrolysis and methanolysis promoted by $\mathbf{3} : \text{Zn}^{2+}(-\text{OH})$ or $\mathbf{3} : \text{Zn}^{2+}(-\text{OCH}_3)$ respectively, the methanolysis reactions are about 1000-fold faster than the hydrolysis reactions with the aryl esters, and somewhat less for the aliphatic esters, again bearing in mind that the hydrolysis data are with methyl acetate and the methanolysis is with ethyl acetate.

The fact that La^{3+} and Zn^{2+} systems react with many of the esters faster than does methoxide gives some clue to the mechanism of reaction. The available data are consistent with a mechanism of catalysis that involves a pre-equilibrium binding of the metal-methoxide complex with the ester followed by an internal delivery of the methoxide *via* a five-coordinate transition state to form an anionic tetrahedral addition intermediate stabilized by a four coordinate Zn^{2+} . This is analogous to the general mechanism that is widely proposed for metal-ion catalyzed hydrolyses, but is kinetically equivalent to a process where an external nucleophilic hydroxide or methoxide attacks the M^{3+} -coordinated ester.³² It is particularly interesting that, where direct comparison can be made with the $\mathbf{3} : \text{Zn}^{2+}(-\text{OH})$ system in promoting the hydrolysis of these esters in water, the corresponding methanolysis promoted by $\mathbf{3} : \text{Zn}^{2+}(-\text{OCH}_3)$ is at least two to three orders of magnitude larger. The likely origins of the rate enhancements are an increased pre-equilibrium binding of the substrate, and a less solvated nucleophile attacking the Zn^{2+} -coordinated C=O unit.

Acknowledgements

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- 31 Given that the rate-limiting step for the methoxide reaction throughout most, if not all of the series of esters is k_1 we can probably replace the denominator in eqn. (8) with $\Delta\log(k'_1)$. In this case the difference in the slopes derived by application of eqn. (8) and (9) stems from the substituent on the k_2/k_1 partitioning constant in the metal catalyzed reactions.
- 32 Suh *et al.*¹¹ have proposed the $3 : \text{Zn}^{2+}$ complex promotes the hydrolysis of aryl esters *via* C=O coordination followed by external attack of methoxide, while Kimura *et al.*¹³ have proposed that the active species is really $3 : \text{Zn}^{2+}(\text{-OH})$. In the present cases, although we favour the internal delivery mechanism, the available pseudo-first order rate constants for the primary kinetic data, along with consideration of reasonable estimates of the pre-equilibrium binding constant and a diffusion limited rate constant for external methoxide attack of $10^{10} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ do not allow us to rule out external methoxide attack.
- 33 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.