Catalysis of the methanolysis of acetylimidazole by lanthanum triflate

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Abstract: Methanolysis of acetylimidazole (1) and *N*-acetylimidazolepentamine-Co(III) (2) was found to be markedly accelerated in the presence of La(OTf)₃. Potentiometric titration of a solution of La³⁺(OTf⁻)₃ gave a pK_a for the metal bound CH₃OH of 7.22. The kinetics of methanolysis of 1 and 2 were measured at 25°C at various pH under buffered conditions as a function of increasing La³⁺. Analysis of both the kinetic and potentiometric data indicates that the catalytically active species is a La³⁺-dimer, bridged by two methoxides, $(CH_3OH)_nLa^{3+}(CH_3O⁻)_2La^{3+}(CH_3OH)_n$. The maximum second-order rate constants for attack of the dimer on 1 and 2 are $1.50 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and $1.42 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ respectively and both processes adhere to titration of a La³⁺(CH₃OH) to generate the active form. The results are explained in terms of a mechanism where the methoxy-bridged La³⁺ dimer transiently breaks a La³⁺-OCH₃ bond to expose both a CH₃O⁻ nucleophile and a La³⁺ which can act as a Lewis acid. Unlike the situation in water, the methanol results indicate that the medium greatly stabilizes and solubilizes the active dimer without the necessity of creating specially designed ligands to stabilize the dinuclear core.

Key words: lanthanum ion, catalysis, methanolysis, activated amide.

Résumé : On a observé que la méthanolyse de l'acétylimidazole (1) et du *N*-acétylimidazopepentamine-Co(III) (2) est fortement accéléré par la présence de La(OTf)₃. Un titrage potentiométrique d'une solution de La³⁺(OTf⁻)₃ permet d'établir que le pK_a du métal lié au CH₃OH est de 7,22. Opérant à divers pH, dans des conditions tamponnées, on a mesuré les cinétiques de méthanolyse des composés 1 et 2 en fonction d'une concentration croissante de La³⁺. L'analyse des données tant cinétiques que potentiométriques indique que l'espèce catalytiquement active est un dimère de La³⁺ comportant un pont par deux molécules de méthylates, (CH₃O)_nLa³⁺(CH₃O⁻)₂La³⁺(CH₃OH)_n. Les constantes de vitesse maximales pour les attaques des composés 1 et 2 sont respectivement de 1,50 × 10³ M⁻¹ s⁻¹ et 1,42 × 10² M⁻¹ s⁻¹ et les deux processus adhèrent au titrage d'un La³⁺(CH₃OH) pour générer la forme active. On explique les résultats en fonction d'un mécanisme dans lequel il se produit une dissociation transitoire d'une liaison La³⁺-OCH₃ du dimère de La³⁺ relié par un pont méthoxy qui permet d'exposer un nucléophile CH₃O⁻ et d'un La³⁺ qui peut agir comme acide de Lewis. Par opposition à la situation dans l'eau, les résultats obtenus avec le méthanol indiquent que le milieu stabilise grandement et solubilise le dimère actif sans avoir à créer des ligands appropriés pour stabiliser le coeur dinucléaire.

Mots clés : ion lanthane, catalyse, méthanolyse, amide activé.

Much recent attention was focussed on the remarkable acceleration provided by lanthanide cations (Ln^{X+}) for the hydrolysis of phosphate esters (1) and, to a lesser degree, amides and peptides (2). However mechanistic study of these Ln^{X+} -promoted hydrolyses is hindered by the fact that in water, formation of insoluble hydroxides and gels of poor definition is a problem, particularly under basic conditions. A few attempts have been made to stabilize the active forms

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¹Author to whom correspondence may be addressed. Telephone and Fax: (613) 533-2624. e-mail: rsbrown@chem.queensu.ca of $Ln^{X+}(OH^{-})_n$ by encapsulation into cyclodextrins (1*h*, 2*a*), macrocycles (1*g*), or micelles (1*d*) but most research has been done at neutral or acidic conditions which limits the catalytic ability of those ions. Only a few examples of Ln^{X+} catalysis of amide bond hydrolysis are known (2), probably due to the poorer M^{X+} -coordinating ability of the neutral > N-C=O moiety compared to that of negatively charged diand monophosphate esters. Indeed, the reported cases of strong M^{X+} -promoted hydrolysis of amide (peptide) substrates are limited to those having additional binding centers that promote preassociation of the metal (3).

Herein we focus on the La³⁺-catalyzed methanolysis of the simple activated amide, acetylimidazole, (1), and its ligand exchange inert Co³⁺-complex, *N*-acetylimidazolepentamine-Co(III), (AcImCo(NH₃)₅³⁺, (2)) (4). These were chosen because their aqueous hydrolyses are well understood, and because it has yet to be shown that the parent compound (1) is subject to metal ion catalysis in water. This combination allows us to investigate the role of electrostatic effects and the possibility of catalysis arising from the binding of the metal ion to the distal nitrogen of **1**. We report here that in methanol, homogeneous solutions can be obtained throughout the entire pH range surrounding ionization of $La^{3+}(CH_3OH)$. Moreover, through the use of buffered media to control the pH, which can be easily measured using a recently reported glass electrode technique (5), we can study the reaction kinetics in methanol as simply as in water without the annoying problems of metal–alkoxide precipitation. To the best of our knowledge, this is the first time such an approach has been used for kinetic investigations in methanol solutions.²



Our preliminary results show that the methanolysis rates³ of 1 and 2 markedly increase in the presence of lanthanum trifluoromethanesulphonate (La(OTf)₃), and this process is very sensitive to pH_{MeOH}. Pseudo-first-order rate constants, k_{obs} , obtained for the methanolysis of **1** and **2** (Fig. 1*a*, *b*) show strong catalysis by La(OTf)₃, with the effect being linearly proportional to [La(OTf)₃] at higher concentrations of metal salt but with significant curvature at concentrations lower than $\sim 2 \times 10^{-4}$ M. This indicates the involvement of second- or possibly higher order terms in [La(OTf)₃]. Unfortunately, direct analysis of all the experimental k_{obs} vs. $[La^{3+}]_t$ data does not provide us with reliable kinetic parameters, particularly in the case of 2 due to the high rate of the background reaction. However the fact that the k_{obs} vs. $[La(OTf)_3]_t$ dependencies look very similar for both substrates eliminates the possibility that the higher reaction order in $[La^{3+}]$ is due to complexation of a La^{3+} ion by the distal nitrogen of 1, and rather indicates the catalysis is due to a concentration dependent change in speciation of La^{3+} in methanol such as formation of active dimers. Dimeric structures were previously observed in methanol solutions of LaCl₃ using La¹³⁹ and Cl³⁵ NMR (6).

Analysis of the linear parts of the plots $([La^3]_t > 2 \times 10^{-4} \text{ M}, Fig. 1b)$ gives the second-order rate constants (k_2) which are then plotted vs. pH_{MeOH} (as in Fig. 2) to reveal similar profiles for both substrates with apparent kinetic pK_a s of 7–7.5. In a separate experiment (not shown), potentiometric titration of La(OTf)₃ (1.33 mmol) between pH_{MeOH} 6 and 9 shows ionization of one proton per metal ion with $pK_a^{MeOH} = 7.22$. In combination with the pH-rate profiles (Fig. 2) and k_{obs} vs. [La(OTf)₃] dependencies (Fig. 1a, b),

Fig. 1. (*a*) Plots of pseudo-first-order rate constants for the methanolysis of AcIm $(pH_{MeOH} = 6.7, \blacksquare, left axis))$ and AcImCo(NH₃)₅³⁺ (pH_{MeOH} = 7.6, $\mu = 0.2$ (NaClO₄) \bullet , right axis) as a function of concentration of [La(OTf)₃] at 25°C. (*b*) Plots of the pseudo-first-order rate constants for methanolysis of AcIm (pH_{MeOH} = 7.33 \blacksquare g, left axis) and AcImCo(NH₃)₅³⁺ (pH_{MeOH} = 7.6 \bullet , right axis) vs. [La(OTf)₃], at 25°C.



this indicates that the kinetically active species is a dimeric complex consisting of two solvated La^{3+} ions and two methoxide anions as shown in Scheme 1.

The equations for the equilibrium constants and the conservation of mass pertaining to the process in Scheme 1 provide the expression given in eq. [1] where k_0 is the

²*N*-methylimidazole ($pK_a^{MeOH} = 7.60$) and *N*-ethylmorpholine ($pK_a^{MeOH} = 8.28$) were used to buffer methanol solutions. Total buffer concentrations were varied between 10⁻³ M and 10⁻² M, and no buffer catalysis was observed. The [CH₃OH₂⁺] was determined using a combination (glass/calomel) electrode, calibrated with Fisher Certified standard aqueous buffers. Values of pH_{MeOH} were calculated by adding a correction constant (2.24) to the experimental meter reading. (R.G. Bates. *In* Determination of pH. Theory and practice. Wiley, New York. (1973); E. Bosch, private communication.)

³UV kinetics were monitored by observing the rate of loss of starting material at 240 nm, under pseudo-first-order conditions of excess metal ([amide] = $0.5 - 1.0 \times 10^{-4}$ M) at 25°C. Pseudo-first-order rate constants (k_{obs}) were evaluated by fitting the Abs. vs. time traces to a standard exponential model.

Scheme 1.



Fig. 2. pH–Second-order rate constant profiles for $La(OTf)_3$ -catalyzed methanolysis of AcIm (\blacksquare) and AcImCo(NH₃)₅³⁺ (\bullet). Curves are the result of NLLSQ fitting of experimental data to eq. [3].



spontaneous rate constant for methanolysis in the absence of metal ion.

[1]
$$k_{obs} = k_0 + (kK_a[H^+]^2/K_d)((1 + 8(K_a + [H^+]^2)K_d[La^{3+}]_t / [H^+]^2)^{0.5} - 1)^2 / (4(K_a + [H^+]^2))^2$$

The linear part of the plots of k_{obs} vs. $[La^{3+}]_t$, (Fig. 1*b*), used to calculate the second-order rate constant k_2 , describe the conditions where $\delta k_{obs} / \delta [La^{3+}]_t$ is constant (eq. [2]),

[2]
$$k_2 = \delta k_{obs} / \delta [La]_t = k \alpha \beta (1 - 1/(1 - \beta [La^{3+}]_t)^{0.5})$$

where $\alpha = K_a [H^+]^2 / (16K_d (K_d + [H^+]^2)^2)$, and $\beta = 8K_d (K_a + [H^+]^2) / [H^+]^2$.

To satisfy the condition that $\delta k_{obs}/\delta[La^{3+}]_t$ is constant, the range of $[La^{3+}]_t$ for analysis must be chosen such that $(1 -\beta [La^{3+}]_t)^{0.5}$ must be much bigger than 1, thereby providing an expression relating k_2 to K_a , the ionization constant of $La^{3+}(HOCH_3)$, eq. [3].

[3]
$$k_2 = kK_a/(2(K_a + [H^+]^2))$$

NLLSQ fitting of $pH-k_2$ data to eq. [3] gives the following parameters:

 $k = (1.50 \pm 0.1) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, $K_a = 10^{(-14.8 \pm 0.1)} \text{ M}^2$ (kinetic $pK_a = 7.40$) for **1**, and $k = (1.42 \pm 0.02) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, $K_a = 10^{(-14.30 \pm 0.02)} \text{ M}^2$ (kinetic $pK_a = 7.15$) for **2**. The lines through the data in Fig. 2 are those generated by the fits to eq. [3]. That the computed kinetic pK_a s are in good agreement with the pK_a^{MOH} obtained from the potentiometric titration lends strong credence to the idea that both processes relate to the ionization of metal-coordinated methanol. Further, the fact that only one inflection point is present in the potentiometric titration of both protons from a dimeric species. While the exact structure of this dimer is uncertain, most reasonable is one having two La³⁺ ions bridged by two methoxide anions as in **3**.

Similar double-bridge structures were suggested for $La_2Cl_6(CH_3OH)_{10}$ (6) (with bridging chloride ions) and a



La³⁺-peroxide complex (with bridging peroxide dianions) (7). Hurst et al. (8), from a study of the hydrolysis of an RNA model dimer promoted by La^{3+} in water, proposed a similar catalytically active metal dimer structure having two lanthanide ions bridged by five HO⁻.

Comparison of the second-order rate constants for La³⁺promoted methanolysis of **1** and **2** ((1.50 ± 0.1) × 10³ M⁻¹ s⁻¹ and (1.42 ± 0.02) × 10² M⁻¹ s⁻¹) clearly indicates that coordination of the (NH₃)₅Co³⁺ to the distal nitrogen does not provide any enhancement of the catalytic effect of La³⁺. Even though **2** has a much better leaving group than does **1** (p K_a = 10.0 for -ImCo(NH₃)₅³⁺ (4) vs. 14 for Im⁻ (9)), the rate of its La³⁺-promoted reaction is 10-fold slower. This is in contrast to our results for CH₃O⁻-catalyzed methanolysis of **2** where the second-order rate constant (k_{CH3O} = 4.69 × 10⁷ M⁻¹ s⁻¹) is four orders of magnitude higher than that for CH₃O⁻ attack on **1** (k_{CH3O} = 7.9 × 10³ M⁻¹ s⁻¹).⁴ Strong acceleration of methoxide attack on **2** relative to **1** can be explained by a combination of leaving group effects and electrostatic interaction between the positively charged substrate (**2**) and a negatively charged nucleophile. The latter

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result thus shows that the La³⁺-promoted methanolysis mechanism cannot involve attack of free methoxide ion since that should result in much higher rate constants for **2** than for **1**, contrary to what is observed. The slower reaction of the lanthanide reaction with **2** can be accommodated by a process involving the dimeric complex $(La^{3+}_2(CH_3O^-)_2(CH_3OH)_m)$ (**3**), having a total positive charge of +4, wherein electrostatic repulsion causes a decrease in the rate for the positively charged substrate **2** relative to neutral **1**.

It has been shown in the case of a structurally similar Co^{3+} -hydroxide dimeric complex, that bridging hydroxides do not possess nucleophilic activity, being at least 10^{10} times less active than the deprotonated oxo-bridged forms (10). For the present methoxy-bridged dimer (3) deprotonation is impossible so the only way to generate an active nucleophile within the dimeric complex requires temporary breakage of a lanthanum—methoxy bond. This creates a scissors-like structure where the La³⁺-bound CH₃O⁻ is delivered to the C=O carbon with the second La³⁺ functioning as a Lewis acid to stabilize the developing negative charge on the carbonyl oxygen as in **4**.



The above study indicates several beneficial features stemming from studying La³⁺-promoted methanolysis relative to La³⁺ in water. Methanolyses have not been studied as extensively as hydrolyses, undoubtedly due to the problems of controlling and measuring the pH which now have been overcome (5). By a combination of potentiometric titration and kinetic data, we have shown that catalytically active La^{3+} dimers (3) are formed above the pK_a of the metal bound CH₃OH. The fact that these dimers are far more soluble in methanol than the corresponding La³⁺-hydroxides are in aqueous solution simplifies kinetic studies and obviates the necessity of creating complex ligands to stabilize the dinuclear catalytically active core, as is the case in aqueous studies (1, 8, 10). The success observed here with the simple amides and the fact that the La^{3+} -dimer acts on the C=O unit suggests that La³⁺-catalyzed methanolyses of more biologically relevant amides, peptides, and oligonucleotides would be interesting, and we will report on these studies in due course.

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