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Reaction pathways for Zn(II)-catalyzed carboxylic acid esters hydrolysis

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Abstract

Reaction pathways have been investigated by quantum-mechanical procedures on gas phase models for the hydrolysis of methyl acetate catalyzed by a monohydroxo-Zn(II) complex formed by a phenanthroline-containing polyamine macrocycle. Based on consideration of energy barrier heights, the hydrolysis process is predicted to be bimolecular, consistently with kinetic data obtained for the hydrolysis of *p*-nitrophenyl acetate promoted by the modelled catalyst. Differences with respect to results of theoretical studies on the more extensively investigated hydrolysis processes catalyzed by the OH^- anion are discussed and appear to be mostly due to the presence of the metal centre close to the OH function in the system now investigated. The pervasive presence and path-controlling role of hydrogen bonds are also discussed.

Keywords: Ester hydrolysis; Macrocyclic ligand; Zn(II) complexes; DFT; Hydrolysis kinetics

1. Introduction

The hydrolysis of carboxylic acid esters is one of the most studied chemical reactions because of its importance both in chemistry and biochemistry [1]. The base-catalyzed hydrolysis of the majority of common esters occurs through the nucleophilic attack of the hydroxide ion at the carbonyl carbon. A variety of experimental investigations have been reported about the ester hydrolysis catalyzed by alkaline solutions [2] and by hydroxide functions activated by an adjacent Lewis acid, mostly the Zn(II) ion [3], while most of the theoretical work is limited to ester hydrolysis catalyzed by alkaline solutions [4].

As a matter of fact, a deprotonated zinc-bound water molecule is involved in many biological processes, such as those catalyzed by alkaline phosphatase, amino- and carboxypeptidase, carbonic anhydrase and P1-nuclease [5,6], where the catalytic role of zinc is generally ascribed to two main functions: (i) binding and/or activation of substrates, and (ii) deprotonation of Zn(II)-coordinated water molecules to give Zn–OH functions, which can act as nucleophiles in the hydrolytic mechanism.

Recently, we have reported the catalytic behaviour of the Zn(II) complexes of a series of polyaza-polyoxacycloalkanes (Scheme 1) towards carboxylic ester hydrolysis, evaluated via spectrophotometric measurements [7]. These ligands are able to form stable Zn(II) complexes, featured by unsaturated coordination spheres and, as a consequence, they can easily form stable hydroxo complexes. The rate constants of the hydrolysis processes, measured for these hydroxo species, reveal a connection between the hydrolytic activity and the pK_a of the coordinated water molecule, since the complexes with higher pK_a give higher rate constants. These findings are in good accord with the simple

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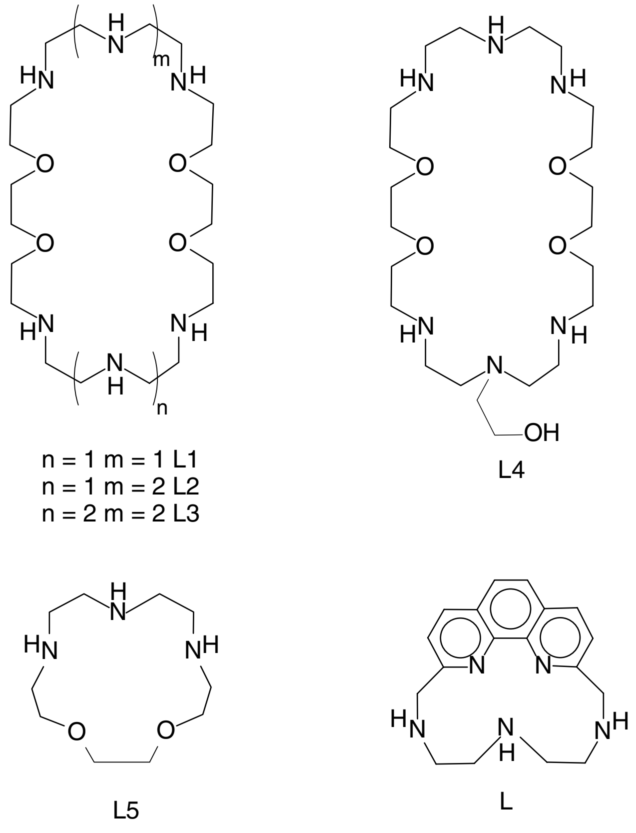

Scheme 1.

nucleophilic mechanism proposed by Kimura and coworkers [3b] for the hydrolysis of carboxylic esters.

In view of the fact that the catalytic sites of several zinc-enzymes (e.g., amino- and carboxypeptidase, carbonic anhydrase) consist of hydrophobic pockets, where the metal is bound to heteroaromatic nitrogens, we have recently synthesized a series of phenanthroline-containing polyamine macrocycles, such as **L** (Scheme 1) [8], suitable to form stable Zn(II) complexes in aqueous solution [9]. The rather high stability of the complexes has been mostly attributed to the arrangement of the heteroaromatic nitrogens, which provide a suitable binding site for the metal ion. At the same time, the rigidity of the phenanthroline unit poses restraints to the simultaneous involvement of all the aliphatic nitrogens in metal coordination, leaving in this way "free" binding sites at the Zn(II) ion. Water molecules, bound to complete the coordination sphere, easily deprotonate to give stable hydroxo species [9].

To the best of our knowledge, the reaction pathways for the nucleophilic attack carried out by the metal-activated OH function have been theoretically investigated for a limited number of systems [10]. Therefore, with the aim to achieve better insight into the reaction mechanism, we undertook the investigation of the catalytic activity of zinc complexes of the **L** ligand toward ester hydrolysis, performing spectrophotometric measurements for the *p*-nitrophenyl acetate hydrolysis reaction and quantum mechanical calculations on systems formed with the smaller methyl acetate molecule as substrate. We are confident, also in view of the results of previous studies on the alkaline hydrolysis of various carboxylic acid esters [4e], that the choice of the simpler substrate for computations should not impair the significance of the conclusions. On the other hand, the use of a non-idealized catalyst complex molecule in the calculations may reduce uncertainties in the interpretation of the results. Our interest has focused on the catalytic behaviour of the monohydroxo $[Zn\mathbf{L}(OH)]^+$ complex, viewed as a potential model system for processes typically performed by hydrolytic enzymes.

2. Results and discussion

2.1. Kinetics of p-nitrophenyl acetate (NA) hydrolysis

Potentiometric measurements showed that Zn(II) complexation by the **L** ligand occurs at acidic pH values to give the mononuclear complex $[Zn\mathbf{L}]^{2+}$ [9]. Deprotonation of a Zn(II)-coordinated molecule affords the monohydroxo complex $[Zn\mathbf{L}(OH)]^+$ at alkaline pHs ($pK_a = 9.39$). NA hydrolysis promoted by the Zn(II) complex with **L** was followed by the appearance of the *p*-nitrophenate anion band at 403 nm (298.1 K, $I = 0.1$ mol dm^{-3} NaCl) in the pH range 5.5–9.5. The complex gives significant enhancement of the hydrolysis rate only above pH 8, where the $[Zn\mathbf{L}(OH)]^+$ species is formed, and second order kinetics is followed. No hydrolytic effect is observed below 8, where the $[Zn\mathbf{L}(H_2O)]^{2+}$ complex or related $[Zn\mathbf{L}(H_2O)_n]^{2+}$ species prevail in solution. A plot of the measured k_{NA} values as a function of the concentration of the hydroxo-complex $[Zn\mathbf{L}(OH)]^+$ gave a straight line. These experimental observations clearly indicate that $[Zn\mathbf{L}(OH)]^+$ is the kinetically active species, i.e., the Zn(II)–OH function is indeed nucleophilic.

The $[Zn\mathbf{L}(OH)]^+$ cation is formed at most in ca. 50% percentage in the pH range of the kinetic measurements. Consequently, in order to compare its hydrolytic activity with that of other Zn(II) complexes, the pertaining second order rate constant k'_{NA} was determined from the maximum k_{NA} value, by using the following equation [7]:

$$
\begin{aligned}
v &= k_{NA}[\text{total Zn(II) complex}][\text{NA}] \\
&= k'_{NA}[Zn\mathbf{L}(OH)^+][\text{NA}]
\end{aligned}
$$

The k'_{NA} value so obtained, 2.16 $M^{-1s\ -1}$, is larger than those found for other monohydroxo complexes where the metal is coordinated by three secondary amine donors, such as $[Zn([12]aneN_3)(OH)]^+$ ($k'_{NA} = 0.041$) [3b]