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Focussed review

Development of the aza-crown ether metal complexes as artificial hydrolase

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ABSTRACT

Hydrolases play a crucial role in the biochemical process, which can catalyze the hydrolysis of various compounds like carboxylic esters, phosphoesters, amides, nucleic acids, peptides, and so on. The design of artificial hydrolases has attracted extensive attention due to their scientific significance and potential applications in the field of gene medicine and molecular biology. Numerous macrocyclic metal complexes have been used as artificial hydrolase in the catalytic hydrolysis of the organic substrate. Aza-crown ether for this comment is a special class of the macrocyclic ligand containing both the nitrogen atoms and oxygen atoms in the ring. The studies showed that the aza-crown complexes exhibited high activity of hydrolytic enzyme. However, the aza-crown ether metal complex as artificial hydrolase is still very limited because of its difficulty in synthesis. This review summarizes the development of the aza-crown ether metal complexes as the artificial hydrolase, including the synthesis and catalysis of the transition metal complexes and lanthanide metal complexes of aza-crown ethers. The purpose of this review is to highlight: (1) the relationship between the structure and hydrolytic activity of synthetic hydrolase; (2) the synergistic effect of metal sites and ligands in the course of organic compound hydrolysis; and (3) the design strategies of the aza-crown ethers as hydrolase.

1. Introduction

Hydrolases have been widely explored because of their high efficiency and selectivity, and biological specificity in biological systems [1,2]. However, their applications are limited by some significant factors such as the complexity of construction, instability out of body, and the high cost [3]. The design and syntheses of the artificial hydrolases have received considerable interests due to their potential applications in molecular biology and drug technology. The exploration of artificial hydrolase not only have important theoretical significance for understanding the mechanism of natural nucleases and designing the biomimetic catalysts with high-efficiency, but also have vast application prospect in many aspects such as molecular genetic tools, the degradation of toxic phosphate esters, the design of medicine and functional materials and so on [4–7].

Considerable amount of work has been done on the syntheses and applications of metal complexes as artificial hydrolase. The metal ions play important roles in the structural integrity of the artificial hydrolytic metalloenzymes [8]. It is generally accepted that there are three direct modes (inner sphere) and three indirect modes (outer sphere) of the activation that a metal ion can provide for accelerating the rate of phosphate ester hydrolysis (Scheme 1) [9,10]. The direct modes include Lewis acid activation (*a*, in which a phosphoryl oxygen atom coordinates to the metal), nucleophile activation (*b*, in which a nucleophile such as a hydroxide coordinates to the metal center), and leaving group activation (*c*, in which a leaving group oxygen atom coordinates to the metal center). The indirect modes of the activation including three modes, namely: metal-coordinated hydroxides acting as intramolecular general base catalyst (*d*), metal-coordinated water molecules acting as an intramolecular general acid catalyst (*e*), and electrostatic interaction between the metal and uncoordinated phosphate ester (*f*) may also provide some rate accelerations for the hydrolytic reaction [11]. Therefore, multitudinous transition metal complexes [12], such as Co^{2+} [13], Cu^{2+} [14,15], Zn^{2+} [16], and Ni^{2+} [17,18]complexes, have been synthesized and used as hydrolytic metalloenzyme models.

Among the designed artificial hydrolase, rare earth metal complexes have also attracted much attention because of their high ionic potential and coordination numbers, and extremely strong Lewis acidity. The studies show that many rare earth metal complexes were highly active at catalyzing the DNA substrate hydrolysis [19,20] and the results were also obtained by our study [21–23].

The structure of the ligand is also the important factor which needs to be considered for designing artificial hydrolase. Because of this, some organic compounds of specific structure, such as Schiff base, porphyrins, oxamido, guanidinium, crown ether, imidazole, aza-crown ethers, macrocyclic polyamine, and bipyridine compounds have been designed and used as the ligand of artificial hydrolase, and most of these ligands possess nitrogen atoms as the coordination atoms in the metal complexes. The studies indicated that the macrocyclic ligands exhibit some unique properties, such as stabilizing metal ions with appropriate radii, introducing side-arms of different functions, which can improve the catalytic

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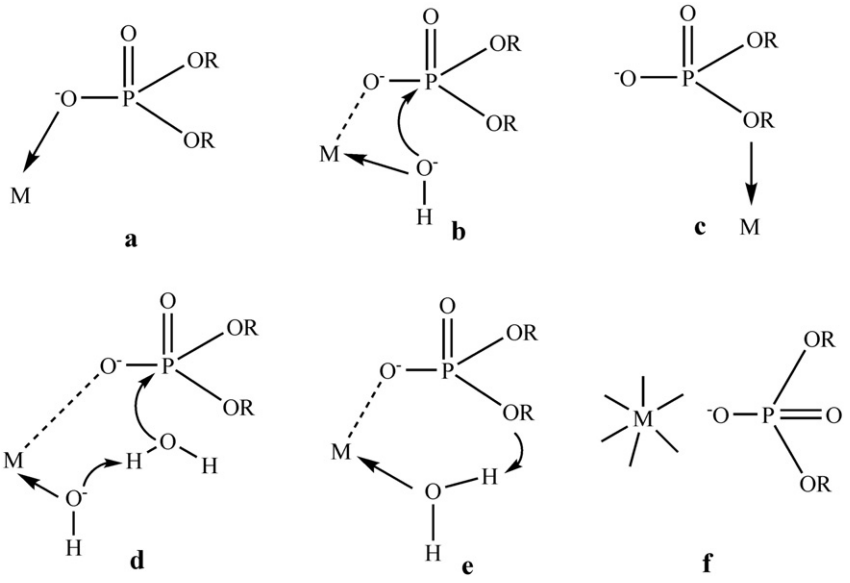

Scheme 1. The mechanisms for substrate activation by metal complexes.

activities of the artificial metalloenzyme. So a large number of macrocyclic metal complexes have been successfully used as the catalysts for the hydrolysis of the ester and as potential catalysts for the detoxification of anticholinesterase agents in chemical warfare [24–27]. Among these macrocyclic ligands, aza-crown ethers, a special class of crown ether which the oxygen atoms are partially replaced by nitrogen atoms in the ring, are known to be good complexing agents of transition-metal ions [28]. In comparison with crown ether, the nitrogen atoms of aza-crown ether are conducive to introducing various pendants such as N-alkylated groups, N-acidic groups and N-basic groups on the ring of ligands, and to form the stable metal complex [29].

The impressive progress in the fields of artificial hydrolases has stimulated the researches of aza-crown ether metal complexes. Among them, the design of the metal complexes, capable of catalyzing ester hydrolysis, is extremely important and has attracted increasing attention in view of their applications. In view of this, this paper reviews the syntheses and applications of the aza-crown ethers metal complexes as artificial hydrolase in catalyzing breakage of many kinds of substrates, such as DNA, proteins, phosphordiesters, 2-hydroxypropyl-4-nitrophenyl phosphate (HpPNP), adenylyl phosphoad-enine (ApA) and so on. Our purpose is to promote the development of aza-crown ethers metal complexes as the artificial hydrolase, which have vast development prospects in many aspects such as molecular genetic tools, the cleavage of toxic phosphate esters and the design of medical materials and anticancer drugs.

2. Syntheses and catalysis of the transition metal complexes of aza-crown ethers as the artificial hydrolase

Metal ions play important roles in the hydrolase based on the natural metalloenzyme, and the selection of metal ions is significant for the design of artificial hydrolase. Transition metal ions, such as Cu^{2+}, Zn^{2+} and Fe^{2+}, are often chosen as the catalytic center of artificial hydrolase on account of the fact that these metal ions were found abundantly in enzymes [30].

2.1. Syntheses and catalytic activity of aza-crown ether Cu^{2+} complexes as artificial hydrolase

Copper ion plays an important structural and catalytic role in numerous biological pathways [31]. Thus, copper complexes provide a potential alternative for artificial hydrolase. Some macrocyclic copper complexes have been employed as the proteolytic center of artificial metalloproteases with potential applicability in protein industry [32]. A number of di-nuclear and tri-nuclear metal complexes, used as hydrolase models catalyzing phosphoryl transfer reactions, have been reported. Here, some specific copper complexes containing the aza-crown ethers were summarized and discussed.

The cooperative catalysis of the functional groups for the complex is an interesting topic in the artificial hydrolase study. For this purpose, Sheng's group [33] synthesized novel ligands, aza-crown ether compounds **1**, **2** (Fig. 1), and their copper complexes Cu^{2+}-**1** and Cu^{2+}-**2** according to the previous literatures [34–37]. Two compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy, and ESI mass spectrometry. The structural characterizations of the compounds are containing two pendant aminoethyl or two pendant guanidinoethyl side arms on the ring of 1,7-dioxa-4,10- diazacyclododecane. These side arms in the complexes may be conducive to activating the substrate and stabilizing phosphorate-like transition states by electrostatic interaction, hydrogen bonding, and/or proton transfer.

Sheng et al. investigated the interactions between these synthesized compounds (or complexes) and calf thymus DNA and the catalytic functions of both the complexes and compounds acting as DNA hydrolytic cleavage agents. The results showed that the DNA binding ability of these complexes and compounds followed the order: Cu^{2+}-**2** > Cu^{2+}-**1** > **2** > **1**, and the catalytic activities of the complexes (Cu^{2+}-**2** and Cu^{2+}-**1**) were remarkably greater than those of the compounds (**1**, **2**), which was attributed to the synergistic effect between the Cu^{2+} cationic center and the proximal functional groups (diamino or bisguanidinium) in the complex [38]. The kinetic study also found that the catalytic efficiency of Cu^{2+}-**2** was remarkably greater than that of Cu^{2+}-**1**, which was ascribed to the binding and electrophilic effect of the guanidinium group of Cu^{2+}-**2** in the reaction [39,40]. The catalytic hydrolysis by applying adenylyl (3′-5′) phosphoadenine (ApA) as nucleic acid model proved that the DNA cleavage promoted by Cu^{2+}-**1** and Cu^{2+}-**2** is a hydrolytic pathway. Based on the experimental results, Sheng et al. proposed a "bifunctional cooperative catalytic hydrolysis" mechanism for the DNA hydrolytic cleavage (Scheme 2). This mechanism reveals that there was a possible equilibrium between the copper-bound water (A) and the copper-bound OH (B); the activated phosphorus atom was attacked by the nucleophilic species Cu-OH in the vicinity off, thus forming the trigonal bipyramidal phosphorous intermediate (steps B–C); one of the P–O bonds of the phosphodiester was cleaved (step C–D); a proton dissociated from the guanidinium