Chemical Papers 67 (4) 365–371 (2013)
DOI: 10.2478/s11696-012-0281-9

ORIGINAL PAPER

Preparation of a new metallomicelle catalyst for the hydrolysis of bis(4-nitrophenyl) phosphate

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Received 3 June 2012; Revised 31 August 2012; Accepted 18 September 2012

A new metallomicellar system containing cerium(III), a macrocylic polyamine ligand, and the non-ionic surfactant Brij35(polyoxyethylene(23) lauryl ether) was prepared and used as a catalyst in the hydrolysis of bis(4-nitrophenyl) phosphate (BNPP). Catalytic rate of the BNPP hydrolysis was measured kinetically using the UV-VIS spectrophotometric method. The results indicate that the metallomicellar system has relatively high stability and excellent catalytic function in the BNPP hydrolysis; also, the reaction rate of the BNPP catalytic hydrolysis increased by a factor of ca. 1×10^{10} compared to the BNPP spontaneous hydrolysis due to the catalytic effect of the active species and the local concentration effect of the micelles in the metallomicellar system. Experimental results also showed that the mono-hydroxy complex containing the macrocyclic polyamine ligand and cerium(III) is the real active species in the BNPP catalytic hydrolysis, and that the micelles provide a useful catalytic environment for the reaction. On basis of the research results, the reaction mechanism of BNPP catalytic hydrolysis has been proposed.
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Keywords: metallomicelles, construction, catalysis, hydrolysis, mechanism

Introduction

Organophosphorus compounds are ubiquitous in nature. To fully understand their behavior it is very important to establish mechanisms of their transformation in biological systems. Many researchers have worked hard to develop biomimetic models for the metalloenzyme with high efficiency and selectivity in order to achieve friendly environment and economically favorable processes (Rossi et al., 2002; Iranzo et al., 2003; Tonde et al., 2006; Ferreira et al., 2008). In this research field, hydrolysis of phosphodiester is of paramount importance in biological and industrial processes (Westheimer, 1987). In recent decades, some metal complexes, such as Mn(III), Cu(II), Zn(II), Ni(II), and lanthanide (Ln(III)) complexes (Luedtke & Schepartz, 2005; Lombardo et al., 2010; Rossi et al., 2002; Patel et al., 2011; Gunnlaugsson et al., 2002; Anbu et al., 2010), have been used as catalysts for the hydrolysis of phosphoric acid esters and as potential catalysts for the detoxification of anticholinesterase agents in chemical warfare. Among these model compounds, the lanthanide ion and its complexes have attracted much attention as catalysts for the hydrolysis of the phosphoric acid ester (Katada et al., 2008; Kuchma et al., 2010) because of their extremely strong Lewis acidity, higher oxidation state and charge density, coordination number, and high ligand exchange rates (Maldonado & Yatsimirsky, 2005; Jurek et al., 2000). These characteristics make the lanthanide ions well-suited to be catalytic centers in the development of artificial enzymes (Franklin, 2001). Cerium is unique among the lanthanides and it has been found to be particularly effective in promoting phosphodiester hydrolysis and DNA hydrolysis (Rammo et al., 1996; Komiyama et al., 1999; Tjioet et al., 2012).

In a many biomimetic models of hydrolytic metalloenzymes, macrocyclic polyamine metal complexes

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*Corresponding author, e-mail: xjq8686@163.com employed as catalysts in the hydrolysis of phosphoric acid esters have attracted considerable attention (Mancin & Tecilla, 2007; Franklin, 2001) due to the unique properties of macrocyclic polyamines; e.g. stabilizing metal ions with appropriate radii, introducing side-arms with different functional groups exhibiting different catalytic activities. Moving along these lines, in order to better mimic both the active sites and the hydrophobic micro-environment of natural enzymes, to elucidate the role of lanthanide ions and the mechanism of phosphate esters hydrolysis catalyzed by the polyamine macrocyclic complex, a new metallomicellar system formed by the cerium(III) ion and the macrocylic polyamine ligand in the presence of surfactant Brij35 micelles.

As it is well known, natural phosphodiesters inside the organism are very complex and stable, so it is very difficult to explore or elucidate the mechanism of natural phosphodiesters cleavage. To understand the cleavage mechanism of the P—O bond of natural phosphodiesters, bis(4-nitrophenyl) phosphate (BNPP), a much more reactive analogue of natural phosphodiester substrates, was used as the reactive substrate in this work.

Experiment

Instrumentation and materials

Melting points were determined on a Yanaco MP-500 micro-melting point apparatus (Yanaco-Mat, USA) and are uncorrected. Infrared spectra were recorded on a Nicolet-1705X IR spectrometer (Nicolet, USA). Mass spectra were obtained on a Finnigan MAT 4510 and a Finnigan LCQ-DECA spectrometers (Bruker, Germany). Elementary analysis was performed on a Carlo Erba 1106 elemental analyzer (Carlo Erba, Italy). pH of the solution was determined by a Radiometer PHM 26 pH meter fitted with G202C glass and K4122 calomel electrodes (Shanghai photics apparatus, China). Spectral analysis and kinetic studies were carried out on a GBC 916 UV-VIS spectrophotometer equipped with a thermostatic cell holder (GBC, Sweden).

Polyoxyethylene(23) lauryl ether (Brij35), 2-ethylhexyl sulfosuccinate sodium (AOT), hexadecyltrimethyl ammonium bromide (CTAB), and bis(p-nitrophenyl) phosphate (BNPP) were purchased from Sigma Chemicals, USA. All reagents, unless otherwise indicated, were of analytical grade. Water used for kinetic experiments was doubly distilled.

Synthesis of the ligand (L, $C_{16}H_{40}N_4O_2$)

5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene perchlorate (10.0 g, 21 mmol), synthesized according to literature (Douglas, 1983), was dissolved in pure methanol (50 mL) and then, $NaBH_4$ (1.9 g, 63 mmol) and NaOH (1.7 g, 42 mmol) were added alternately while stirring at 0 ℃. After the addition was completed, the solution was stirred mechanically for 2 h, and then heated to reflux for 8 min. After the solution was cooled to room temperature, pure water (100 mL) and NaOH (5.0 g, 125 mmol) were added and the solution was stirred vigorously until precipitation occurred. The solution was then filtered and the residue was washed with cold water and dried. The product (5.2 g), 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane dihydrate, was obtained as white crystals: yield 88.0 %, m.p. 148–149 ℃. IR (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3325 υ(NH), 3416 υ(OH). MS: $m/z = 284$ [M^+]. Composition found (calc.) (w_i/%): C 59.95 (60.00), H 12.46 (12.50), N 17.63 (17.50).

Methodology

Concentrated solution of Ce(III) nitrate, 5×10^{-2} mol dm^{-3}, was prepared in diluted HNO_3 solution of the desired pH, and concentrated solution of the ligand, 5×10^{-2} mol dm^{-3}, was freshly prepared in pure ethanol. The metallomicellar system was prepared by adding concentrated Ce(III) nitrate and the ligand solution to the surfactant Brij35 solution of the desired pH under stirring. Stock solutions of BNPP were prepared in water in the concentration of 5.0×10^{-3} mol dm^{-3}.

Kinetic studies were carried out on a GBC 916 UV-VIS spectrophotometer equipped with a thermostated cell holder. The mixture solution (3 cm^3) of Ce(III) nitrate and the ligand of the desired concentration were added in a cuvette (4 cm^3) with a temperature control system and the reactions were initiated by injecting 30 mm^3 of a 5.0×10^{-2} mol dm^{-3} stock solution of BNPP into the cuvette. The characteristic spectrum of p-nitrophenol (product of BNPP hydrolysis) was detected at the wavelength of 404 nm. Therefore, the kinetics of BNPP cleavage was monitored spectrophotometrically by the absorbance change of the p-nitrophenol at 404 nm. To obtain reliable trends of k_{obsd}, measurements were performed using the same cells and stock solutions in one day. BNPP catalytic hydrolysis is considered to be a first-order reaction as the concentration of the catalyst is at least ten times higher than that of BNPP and the observed first-order rate constants were calculated by the integral method from the kinetic curves followed by up 95 % or higher conversion of the substrate.

Results and discussion

Activity and preparation of the metallomicellar system

In preliminary experiments on the BNPP cleavage, either the stock solution of $Ce(NO_3)_3$ or the nitrogen heterocyclic ligand was employed as the catalyst in the pH range of 5.7–8.0. Experimental results show that the nitrogen heterocyclic ligand has no activity and the $Ce(NO_3)_3$ solution shows low stability and activity. Therefore, the metallomicellar systems used as the catalyst consisting of the cerium(III) ion, the ligand, and the surfactant (including anionic AOT, cationic CTAB, non-ionic Brij35) were tested in our work. The results indicate that the anionic and cationic metallomicellar systems display low stability and activity. Surprisingly, the non-ionic Brij35 metallomicellar system showed reproducible and remarkable catalytic activity and stability in the phosphodiester cleavage. The observed first-order rate constant (k_{obsd}) of the BNPP catalytic cleavage was 4.18×10^{-1} s^{-1} and it is ca. 1×10^{10} times the rate of the BNPP spontaneous hydrolysis at 25 °C ($k_{\text{obsd}} = 10^{-11}$ s^{-1} (Jones et al., 1983)).

To get more information on the reaction mechanism and the final products, hydrolytic rate of the *p*-nitrophenyl phosphate (NPP) catalyzed by the metallomicellar system was also examined in this work. The experimental results show that the hydrolytic rate of the *p*-nitrophenyl phosphate (NPP) is ten times higher than that of BNPP under the same conditions. This indicates that one mole of BNPP liberates two moles of *p*-nitrophenol in the BNPP catalytic hydrolysis.

Analysis of the active species as catalyst in the aqueous solution reaction system

Spectral analysis is an effective method for the analysis of the species from the given reactive process, and it was used in the analysis of the reaction intermediate (Li et al., 2005). According to the literature method, the characteristic spectra of ligand $C_{16}H_{40}N_4O_2$ (the reference solution is the solvent of the ligand) and those of the mixture solution of $Ce(NO_3)_3$ + ligand (the reference solution is $Ce(NO_3)_3$ solution with the same concentration) were recorded on a UV-VIS absorption spectrophotometer in the range of 190∼400 nm. The results are shown in Fig. 1.

Comparing the characteristic spectra of the ligand solution and the mixture solution in Fig. 1, it can be seen that the characteristic peak of the ligand at $\lambda = 220$ nm disappears and a new characteristic peak appears at $\lambda = 238$nm in the mixture solution. The signal of the ligand undergoes a very strong downfield shift to $\lambda = 238$nm due to the complexation with the cerium(III) ion. Apparently, this result indicates tight binding and the formation of a new complex, Ce_mL_n, between the cerium ion and the ligand. From curves B and C it can be seen that the characteristic spectra of complex Ce_mL_n do not change in the aqueous solution and in surfactant Brij35. This shows that the structure of complex Ce_mL_n is the same in water and also in surfactant Brij35.

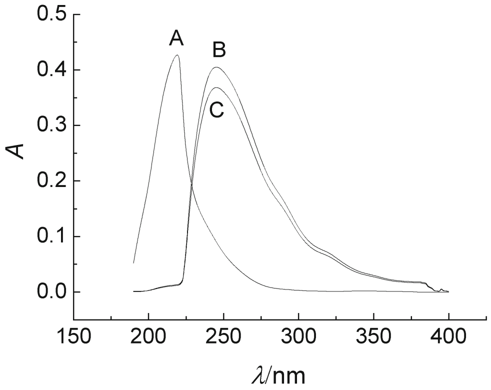

Fig. 1. Characteristic spectra of ligand (A), ligand + Ce(III) in aqueous solution (B), and ligand + Ce(III) in Brij35 solution (C): [Ce(III)] = [ligand] = 1.5×10^{-5} mol dm^{-3}, [Brij35] = 4.0×10^{-3} mol dm^{-3}, pH = 7.0, t = 25 °C.

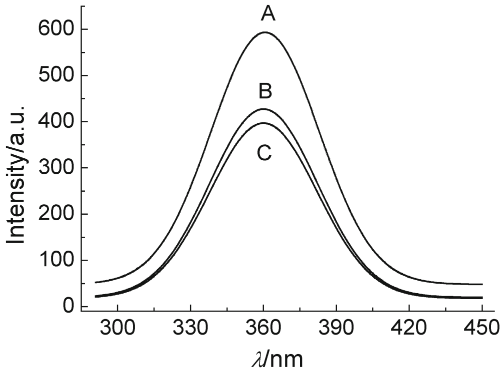

Fig. 2. Fluorescence spectra of three catalytic systems Ce(III) (A), Ce(III) + L (B), and Ce(III) + L + Brij35 (C): [Brij35] = 4.0×10^{-3} mol dm^{-3}, [Ce(III)] = [ligand] = 1.6×10^{-6} mol dm^{-3}, pH = 7.5, t = 25 °C.

Fluorescence spectroscopy can also be used to study the interaction between the metal ion and the ligand. When the binding interaction between the metal ion and the ligand occurs, the fluorescence intensity of the system is enhanced or weakened due to the energy transfer between the metal ion and the ligand, which decreases or increases complexes' fluorescence (Wang et al., 2008). In order to further demonstrate the interaction between metal ions and ligands, the fluorescence intensity of three systems was analyzed and the results are shown in Fig. 2. As it can be seen from the graph, the metal cerium ion fluorescence intensity strongly decreases with the addition of the ligand. The fluorescence intensity decrease shows that the metal ion and the ligand promote the binding interaction. The results also show that, in the surfactant as well as in the aqueous solution, the complex fluorescence is the same, indicating that the complex structure in the micellar solution did not change.

Kinetic version of the Job-plot is a convenient method for the determination of the chelating stoi-

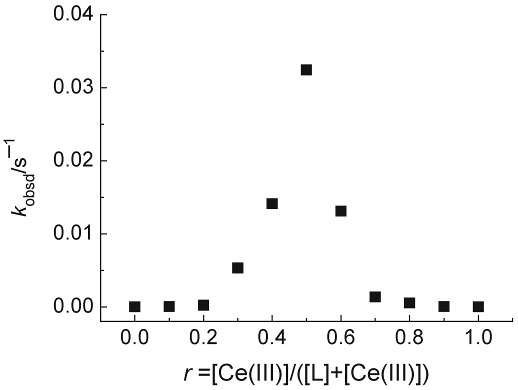

Fig. 3. Job-plot for BNPP hydrolysis catalyzed by the system Ce(III) + L: [Ce(III)] + [L] = 1×10^{-2} mol dm^{-3}, [Brij35] = 4.0×10^{-3} mol dm^{-3}, [BNPP] = 5.0×10^{-5} mol dm^{-3}, pH = 7.5, t = 25 °C.

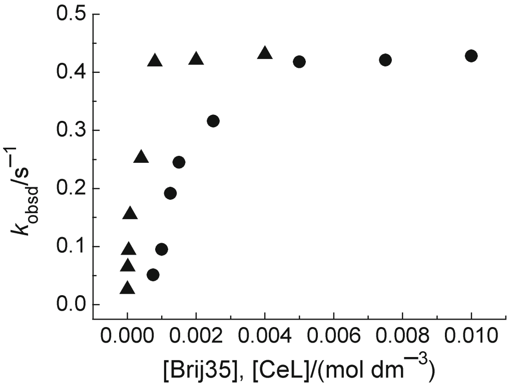

Fig. 4. Dependence of k_{obsd} on the concentration of the CeL complex (●) and surfactant Brij35 (▲): [BNPP] = 5×10^{-5} mol dm^{-3}, pH = 7.5, t = 25 °C: [CeL] = 5×10^{-3} mol dm^{-3} (▲), [Brij35] = 4×10^{-3} mol dm^{-3} (●).

chiometry of metal complexes; here, the observed rate constants (k_{obsd}) are plotted as a function of the mole fraction (r) of the ligand or metal ion to achieve constant total concentrations (Jiang et al., 2004). Thus, to confirm the stoichiometry of the active species in the hydrolysis of BNPP, the kinetic version of a Job plot was drawn and it is shown in Fig. 3. This figure indicates that the r value is 0.5 for the maximum rate constant obtained, which corresponds to the stoichiometry of the metal ion to ligand of 1 : 1 for the kinetically active species. This result also verifies the presence of the complex in the catalytic hydrolysis of BNPP. Due to the extremely strong Lewis acidity of the cerium(III) ion, complex CeL can coordinate the water molecule to form hydrated complex CeL(H_2O)$_2$ in the mixture solution of the cerium(III) ion and the ligand. Thus, complex CeL or hydrated complexes CeL(H_2O)OH$^-$ and CeL(H_2O)$_2$ can be applied as the active species, catalysts, in the mixture solution.

Effects of the non-ionic Brij35 micelles in BNPP catalytic hydrolysis

Micelles play a very important role in the enzyme catalytic process owing to the hydrophobic microenvironment (Taşcioğlu, 1996). The effects of non-ionic Brij35 micelles on the BNPP reaction rate constant, k_{obsd}/s^{-1}, of the BNPP hydrolysis in different catalytic systems were investigated and they are shown in Table 1.

Experimental results presented in Table 1 show that the catalytic systems of Brij35 micelles solution (critical micellar concentration (cmc) of 5.22×10^{-5} mol dm^{-3} (Xiang et al., 2002)) and L + Brij35 have no catalytic activity, and the catalytic system Ce(III) + Brij35 has low activity, indicating that the non-ionic Brij35 micelles have no catalytic activity. From Table 1 it can be also found that the rate of catalytic hydrolysis of BNPP is more than ten times higher in the system Ce(III) + L + Brij35 compared to the system Ce(III) + L. The Job-plot in Fig. 3 shows that the complex CeL can be considered as the active species in the mixture solution. One of the most important processes leading to micellar effects on the reactions is the solubilization of solutes in the micelle phase (Taşcioğlu, 1996). In the present work, water-solubility of both substrate (BNPP) and active species (CeL) are low, so that an addition of surfactants leads to better solubilization of BNPP and the catalyst in the Stern layer of micellar aggregates by the hydrophobic interaction increasing thus the local concentration and the collision frequency of the reagents and facilitating the BNPP catalytic hydrolysis. So, the catalytic active species is still the complex in the non-ionic Brij35 micelle, and the catalytic acceleration of BNPP hydrolysis is ascribed to the solubilization effect of the Brij35 micelle.

Dependence of k_{obsd} on the concentration of the CeL complex and the surfactant in the metallomicellar system

Effects of different concentrations of the CeL complex and those of the surfactant on k_{obsd} are shown

Table 1. BNPP hydrolysis reaction rate constant, k_{obsd}, using different catalytic systems

System	Brij35	L + Brij35	Ce(III) + Brij35	Ce(III) + L	Ce(III) + L + Brij35
k_{obsd}/s^{-1}	inactive	inactive	4.45×10^{-7}	2.64×10^{-2}	4.18×10^{-1}

[Ce(III)] = [L] = 5×10^{-3} mol dm^{-3}, [BNPP] = 5×10^{-5} mol dm^{-3}, [Brij35] = 4×10^{-3} mol dm^{-3}, pH = 7.5, t = 25 °C.

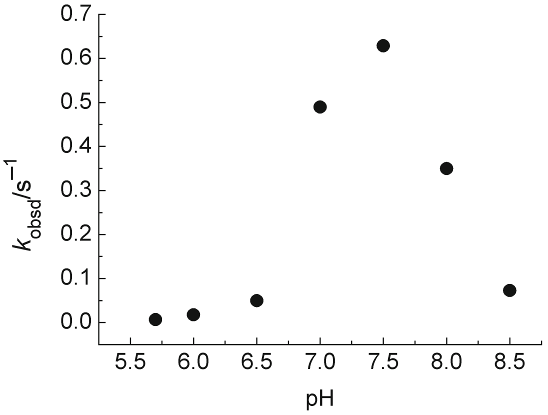

Fig. 5. pH–reaction rate constant profile for BNPP catalytic hydrolysis: [BNPP] = 5×10^{-5} mol dm^{-3}, [CeL] = 5×10^{-3} mol dm^{-3}, [Brij35] = 4×10^{-3} mol dm^{-3}, $t = 25\,^{\circ}$C.

in Fig. 4; catalytic reaction rate of BNPP increased abruptly with the increasing Brij35 concentration below the critical micellar concentration of Brij35 and then stabilized at or above the cmc value of Brij35. The results can be ascribed to the following reasons: when the concentration of Brij35 increases above its cmc value, the solubilization does not change significantly so that the catalytic hydrolytic reaction rate of BNPP remains almost constant.

From Fig. 4 it can also be found that the observed rate constants of the catalytic hydrolysis of BNPP increase with the increasing complex concentration below 5×10^{-3} mol dm^{-3}, stabilizing with the increasing complex concentration between 5×10^{-3} mol dm^{-3} and 1×10^{-2} mol dm^{-3}. This implies that the maximum catalytic efficiency of the catalytic system is achieved at complex concentrations higher than 5×10^{-3} mol dm^{-3}.

Acid effect and catalytic mechanism of BNPP hydrolysis in metallomicelles

The observed first-order rate constants of the hydrolytic reaction were obtained from experiments at various pH values, and the results are shown in the pH-rate profile in Fig. 5. From Fig. 5, the system's optimal catalytic efficiency in the reactive medium can be obtained at pH of ca. 7.5. This indicates that k_{obsd} of the catalytic hydrolysis of BNPP is correlated to the acidity of the reaction system, implying that the active species is neither the hydrated complex CeL$(H_2O)_2$ nor the CeL in the metallomicelles.

From the complex structure profile results that two H_2O molecules of the hydrated complex CeL$(H_2O)_2$ can dissociate in the metallomicelle solution, Fig. 6. Therefore, the complex exists in three different protonization states with the first and the second order acidic dissociation of H_2O molecules coordinated to the cerium(III) ion in the metallomicelle solution. The 2-hydroxy complex CeL$(OH^-)_2$ is easily formed in the exorbitant alkali solution, and the hydrated complex CeL$(H_2O)_2$ is easily formed in the acidic solution; however, neither environment is favorable for the formation and stabilization of the mono-hydroxy complex CeL$(H_2O)OH^-$. Therefore, it is apparent that the mono-hydroxy complex is most likely the real active species (Jiang et al., 2008) promoting the BNPP hydrolysis since the k_{obsd} maximum of the bell-shaped curve in Fig. 5 is achieved at ca. pH 7.5.

Experimental results indicate that the reaction pathway of the BNPP catalytic hydrolysis is different from that of its spontaneous hydrolysis because the oxygen atom of the BNPP molecule has strong affinity to the metallic ions. Phosphoryl oxygen of the BNPP molecule can bind to the metal ion of the complex when the BNPP is injected into the metallomicelle solution, which promotes the formation of a

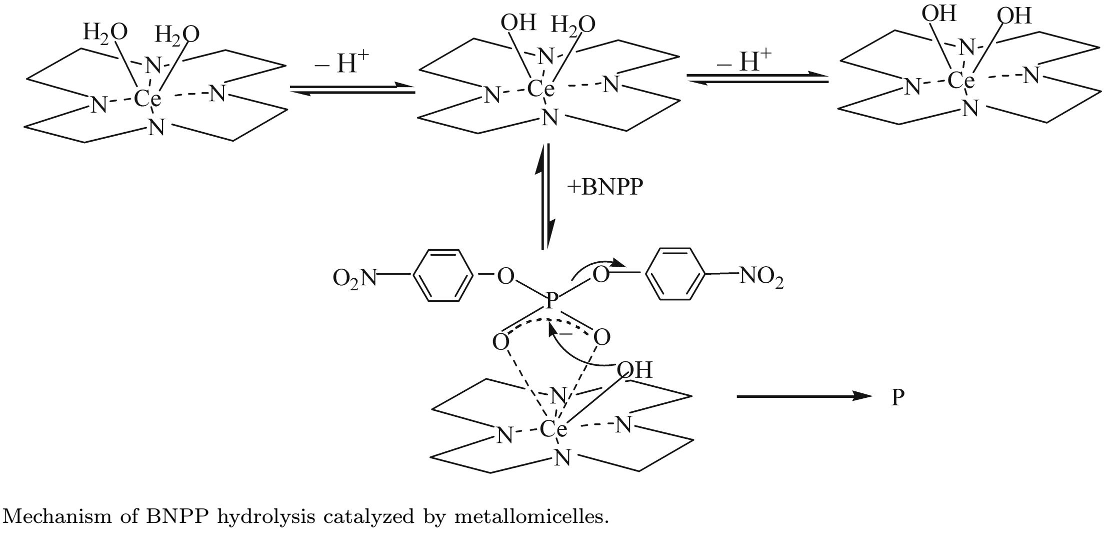

Fig. 6. Mechanism of BNPP hydrolysis catalyzed by metallomicelles.

Table 2. Changes of the BNPP catalytic hydrolysis rate with temperature

T/K	288.15	293.15	298.15	303.15	308.15	313.15	318.15	323.15
$k_{\mathrm{obsd}}/\mathrm{s}^{-1}$	0.299	0.365	0.418	0.519	0.603	0.389	0.169	0.129

[CeL] = 5×10^{-3} mol dm^{-3}, [BNPP] = 5×10^{-5} mol dm^{-3}, [Brij35] = 4×10^{-3} mol dm^{-3}, pH = 7.5.

reaction intermediate containing the BNPP molecule and the mono-hydroxy complex. In this process, there are two modes of activation provided by the Ce(III) ion accelerating the rate of the BNPP hydrolysis: the Lewis acid activation, where the negative charge of the substrate molecule is dispersed and the intermediate is stabilized by coordination of the phosphoryl oxygen to the Ce(III) ion; the Ce(III) hydroxide activation, where the hydroxyl coordinated to the Ce(III) ion is activated by the Ce(III) ion, promoting thus the intramolecular nucleophilic reaction. The rate of the BNPP hydrolysis is strongly accelerated by the synergistic effects of the Lewis acid and the metal hydroxide activation.

Temperature effect on the BNPP hydrolysis

The activity of enzymes is closely related to the temperature. Generally speaking, natural enzymes have each their own optimal temperature at which they exhibit excellent catalytic activity (Daniel, 1996). In order to investigate the effect of temperature on the catalytic activity of the present metallomicellar system, and kinetic measurements of the BNPP hydrolysis were performed in the temperature range from 288 K to 323 K; the results are shown in Table 2. The data in Table 2 indicate that the reaction rate of BNPP catalyzed by the metallomicellar system increases with the increasing temperature to the maximum rate achieved at 308 K and then decreases quickly when the temperature continues increasing. This is probably caused by the higher temperature of the reaction system compensating for the reaction energy barrier and providing more activated molecules increasing the collision frequency between the molecules, which is apparently favorable for the catalytic hydrolysis of BNPP. Meanwhile, a reaction rate decrease was observed at $T > 308$ K caused by the deactivation of the catalysts because of the complex structure changes at such relatively high temperature.

On basis of the linearized form of the Arrhenius equation, $-\ln k_{\mathrm{obsd}} = E_{\mathrm{a}}/(RT) - \ln A$, the observed activation energy $E_{\mathrm{a}} = 25.91$ kJ mol^{-1} was calculated for the temperature range of 15 ℃ – 35 ℃. $R = 8.314$ J K^{-1} mol^{-1} is the universal gas constant and A/s^{-1} the pre-exponential factor.

Conclusions

The effect of metallomicelles formed by Brij35, cerium(III) and nitrogen-hetercyclic lignad complex on the hydrolysis of BNPP was investigated kinetically. Some interesting results were obtained:

i) the metallomicellar system presented in this work is quite stable in the BNPP hydrolysis at neutral pH when compared with other catalytic systems containing lanthanide ions in the absence of micelle;

ii) the metallomicellar system containing the cerium(III) ion and the macrocyclic ligand shows remarkable catalytic activity in the BNPP hydrolysis under very mild conditions at pH 7.5 and 25 ℃, while the hydrolytic rate of BNPP was by almost 10^{10} fold higher than that of its spontaneous hydrolysis in water;

iii) catalytic efficiency of the metallomicellar system correlates with pH values and temperature, and the optimal catalytic efficiency is achieved in the reactive medium at pH of ca. 7.5 and temperature of ca. 35 ℃.

Acknowledgements. The authors gratefully acknowledge financial support from the Chinese National Natural Science Foundation (21173274), Natural Science Foundation Project of CQ CSTC (2009BB5052), Scientific Research Foundation for Returned Scholars, Ministry of Education of China, and the Start-up Fund of Chongqing University of Technology.

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