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Research Article

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Novel Zn(II) and Cu(II) complexes of the tetraaza-cyclododecane derivatives: Synthesis, characterization and catalytic activity

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ABSTRACT

A series of Zn(II) and Cu(II) complexes of the tetraaza-cyclododecane derivatives were synthesized and characterized with the synthetic routes designed in this work. Azole groups have been designed to work as auxiliary hydrolytically active units in the complexes. The comparison of the catalytic activity in the p-nitrophenyl picolinate (PNPP) hydrolysis was made between the Zn(II) and Cu(II) complexes bearing the tetraaza-cyclododecane derivatives with benzimidazole unit and imidazole unit. The complexes carrying cyclen-benzimidazole showed significant rate acceleration by about 13.6-223 fold larger than the hydrolytic rate catalyzed by Zn(II) cation, and about 43.8-718 times faster than the hydrolysis rate of PNPP without any catalyst. The catalytic activity of the complexes carrying cyclen-benzimidazole was also much stronger than that of cyclen-imidazole. The catalytic function of each group among the catalyst was discussed, and the synergetic effect between cation center and azole group was also proposed in this paper.

Keywords: Cyclen, azole groups, metal complex, catalytic activity, synergetic catalysis

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INTRODUCTION

Natural enzymes set a high standard for chemists to synthesis catalysts accompanying with high selectivity and simultaneous enormous acceleration of relative reactions, but this goal is very difficult to achieve. These enzymes often require metal cations for their activity [1-3], and many metal-ion-based model systems have been reported, generally featuring tridentate or tetradentate ligands with free coordination sites on the metal cation. The proposed general mechanism of the hydrolytic reaction promoted by these complexes is based on the Lewis acidic metal ion reducing the pKa of the coordinated water, thus providing a metal-bound hydroxide nucleophile at neutral pH and at the same time activating the substrate toward nucleophilic attack by charge neutralization [4-6].

As a well-known macrocyclic polyamine, 1,4,7,10-tetraazacyclododecane (cyclen), which was often used as chemical nuclease enzymes for DNA recognition and cleavage, and polymers contained cyclen were prepared for gene vectors [7,8]. Akkaya *et.al.* reoported that xanthene derivative conjugated imidazole group and cyclen could hydrolysze *p*-nitrophenylacetate (NA) efficiently [9]. Recently, it had been reported that Zn (II) cyclen complex was further improved to be used as a small-molecule carbon capture catalyst by mimic the property of carbonic anhydrase (CA) [10], which could expand the usage of cyclen complex from bioorganic & medicinal chemistry to

energy conservation and emission reduction aspect. Therefore, the research of interaction between cyclen complex and carbonate model attracted our attention very much.

It has been demonstrated that additional interactions in the active site influence the properties of the metal complexes and that the hydrolytic activity may increase by attachment of functional groups to a chelate ligand [11], such as a basic or nucleophilic auxiliary group [12] or an NH acidic group [13-19]. Herein, we presented a series of compounds **8a-8e** and **9a-9e**, which included cyclen, imidazole and benzimidazole as hydrolytic catalysts. This work has been focused on the syntheses and properties of these tetraaza-cyclododecane macrocyclic polyamine derivatives. The primary aim of the current studies was to investigate the catalytic hydrolysis abilities of these compounds, especially for these benzimidazole complexes, and the hydrolysis substrate was *p*-nitrophenyl picolinate (PNPP). The influence of the following parameters on the hydrolytic efficiency and the mechanism of the hydrolysis reaction were analyzed: (i) spacer type and length of metal complex; (ii) metal ion and its properties (synthesis of Zn (II) and Cu (II) complexes of different ligand); (iii) contrast assisting effects between different azole groups.

EXPERIMENTAL SECTION

Instrumentation and materials

All of reagents and solvents used were commercially available without further purification. UV spectra were recorded on a JASCO U-530 UV/vis spectrophotometer at 30 °C. MS spectra data were recorded on Finnigan MAT-4510 and VG Auto spectrometer 3000 mass spectrometer, respectively. ^{1}H NMR spectra were recorded on Brucker AV-300 MHz and chemical shifts are reported relative to internal Me_4Si. Elemental analyses were performed by using a Carlo-Elba 1106 elemental analytical instrument. Melting points were determined by using a micro-melting point apparatus without any corrections. $CHCl_3$ and THF were purified according to the standard method. Halide **2a** was purchased from Sigma and Acros. All aqueous solutions were prepared using doubly distilled water. The buffer solution of UV titration was Tris-base (pKa = 10.0, at 20 °C). The ionic strength of solution was adjusted to 0.1 with $NaNO_3$ ($NaNO_3$ was recystalized with deionized water). Halide **2b** and **2c** was synthesized as previously described [20]. 1,4,7-tris(tert-butyloxycarbony1)-1,4,7,10-tetraaza cyclododecane and its derivatives **3a-3c** were prepared according to literature [21].

Synthesis of the ligand

tri-tert-butyl-10-(4-(bromomethyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (3a)

The synthesis of **3a** is according to the reference [21]. Yield 62.0%, m.p. 71−73 °C. MS(ESI) *m/z*:627 [$(M+H)^+$, 100]. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.48−1.69 (s, 27H, OC (CH_3)$_3$), 2.65 (brs, 4H, NCH_2CH_2N), 3.25−3.39 (m, 8H, NCH_2CH_2N), 3.58 (s, 4H, NCH_2CH_2N), 3.72 (s, 2H, NCH_2Ph), 4.47 (s, 2H, BrCH_2Ph), 7.21−7.34 (q, J = 7.9 Hz, 4H, Ph-*H*).

Tri-tert-butyl-10-(3-(bromomethyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (3b)

The synthesis is according to the reference [21]. Yield 65.0%. m.p. 83−84 °C. MS(ESI) *m/z*:627 [$(M+H)^+$, 100]. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.43−1.47 (d, 27H, OC(CH_3)$_3$), 2.66 (br, 4, NCH_2CH_2N), 3.22 − 3.72 (m, 12H, NCH_2CH_2N), 3.82 (br, 2H, NCH_2Ph), 4.46 (s, 2H, BrCH_2Ph), 7.18 − 7.31 (m, 4H, Ph-*H*).

tri-tert-butyl-10-((6-(chloromethyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (3c)

The synthesis is according to the reference [21]. Yield 85.6%. m.p. 101−102 °C. MS(ESI) *m/z*: 634.19 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{30}H_{50}ClN_5O_6\cdot H_2O$: C 57.17, H 8.32, N 11.11; found: C 57.99, H 7.97, N 11.18. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44−1.50 (s, 27H, OC (CH_3)$_3$), 2.71−2.79 (br, 4, NCH_2CH_2N), 3.34−3.66 (m, 12H, NCH_2CH_2N), 3.84 (s, 2H, NCH_2Py), 4.65 (s, 2H, ClCH_2Py), 7.24−7.70 (m, 3H, Py-*H*).

Tri-tert-butyl-10-(4-((1H-benzo[d]imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5a)

Benzimidazole (**4b**) (0.38 g, 3.21 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.12 g, 5.00 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3a** (2.10 g, 3.20 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: Petroleum (60−90 °C): Ethyl Acetate = 1 : 4 (V/V)] to give the desired compound **5a** (1.99 g) as white amorphous solid. Yield 89.9%. m.p. 91−93. MS(ESI) *m/z*: 715.22 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{38}H_{56}N_6O_6\cdot 2H_2O$: C 62.61, H 8.30, N 11.53; found: C 62.95, H 7.96, N

11.37. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.41−1.47 (s, 27H, OC(C*H*$_3$)$_3$), 3.01 (brs, 4H, NC*H*$_2$C*H*$_2$N), 3.29−3.44 (m, 8H, NC*H*$_2$C*H*$_2$N), 3.56 (s, 4H, NC*H*$_2$C*H*$_2$N), 3.71 (s, 2H, NC*H*$_2$Ph), 5.33 (s, 2H, PhC*H*$_2$BIm), 7.11−7.24 (q, J = 8.8 Hz, 4H, Ph-*H*), 7.26−7.81 (m, 4H, BIm-*H*), 7.93(s, 1H, BIm-H).

tri-tert-butyl-10-(3-((1H-benzo[d]imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5b)

Benzimidazole (**4b**) (0.11 g, 0.93 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.03 g, 2.20 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3b** (0.60 g, 0.92 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: Petroleum (60−90 °C): Ethyl Acetate = 1 : 2 (V/V)] to give the desired compound **5d** (0.42 g) as white amorphous solid. Yield 66.4%. m.p. 86−87 °C. MS(ESI) *m/z*: 715.42 [(M+Na)$^+$, 100]. Anal. Calcd. for $C_{38}H_{56}N_6O_6$: C 65.87, H 8.15, N 12.13; found: C 65.38, H 8.05, N 11.65. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.42−1.48 (s, 27H, OC(C*H*$_3$)$_3$), 2.59 (br, 4, NC*H*$_2$C*H*$_2$N), 3.19−3.55 (m, 12H, NC*H*$_2$C*H*$_2$N), 3.70 (s, 2, NC*H*$_2$Ph), 5.35 (s, 2H, BImC*H*$_2$Ph), 7.03−7.31 (m, 7H, Bim-*H*, Ph-*H*), 7.81−7.84 (d, J = 8.3 Hz, 1H, BIm-*H*), 7.95 (s, 1H, BIm-*H*).

tri-tert-butyl-10-((6-((1H-benzo[d]imidazol-1-yl)methyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5c)

Benzimidazole (**4b**) (0.27 g, 2.29 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.07 g, 3.00 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3c** (1.50 g, 2.23 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: CH_2Cl_2 : CH_3OH = 40 : 1 (V/V)] to give the desired compound **5c** (0.90 g) as white amorphous solid. Yield 58.1%. m.p. 91−92 °C. MS(ESI) *m/z*: 716.23 [(M+H)$^+$, 100]. Anal. Calcd. for $C_{37}H_{55}N_7O_6\cdot H_2O$: C 62.42, H 13.77, N 8.07; found: 62.87, H 13.37, N 7.96. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.42−1.48 (s, 27H, OC(C*H*$_3$)$_3$), 2.66 (br, 4, NC*H*$_2$C*H*$_2$N), 3.32−3.58 (m, 12H, NC*H*$_2$C*H*$_2$N), 3.85 (s, 2H, NC*H*$_2$Py), 5.44 (s, 2H, BImC*H*$_2$Py), 6.79−6.82 (d, 1H, J = 7.7 Hz, Py *3*-*H*), 7.18−7.32 (m, 4H, BIm*H*), 7.51−7.56 (t, 1H, J = 7.2 Hz Py 4-*H*), 7.81−7.85 (d, J = 8.3 Hz, 1H, Py *5*-*H*), 8.05 (s, 1H, BIm-*H*).

tri-tert-butyl-10-(4-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5d)

Imidazole (**4a**) (0.22 g, 3.05 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.12 g, 5.00 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3a** (1.73 g, 2.64 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: Petroleum (60−90 °C): Ethyl Acetate = 2 : 1 (V/V)] to give the desired compound **5d** (1.61 g) as white amorphous solid. Yield 95.3%. m.p. 84−87 °C. MS(ESI) *m/z*: 643.35 [(M+H)$^+$, 100]. Anal. Calcd. for $C_{34}H_{54}N_6O_6\cdot 1.5H_2O$: C 60.96, H 8.58, N 12.55; found: C 60.84, H 8.27, N 12.38. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.43−1.48 (s, 27H, OC(C*H*$_3$)$_3$), 2.64 (br, 4H, NC*H*$_2$C*H*$_2$N), 3.27−3.58 (m, 12H, NC*H*$_2$C*H*$_2$N), 3.73 (s, 2H, NC*H*$_2$Ph), 5.09 (s, 2H, ImC*H*$_2$Ph), 6.87−6.88 (s, 1H, Im-*H*), 7.08−7.28 (m, 5H, Im-*H*, Ph-*H*), 7.53 (s, 1H, Im-*H*).

tri-tert-butyl-10-(3-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5e)

Imidazole (**4a**) (0.16 g, 2.35 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.07 g, 5.00 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3b** (1.50 g, 2.30 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: CH_2Cl_2: CH_3OH = 50 : 1 (V/V)] to give the desired compound **5e** (0.60 g) as white amorphous solid. Yield 37.0%. m.p. 77−78 °C. MS(ESI) *m/z*: 643.35 [(M+H)$^+$, 100]. Anal. Calcd. for $C_{34}H_{54}N_6O_6\cdot 1.5H_2O$: C 60.96, H 8.58, N 12.55; found: C 61.11, H 8.24, N 12.30. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.43−1.48 (s, 27H, OC(C*H*$_3$)$_3$), 2.64 (br, 4H, NC*H*$_2$C*H*$_2$N), 3.28−3.58 (m, 12H, NC*H*$_2$C*H*$_2$N), 3.75 (s, 2H, NC*H*$_2$Ph), 5.16 (s, 2H, triazoleC*H*$_2$Ph), 7.12−7.31 (q, J = 7.83Hz, 4H, Ph-*H*), 7.08−7.28 (m, 5H, Im-H, Ph-*H*), 7.53 (s, 1H, Im-*H*).

tri-tert-butyl-10-((6-((1H-imidazol-1-yl)methyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (5f)

Imidazole (**4a**) (0.17 g, 2.45 mmol) was dissolved in 50 mL anhydro-THF in 100 mL flask. NaH (0.10 g, 4.17 mmol) was added by steps with the ice bath. Then stirred under the room temperature for 1h, compound **3c** (1.50 g, 2.45 mmol) was added and stirred under reflux for another 48h. After the reaction was completed, the insoluble substance was removed by filtration, and subsequently the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [Eluent: CH_2Cl_2: CH_3OH = 40 : 1 (V/V)] to give the desired compound **5f** (0.60 g) as colourless oil. Yield 37.0%. MS(ESI) *m/z*: 644.44 [$(M+H)^+$, 100]. ^1H NMR ($CDCl_3$, 300MHz) δ: 1.42−1.48 (s, 27H, OC(CH_3)$_3$), 2.69 (br, 4, NCH_2CH_2N), 3.33−3.61 (m, 12H, NCH_2CH_2N), 3.84 (s, 2H, NCH_2Py), 5.20 (s, 2H, ImCH_2Py), 6.83−7.31 (m, 4H, Im-*H*, Py-*H*), 7.57−7.61 (br, 2H, Im-*H*).

1-(4-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole bromide (6a)

C To a solution of **5a** (1.75 g, 2.52 mmol) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C. The desired compound **6a** (1.77 g) was obtained as white soild. Yield 98.0%. m.p. 282−284 °C. MS(ESI) *m/z*: 716.24 [$(M+4HBr+H)^+$, 26]. Anal. Calcd. for $C_{23}H_{37}Br_5N_6\cdot 3H_2O$: C 32.46, H 5.09, N 9.87; f.ound: C 32.22, H 5.04, N 9.84. ^1H NMR (D_2O, 300MHz) δ: 2.78−3.11 (m, 16H, NCH_2CH_2N), 3.76 (s, 2H, NCH_2Ph), 5.66 (s, 2H, PhCH_2BIm), 7.29−7.32 (q, J = 8.3 Hz, 4H, Ph-*H*), 7.36−7.53 (m, 4H, Ph-*H*, BIm-*H*), 9.22 (s, 1H, BIm-*H*).

1-(3-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole bromide (6b)

To a solution of **5b** (1.30 g, 1.88 mmol) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C. The desired compound **6b** (1.23 g) was obtained as white soild. Yield 82.6%. m.p. 220−221 °C. MS(ESI) *m/z*: 393.36 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{23}H_{32}N_6\cdot 5HBr\cdot 2H_2O$: C 33.16, H 4.96, N 10.09; found: C 33.27, H 4.72, N 9.94. ^1H NMR ($CDCl_3$, 300MHz) δ: 2.67−3.06 (m, 16H, NCH_2CH_2N), 3.74 (s, 2H, NCH_2Ph), 5.69 (s, 2H, BImCH_2Ph), 7.21−7.59 (m, 8H, Bim-*H*, Ph-*H*)，7.77−7.81 (d, J = 7.0 Hz, 1H, BIm-*H*).

1-((6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole bromide (6c)

To a solution of **5c** (0.80 g, 1.15 mmoL) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C. The desired compound **6c** (0.70 g) was obtained as white soild. Yield 63.5%. m.p. 211−213 °C. MS(ESI) *m/z*: 394.26 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{22}H_{31}N_7\cdot 5HBr\cdot 3H_2O$: C 31.01, H 4.97, N 11.51; found: C 30.69, H 4.66, N 11.48. ^1H NMR ($CDCl_3$, 300MHz) δ: 2.56−3.04 (m, 16H, N*H*CH_2CH_2N), 3.79 (s, 2H, NCH_2Py), 5.83 (s, 2H, BImCH_2Py), 7.20−7.77 (m, 7H, Bim-*H*, Py-*H*), 9.31 (s, 1H, BIm-*H*).

1-(3-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane bromide (6d)

To a solution of **5d** (1.10 g, 1.71 mmol) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C. The desired compound **6d** (1.18 g) was obtained as white soild. Yield 92.2%. m.p. 260−264 °C. MS(ESI) *m/z*: 344.32 [$(M+H)^+$, 19]. Anal. Calcd. for $C_{19}H_{30}N_6\cdot 5HBr\cdot 2H_2O$: C 29.14, H 5.02, N 10.73; found: C 28.83, H 4.80, N 10.51. ^1H NMR (D_2O, 300MHz) δ: 2.76−3.12 (m, 16H, NCH_2CH_2N), 3.77 (s, 2H, NCH_2Ph), 5.35 (s, 2H, ImCH_2Ph), 7.27−7.40 (m, 6H, Im-*H*, Ph*H*), 8.69 (s, 7H, Im-*H*).

1-(4-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane bromide (6e)

To a solution of **5e** (1.50 g, 2.33 mmol) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C to afrord white soild 1.44 g. Yield 82.0%. m.p. 196−200 °C. MS(ESI) *m/z*: 343.33 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{19}H_{30}N_6\cdot 5HBr\cdot 2H_2O$: C 29.14, H 5.02, N 10.73; found: C 28.90, H 4.74, N10.55. ^1H NMR ($CDCl_3$, 300MHz) δ: 2.77−3.11 (m, 16H, NCH_2CH_2N), 3.77 (s, 2H, NCH_2Ph), 5.34 (s, 2H, ImCH_2Ph), 7.33−7.36 (m, 6H, Im-*H*, Ph-*H*), 8.68 (s, 1H, Im-*H*).

1-((6-((1H-imidazol-1-yl)methyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane bromide (6f)
To a solution of **5f** (0.65 g, 1.01 mmoL) and anhydroethanol 5 mL at 0 °C, aqueous hydrobromic acid (40 %, 15 mL) was added slowly and stirred overnight at room temperature. The resulting crude powder was collected by filtration, and then the material was dried *in vacuum* below 40 °C. The desired compound **6f** (0.64 g) was obtained as white soild. Yield 84.6%. m.p. 220−222 °C. MS(ESI) *m/z*: 344.35 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{18}H_{29}N_7 \cdot 6HBr$: C 26.08, H 4.26, N 11.83; found: C 26.04, H 4.49, N 11.69. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.85−3.11 (m, 16H, NCH_2CH_2N), 3.87 (s, 2H, NCH_2Py), 5.51 (s, 2H, ImCH_2Py), 7.18−7.20 (d, 1H, Py*3*-*H*), 7.36−7.38 (d, 1H, Py *5*-*H*), 7.43−7.44 (d, J = 7.9 Hz, 2H, Im-*H*), 7.81−7.86 (t, J = 7.6 Hz, 1H, Py 4-*H*), 8.79 (s, 1H, Im-*H*).

(1-(4-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole) (7a)
The hydrobromide **6a** (1.57 g, 2.40 mmol) was dissolved in water (20 mL), and the pH of the solution was adjusted to 12 with aqueous NaOH. The alkaline solution was extracted with CH_2Cl_2 (30 mL ×5), and then the solvent was dried by anhydro-Na_2SO_4 and evaporated. The desired compound 0.80 g was obtained as yellow oil. Yield 93%. MS(ESI) *m/z*: 393.26 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{23}H_{32}N_6 \cdot NaOH \cdot 2H_2O$: C 61.31, H 7.83, N 18.65; found: C 62.01, H 7.74, N 17.83. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.51−2.86 (m, 16H, N*H*CH_2CH_2N), 3.64 (s, H, NCH_2Ph), 3.79 (s, H, NCH_2Ph), 5.34−5.36 (d, J = 6.0 Hz, 2H, PhCH_2BIm), 7.12−7.81 (m, 8H, Ph-*H*, BIm-*H*), 7.96 (s, 1H, BIm-*H*).

(1-(3-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole) (7b)
The hydrobromide **6b** (1.23 g, 1.54 mmol) was dissolved in water (20 mL), and the pH of the solution was adjusted to 12 with aqueous NaOH. The alkaline solution was extracted with CH_2Cl_2 (30 mL ×5), and then the solvent was dried by anhydro-Na_2SO_4 and evaporated. The desired compound 0.57 g was obtained as yellow oil. Yield 94.1%. MS(ESI) *m/z*: 393 [$(M+H)^+$, 52]. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.17−3.49 (m, 16H, N*H*CH_2CH_2N), 3.67−3.72 (d, 2H, NCH_2Ph), 5.39−5.55 (m, 2H, BImCH_2Ph), 7.19−7.37 (m, 7H, BIm-*H*, Ph-*H*), 8.19−8.21 (q, J = 8.6 Hz, 4H, BIm-*H*).

(1-((6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole) (7c)
The hydrobromide **6c** (0.80 g，1.00 mmol) was dissolved in water (20 mL), and the pH of the solution was adjusted to 12 with aqueous NaOH. The alkaline solution was extracted with CH_2Cl_2 (30 mL ×5), and then the solvent was dried by anhydro-Na_2SO_4 and evaporated. The desired compound 0.31g was obtained as yellow oil. Yield 78.7%. MS(ESI) *m/z*: 394 [$(M+H)^+$, 36]. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.42−3.06 (m, 16H, N*H*CH_2CH_2N), 3.91−3.93 (d, J = 4.83Hz, 2H, NCH_2Py), 5.51−5.53 (d, J = 5.45Hz, 2H, BImCH_2Py), 7.03−7.05 (d, J = 7.7 Hz, 1H, Py *3*-*H*), 7.23−7.30 (m, 4H, BIm*H*), 7.63−7.65 (t, J = 7.7 Hz, 1H, Py 4-*H*), 7.79−7.82 (d, J = 6.5 Hz, 1H, Py *5*-*H*), 8.09 (s, 1H, BIm-*H*).

Synthesis of the metal complexes 8a-8e and 9a-9e
The obtained acid free ligand and equal or double molar weight of $Zn(ClO_4)_2 \cdot 6H_2O$ or $Cu(ClO_4)_2 \cdot 6H_2O$ were stirred at room temperature for 24 h. After that, the solids were filtered off, washed with cooled EtOH, the residue was crystallized from H_2O/EtOH to obtained crystals. The product was dried in vacuum.

1-(4-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole Zn (Ⅱ) complex (8a)
An solution of EtOH (10 mL), the obtained acid free ligand **7a** (0.36 g, 0.99 mmoL) and $Zn(ClO_4)_2 \cdot 6H_2O$ (0.37 g, 0.99 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. White solid (yield 68.3%). m.p. > 290 °C (dec.). MS(ESI) *m/z*: 496.14 [$(M+K^+-2H^+-2ClO_4^-)^+$, 57]. Anal. Calcd. for $C_{23}H_{33}Cl_3N_6O_{12}Zn$: C 36.48, H 4.39, N 11.10; found: C 36.70, H 4.81, N 10.94. ^{1}H NMR (D_2O, 300MHz) δ: 2.66−3.07 (m, 16H, NCH_2CH_2N), 3.74 (s, 2H, NCH_2Ph), 5.65 (s, 2H, PhCH_2BIm), 7.33−7.81 (m, 8H, Ph-*H*, BIm-*H*), 8.81(s, 1H, BIm-*H*).

1-(4-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole Cu (Ⅱ) complex (8b)
An solution of EtOH (10 mL), the obtained acid free ligand **7a** (0.34 g, 0.97 mmoL) and $Cu(ClO_4)_2 \cdot 6H_2O$ (0.37 g, 0.99 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. Blue solid (yield 65.8%). m.p. 231−233 °C. MS(ESI) *m/z*: 455 [$(M-H^+-2ClO_4^-)^+$, 32]. Anal. Calcd. for $C_{23}H_{32}Cl_2N_6O_8Cu \cdot 4H_2O$: C 38.00, N 11.56, H 5.55; found: C 38.02, N 11.00, H 4.92.

1-(3-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)-1H-benzo[d]imidazole Cu (Ⅱ) complex (8c)
An solution of EtOH (10 mL), the obtained acid free ligand **7b** (0.28 g, 0.68 mmoL) and $Cu(ClO_4)_2·6H_2O$ (0.25 g, 0.69 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. Blue solid (yield 62.4%). m.p. 239−241 °C. MS(ESI) *m/z*: 573 $[(M+H_2O\text{-}ClO_4^-)^+$, 52]. Anal. Calcd. for $C_{23}H_{32}Cl_2N_6O_8Cu·2.5H_2O$: C 39.46, N 12.01, H 5.33; found: C 39.97, N 11.58, H 5.02.

1-((6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole Zn (Ⅱ) complex (8d)
An solution of EtOH (10 mL), the obtained acid free ligand **7c** (0.17 g, 0.45 mmoL) and $Zn(ClO_4)_2·6H_2O$ (0.17 g, 0.45 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. White solid (yield 58.0%). m.p. 226−229 °C. MS(ESI) *m/z*: 560 $[(M\text{-}ClO_4^-)^+$, 27]. Anal. Calcd. for $C_{22}H_{32}Cl_3N_7O_{12}Zn·C_2H_5OH$: C 35.84, N 12.19, H 4.76; found: C 35.84, N 12.22, H 4.69. ^{1}H NMR (D_2O, 300MHz) δ: 2.59−3.04 (m, 16H, NCH_2CH_2N), 4.19 (s, 2H, NCH_2Py), 6.37−7.88 (m, 6H, Bim-*H*, Py-*H*).

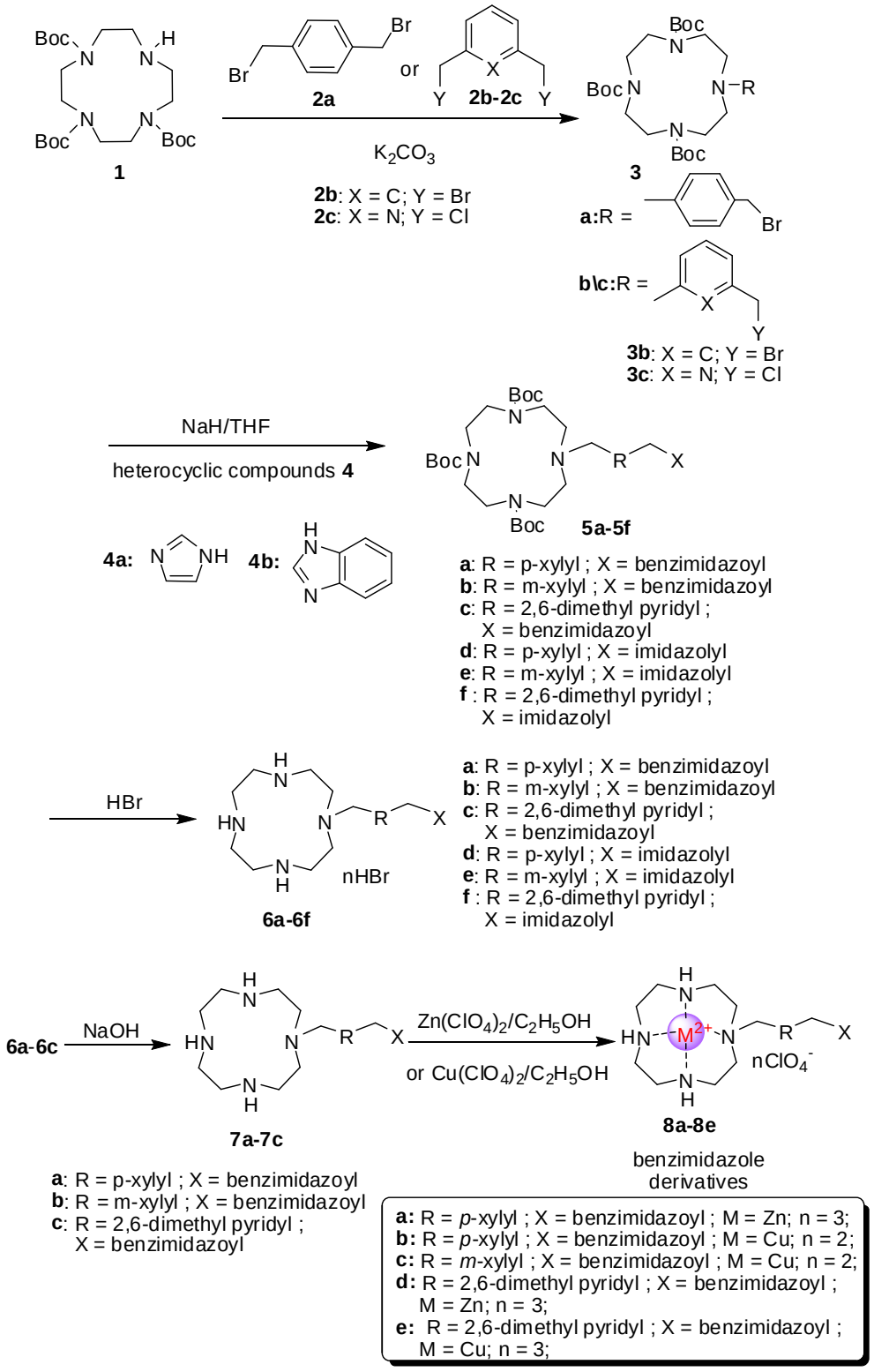
1-((6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole Cu (Ⅱ) complex (8e)
An solution of EtOH (10 mL), the obtained acid free ligand **7c** (0.17 g, 0.45 mmoL) and $Cu(ClO_4)_2·6H_2O$ (0.17 g, 0.45 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. Blue solid (yield 37.9%). m.p. 251−255 °C. MS(ESI) *m/z*: 558 $[(M\text{-}ClO_4^-)^+$, 22]. Anal. Calcd. for $C_{22}H_{32}Cl_3N_7O_{12}Cu·C_2H_5OH$: C 35.92, N 12.22, H 4.77; found: C 35.89, N 12.60, H 4.67.

1-(4-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane Zn (Ⅱ) complex (9a)
An solution of EtOH (10 mL), the obtained acid free ligand (0.34 g, 0.99 mmoL) and $Zn(ClO_4)_2·6H_2O$ (0.37 g, 1.0 mmo1) was stirred at room temperature for 24 h. After that, the solids were filtered off, washed with cool EtOH, the residue was crystallized from H_2O/EtOH to obtained colorless crystals. The product was dried *in vacuum*. White solid (yield 68.3%). m.p. > 290 °C (dec.). MS(ESI) *m/z*: 457 $[(M+OH^-\text{-Im-}HClO_4^-)^+$, 8]. Anal. Calcd. for $C_{19}H_{30}Cl_2N_6O_8Zn·H_2O$: C 36.52, N 13.35, H 5.16; found: C 36.68, N 13.45, H 4.98. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.79−4.50 (m, 16H, NCH_2CH_2N), 4.75 (s, 2H, NCH_2Ph), 5.36 (s, 2H, ImCH_2Ph), 6.92−8.66 (m, 7H, Im-*H*, Ph-*H*).

1-(4-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane Cu (Ⅱ) complex (9b)
An solution of EtOH (10 mL), the obtained acid free ligand (0.34 g, 0.99 mmoL) and $Cu(ClO_4)_2·6H_2O$ (0.36 g, 1.0 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. Blue solid (yield 65.8%). m.p. 218−221 °C. MS(ESI) *m/z*: 621 $[(M+H_2O)^+$, 29]. Anal. Calcd. for $C_{19}H_{30}Cl_2N_6O_8Cu·0.5H_2O·3.5C_2H_5OH$: C 35.83, N 11.16, H 5.83; found: C 34.94, N 11.78, H 5.06.

1-(3-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane Zn (Ⅱ) complex (9c)
An solution of EtOH (10 mL), the obtained acid free ligand (0.25 g, 0.73 mmoL) and $Zn(ClO_4)_2·6H_2O$ (0.27 g, 0.73 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. White solid (yield 75.0%). m.p. 221−223 °C. MS(ESI) *m/z*: 627 $[(M+Na)^+$, 100]. Anal. Calcd. for $C_{19}H_{30}Cl_2N_6O_8Zn·H_2O$: C 36.52, N 13.45, H 5.16; found: C 36.70, N 12.74, H 5.19. ^{1}H NMR (D_2O, 300MHz) δ: 2.59−3.11 (m, 16H, NCH_2CH_2N), 3.80−3.94 (br, 2H, NCH_2Ph), 5.39 (s, 2H, ImCH_2Ph), 7.28−8.71 (m, 7H, Im-*H*, Ph-*H*).

1-(3-((1H-imidazol-1-yl)methyl)benzyl)-1,4,7,10-tetraazacyclododecane Cu (Ⅱ) complex (9d)
An solution of EtOH (10 mL), the obtained acid free ligand (0.25 g, 0.73 mmoL) and $Cu(ClO_4)_2·6H_2O$ (0.27 g, 0.73 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. Blue solid (yield 54.5%). m.p. 210−212 °C. MS(ESI) *m/z*: 404 $[(M\text{-}H^+\text{-}2ClO_4^-)^+$, 70]. Anal. Calcd. for $C_{19}H_{30}Cl_2N_6O_8Cu·3H_2O·0.5C_2H_5OH$: C 35.22, N 12.32, H 5.76; found: C 35.17, N 11.77, H 5.11.



Scheme 1 The synthetic routes of benzimidazolyl compounds 8a-8e

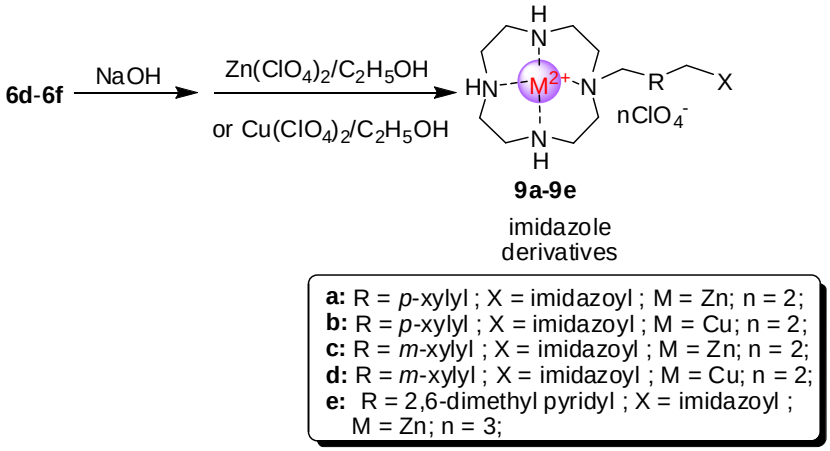
1-((6-((1H-imidazol-1-yl)methyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecan-e Zn (II) complex (9e)
An solution of EtOH (10 mL), the obtained acid free ligand (0.28 g, 0.82 mmoL) and $Zn(ClO_4)_2 \cdot 6H_2O$ (0.31 g, 0.83 mmo1) was stirred at room temperature for 24 h. After that, the process followed the procedure described above. White solid (yield 56.7%). m.p. 241−244 °C. MS(ESI) *m/z*: 406 [$(M\text{-}H^+\text{-}2ClO_4^-)^+$, 18], 520 [$(M\text{-}Im\text{-}H_2O)^+$, 23]. Anal. Calcd. for $C_{18}H_{29}Cl_2N_7O_8Zn \cdot 0.5HClO_4 \cdot H_2O$: C 31.98, N 14.50, H 4.70; found: C 32.28, N 14.29, H 4.56. ^{1}H NMR (D_2O, 300MHz) δ: 2.71−3.09 (m, 16H, NC*H*$_2$C*H*$_2$N), 4.15 (s, 2H, NC*H*$_2$Ph), 5.44 (s, 2H, ImC*H*$_2$Ph), 6.92−6.95 (d, J = 7.8 Hz, 1H, Py 3-*H*), 7.09 (s, 1H, Im-*H*), 7.15 (s, 1H, Im-*H*), 7.44−7.47 (d, J = 7.7 Hz, 1H, Py 5-*H*), 7.93−7.98 (d, J = 8.3 Hz,1H, Py 4-*H*).

Study of the kinetics of the hydrolysis reaction
Absorption spectrometry was performed using JASCO U-530 UV/vis spectrophotometer at 30 ± 0.1 °C. Kinetics of the reactions was carried out in aqueous buffer solutions with different pH and temperatures and calculated by following the increase in the absorption at 400 nm due to the release of the *p*-nitrophenolate ion. The kinetic data were collected under pseudo-first-order conditions (excess of the metal complex). The initial rate of 4-nitrophenolate release was calculated and the results were the average of three independent measurements. Hence, K_{obs1} was determined by the regression equation with $\ln(A_\infty\text{-}A_t)$ and time. In this equation the A_∞ or A represents the absorbance values of 4-nitrophenolate at equilibrium state and any time in the reaction respectively.

RESULTS AND DISCUSSION

The general synthesis procedures of the metal complexes
All target complexes were synthesized following the routes described in **Scheme 1** and **Scheme 2**. The target derivatives were synthesized from 3Boc-cyclen. The reaction mixture of protected cyclen with different halogenides was purified by column chromatography with different eluent. The azoles, such as **4a-4d**, were reacted with **3a-3b** on the conditions of NaH/THF to get the crude products **5a-5f**, and the yields after being processed ranged from 37.0 % to 95.3 %. Then compounds **5a-5f** were stirred with saturated HBr/C_2H_5OH, and their corresponding hydrobromates **6a-6f** were filtrated and collected. At last these compounds were dried in vacuum below 40 °C.

The hydrobromide was dissolved in water (10 mL), and the pH of the solution was adjusted to 12 with aqueous NaOH. The alkaline solution was extracted with CH_2Cl_2 (30 mL×5), then dried by anhydro-Na_2SO_4 and evaporated. Solution of EtOH (10 mL), the obtained acid free ligand and equal molar weight of perchlorate were mixed and stirred at room temperature for 24 h. After that, the solid was filtered off, washed with cool EtOH, the residue was crystallized from H_2O/EtOH to obtained crystals, and the product was dried in vacuum.



Scheme 2 The synthetic routes of imidazolyl compounds 9a-9e

Comparison of the catalytic activity of different metal complexes in PNPP catalytic hydrolysis
It is well known that the enzymatic catalytic activity and selectivity are correlative to the enzymatic structure. The mimic hydrolase used in this study exhibited similar effects as that of the natural hydrolase in PNPP catalytic hydrolysis. The complexes **8a-8b** linked with *p*-xylyl and other compounds **8c-8e** conjugated with different linkers

were all tested as hydrolytic catalysts at neutral pH 7.0. Among all the benzimidaole complexes **8a**-**8e**, the **8d** showed the best catalytic efficiency at pH 7.0 (**Table 1**). In a word, the K_{obs1} values of PNPP hydrolysis accelerated by **8a**-**8e** were 718~43.8 times larger than the hydrolysis rate without catalyst, and 223~13.6 times larger than K_{obs1} value of Zn (II) cation hydrolysis. The maximum hydrolytic rate of complex **9d** was 8.7×10^{-4} s^{-1} at pH 7.0. Moreover, data in **Table 2** showed that the K_{obs1} values of target imidazolyl compounds **9a**-**9e** were ranging from 3.9×10^{-4} s^{-1} to 26.0×10^{-4} s^{-1} at pH 7.0, and the K_{obs1} values were about 77-11.5 times larger than that of Zn (II) hydrolysis and 247.6~37.1 fold of the uncatalyzed reaction under the same conditions.

The changing tendency of K_{obs1} values of imidazolyl compound **9a**-**9e** was as the same as the variety of K_{obs1} values of **8a**-**8e** described above. This may be ascribed to the following reason: the closer of cyclen and azole, the better efficiency of the target complex hydrolyzing PNPP. As for the compound **8d**, the best catalyst of all, the 2,6-dimethyl pyridyl linker was the key factor in favor of catalytic function of hydrolysis. This may be due to the fact that the nitrogen atom in pyridyl could reduce the interaction between Zn (II) center and azole arm, and they could produce marked effects as synergetic catalyst on PNPP hydrolyzing. Compound **9d** with Cu (II) center exhibited the highest efficiency among all these imidazole complexes, and as we know, few Cu (II) cyclen complexes promoting the hydrolysis of carboxyester were reported, except that some Cu[9]aneN_3 complexes showing catalytic efficiency on phosphate ester hydrolysis [22]. Due to the fact that Cu (II) was a weak Lewis acidic metal ion, and the pKa of water bound to Cu (II)-cyclen complex was about 8.34 and was hard to form functional Cu (II)-OH center [22]. So that the catalysis mechanisms of Cu (II) complexes were quit different from that of Zn (II) compounds. Finally, these results showed that benzimidazolyl compounds **8a**-**8e** generally had higher K_{obs1} values than that of imidazolyl compounds **9a**-**9e**. The relative stronger π-π stack effect between benzimidazole arm and 4-nitrophenolate than imidazole was the major reason for the difference observed in these azole compounds.

Table. 1 The max-value of pseudo-frist-order constants for hydrolysis of PNPP by benzimidazole complexes in aqueous solution and the corresponding pH

Entry	Complex	$K_{obs1}/10^{-4}$ (s^{-1})	pH
1	**8a**	4.6	7.0
2	**8b**	54.3	7.0
3	**8c**	28.1	7.0
4	**8d**	75.4	7.0
5	**8e**	5.3	7.0
6	**Zn^{2+}**	0.338 [24]	7.0
7	**no**	0.105 [24]	7.0
8	**benzimidazle**	Not detected	7.0

Conditions: [complex] = 1.00×10^{-4} mol·dm^{-3}, [substrate] = 5.00×10^{-5} mol·dm-3； Tris-HCl buffer (0.10 mol·dm^{-3}), I = 0.10 ($NaNO_3$), PNPP: p-nitrophenyl picolinate.

Table. 2 Pseudo-frist-order constants for PNPP hydrolysis catalyzing by different imidazole complexes in aqueous solution

Entry	Complex	$K_{obs1}/10^{-4}$ (s^{-1})	pH
1	**9a**	8.7	7.0
2	**9b**	4.3	7.0
3	**9c**	3.9	7.0
4	**9d**	26.0	7.0
5	**9e**	7.1	7.0
6	**Zn^{2+}**	0.338 [24]	7.0
7	**no**	0.105 [24]	7.0
8	**imidaozle**	Not detected	7.0

Conditions: [complex] = 1.00×10^{-4} mol·dm^{-3}, [substrate] = 5.00×10^{-5} mol·dm^{-3}； Tris-HCl buffer(0.10 mol·dm^{-3}， pH = 7.0), I = 0.10 ($NaNO_3$), PNPP: p-nitrophenyl picolinate

Acid effect and synergetic catalytic mechanism of the complexes

In order to understand the mechanism of this kind of catalysis, the kinetics of PNPP catalytic hydrolysis was studied by complexes **8a** and **9a** as examples at different pH values. The results were shown in **Fig. 1.** The **Fig. 1** exhibited that the K_{obs1} of PNPP hydrolysis catalyzed by compound **8a** and **9a** did not always increase with the increase of pH from pH 6.5 to 7.5. The maximum hydrolytic rates of both compound **8a** and **9a** appeared at pH 7.0, and the K_{obs1} values were 4.6×10^{-4} s^{-1} and 8.7×10^{-4} s^{-1}, respectively. This result was in accordance with the reference 6. This tendency proved that the azole unit could bind proton and act as a general acid for a nucleophilic attack in catalysis process. Meanwhile, benzimidazolyl group in compound **8a** could conjugate the 4-nitrophenolate group through the π-π stack effect to stabilize the host-guest complex at the same time. It was reported that cyclen derivative

coordinated with Zn (II) carried a water molecule as an additional ligand in aqueous solution [23], and it is believed that the metal bound hydroxide (M–OH) is the source for nucleophilic attack around pH 7.0 [9]. As many examples of metallic-enzyme mimetic models, the metal-bound hydroxide appears as the critical nucleophile at pH 7.0 [24]. But in solutions with higher pH, azolyl arm was deprotonated, and could not act as a general acid catalyst. The K_{obs1} value of **8a** and **9a** decreased to 3.9×10^{-4} s^{-1} at pH 7.2 and 8.0×10^{-4} s^{-1} at pH 7.5 respectively, and they were apparently smaller than that corresponding data at pH 7.0. Furthermore, it must be pointed out that the free OH^- in solution was the primary nucleophilic reagent at pH 8.0, and the hydrolysis rate was significantly large.

In certain model systems, the cooperative action had been demonstrated, such as dinuclear species, the two metal ions act cooperatively in the catalytic process; either one metal ion provides the nucleophile and the other one coordinates the substrate or both metal ions participate in substrate binding, activation, and cleavage [25]. From these hydrolytic data of benzimidazole and imidazole alone in **Table 1** and **Table 2**, it may be concluded that azole group showed no direct catalytic effect and worked as assistant to capture the substrate and cleave the ester bond. So that, in this synergetic catalysis model, the two functional groups among the azole cyclen compound could work respectively to complement each other and accomplish the hydrolysis process. The azoles groups were considered to array of stabilizing and activating interactions with H^+. From the results described above, the proposed catalysis mechanisms of **8a** and **9a** were depicted in **Fig. 2**, which showed the two kinds of complexes acted as hydrolytic enzymes with two functional catalytic centers, one was the cation nucleus, and the other was the heterocyclic arm. So that the target materials discussed in this paper were indeed synergetic catalysts.

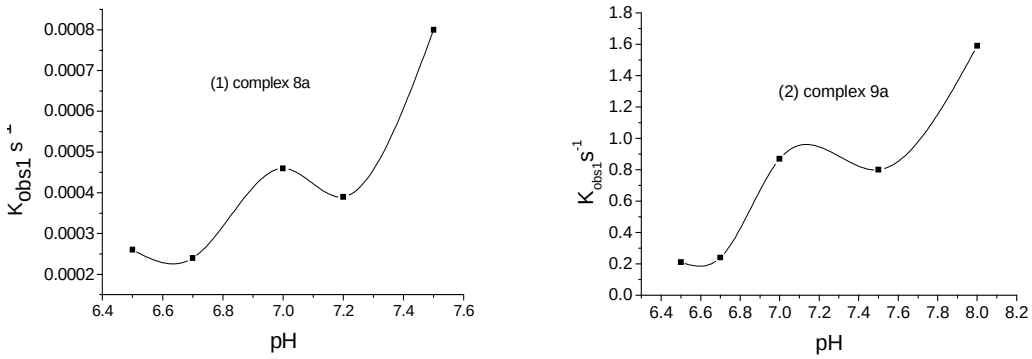


Fig. 1 K_{obs1} *versus* pH for the hydrolysis of PNPP by complex 8a and 9a at I = 0.10 ($NaNO_3$), T = 303.2±0.1 K

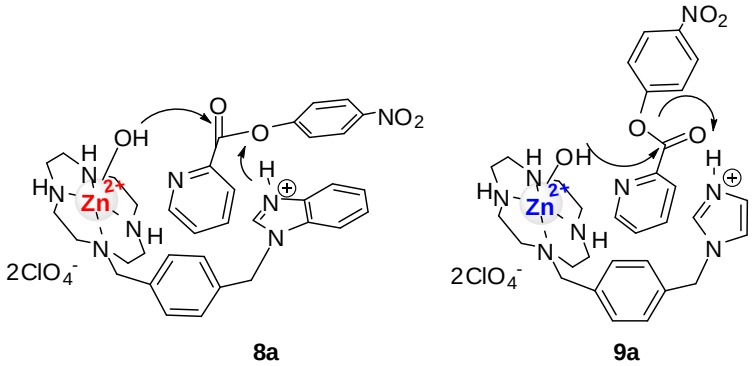


Fig. 2. Synergetic catalysis of *p*-nitrophenylacetate hydrolysis with the enzyme model 8a and 9a

CONCLUSION

In this work, a number of Zn(II) and Cu(II) complexes of the tetraaza-cyclododecane with benzimidazole or imidazole unit were synthesized and characterized and used as artificial enzyme mimetic models to catalyze PNPP hydrolysis. There are several interesting results obtained in this work: (1) the Zn(II) complexes bearing cyclen-benzimidazole showed marked rate acceleration by 13.6 to 223 fold larger than hydrolytic rate catalyzed by Zn(II)

cation, and 43.8~718 times faster than the hydrolysis rate without any catalyst; (2) the catalytic activity of the complexes carrying cyclen-benzimidazole was much higher than that of cyclen-imidazole derivatives; (3) the PNPP hydrolysis catalyzed by synthetic enzyme model **8a** and **9a** was most probably through synergistic hydrolytic mechanism; (4) the largest rate acceleration obtained with benzimidazolyl compound **8b** (75.4×10^{-4} s^{-1}) at pH 7.0 clearly demonstrates the potential of such multifunctional enzyme models.

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