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Chiral imidazole metalloenzyme models: Synthesis and enantioselective hydrolysis for α-amino acid esters

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Abstract

Chiral imidazole hydrolytic metalloenzyme models with characteristics of chiral centers directly link to imidazole N-atoms and varieties in both alkyl chain length and number of alkyl chains, have been synthesised and investigated for enantioselective hydrolysis of Boc-α-amino acid esters. The result indicates that both hydrolysis rates and enantioselectivities are increased with increases in the alkyl chain length and the number of the alkyl chains in the lipophilic chiral imidazole-type surfactants in many cases. The lipophilic chiral imidazole **4d** ((*S*)-1-hexadecoxy-2-(1-imidazolyl)-propane), which has one long alkyl chain, shows higher hydrolysis rate and enantioselectivity ($k_D = 132.5 \times 10^{-5}$, $k_D/k_L = 5.38$), **5d** ((*S*)-1,5-dihexadecoxy-2-(1-imidazolyl)-pentane), which has two long alkyl chains, shows the highest hydrolysis rate and enantioselectivity ($k_D = 201.5 \times 10^{-5}$, $k_D/k_L = 11.72$). Additionally, the effects of the metals, the additives, the solvents and the substrates on the hydrolysis rates and enantioselectivities are examined.

Keywords: Chiral imidazole; Enantioselective hydrolysis; Metallomicelles; α-Amino acid esters; Synthesis

1. Introduction

During the past few decades, enantioselective reactions in metallomicelle medias have attracted much attention because of their usefulness as models for enzyme catalysis [1] and as tools for asymmetric synthesis [2]. Of particular interest is the micellar model of hydrolytic metalloenzymes [3] that are able to promote the cleavage of phosphoric and carboxy esters or amides. Tonellato [4] reported that excellent enantioselectivities were obtained in the hydrolysis of PhgPNP (*p*-nitrophenyl esters of phenylalanine), catalyzed by (*S*)-1,2-diamino-[*N*-tetradecyl-*N*′-((*S*)-1-benzyl-2-hydroxyethyl)]-1-methylethane metallomicelles. Tagaki [5] developed some binuclear metal complexes as artificial hydrolytic enzyme models that also showed very high catalytic activities. Engbersen used chiral 1,l0-phenanthroline metallomicelles to study the characteristics of rigid structure in hydrolysis of esters [6]. Among these hydrolytic metalloenzyme models, considerable attention has been paid to the imidazole-containing models because the imidazole residue is well recognized as the active sites of a lot of enzymes [7].

We previously reported the enantioselective hydrolysis of amino acid esters by chiral metallomicelles composed of chiral sulfur-containing macrocyclic ligands [8], chiral lipophilic pyridyl-containing amino alcohol ligands [9] and lipophilic L-histidinol ligands [10]. As a continuing research in the enantioselective hydrolysis of amino acid esters [8–10], in this paper, we present the first example of the use of chiral imidazole metalloenzyme models, in which chiral center directly link to imidazole N-atom, catalyze the enantioselective hydrolysis of amino acid esters. Three series of lipophilic chiral imidazoles **3**–**5**, are studied to clarify the structural variation effects of chiral imidazole surfactants, including alkyl chain length, number of alkyl chains, as well as the effects of solvents, metals, additives, and substrates, on the hydrolysis rates and enantioselectivities.

2. Results and discussion

2.1. General methods and materials

^{1}H NMR spectra were recorded at 300 MHz, and chemical shifts in ppm were reported relative to internal Me_4Si. Mass

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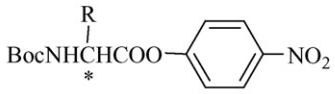


substrate	R
D(L)-Boc-PhePNP	$PhCH_2$
D(L)-Boc-LeuPNP	$(CH_3)_2CHCH_2$
D(L)-Boc-AlaPNP	CH_3

Scheme 1.

spectra datum were recorded on a Finnigan-LCQ^{DECA} spectrometer. Optical rotations were taken on a Perkin-Elmer Model 341 polarimeter. Kinetic runs were conducted on a Shimadzu TU-1901 spectrophotometer equipped with a thermostated cell compartment. Solutions of the ligands, metal ions and cosurfactants were prepared in the proper buffer (0.05 M). Reaction temperature was maintained at $25 \pm 0.1\,^{\circ}C$. Kinetics was typically started by injecting an acetonitrile solution (0.01 M) of substrate ester into a 1 cm cuvette containing 3 ml of buffered micellar solution and the desired concentration of metal ion and ligand. Pseudo-first-order rate constants (k_D and k_L) for the hydrolysis of substrate esters were determined by monitoring the release of *p*-nitrophenol at 320 nm (pH 5.0–6.3) or 400 nm (pH 6.3–9.5) for at least five half-lives, and obtained by linear plots of $\ln(A_\infty - A_t)$ versus time. The rate constants for each reaction were determined three times from three separate runs with an uncertainty of less than 5%. The critical micellar concentrations (cmc) are 2.7×10^{-5} M(**4c**) and 1.8×10^{-5} M(**5d**), respectively.

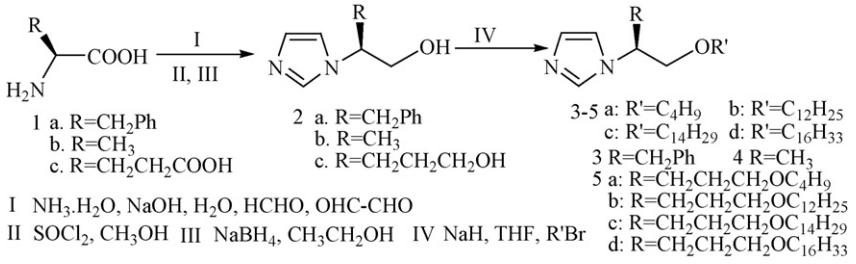
$Zn(NO_3)_2{\cdot}6H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $MnCl_2{\cdot}3H_2O$, *n*-dodecyl sodium sulfate (SDS), *n*-hexadecyltrimethylammonium bromide (CTABr) and polyethylene glycol dodecyl ether (Brij35) were purchased from commercial sources and used without further purification. The buffer was Tris (pH 6.0–9.0). The *p*-nitrophenyl esters of the Boc-α-amino acids were prepared according to literature procedures [11]. Scheme 1 shows the substrates. All other chemicals and reagents were obtained commercially and used without further purification.

The lipophilic chiral imidazoles were synthesized according to the procedures outlined in Scheme 2 using L-alanine, L-phenylalanine and L-glutamic acid as starting materials. **2a–c** were prepared according to literature [12].

2.2. Kinetics

Rates of hydrolysis were obtained from observing the release of *p*-nitrophenol spectrophotometrically under pseudo-first-order conditions. Pseudo-first-order rate constants (k_D and k_L) for the enantioselective cleavage of D- and L-α-amino acid *p*-nitrophenyl esters promoted by metal complexes comicellized with Brij35 are summarized in Table 1 along with enantioselectivities k_D/k_L. The results show that these chiral metallomicelles can effectively catalyze the enantioselective hydrolysis of D- and L-α-amino acid esters with good enantioselectivities, and that all of D-substrates are hydrolyzed faster than the corresponding L-isomers. Both rates and enantioselectivities are low when catalyzed singlely by ligands or metal ions. Large rate enhancements are observed in the presence of both ligands and metal ions, and the enantioselectivities may depend on the nature of the transition metal ion, in the order of $Zn^{2+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$, which is similar to lipophilic L-histidinol system [10]. Ligands **3–5** with better dimensional orientation lead to better enantioselectivities, but hydrolysis rates are lower than lipophilic L-histidinol system [10], it could be attributed to that ligands **3–5** lack hydroxyl groups, which lead to rate enhance [13].

Structural effects of ligands on the hydrolysis catalyzed by comicelles are also depicted in Table 1. Increases in the alkyl chain length and the number of the alkyl chains promote both the hydrolysis rates and the enantioselectivities except for from **3c** to **3d** and from **5c** to **5d**. Lipophilic metallmicelles **4d**-Zn^{2+} containing a long alkyl chain gives higher rate enhancements and enantioselectivities (entry 18). **5d**-Zn^{2+} containing two long alkyl chains gives the highest rate enhancements and enantioselectivities (entry 19). **2a–c**-Zn^{2+} lacking alkyl chains are less reactive and enantioselective (entries 5–7). The result indicates that the hydrophobic interactions between substrates and metallmicelles are favorable for both high rate accelerations and good enantioselectivities. Since the microviscosity of micells is higher than the viscosity of the surronding homogeneneous solvent. When substrate molecules incorporated in micelles, longer the alkyl chains of micelles are, less translational and rotational freedom are. And these are reflected in their reactivity, regio-, stereo- and product selectivity [14]. The hydrolysis rates decrease from **3c** to **3d**, or from **5c** to **5d** is because **3d** and **5d** are poorly soluble in water and mixed solutions have to be used, which inhibit the hydrolysis rates of both D- and L-substrates. Enantioselectivities of **3** are worse than **4**, which indicate that



Scheme 2.

Table 1
Pseudo-first-order constants (k_D and k_L, s^{-1}) and enantioselectivities (k_D/k_L) for the cleavage of D(L)-Boc-PhePNP by ligands and M^{2+} comicellized with Brij35

Entry[a]	Ligand	M^{2+}	k_D (10^{-5})	k_L (10^{-5})	k_D/k_L
1	None	None	2.01	2.02	1
2	None	Zn^{2+}	3.43	3.43	1
3[b]	None	None	1.82	1.82	1
4[b]	None	Zn^{2+}	3.97	4.06	0.98
5	2a	Zn^{2+}	7.8	5.3	1.47
6	2b	Zn^{2+}	8.3	5.9	1.41
7	2c	Zn^{2+}	15.2	9	1.69
8	3a	Zn^{2+}	20.6	12.7	1.62
9	4a	Zn^{2+}	43.2	24.1	1.79
10	5a	Zn^{2+}	63	32.8	1.92
11	3b	Zn^{2+}	154	57.9	2.66
12	4b	Zn^{2+}	103.3	25.7	4.02
13	5b	Zn^{2+}	481.8	189.7	2.54
14	3c	Zn^{2+}	170.9	60.8	2.81
15	4c	Zn^{2+}	119.5	26.4	4.53
16	5c	Zn^{2+}	504	191	2.64
17[b]	3d	Zn^{2+}	64	13.5	4.74
18[b]	4d	Zn^{2+}	132.5	24.6	5.38
19[b]	5d	Zn^{2+}	201.5	17.2	11.72
20[c]	3c	Zn^{2+}	595	210	2.83
21[b]	3c	Zn^{2+}	68.5	16.7	4.1
22[c]	5c	Zn^{2+}	341	257.5	1.32
23[b]	5c	Zn^{2+}	221.5	29.7	7.9
24[c]	5d	Zn^{2+}	333.5	103.5	3.22
25[d]	5d	Zn^{2+}	68	16.3	4.17
26	4c	Co^{2+}	80	26	3.08
27	4c	Cu^{2+}	168.5	47.9	3.52
28	4c	Mn^{2+}	86.5	31.9	2.71
29	4c	Ni^{2+}	83	25.4	3.27
30[b]	5d	Co^{2+}	175	29.6	5.92
31[b]	5d	Cu^{2+}	485	69.2	7.01
32[b]	5d	Mn^{2+}	224	43.3	5.17
33[b]	5d	Ni^{2+}	173	25.8	6.7

[a] 25 ± 0.1 °C, pH 8.60 [0.01 mol dm^{-3} Tris] (**2a–b**, **3–4**), pH 8.70 [0.01 mol dm^{-3} Tris] (**2c**, **5**) [ligand] = 3.33×10^{-4} mol dm^{-3}, [substrate] = 2.5×10^{-5} mol dm^{-3}, [M^{2+}] = 1.67×10^{-4} mol dm^{-3}, [Brij35] = 4.0×10^{-3} mol dm^{-3}.
[b] In water/THF 9:1.
[c] In water/EtOH 9:1.
[d] In water/DMSO 9:1.

the hydrophobic phenyl function in **3** is not favorable for the formation of micelles.

Subsequently, the effects of solvent are examined. Proper solvent can greatly increase the enantioselectivities, but hydrolysis rates are decreased in some degree. Lipophilic chiral imidazole ligand **3c**, which is very difficult to dissolve in water, shows bad enantioselectivity (entry 14). When a small quantity of THF is added (H_2O/THF 9:1), enantioselectivity is greatly enhanced but hydrolysis rates are decreased (entry 14, 21). However, H_2O/EtOH or H_2O/DMSO (entries 24–25) is used for ligand **5d**, enantioselectivities are no better than THF is added.

Kinetic data are observed for the cleavage of D(L)-Boc-PhePNP in the presence or absence of nonionic polyethylene glycol dodecyl ether (Brij35), cationic *n*-hexadecyltrimethylammonium bromide (CTABr) and anionic *n*-dodecyl sodium sulfate (SDS). For lipophilic chiral imidazole ligand **5d**, enantioselectivity is higher in the Brij35 additive ($k_D/k_L = 11.72$) than in CTABr ($k_D/k_L = 7.25$), SDS ($k_D/k_L = 4.18$) and without additive ($k_D/k_L = 2.96$). However, hydrolysis rate is higher in the CTABr micelle ($k_D = 1261.5 \times 10^{-5}$) than without additive ($k_D = 858.5 \times 10^{-5}$), Brij35 ($k_D = 201.5 \times 10^{-5}$) and SDS ($k_D = 76.5 \times 10^{-5}$). These can be mainly explained that in CTABr, the folding back of the alkyl groups at the head groups towards the micellar surface reduces water–alkyl group contact so that the reaction takes place in a region of relatively low polarity [15]. And the low polarity environment in CTABr additive can decrease the free energy of bulky anionic transition state, with more delocalized charge, relative to that of the ground state. An anionic additive SDS has the opposite effect [16]. In nonionic Brij35, substrate molecules have less rotational freedom due to the twisted chain of polyoxyethylene [3]. This result in lower hydrolysis rates than CTABr and the highest enantioselectivities. So, we can conclude that the micellar microenvironments are of importance for the hydrolysis activities and the enantioselectivities.

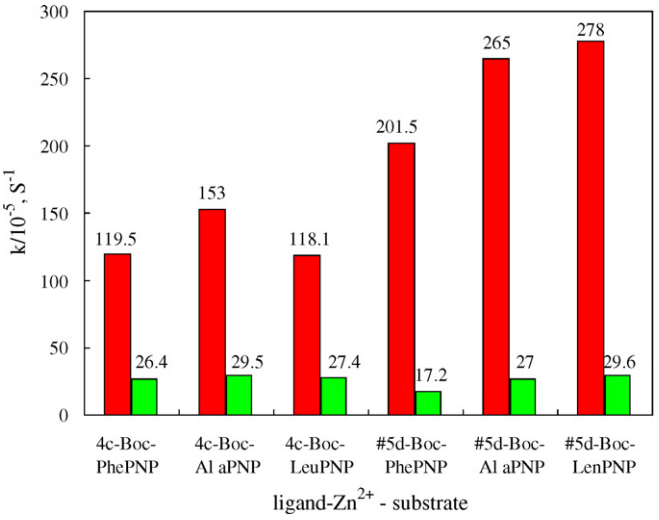


Fig. 1. Pseudo-first-order constants (k_D(■) and k_L(■), s^{-1}) for the cleavage of Boc-α-amino acid esters by ligands and Zn^{2+} comicellized with Brij35. Conditions: 25 ± 0.1 °C, pH 8.60[0.01 mol dm^{-3} Tris](**4c**), pH 8.70[0.01 mol dm^{-3} Tris](**5d**) [ligand] = 3.33×10^{-4} mol dm^{-3}, [substrate] = 2.5×10^{-5} mol dm^{-3}, [M^{2+}] = 1.67×10^{-4} mol dm^{-3}, [Brij35] = 4.0×10^{-3} mol dm^{-3}. # Water/THF 9:1.

Fig. 1 shows the Pseudo-first-order constants for the cleavage of Boc-PhePNP, Boc-LeuPNP and Boc-AlaPNP by ligands-Zn^{2+} with Brij35. Selectivities are almost exclusively due to the increasing rates of the D-substrate whereas the rates of L-substrate are hardly affected in the presence of ligands and Zn^{2+}. The structure of D-Boc-AlaPNP may match to ligand **4c**, which shows better enantioselectivity. On the other hand, ligand **5d** shows the best enantioselectivity to D-Boc-PhePNP may due to the good sterical orientative effect between hosts and guests.

2.3. *Concentration effect of Zn^{2+} on the hydrolysis rate*

When fixing concentration on lipophilic chiral imidazole ligands **4c** and **5d**, concentration effects of Zn^{2+} on the deacylation rates of D-Boc-PhePNP are studied in Fig. 2. Initially,

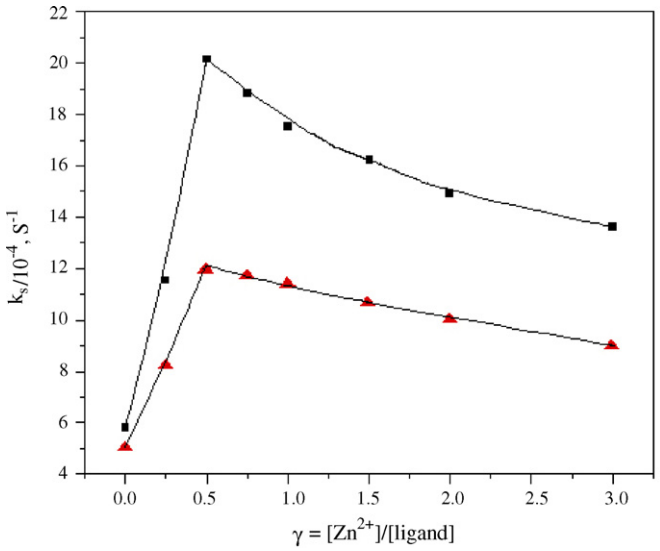


Fig. 2. Pseudo-first-order constants for the hydrolysis of D-Boc-PhePNP as a function of $[Zn^{2+}]$ under fixed concentration of ligand **4c**(▲) in Brij35 micelles and **5d**(■) in Brij35 micelles (water/THF 9:1). Conditions: 25 ± 0.1 °C, pH 8.60[0.01 mol dm^{-3} Tris](**4c**), pH 8.70[0.01 mol dm^{-3} Tris](**5d**) [ligand] = 3.33 × 10^{-4} mol dm^{-3}, [substrate] = 2.5 × 10^{-5} mol dm^{-3}, [M^{2+}] = 1.67 × 10^{-4} mol dm^{-3}, [Brij35] = 4.0 × 10^{-3} mol dm^{-3}.

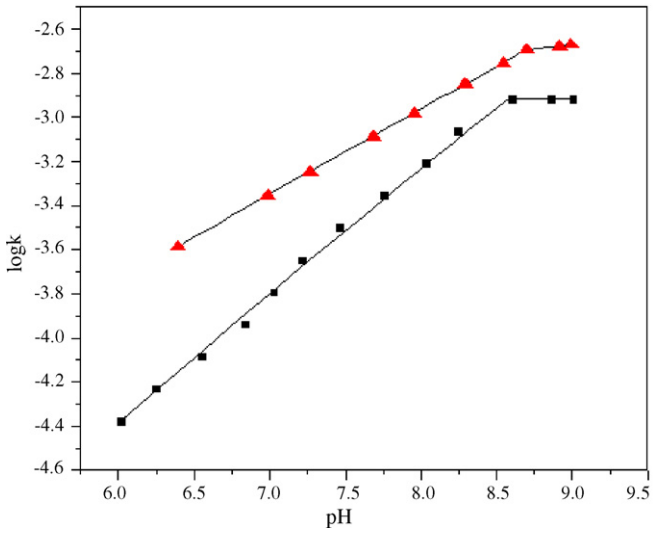


Fig. 3. log K vs. pH for the cleavage of D-Boc-PhePNP by **4c**-Zn^{2+}(■), **5d**-Zn^{2+}(▲)(water/THF 9:1). Conditions: 25 ± 0.1 °C, [ligand] = 3.33 × 10^{-4} mol dm^{-3}, [substrate] = 2.5 × 10^{-5} mol dm^{-3}, [M^{2+}] = 1.67 × 10^{-4} mol dm^{-3}, [Brij35] = 4.0 × 10^{-3} mol dm^{-3}.

a small quantity addition of Zn^{2+} to ligands **4c** and **5d** leads to a fast increase in reaction rates. Ratios reach maximums when [Zn^{2+}]:[**4c** or **5d**] are 1:2. Rates decreases are observed with further increase in the concentration of Zn^{2+}. These are similar to lipophilic L-histidinol system [10]. For ligands **4c** and **5d**, addition of Zn^{2+} may activate the hydroxyl group of water for nucleophilic attacks to cause the rate enhancements [2]. Hydrolysis rates are lower than lipophilic L-histidinol system [10], this can be explained that the chiral imidazole ligands lack hydroxyl groups, which lead to rate enhance [13].

2.4. pH-rate profile

pH-rate constant profiles are determined for reactions of D-Boc-PhePNP with catalysts lipophilic chiral imidazole ligands **4c** and **5d**-Zn^{2+}. The pH value is checked before and after any kinetic run and proved to be constant within ±0.05 pH unit. The inflections in the rate-pH profiles are diagnostic of operative pK_a value of ca. 8.6(**4c**) and 8.7(**5d**) (Fig. 3). They are taken as, ligands **2a–b**, **3a–b**, **4a–c** in Tris buffer (0.05M, pH 8.60), **2c**, **5a–b**, in Tris buffer (0.05M, pH 8.70), **3c–d**, **4d**, **5c–d** in Tris buffer (water/THF 9:1)(0.05M, pH 8.70), under our micellar reaction conditions.

2.5. Stoichiometry of the reactive complexes

To know stoichiometries of the kinetically reactive complexes, kinetic versions of job plots are examined by plotting k_D and k_L as functions of molar fraction of ligands (γ), keeping total concentrations of ligands and metal ion constants. The results shown in Fig. 4 indicate that in the case of Zn^{2+} and lipophilic chiral imidazole ligands **4c** or **5d**, the rate maximas are observed at $\gamma = 0.67$, which is correspond to stoichiometry of ligands:Zn^{2+} = 2:1. Moreover, stable Zn^{2+} complexes could be formed as indicated by the sharp maxima in the job plots. We also obtained direct evidence for these complexes by the ESI mass data and the peak at 712.6 (**4c**-Zn^{2+}) and 1303.1 (**5d**-Zn^{2+}) show the existence of complexes formed by two ligands and one Zn^{2+}.

2.6. Mechanism

Normal micelles have loose and mobile structures that are not very effective at inducing stereoselectivities. However, in this system, good enantioselectivities are obtained. We speculate

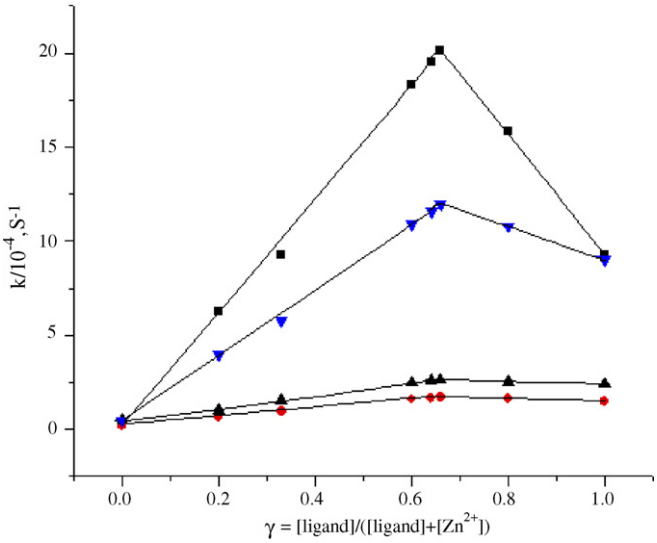
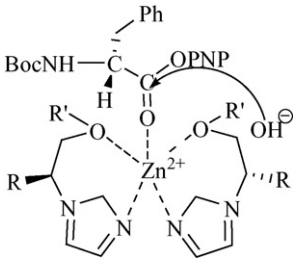


Fig. 4. Kinetic job plots for the cleavage of L-Boc-PhePNP and D-Boc-PhePNP by ligand **4c** + Zn^{2+} in Tris buffer, pH 8.60 and **5d** + Zn^{2+} in Tris buffer (water/THF 9:1), pH 8.70, 25 ± 0.1 °C. ([**4c**] + [Zn^{2+}]) = ([**5d**] + [Zn^{2+}]) = 5.0 × 10^{-4} mol dm^{-3}. **4c**-L(♦), **4c**-D(▼), **5d**-L(▲), **5d**-D(■).



Scheme 3. The ternary complex of **5**-Zn^{2+}-D-Boc-PhePNP.

that these are caused by highly oriented substrate–metallmicelle ternary complexes (**3**(**4**, **5**)-Zn^{2+}-PhePNP). In these ternary complexes, motional freedom substrates are restricted by template effects of metal ions. The possible **5**-Zn^{2+}-catalyzed hydrolysis of D-Boc-PhePNP formed ternary complexes is indicated in Scheme 3 [5]. These models show that alkyl chains of chiral imidazoles are sterically orientated to coordinate to metal ions, and therefore the function of these groups will primarily incorporating the ligands into the micellar phases and directing the approaching substrates. Enantioselectivities in the hydrolysis are mainly caused by differences in steric orientation effects of the diastereomeric transition states, which are possibly generated by the nucleophilic attack of hydroxyl group upon the carbonyl atom of D-Boc-PhePNP. In these ternary complexes, the motional freedom substrates are restricted by the template effects of the metal ions and ligands. Additionally, the coordination geometry of the metal ions in these ternary complexes has direction effects to stereoselectivities in some degree.

3. Conclusion

We have developed a novel and high efficient catalytic system for enantioselective hydrolysis of α-amino acid esters. Enantioselectivities and hydrolysis rates are remarkably influenced by the alkyl chain length, the number of alkyl chains of ligands and the matching degree between ligands and substrates. Enantioselectivities and hydrolysis rates are also sensitive to the proper selectivity of solvents, surfactants and metal ions. Studies of the kinetic parameter suggest that enantioselectivities are caused by both steric orientation effects and binding strengths between chiral imidazole metallmicelles and D- or L-substrates. These micellar systems may also be applicable to other types of enantioselective reactions. Further works are being in progress.

4. Experimental section

*4.1. General procedure for the synthesis of **3–5***

3–5 were prepared according to the following procedure described for **3a**. 1.1 mmol NaH was added to 1 mmol compound **2a** in 10 ml THF in ice bath. 1 mmol C_4H_9Br in 5 ml THF was then added drop wise. The mixture was stirred at this temperature for 5 h. The mixture was filtered. And the resulting solid was washed five times with EtOAc. The filtrates were combined and concentrated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give a white oil. Their structures are supported by the data from MS, ^{1}H NMR and HRMS.

*4.1.1. (S)-1-Phenyl-2-(1-imidazolyl)-3-butoxy-propane (**3a**)*

78% yield: $[\alpha]_D^{25} = -57.1$ ($c = 1.0$, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.89–0.97 (m, 3H, $(CH_2)_3CH_3$), 1.26–1.43 (m, 2H, $O(CH_2)_2CH_2$), 1.51–1.58 (m, 2H, OCH_2CH_2), 2.98–3.05 (q, $J = 8.28$, 1H, $PhCH_{2a}$), 3.16–3.22 (q, $J = 6.51$, 1H, $PhCH_{2b}$), 3.36–3.44 (m, 2H, OCH_2), 3.61–3.65 (m, 2H, CH_2O), 4.28–4.32 (m, 1H, $ImCHCH_2O$), 6.97–7.03 (m, 4H, 4, 5-Im*H*, Ph), 7.20–7.27 (m, 3H, Ph), 7.42 (s, 1H, 2-Im*H*). MS *m*/*z* 259 ($M^+ + 1$, 100). HRMS calcd. for $C_{16}H_{22}N_2O$ [$M^+ + H$] 259.1810; found 259.1811.

*4.1.2. (S)-1-Phenyl-2-(1-imidazolyl)-3-dodecoxy-propane (**3b**)*

82% yield: $[\alpha]_D^{25} = -41.8$ ($c = 1.0$, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.86–0.90 (t, $J = 6.51$, 3H, $(CH_2)_{11}CH_3$), 1.26 (s, 18H, $OCH_2CH_2(CH_2)_9$), 1.54–1.56 (d, $J = 6.81$, 2H, OCH_2CH_2), 2.98–3.05 (q, $J = 8.28$, 1H, $PhCH_{2a}$), 3.16–3.22 (q, $J = 6.51$, 1H, $PhCH_{2b}$), 3.36–3.44 (m, 2H, OCH_2), 3.61–3.65 (m, 2H, CH_2O), 4.28–4.32 (m, 1H, $ImCHCH_2O$), 6.98–7.03 (m, 4H, 4, 5-Im*H*, Ph), 7.20–7.27 (m, 3H, Ph), 7.43 (s, 1H, 2-Im*H*). MS *m*/*z* 371 ($M^+ + 1$, 100). HRMS calcd. for $C_{24}H_{38}N_2O$ [$M^+ + H$] 371.3062; found 371.3063.

*4.1.3. (S)-1-Phenyl-2-(1-imidazolyl)-3-tetradecoxy-propane (**3c**)*

82% yield: $[\alpha]_D^{25} = -36.9$ ($c = 1.0$, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.86–0.92 (q, $J = 4.26$, 3H, $(CH_2)_{13}CH_3$), 1.15–1.26 (q, $J = 14.85$, 22H, $OCH_2CH_2(CH_2)_{11}$), 1.52–1.58 (q, $J = 6.18$, 2H, OCH_2CH_2), 2.99–3.06 (q, $J = 8.28$, 1H, $PhCH_{2a}$), 3.19–3.23 (q, $J = 6.51$, 1H, $PhCH_{2b}$), 3.35–3.43 (m, 2H, OCH_2), 3.58–3.67 (m, 2H, CH_2O), 4.28–4.33 (m, 1H, $ImCHCH_2O$), 6.98–7.03 (m, 4H, 4, 5-Im*H*, Ph), 7.20–7.28 (m, 3H, Ph), 7.45 (s, 1H, 2-Im*H*). MS *m*/*z* 399 ($M^+ + 1$, 100). HRMS calcd. for $C_{26}H_{42}N_2O$ [$M^+ + H$] 399.3375; found 399.3374.

*4.1.4. (S)-1-Phenyl-2-(1-imidazolyl)-3-hexadecoxy-propane (**3d**)*

85% yield: $[\alpha]_D^{25} = -32.0$ ($c = 1.0$, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.84–0.90 (q, $J = 6.39$, 3H, $(CH_2)_{15}CH_3$), 1.26 (s, 26H, $OCH_2CH_2(CH_2)_{13}$), 1.52–1.59 (q, $J = 6.9$, 2H, OCH_2CH_2), 2.99–3.06 (q, $J = 8.28$, 1H, $PhCH_{2a}$), 3.16–3.23 (q, $J = 6.51$, 1H, $PhCH_{2b}$), 3.35–3.43 (m, 2H, OCH_2), 3.61–3.66 (m, 2H, CH_2O), 4.28–4.33 (m, 1H, $ImCHCH_2O$), 6.98–7.03 (m, 4H, 4, 5-Im*H*, Ph), 7.20–7.28 (m, 3H, Ph), 7.45 (s, 1H, 2-Im*H*). MS *m*/*z* 427 ($M^+ + 1$, 100). HRMS calcd. for $C_{28}H_{46}N_2O$ [$M^+ + H$] 427.3684; found 427.3684.

*4.1.5. (S)-1-Butoxy-2-(1-imidazolyl)-propane (**4a**)*

75% yield: $[25]_D^{25} = +18.0$ (c = 1.0, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.86–0.94 (m, 3H, $(CH_2)_3CH_3$), 1.26–1.38 (m, 3H, $ImCHCH_3$), 1.49–1.55 (m, 4H, $OCH_2(CH_2)_2CH_3$), 3.31–3.44 (m, 2H, OCH_2), 3.49–3.60 (m, 2H, CH_2O), 4.30–4.36 (m, 1H, $ImCHCH_3$), 7.00 (s, 1H, 5-Im*H*), 7.04 (s, 1H, 4-Im*H*), 7.58

(s, 1H, 2-Im*H*). MS *m*/*z* 183 ($M^+ + 1$, 100). HRMS calcd. for $C_{10}H_{18}N_2O$ [$M^+ + H$] 183.1497; found 183.1498.

*4.1.6. (S)-1-Dodecoxy-2-(1-imidazolyl)-propane (**4b**)*

79% yield: $[\alpha]_D^{25} = +10.4$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.94 (m, 3H, $(CH_2)_{11}CH_3$), 1.26–1.38 (m, 18H, $OCH_2(CH_2)_9CH_3$), 1.49–1.55 (m, 5H, OCH_2CH_2, ImCHCH_3), 3.30–3.42 (m, 2H, OCH_2), 3.49–3.60 (m, 2H, CH_2O), 4.29–4.35 (m, 1H, ImC*H*CH_3), 6.99 (s, 1H, 5-Im*H*), 7.04 (s, 1H, 4-Im*H*), 7.58 (s, 1H, 2-Im*H*). MS *m*/*z* 295 ($M^+ + 1$, 100). HRMS calcd. for $C_{18}H_{34}N_2O$ [$M^+ + H$] 295.2749; found 295.2749.

*4.1.7. (S)-1-Tetradecoxy-2-(1-imidazolyl)-propane (**4c**)*

80% yield: $[\alpha]_D^{25} = +6.9$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.92 (m, 3H, $(CH_2)_{13}CH_3$), 1.17–1.30 (m, 25H, $OCH_2CH_2(CH_2)_{11}$, ImCHCH_3), 1.49–1.54 (m, 2H, OCH_2CH_2), 3.32–3.40 (m, 2H, OCH_2), 3.48–3.60 (m, 2H, CH_2O), 4.31–4.33 (m, 1H, ImC*H*CH_3), 6.99 (s, 1H, 5-Im*H*), 7.05 (s, 1H, 4-Im*H*), 7.58 (s, 1H, 2-Im*H*). MS *m*/*z* 323 ($M^+ + 1$, 100). HRMS calcd. for $C_{20}H_{38}N_2O$ [$M^+ + H$] 323.3062; found 323.3063.

*4.1.8. (S)-1-Hexadecoxy-2-(1-imidazolyl)-propane (**4d**)*

83% yield: $[\alpha]_D^{25} = +4.9$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.90 (m, 3H, $(CH_2)_{15}CH_3$), 1.20–1.26 (m, 26H, $OCH_2CH_2(CH_2)_{13}$), 1.48–1.54 (m, 5H, OCH_2CH_2, ImCHCH_3), 3.32–3.40 (m, 2H, OCH_2), 3.49–3.59 (m, 2H, CH_2O), 4.31–4.33 (m, 1H, ImC*H*CH_3), 6.99 (s, 1H, 5-Im*H*), 7.04 (s, 1H, 4-Im*H*), 7.57 (s, 1H, 2-Im*H*). MS *m*/*z* 351 ($M^+ + 1$, 100). HRMS calcd. for $C_{22}H_{42}N_2O$ [$M^+ + H$] 351.3375; found 351.3377.

*4.1.9. (S)-1,5-Dibutoxy-2-(1-imidazolyl)-pentane (**5a**)*

71% yield: $[\alpha]_D^{25} = -1.8$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.90 (m, 6H, $(CH_2)_3CH_3$, $(CH_2)_3CH_3$), 1.25–1.56 (m, 10H, $OCH_2(CH_2)_2CH_3$, $OCH_2(CH_2)_2CH_3$, $ImCHCH_2CH_2$), 1.86–1.88 (m, 2H, ImCHCH_2), 3.32–3.43 (m, 6H, $CH_2CH_2CH_2O$, OCH_2, OCH_2), 3.58–3.61 (m, 2H, CH_2O), 4.14–4.17 (m, 1H, ImC*H*CH_2O), 6.98 (s, 1H, 5-Im*H*), 7.05 (s, 1H, 4-Im*H*), 7.55 (s, 1H, 2-Im*H*). MS *m*/*z* 283 ($M^+ + 1$, 100). HRMS calcd. for $C_{16}H_{30}N_2O_2$ [$M^+ + H$] 283.2386; found 283.2366.

*4.1.10. (S)-1,5-Didodecoxy-2-(1-imidazolyl)-pentane (**5b**)*

73% yield: $[\alpha]_D^{25} = -1.3$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.90 (t, $J = 6.42$, 6H, $(CH_2)_9CH_3$, $(CH_2)_9CH_3$), 1.26 (s, 36H, $OCH_2CH_2(CH_2)_9CH_3$, $OCH_2CH_2(CH_2)_9CH_3$), 1.51–1.52 (d, $J = 2.43$, 6H, OCH_2CH_2, OCH_2CH_2, $ImCHCH_2CH_2$), 1.86–1.88 (m, 2H, ImCHCH_2), 3.33–3.37 (m, 6H, OCH_2, OCH_2, $CH_2CH_2CH_2O$), 3.59–3.60 (m, 2H, CH_2O), 4.14–4.17 (m, 1H, ImC*H*CH_2O), 6.97 (s, 1H, 5-Im*H*), 7.05 (s, 1H, 4-Im*H*), 7.55 (s, 1H, 2-Im*H*). MS *m*/*z* 507 ($M^+ + 1$, 100). HRMS calcd. for $C_{32}H_{62}N_2O_2$ [$M^+ + H$] 507.4890; found 507.4871.

*4.1.11. (S)-1,5-Ditetradecoxy-2-(1-imidazolyl)-pentane (**5c**)*

76% yield: $[\alpha]_D^{25} = -0.8$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.90 (t, $J = 6.39$, 6H, $(CH_2)_{13}CH_3$, $(CH_2)_{13}CH_3$), 1.26 (s, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.45–1.54 (m, 6H, OCH_2CH_2, OCH_2CH_2, $ImCHCH_2CH_2$), 1.86–1.88 (m, 2H, ImCHCH_2), 3.31–3.41 (m, 6H, CH_2CH_2O, OCH_2, OCH_2), 3.58–3.60 (q, $J = 2.19$, 2H, CH_2O), 4.15–4.17 (m, 1H, ImC*H*CH_2O), 6.97 (s, 1H, 5-Im*H*), 6.98 (s, 1H, 4-Im*H*), 7.56 (s, 1H, 2-Im*H*). MS *m*/*z* 363 ($M^+ + 1$, 100). HRMS calcd. for $C_{36}H_{70}N_2O_2$ [$M^+ + H$] 563.5516; found 563.5498.

*4.1.12. (S)-1,5-Dihexadecoxy-2-(1-imidazolyl)-pentane (**5d**)*

80% yield: $[\alpha]_D^{25} = -0.5$ ($c = 1.0$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.86–0.90 (t, $J = 6.42$, 6H, $(CH_2)_{15}CH_3$, $(CH_2)_{15}CH_3$), 1.26 (s, 52H, $OCH_2CH_2(CH_2)_{13}CH_3$, $OCH_2CH_2(CH_2)_{13}CH_3$), 1.46–1.54 (m, 6H, OCH_2CH_2, OCH_2CH_2, $ImCHCH_2CH_2$), 1.86–1.88 (m, 2H, ImCHCH_2), 3.32–3.40 (m, 6H, CH_2CH_2O, OCH_2, OCH_2), 3.58–3.61 (m, 2H, CH_2O), 4.14–4.17 (m, 1H, ImC*H*CH_2O), 6.98 (s, 1H, 5-Im*H*), 7.07 (s, 1H, 4-Im*H*), 7.59 (s, 1H, 2-Im*H*). MS *m*/*z* 620 ($M^+ + 1$, 100). HRMS calcd. for $C_{40}H_{78}N_2O_2$ [$M^+ + H$] 619.6142; found 619.6122.

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