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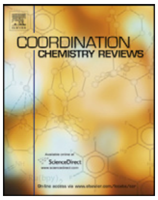

Review

# Metallomicelles as potent catalysts for the ester hydrolysis reactions in water

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**Contents**

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ABSTRACT

Synthetic amphiphiles have been employed for the investigation of diverse topics, *e.g.* membrane mimetics, drug delivery, ion sensing and even in certain separation processes. Metal-complexing amphiphiles comprise an interesting class of compounds possessing multiple utilities. Upon solubilization in water they form metallomicelles. For achieving specific catalysis of a variety of reactions, metallomicelles were utilized by applying the principles of coordination chemistry and self-organizing systems. Because of their certain similarities with the natural enzymes, metallomicelles were synthesized as catalysts for many reactions. In particular the metallomicelles play a catalytic role in reactions involving the hydrolysis of activated carboxylate esters, phosphate esters and amides at ambient conditions near neutral pH. Apart from the hydrolysis reactions, these were exploited to play pertinent role as Lewis acid catalysts in cycloaddition reactions, and in other reactions such as phenolic oxidation in presence of hydrogen peroxide. In this review we emphasize with the help of assorted examples, the design, synthesis of metal-complexing amphiphiles and their aggregation behavior leading to catalytic hydrolysis reactions in aqueous media.

## 1. Introduction

Many hydrolytically active metalloenzymes are found in nature [1]. The understanding of the structure function relationship of these enzymes inspired extensive studies on the design and synthesis of novel metal complexes that miniaturize and mimic enzyme active sites [2]. Several of these investigations focus on the role of metal complexes toward catalyzing hydrolysis reactions of activated esters of carboxylic acid and phosphate esters or amides [3]. Some other metal complexing systems such as metallomicelles function as Lewis-acid catalysts in the cyclo-addition reactions, *e.g.* Diels-Alder reaction [4]. Apart from these, the metallomicelles also show potential in the complexation of molecular oxygen [5], and in certain photochemical processes [6]. In this article, we concentrate on the hydrolase mimic properties of various metallomicellar systems.

Hydrolysis of carboxylic acid esters plays an important role in many biochemical processes [7,8]. For many decades, several groups

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have focused on the hydrolysis of carboxylic acid esters, using a variety of catalytic systems. However, it undoubtedly remains to be a major challenge to achieve the activity of the natural enzymes. Since the metallomicelles are able to mimic some of the useful attributes of the enzymes, the investigations involve the metallomicellar systems, which comprise an interesting area of research [9].

The metal ions play an important role in the metalloenzyme-based hydrolases. Similarly in a model system that calalyzes a hydrolysis reaction, a metal ion such as $Cu^{2+}$ or $Zn^{2+}$ should be capable of stabilizing the tetrahedral transition state (T.T.S.) through which the hydrolysis of an ester or an amide takes place. Thus the metal ion has to stabilize the T.T.S. via coordination with the charged oxyanionic tetrahedral intermediate. The oxyanionic intermediate of an electrophilic carbonyl carbon is able to interact effectively with a metal ion if there is an O/N on an adjacent atom. This charge stabilization of the developing negative charge in the T.T.S. and the full negative charge in the intermediate are often called an electrostatic catalysis. Such a strategy is indeed employed by several enzymes since nearly one third of all enzymes require metal ions.

## 2. How do metallomicelles help in the hydrolysis reactions?

Metallomicelles are made up of 'functionalized' surfactants endowed with ligands at the level of polar head group that make effective chelation with certain metal ions. Upon aggregation in aqueous medium, these mimic certain functional properties of hydrolytic metalloenzymes. The natural enzymes employ metal ions in their active sites which result in the formation of more acidic water molecules [10]. The metal ion in the active site coordinates a water molecule and increases the acidity of the bound water by further polarizing the H–O bond. This in turn enhances the effective nucleophilicity.

Thus metal ions serve dual purposes, firstly act as a Lewis acid to bind and activate carbonyl or phosphoryl bond of the ester/amide or the phosphate substrate, respectively. This makes the carbonyl C or phosphoryl P more vulnerable to nucleophilic attack. Thus they simultaneously furnish the metal bound water or $HO^-$ nucleophile to attack on to the substrate's phosphoryl or carbonyl group during the hydrolysis reaction.

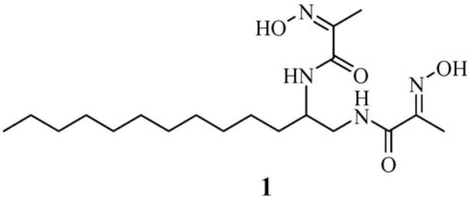
## 3. Catalysis in metallomicellar aggregates

Following the accepted definition, catalysis indicates the occurrence of notable rate enhancements due to the presence of a species (catalyst) that remains chemically unaffected or fully and rapidly regenerated at the end of the reaction. In many cases of hydrolytic reactions accelerated by metallomicelles, the first and fast step involves the attack onto the substrate by the "catalytic species" that is then chemically affected to give an intermediate species which, in the following step(s), is eventually hydrolyzed to regenerate the catalyst with a rate expressed as turnover rate or the like. Although slow turnover is reported in instances to illustrate the mechanism by which the hydrolysis takes place, catalysis in the absence of a fast turnover is rather impractical and almost useless. Yet in the literature, the term catalysis is widely used almost everywhere even where only rate enhancements were only observed and no evidence of catalytic turnover was presented. So it makes it a rather difficult job to sort out among the many papers reviewed here those reacting through an authenticated catalysis. In the following we present several examples from literature where significant rate enhancements in the hydrolysis reactions mediated by metallomicelles were documented. Of them those with specific evidence that the reactions proceed with "tested" turnover should be considered as truly catalytic.

## 4. Early examples of metallomicelles

The metallomicelles possess both the metal ion and the lipophilic tail to provide a hydrophobic ambience of the natural enzymes. The first report of the catalysis of a hydrolysis reaction by metallomicelles appeared in 1978 by Gutsche et al. These authors examined the effects of metal ions in micellar systems on the hydrolysis reactions of acetyl phosphate, using amine-ammonium micelles, chelate-forming micelles, metal-chelated polyamines and polyamides containing nucleophilic moieties [11]. The hydrolysis rate can be modulated by optimization of the pH of the medium.

In a subsequent study with l-undecyl-*N*,*N*′-bis[2-(hydroxyimino)propanoyl] ethylene diamine (**1**) in presence of metal ions such as $Zn^{2+}$, $Cu^{2+}$, or $Ni^{2+}$, the rate of hydrolysis of acetyl phosphate increased by factors of ∼60–140 at pH 11.5 in which the compound **1** existed in the hydroxamate form [12].

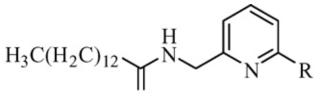


**1**

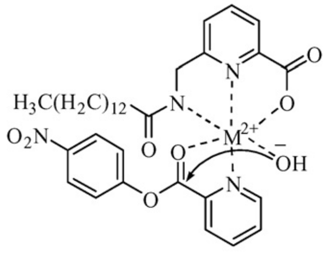
For the hydrolyses of ester/amide substrates, the most widely studied oxyanion in the biological system is the serine hydroxyl ($-CH_2OH$) group. On this basis, many nucleophile functionalized surfactants have been synthesized. These include hydroxide [13], and phenoxide functionalized amphiphiles [14]. Most of the metallomicelles developed along these lines therefore feature a hydroxy function located in the proximity of the chelating ligand to allow coordination with appropriate metal ions. Such metal ion complexation leads to activation of $-CH_2OH$ leading to its facile alkoxide ion formation by p*K*a lowering. Other functional surfactants possessing hydroxamate [15], oximate [16], imidazole [17], 4,4′-dialkylaminopyridine [18], hydroxybenzotriazole [19], tetrazole [20], peroxide and related nucleophiles [21] were also developed and their esterolytic properties were investigated. The results from these investigations provide critical insights for comparison with the activities of various metallomicellar systems. Few of these functional systems have also been examined towards the hydrolysis reactions under metal complexing conditions. In the following we present different types of ligands, functionalized ligands and their metal complexes, and their role in the hydrolysis of various carboxylate and phosphate esters as substrates in organized media.

### 4.1. *Pyridine-based ligand amphiphiles*

Tonellato and co-workers have systematically studied substituted pyridine-based amphiphiles (**2** and **3**) and their catalytic efficiency in the hydrolysis of carboxylic acid esters under comicellar conditions. In such systems the hydroxyl function bound to the pyridine moiety acts as a nucleophile which leads to the formation of a transacylation intermediate. The metal ion introduction to the micellar nucleophiles increases the hydrolysis rates up to 1200 times [22]. The change from the comicellar to homomicellar environment does not affect much in the way of rate acceleration. Based on the kinetic job plot, these authors demonstrated the evidence of a ternary complexation model (**4**, **5**) involving the ligand, the metal ion and the substrate. The metal complex works as a nucleophile which leads to an increased rate of transacylation of the substrate. The corresponding studies were also performed with the corresponding holomicellar system [23].



**2**; R = COOH
**3**; R = $CH_2OH$



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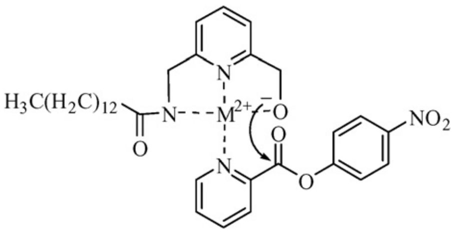
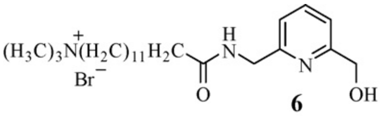
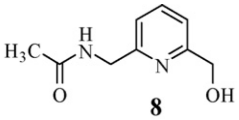


**5**

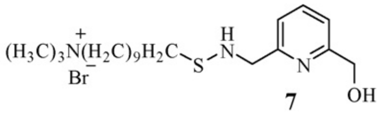
A comparative study using the micellar ligands **6** and **7** and the non-micellar ligands **8** and **9** confirmed the catalytic effectiveness of the micelle forming ligands toward the hydrolysis of *p*-nitrophenyl picolinate (PNPP) [23]. This shows the importance of hydrophobicity of the ligands which bring the substrate in a small volume together and the enhanced electrophilicity of divalent metal ions toward micellar-bound substrates. The local pH at the micellar surface is higher compared to that of the bulk which again favors the acid dissociation of the hydroxyl group in the ternary complex. In all the hydroxymethyl pyridine complexes, the ternary complex acts as an active species in the form of a transacylation intermediate. But here the importance of the substrate structure is worth mentioning. The correct geometry is required for the effective ternary complex formation and then only its catalytic activity could be observed. Some of the metallomicelles have been reported to show their enantioselective catalytic activity with *p*-nitrophenyl picolinate ester of naturally chiral α-amino acids [24]. Under similar conditions non-ligand substrates like *p*-nitrophenyl acetate (PNPA) or hexanoate (PNPH) have not been cleaved at significant rates even by micellized **6** or **7**.



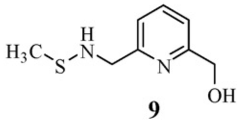
**6**



**8**



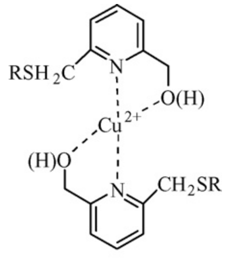
**7**



**9**

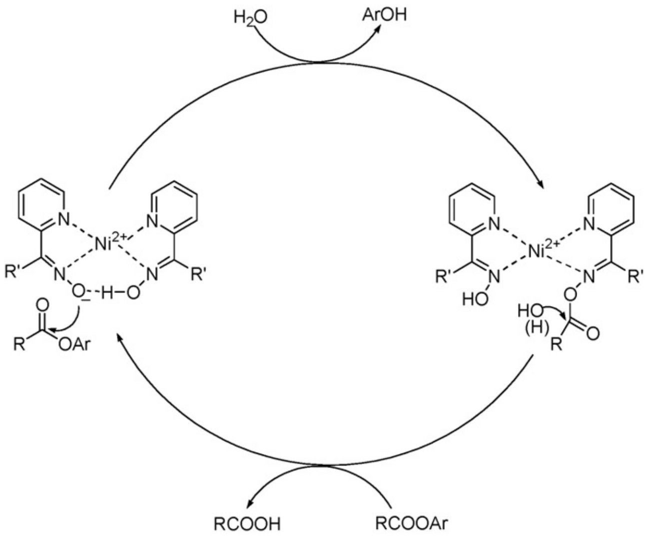
Interestingly three-dimensional supramolecular assemblies of the amphiphilic ligand and the substrate act differently in presence of different metal ions and show significantly different catalytic activity. Tonellato and co-workers have further shown that the micellization plays an important role in eliciting the catalytic activity with Cu(II) complexes [25]. With the same ligand, a variation of metal ions for instance from Cu(II) to Zn(II), manifests different levels of catalytic activity. Thus only the Cu(II) complex did not show any catalytic activity with the non-micellized ligands. Molecular models have suggested that central Zn(II) adopts a ternary complex in the form of a tetrahedral geometry, whereas Cu(II) replaces the weakest donor of the ligand to form a preferred planar complex [26].

Even the nature of the metallomicellar aggregate that is formed plays an important role. The ratio of the ligand to metal ion influences the catalytic power via formation of esterolytically 'active' complexes. An excess amount of the ligand leads to the formation of the 'inactive' ternary complex such as $L_2Cu$ (**10**) [27].



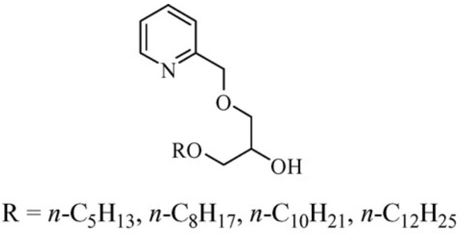
**10**

Cheng et al. have also investigated the effect of introducing a long chain in the pyridine ligands [28]. The rate enhancements were dependent on the type of metal ion, ligand and pH, which clearly indicated the formation of metal-based complexes. Interestingly the effect of long chain was different for various metal ion complexes. Among the metal ions $Cu^{2+}$, $Zn^{2+}$, and $Ni^{2+}$ the association constant between the ligand and the metal ion increases with Zn(II) and Ni(II), and decrease with the Cu(II) [28]. As mentioned earlier Cu(II) generally requires square planar geometry for activation, which might lead to steric hindrance. However, the association constant for the ternary complex increases with the increasing chain length of the alkyl group in the ligand (**11**) for all the metal complexes. This is rationalized on the basis of a steric strain, according to



**Scheme 1.** Catalytic cycle of hydrolyzing an ester substrate involving oxime-based ligands.

which the metal ion activates differently located hydroxyls based on its geometrical requirement of the complex in the microenvironment (similar to that of enzyme). This indicates that a metal ion can change the geometry in the micellar medium to activate the hydroxyl group of the ligand like that of metalloenzymes (**12**).



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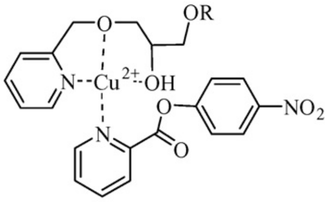
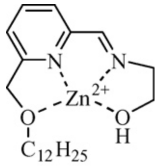


**12**

The catalytic activity depends not only on the metal ion and the ligand involved but also on the substrate. For instance a comparison between the PNPA and PNPP reveals that the catalytic activity is better for PNPP and less effective for PNPA [28]. It seems reasonable as the substrate PNPA possesses poor metal ions complexing ability. Regarding the catalytic activity of the metal ions, the Cu(II) was the best metal ion [29] among other transition metal ions examined. The possible reason is the low p*K*a value of the Cu complexes which allows dissociation of the ligand hydroxyl completely at relatively lower pH value. But at the same time, such effect produces less nucleophilic species. Depending on the factor which prevails, the catalytic activity of different metal ion complexes are observed. In some metallomicelles (*e.g.* **13**), the Zn(II) complexes have shown nearly 2-fold and 2.5-fold greater catalytic activity for the hydrolysis of PNPP and PNPA, respectively than the corresponding metallomicelles based on Cu(II) [30].

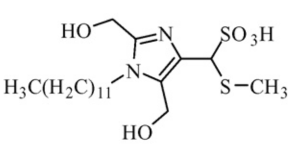


**13**

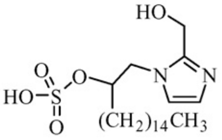
Apart from the hydroxyl function, other functional groups have also been examined by Tonellato et al. The other most effective function acting as a hydrolyzing catalyst is oxime [31,32], more particularly the pyridine ketoxime. The concept of choosing the oxime comes from the PAM (2-[(hydroximino)-methyl]-1-methyl pyridinium iodide), which acts as a powerful hydrolytic agent towards the phosphorylated serine of enzyme cholinesterase poisoned by organophosphorous inhibitors. Many metal ions such as Cu(II), Co(II), Ni(II), and Zn(II) in combination with oxime have been tested for this purpose. Among them the Ni(II) and the Zn(II) were the best and the system showed truly catalytic hydrolytic behavior with a sizable turnover rate [31]. The mode of action by the oxime ligand in the catalytic complex is different from the ternary complexes involving hydroxymethyl pyridine ligands (L) as discussed earlier. Here the metal ion does not assist in the hydrolysis directly as in the ternary complex. In case of the complex with Ni(II), the complex formed has a stoichiometry of $L_2Ni$, so the metal ion most likely forms a binary complex with ligands. Also the optimum rate accelerations occur in the pH range of 3–5 indicating the mode of action involving nucleophilic attack via the oxime function at the carbonyl carbon of the ester substrate. Accordingly the catalytic cycle involves the formation of a 2:1 complex which remains in partly dissociated form bound to the acylated species first. Then it gets dissociated to the hydrolyzed product by the action of a bound water molecule (Scheme 1). The 2:1 stoichiometry was ineffective towards the hydrolysis of phosphate esters, which could be due to the steric crowding.

### 4.2. Imidazole-based ligand amphiphiles

Tagaki and co-workers synthesized a series of lipophilic ligands bearing hydroxyl groups for achieving the hydrolysis of carboxylic acid esters [30,33–35]. Each of these ligands (**14**–**18**) possessed functional imidazole and a hydroxyl moiety, and were examined with regard to their catalytic activities toward the hydrolysis of *p*-nitrophenyl-2-pyridine carboxylate in presence of either $Zn^{2+}$ or $Cu^{2+}$ ions and also under co-micellar conditions with cetyl trimethyl ammonium bromide (CTAB). The observed acceleration in the rate was attributed to the formation of a reactive mixed chelate in which the activated ligand hydroxyl function bound to metal ion acted as an effective nucleophile.



**14**



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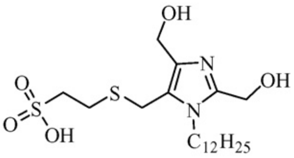

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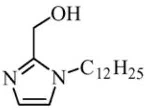

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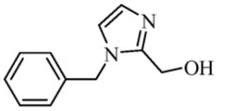
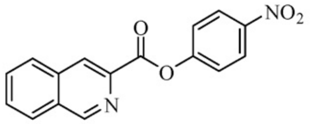
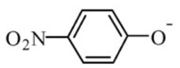


**18**

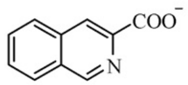
Most of the studies for the hydrolysis of activated esters were performed by monitoring the time-dependent release of leaving group (generally *p*-nitrophenoxide ion) using UV–vis spectroscopy. But the spectrophotometric determination of the rate of deacylation was not been possible in most of the cases as the leaving carboxylate species is often colorless in the UV–vis region. Toward this end, *p*-nitrophenyl isoquinoline-3-carboxylate (PNIQ) **19** was introduced by Tagaki and co-workers [36] as a versatile ester substrate which enabled the kinetic study of both acylation and deacylation steps as the released carboxylate ion was able to complex with the $Zn^{2+}$ ion and was fluorescence active. Several hydroxymethyl imidazole-based ligands (**20**–**23**) were developed and among them **21** and **22** showed better activity for the hydrolysis of PNPP [37]. These ligands formed ternary complexes in which the secondary OH group was selectively activated by coordination with the $Zn^{2+}$ ion to fit into a tetrahedral geometry. The deacylation rate of the ligand–$Zn^{2+}$complex was highest for the ligand **21** which indicated that the deacylation step occurred through an acylated intermediate **24** where the $Zn^{2+}$ ion could attack the carbonyl group in a pseudo-intramolecular manner. Thus the true catalysis of such hydrolysis reactions of PNIQ could be demonstrated by monitoring the rates of both acylation (first step) of a catalyst complex by a UV method and deacylation of the acylated intermediate to regenerate the catalyst-complex by a fluorescence method.



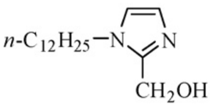
**19** ( PNIQ)



UV detection @ 400 nm



Fluorescent detection @ 344 nm (emission)



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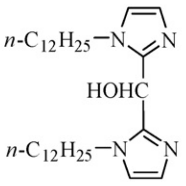
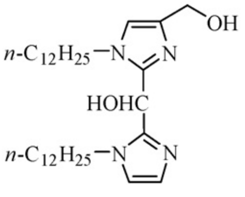


**21**



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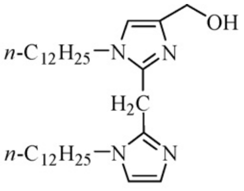

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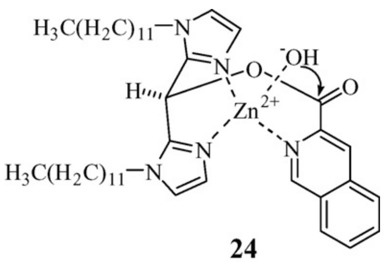
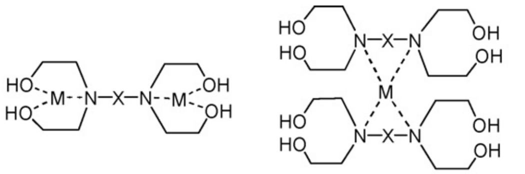


**24**



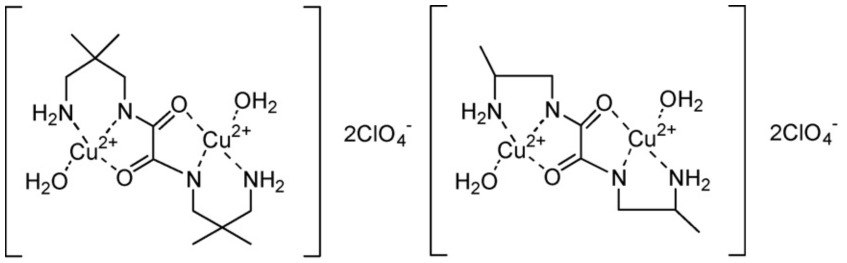
M = Zn, Ni, Cu

(A): X = $CH_2CH_2CH_2$; (B): X = $CH_2(CH_2)_8CH_2$; (C): X = $CH_2PhCH_2$

**Scheme 2.** The structure of complexes in CTAB and Brij 35 micellar solution.

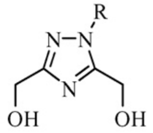
### 4.3. Triazole-based amphiphilic ligands

Recently other function such as 1,2,4-triazole-based hydroxymethyl ligand (**25**) has also been employed to study the hydrolysis reactions in CTAB micelle [38]. In this case the Cu(II) ion showed better catalytic activity compared to Ni(II) toward PNPP hydrolysis. Also an increase in the chain length of the hydrophobic tail manifested better complexing ability leading to the formation of a ternary complex. An extension of this study of the triazole-based ligands was performed using gemini surfactant micelles [39]. The gemini surfactant micelles showed catalytic activity only at optimum concentrations and there was a decrease in activity beyond that concentration of the gemini. This was attributed to the variation of microviscosity of the host gemini surfactants, since the microviscosity increases significantly from single chain surfactant to the gemini [40,41]. The presence of alkyl chain (R) in such ligands also changes the stoichiometry of the complex. In ligand **25**, when there is no alkyl group (R = H), it shows a catalytically active complex with a 2:1 (metal:ligand) stoichiometry (**26**) in gemini surfactant micelle. Interestingly with *N*-alkylated ligands, *i.e.* R = $CH_3$, $C_{10}H_{21}$, or $C_{12}H_{25}$, the stoichiometry changes and forms a 1:1 complex (**27**).

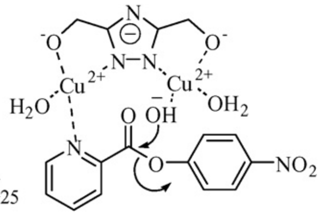


**37** **38**

**Scheme 3.** Structure of oxamido-bridged dinuclear copper(II) complexes.


R = H; $CH_3$; n-$C_{10}H_{21}$; n-$C_{12}H_{25}$

**25**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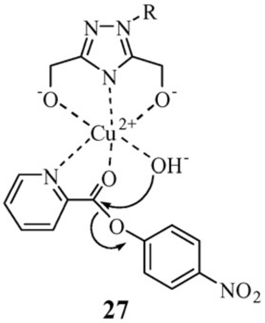
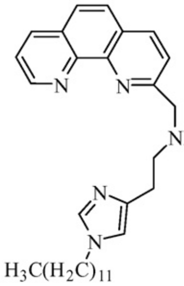
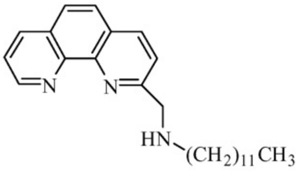

**27**

In ligand **25** when R changes from H to $CH_3$ the efficiency of the catalyst system decreases comparatively. Both the values of the association constant between the metal ion and the ligand and between the substrate and the binary complex for the ligand having R = H were considerably larger. However, the rate enhancement was still not significant. The possible reason for this could be due to the higher solubility of the ligand in bulk aqueous medium due to the absence of an alkyl chain. This rendered the existence of the active complex in the micellar medium untenable, leading to the separation of the reactants. Between the ligands containing long alkyl chains like $C_{10}H_{21}$ or $C_{12}H_{25}$, the rates were remarkably higher than those containing H or $CH_3$ which clearly demonstrated the role of hydrophobicity.

### 4.4. *Phenanthroline-based ligand amphiphiles*

Metallomicelles based on phenanthroline **28**–**33** [42,43] have been developed by Engbersen and co-workers. Of these the ligands **28**–**30** showed their maximum catalytic activity in mixed micellar medium in presence of Zn(II). In contrast between **31** and **32**, the ligand **31** possessing a lipophilic chain was soluble in micellar medium easily and manifested maximum activity in presence of Zn(II) by forming a 1:1 complex. However, **32** showed esterolytic activity in presence of Co(II) with either 1:1 or 2:1 complexation stoichiometry. In comparison to **31** and **32**, the catalytic activity of **33** was 25 times lower demonstrating the involvement of the hydroxyl group in the active complex.


**28**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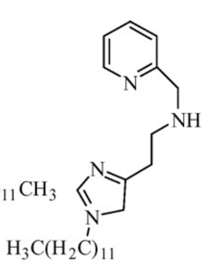
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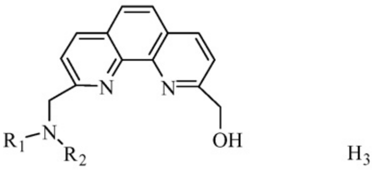
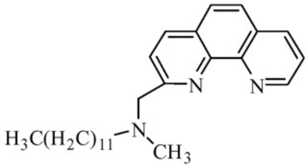
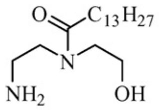
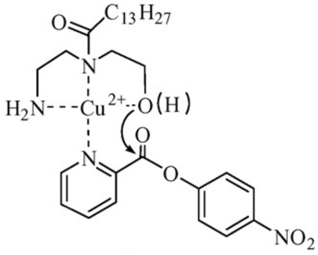

**31** $R_1$ = n-$C_{12}H_{25}$; $R_2$ = $CH_3$
**32** $R_1$ = $CH_3$; $R_2$ = $CH_3$


**33**

### 4.5. *Other ligand amphiphiles*

Instances of other ligands are also known. One such ligand, *N*-myristoyl-*N*-($\beta$-hydroxyethyl)ethylenediamine (**34**) in presence of $Cu^{2+}$-induced cleavage of PNPP [44]. Kinetic studies showed that here also a ternary complex "intermediate" (**35**) was involved in the hydrolysis of the ester substrates.

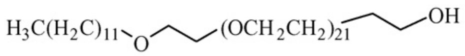

**34**


**35**

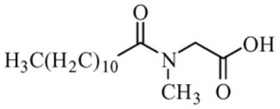
Upon variation of the charge type of micelle, some interesting results were observed. Thus the existence of different complexes **36** (Scheme 2) was evident due to the change in the micellar medium [45]. By performing experiments with various lengths of the bridging ligand, many mechanistic aspects of the catalysis of the hydrolytic reactions were elucidated.

The same metal complex shows a 1:2 stoichiometry between the ligand and the metal ion in the cationic CTAB micelle whereas it is reverse in case of the neutral Brij 35 micellar medium. In both types of micelle the catalytic activity follows the order, Zn(II) < Co(II) < Ni(II) which is in accordance with the polarizability of the metal ions. Thus the stronger is the polarization of the metal ions in the complex, the higher is the esterolytic activity. The effect of bridging ligands shows a trend of activity in the order (C) > (A) > (B). This suggests that with increasing rigidity of the bridge, the rate of hydrolysis of PNPP increases. The rigidity of the ligand makes the two metal ions lie farther from each other and thus minimizes mutual influence of the metal ions on each other. This in turn helps in increasing the activity as in this case the two metal ions in the complex can act on two different substrates.

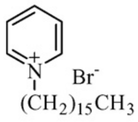
Another class of metallomicelles formed from the oxamido-bridged dinuclear copper(II) complex (**37**, **38**) was developed by Xie et al. [46]. A comparative study of the hydrolysis of substrates, *e.g.* PNPP and PNPA has shown that the rate is higher for PNPP compared to PNPA. Two factors seem to be involved here. One is the presence of a pyridine moiety in the PNPP which is a better ligand for metal ion coordination than an acetate in PNPA. Another factor involves the coordination of hydroxide ion or water molecule with the metal ion. Synergisms of these two effects enhance the catalytic activity in the micellar medium. The better coordination property of the pyridine makes the reaction to occur intramolecularly requiring lesser activation energy barrier. Also the two substrates, PNPP and PNPA show different reactivity order in different micellar conditions. For PNPP hydrolysis, the surfactant hosting metallomicelles follow the order: LSS (*N*-lauroylsarcosine sodium salt) > Brij 35 > CPB (cetyl pyridinium bromide). Thus the surface charge of the micelles plays a key role toward the PNPP hydrolysis. In contrast for PNPA, the order is Brij 35 > LSS > CPB and the effect that plays the major role is the polarity effect of the micelle. When PNPA is used as a substrate, which is more hydrophobic in nature, it gets more solubilized in the Brij 35 micelles. Also the active species generated during the reaction is either cationic or neutral in nature which causes depletion in concentration of the active species in the cationic micelle. This explains why the lowest reaction rate is observed in the cationic micelle, CPB. Between the two complexes **37** and **38** investigated (Scheme 3); **37** have shown better reactivity than **38** toward the PNPP hydrolysis, whereas **38** show higher reactivity toward the PNPA hydrolysis. As mentioned previously PNPA undergoes an intermolecular reaction and hence it is easier to approach PNPA via complex **38** due to less steric hindrance which causes better catalytic activity of the complex **38** toward PNPA. In contrast PNPP undergoes an intramolecular reaction and therefore the *p*Ka of water molecules that are coordinated plays a more effective role here. The *p*Ka of water molecules coordinated with the complex **37** is lower than that of **38** and this increases the concentration of the active species of **37** over that of **38** and consequently leads to better catalytic activity.



Brij 35



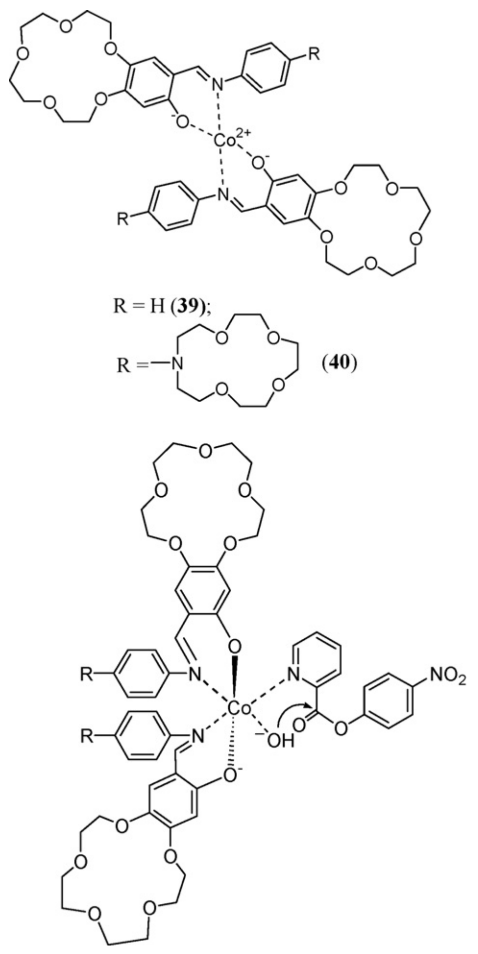
LSS



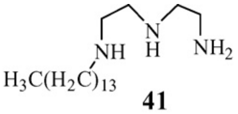
CPB

Another class of benzocrown ether ligand based on aromatic Schiff base has been synthesized by Jiang et al. [47]. These authors investigated the metallomicelles made up of Schiff base Co(II) complexes (**39**, **40**) in monomeric CTAB micelles and in the corresponding gemini micelles of $C_{16}H_{33}–NMe_2{}^+–(CH_2)_6–NMe_2{}^+C_{16}H_{33}$ to effect the hydrolysis of PNPP [47]. The hydrolysis rates were higher in the gemini micellar media in comparison that in the monomeric surfactant micelles [48] and it could be due to the intrinsic differences in the organizations inside two types of micelle. Compound **39** showed greater catalytic activity than that of **40**. In gemini micelles, **39** showed twofold higher activity than that of **40**. This indicates that the steric bulk of the aza-crown moiety in **40** presumably hinders the rate. A mechanism has been proposed in which the metal bound hydroxyl group attacks the substrate in the key rate-determining step (Scheme 4). The steric bulk can also block the active site in the micellar medium. The role of the host surfactant is thus crucial as it provides a hydrophobic pocket for the solubilization of the substrate and also due to the presence of two dimethylammonium head groups in gemini surfactants, which holds ionic part and generates a higher local concentration which enhances the collision frequency among the nucleophile and the substrate. This in turn significantly increases the rate compared to that in the monomeric surfactant micelle, *e.g.* in CTAB.

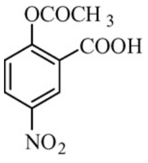
Investigations were also carried out with the metallomicelle mediated esterolysis of different substituents on the substrate [49]. The study showed the effect of metallo-surfactant **41** on the hydrolysis of different aryl esters possessing various substitutions in different positions of the aromatic skeleton (A–D). The presence of a carboxylate anion on the aryl ester manifested an increase in the rate of hydrolysis over the neutral one. The increased rate has been attributed to the favorable electrostatic disposition of the anionic substrate enabling its strong interaction with the metal ion and the cationic surfactant. It was also evident from the rates of ester hydrolysis for the series, which showed the order A ∼ B > C > D. The location of the COO⁻ anion ortho or para to the acyl ester group in the aromatic backbone had little effect on the magnitude of rate enhancement. This suggested a role of stereochemical constraints in the ternary complex for the intramolecular attack. A more appreciable effect has been observed with the addition of surfactant. The influence of cosurfactant on the rate enhancement was dependent on the concentration of metallomicelle or cosurfactant in addition to the substrate structure.



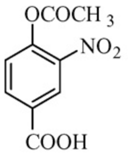
**Scheme 4.** Catalytically active complex formed by crown ether-based Schiff base ligand.



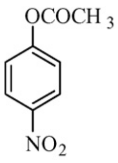
**41**



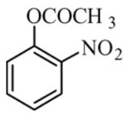
A



B



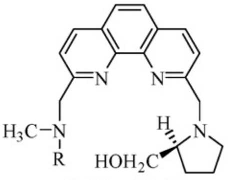
C



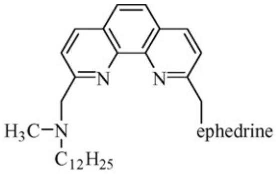
D

## 5. Enantioselective cleavage of esters

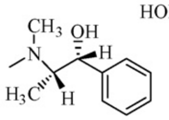
The phenanthroline-based ligands have also been used in exploring the catalytic, enantioselective cleavage of *p*-nitrophenyl esters of *N*-protected amino acids addressing the mechanistic aspects and the effect of different micelles, metal ions, activated complexes and most importantly the origin of stereoselectivity [50]. Each ligand of **42**–**48** possessed one or more chiral centre and showed enhanced catalysis for the hydrolysis of PNPP. Best among them was **42**, which in presence of Zn(II), showed about 6780 times rate enhancement. The ligands when used against the *N*-protected *p*-nitrophenyl esters of D- and L-phenylalanine and D- and L-leucine dissolved in Brij 35 micelles, there was only low rate enhancement toward ester hydrolysis and poor enantioselectivity in absence of metal ions. Metal coordinated complex of **42** however, showed good catalytic rate with significant enantioselectivity. The degree of enantioselectivity obtained was dependent on the nature of the metal ion and also on the rigidity of the complex formed. The nature of the metal ion determined not only the degree of enantioselectivity but also the direction of enantioselectivity. **42**-Co(II) and **42**-Cu(II) hydrolyzed both D-$C_{12}$-Phe-PNP and D-$C_{12}$-Leu-PNP more rapidly than their L-enantiomers.



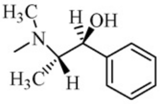
**42**; R = $C_{12}H_{25}$;
**43**; R = $CH_3$

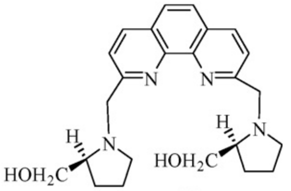


(**44**): (1R,2S)-ephedrine

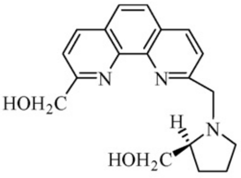


(**45**): (1S,2S)-ephedrine

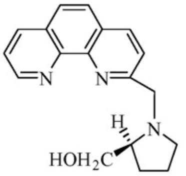




**46**



**47**

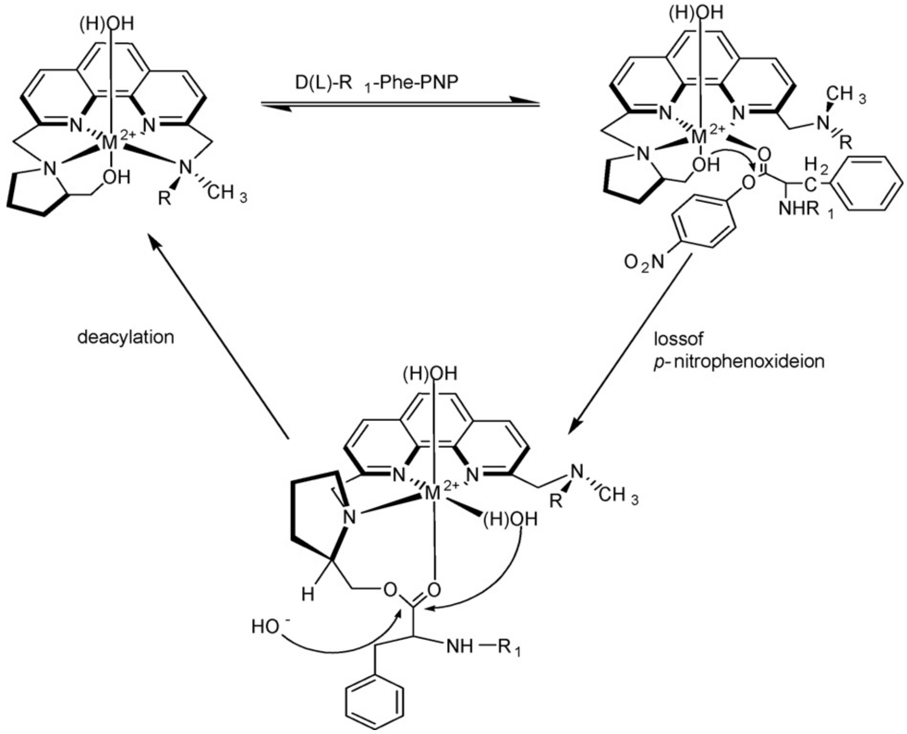


**48**

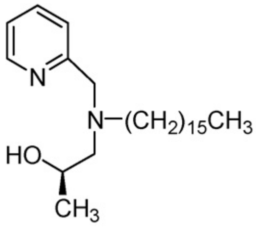
However, the rate and enantioselectivity were different when the corresponding Zn(II) complex was used and inversion in the enantioselectivity was observed. Even the micellar microenvironment influences the stereochemical control. Thus the **42**-Co(II) system in Brij 35 micelles showed higher enantioselectivity. However, it did not show an inversion of enantioselectivity in presence of Zn(II) in Brij 35 micellar system. The ratio of the ligand and the metal ion also influenced the stereoselectivity and different metal ions showed maximal activity at different ratios. The rigidity of the active complex increased as the ligand **42** showed higher activity than others, even better than its non-micellar analog indicating that the micellar microenvironment contributed to the catalytic activity. A plausible reason could be the increased concentration of the reactants in the micellar pseudophase. In addition the increased concentration of $OH^-$ at the cationic micellar interface raises the concentration of the ligand-oxido anion nucleophile.

Along with this the positive charge of CTAB at the stern layer increases the electrophilicity of the metal ion which also boosts the rate. The enantioselectivity of the product formation is mainly caused by the changes in the free energy of different diastereomeric complexes formed, and the proposed model for the complex (Scheme 5) shows the involvement of an octahedral complex. The coordination geometry of the metal ion plays an important role in determining the enantioselectivity as it restricts the motional freedom of the hydroxyl group of the ligand and the substrate. Also the change in the direction of enantioselectivity as in case of **42**-Zn(II) complex demonstrates the crucial role of the metal ions. This originates because of the possibility of different coordination geometry, observed for other reactions also, for instance, with the hydrogenation of prochiral alkene catalyzed chiral $Rh^+$ and $Ru^{2+}$ diphosphine complexes [51]. But there is no evidence which suggests that the individual metal ions operate via different mechanism. Also there is no proof whether a change in the micellar microenvironment affects the coordination geometry of the activated complex. The multi-site interaction in the active complex increases the efficiency of the hydrolytic catalysts [52]. Availability of more number of sites for interactions should give more rigidity to the active complex and increase the selectivity ultimately leading to the enhancement of the enantioselectivity. The involvement of the hydroxyl group in ligand has been extensively studied by Tonellato and coworkers [53]. The ligands based on 2-pyridyl unit and tertiary amine incorporating hydroxyl group (**49**–**54**) were utilized for the cleavage of *p*-nitrophenyl esters of α-amino acids (Phe, Phg, Leu). A comparison of ligands elucidates many mechanistic points. The enantiomers which react faster are the (R)-ligand and (S)-substrate (or vice versa) showing complementarity of the substrate and the ligand interaction. The unprotected amino groups of the amino acids were more enantioselective than the protected ones showing the effect of multi-site binding. An important effect is the disappearance of the enantioselectivity with the alkylation of the hydroxyl group. But in the absence of micellar medium, no appreciable difference in rate has been observed between the hydroxyl and the *O*-methylated species, indicating that in water the hydroxyl group is no longer the nucleophile or it may be possible that amino group in the substrate and the hydroxyl group in the micellar medium. The manifestation of the enantioselectivity could be explained on the basis of an activated complex model (Scheme 6).

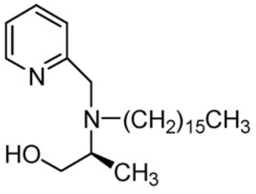
Overall several pieces of experimental evidence indicate that effective hydrolysis in micellar aggregates with **49**–**54** involve



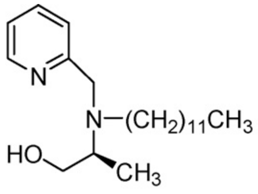
**Scheme 5.** Possible mechanism of hydrolysis of amino acid ester.



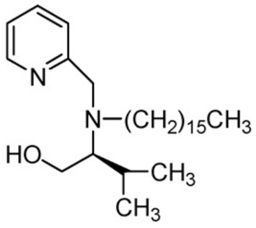
**49**



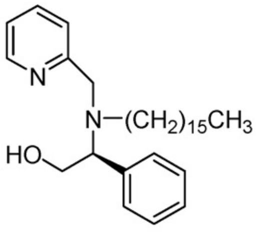
**50**



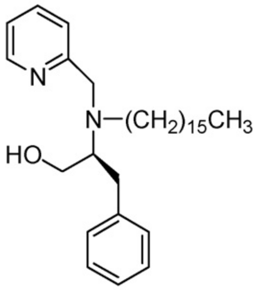
**51**



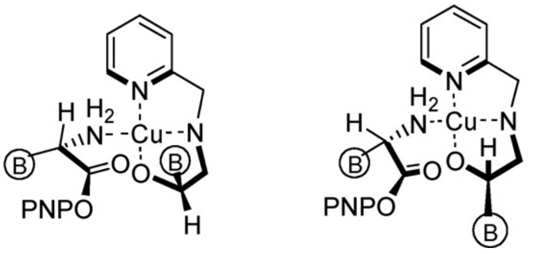
**52**



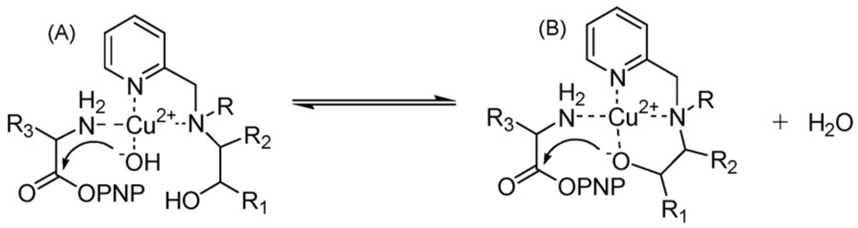
**53**



**54**

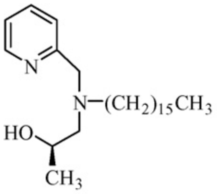


**Scheme 6.** Proposed model showing enantioselectivity.

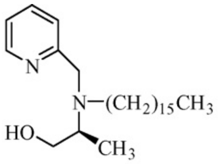


**Scheme 7.** Equilibrium between the active complexes in water and in surfactant aggregate.

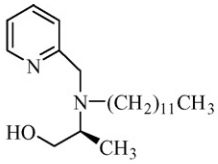
the following: (a) the formation of a ternary (ligand–metal ion-substrate) complex; (b) within such a complex, a nucleophilic attack of the ligand hydroxyl on the substrate to give a transacylation intermediate; (c) the metal ion promoted hydrolysis of the transacylation intermediate with a relatively fast turnover of the catalyst.



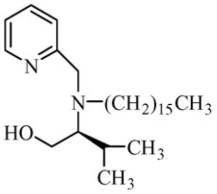
**49**



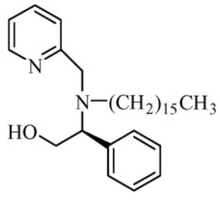
**50**



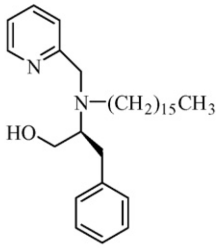
**51**



**52**



**53**

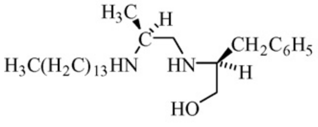


**54**

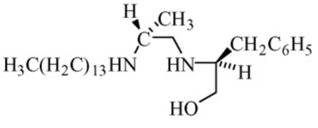
Further the catalytic activities of these ligands were explored in different surfactant micelles such as Brij, SDS and CTAB, and also in vesicles. The surface charge profoundly affects the reactivity [54]. The cationic micelles showed maximum rate enhancement along with moderate enantioselectivity, and the anionic micelles showed the reverse while these parameters were by and large unaffected by the nonionic micelles. In vesicles, the fluidity of the aggregate bilayers affects the enantioselectivity when the surface was cationic in nature. The manifestation of this behavior has been explained on the basis of compartmentalization of the active complex in different loci of the aggregate. On this basis the formation of a ligand–metal ion-substrate complex in water and the aggregate is different and there exists an equilibrium between these compartments (Scheme 7). In water the complex mostly exists as complex, "A" while in the micellar aggregates the complex, "B" prevails. The confinement of the complex in the vesicles is more effective in gel state rather than in the fluid state or in the micelles. The difference in the rate for the hydrolysis of two enantiomers is due to the relative amount of the reaction going via the complex B than the complex A.

In another series of design of amphiphilic ligands, the ligands comprising the 1,2 ethylenediamine as chelating subunit and hydroxyl group have shown remarkable enantioselectivity in their hydrolysis reactions of suitable substrates [55]. The ligands **55**(**a** and **b**) showed the enantioselectivity as high as ~35 in presence of a cosurfactant DMDBAB (ditetradecyl dibutylamonium bromide) when the absolute configuration of both the chiral carbons of the ligand and the substrate was the same. These ligands exist in two forms I (in aggregate) and II (mostly in bulk water) which remain in equilibrium (Scheme 8) as has been discussed earlier. The enantioselection again here is due to the competition between the two forms in equilibrium. The slower process occurs through the complex B where the ligand hydroxyl is displaced by a water molecule and the competition is driven by the interaction of the ternary complex with the surfactant aggregate. But the reason why only one particular complex reacts faster over another in micellar medium is not so apparent.

A remarkable amplification of enantioselectivity was observed upon rapidly decreasing the pH ("pH-jump") of the reaction medium [56]. The strength of the ligand-complex formed was largely affected by the pH of the system, and at low pH, the competition with proton might occur, so that the complex would not form. The ligand **55**(**a** and **b**) co-micellized in CTAB and in presence of metal Cu(II) manifested an amplification in the enantioselectivity from 24 to 58 (ratio of the rate constants for the faster and slower reacting enantiomer, respectively) upon decreasing the pH from 9 to 5. This change occurs because the rate of decomplexation lies between the rates of cleavage of the two enantiomers, and as pH is abruptly decreased, it causes the complex to undergo decomplexation again.

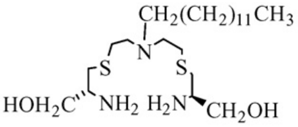


**55a**

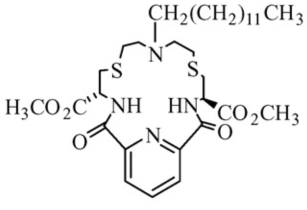


**55b**

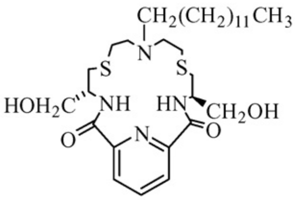
A good deal of work has been done by You et al. in eliciting the enantioselective cleavage of the α-amino acid esters. Many different types of ligands based on chiral sulfur containing moieties including macrocycles **56**–**58** [57], pyridyl β-amino and other related ligands **59**–**63** [58] have been utilized for the evaluation of the cleavage kinetics. Each ligand of **56**–**63** exhibited moderate enantioselectivity and possessed certain common features. The enantioselectivity was highly affected by the micellization, and by the rigidity of the complex along with the choice of the transition metal ion. The catalytic effect is a result of the synergistic co-operation between the ligand and the metal ion. The ligands containing hydroxyl group show that the hydroxyl group acts as a nucleophile if it is in proximity with the metal ion. Thus alkylation of the OH group almost diminishes the catalytic activity, even sometimes causes an inversion of the enantioselectivity. The substrate structure also influences the rate of hydrolysis. Thus an increase in the size of the side chain in the amino acid ester from methyl (in alanine) to benzyl (in phenylalanine) increased the selectivity from 2.55 to 7.81 [58].



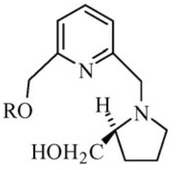
**56**



**57**

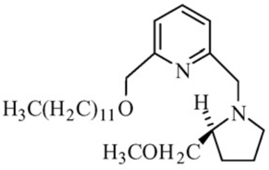


**58**

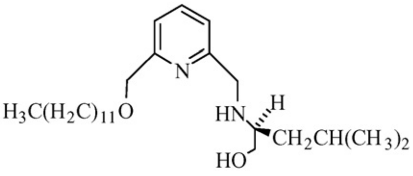


R = $CH_3$; $n$-$C_{12}H_{25}$

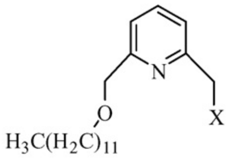
**59**



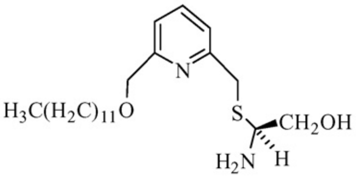
**60**



**61**



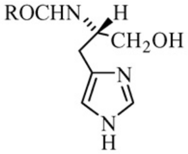
**62a;** X = (1R, 2S)- ephedrine
**62b;** X = (1S, 2S)-ephedrine



**63**

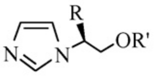
A similar observation is noted where the reactivity follows the order Ala < Leu < Pro (amino acid esters) [59]. Thus the hydrophobic interaction increases both the rate and the enantioselectivity. Almost all the ligands undergo the catalytic cycle through formation of a ternary complex intermediate.

Imidazole-based ligands have evolved special interest because imidazole (histidine) is found in the active sites of many hydrolytic enzymes. Ligands **64**–**65** [59,60] were developed and these showed good catalytic power along with enantioselectivity. The ligands incorporate one chiral centre in it and show similar characteristic as discussed earlier although these form different ligand:metal (2:1) stoichiometry in the kinetically active ternary complex (Scheme 9) [59]. The choice of an appropriate solvent increases the enantioselectivity to a great extent, but at the same time, the rate decreases considerably mainly for the lipophilic ligands [60]. These complexes were less soluble in water and when the solvent composition was changed from pure water to a 9:1 water/THF mixture, there was an increase in the enantioselectivity. However the rates decreased due to this change [60].



**64**

R = $n$-$C_{11}H_{23}$; $CH_3$

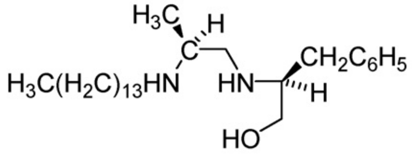


**65**

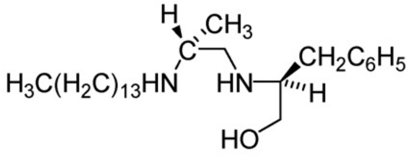
R = $CH_3$; $CH_2CH_2CH_2O(CH_2)_{15}CH_3$
R' = $n$-$C_{16}H_{33}$

## 6. Hydrolysis of phosphate esters

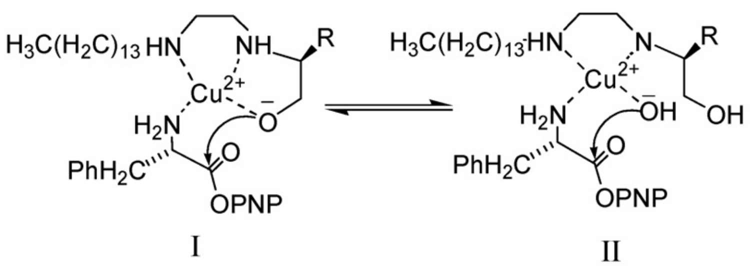
Along with the hydrolysis of the activated esters and the amino acid esters, extensive studies were performed on achieving the hydrolysis of phosphate esters by metallomicellar catalysts. These studies are very important as many of the lethal compounds used as chemical weapons are organophosphorous compounds known as nerve agents, *e.g.* Sarin, Soman or Tabun, etc. Metallomicellar catalysis has been exploited extensively for effecting the hydrolysis of phosphate ester because of their apparent similarity with some natural enzymes. The first experimental demonstration of metallomicellar catalysis for the phosphate triester PNPDPP (*p*-



**55a**



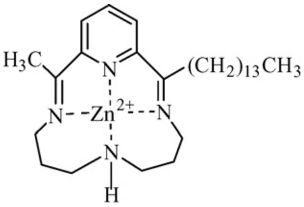
**55b**



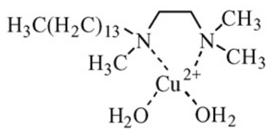
**Scheme 8.** Equilibrium of the active species of ethylene diamine ligand in aggregate (I) and in water (II).

nitrophenyl diphenyl phosphate) hydrolysis was reported in 1986 by Gellman et al. These authors employed a ligand having surfactant like nature **66** enclosed with a head group that could complex specific metal ions [61]. The $Zn^{2+}$ complex of **66** showed significant reactivity towards the PNPDPP cleavage at mildly alkaline pH with catalytic turnover.

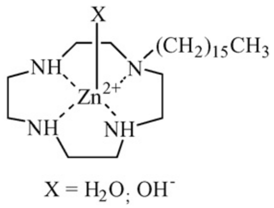
Menger et al. synthesized a $Cu^{2+}$ metallomicellar system **67** which showed effective catalysis towards the hydrolysis of phosphotriester PNPDPP [62]. The metallomicellar aggregate **67** showed ~$10^5$ fold rate enhancement with catalytic turnover behavior in the cleavage of PNPDPP over the buffer solution devoid of micelles. The metallomicelles here act as catalysts for the hydrolysis of phosphate ester in a similar way as they do for activated carboxylate esters. The central metal ion acts as a Lewis acid coordinate with the P = O oxygen, neutralizes the negative charge of the phosphate mono or diesters and along with it decreases the *p*Ka of bound water and help in generating the nucleophile in mild condition of pH. It also helps in the departure of the alcoholic leaving group.



**66**



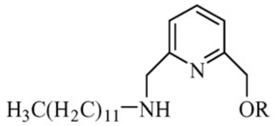
**67**



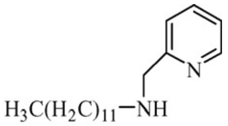
**68**

Kimura et al. also synthesized a lipophilic hexadecylcyclen Zn(II) complex **68** [63]. It showed nucleophilic reactivity towards the cleavage of *tris*(*p*-nitrophenyl) phosphate (TNP) in the comicellar solution of the Triton-X (10 mM). The p*K*a of the Zn bound water was ~7.5. The activity of **66** showed potency for the cleavage of lipophilic substrate, TNP by favorable formation of a supramolecular assembly in the micellar medium (Scheme 10).

The ligands work in a different manner for the cleavage of phosphotriester than the way they act for the hydrolysis of carboxylate and amino acid ester substrates. Scrimin et al. emphasized on the difference of catalyzing activity of pyridine-based ligands for the hydrolysis of different esters [64]. Ligand **69** bearing a hydroxyl group was a very efficient catalyst for the cleavage of carboxylic acid ester. However, the corresponding methylated analogue, **70** or the analogue **71**, which did not have the hydroxyl moiety, could not cleave the PNPH effectively. The reactivity of **70** was ~21 times lesser than that of **69** for the carboxylate ester hydrolysis. However, for the hydrolysis of PNPDPP, **70** was two times more reactive than **69**. The hydroxyl moiety plays a crucial role in the hydrolysis of carboxylate ester but not required for the hydrolysis of phosphotriester. The difference in the behavior originates from the differences in the stoichiometry of the activated complex formed during the hydrolysis. The most efficient stoichiometry for ligand **69**, either in the cleavage of PNPH or PNPDPP, was 2 (ligand):1 ($Cu^{2+}$). Surprisingly, in case of the methylated ligand **70**, the optimum stoichiometry switched to 1:1.



**69**; R = H
**70**; R = $CH_3$



**71**

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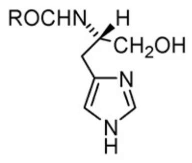
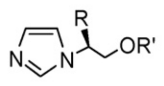
Two different types of ligands, one bearing a hydroxyl and the other devoid of it form different types of active complexes for the catalysis (Scheme 11). The hydroxyl bearing ligands forms ternary complexes, *e.g.* (I) and (II) as effective species whereas (III) and (IV) are the type of complexes formed by those ligands which do not possess any hydroxyl group. Similar observation was also reported by Menger and co-workers [62,65] and Morrow and Trogler [66]. The difference in the behavior could be because of the differences in the binding constants of the carboxylic acid ester and the phosphate ester with the central metal ion. Chin and Jubian evaluated the binding constant of methyl acetate with $Cu^{2+}$. 2,2′-Dipyridylamine complex to be low [67]. But the affinity of P = O in phosphate ester for the $Cu^{2+}$ was much greater [68].

Different phosphate esters show variable reactivity towards the metallomicellar catalyst. Scrimin et al. have addressed this issue



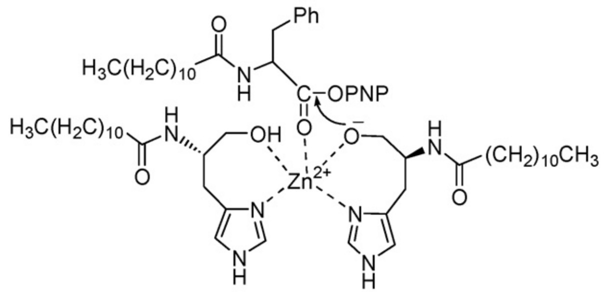
**64**

$R = n\text{-}C_{11}H_{23}$; $CH_3$

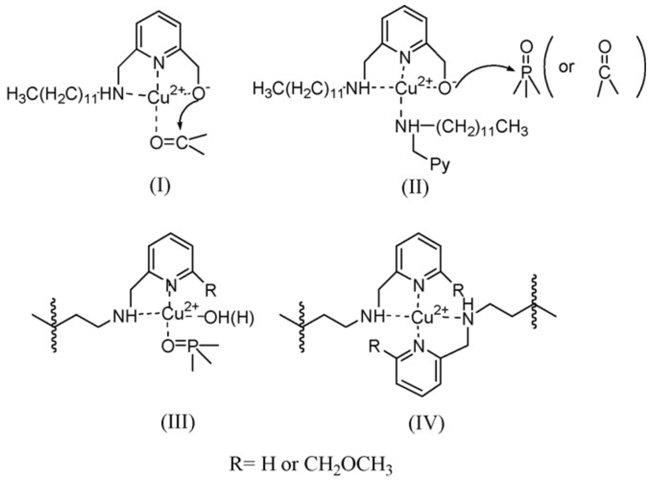


**65**

$R = CH_3$; $CH_2CH_2CH_2O(CH_2)_{15}CH_3$
$R' = n\text{-}C_{16}H_{33}$

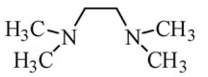


**Scheme 9.** Hydrolysis of the activated ester by the micellized imidazole-based ligands.

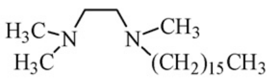


**Scheme 11.** Active complexes formed by the ligands containing hydroxyl groups (I and II) and those devoid of hydroxyl moiety (III and IV).

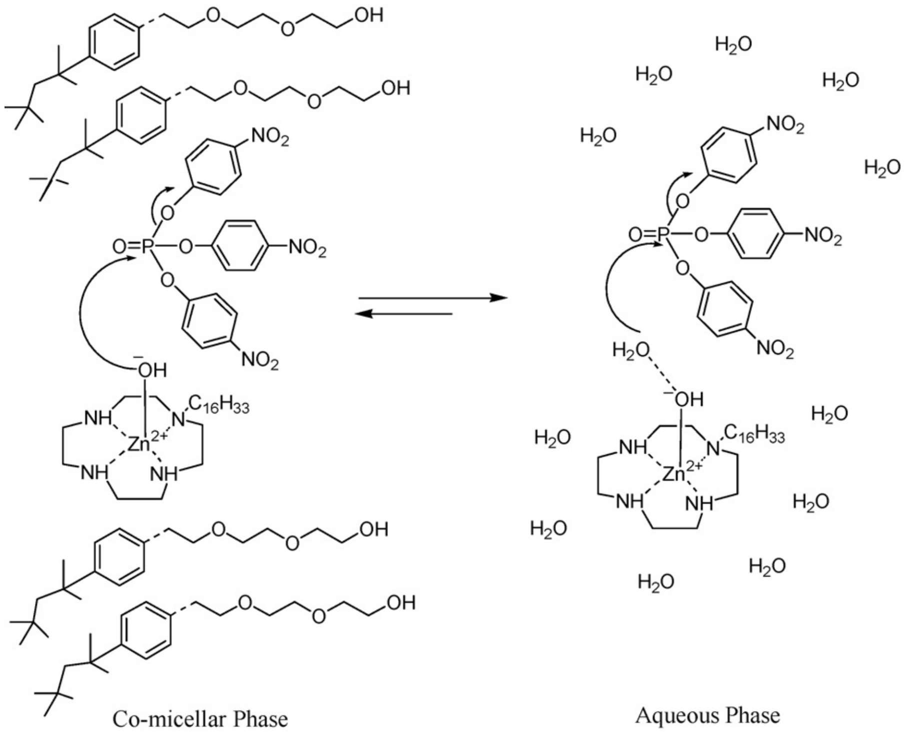
using the Cu(II) complex of tetramethylethylenediamine **72** and the amphiphilic *N*-*n*-hexadecyl-*N*,*N*′,*N*′-trimethyl ethylene diamine **73** in comicelles of $CTANO_3$ to investigate the comparative reactivities of phosphodi- and tri-esters and also to access effect of the amphiphilicity of the ligand involved [69]. The pseudo-first-order rate constant for the hydrolysis was almost one order of magnitude larger for the micellar catalyst, **73** than that of **72** although the second-order rate constants were higher for the hydrophilic catalyst **72**. The electrophilic assistance of the metal centre plays a major role in the hydrolysis of the phosphotriester, as the ligand **72** bound hydroxyl works better than the free hydroxyl. In contrast, the hydroxyl bound to **73** was even poorer regardless of the structure of the ester, as electrophilic assistance diminishes in the micellar medium. But in case of the phosphodiester, the hydroxyl bound to both the **72** and **73** are better nucleophiles than the free $HO^-$ ion. Partial neutralization of the negative charge on the diester could be responsible for the manifestation of this behavior. Indeed in many micellar mediated bimolecular reactions the second-order rate constant at the micelle–water interface are similar to, or somewhat lower than corresponding reactions of the monomeric species in water [70,71].



**72**

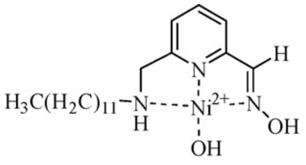


**73**



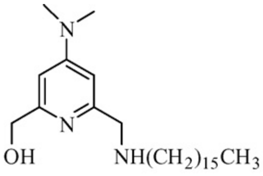
**Scheme 10.** Favorable attack mediated by $Zn^{2+}$-based catalysts in the micellar medium.

Tecilla and co-workers have prepared ligands featuring a 6-alkylaminomethyl-2-pyridinealdoxime moiety, **74**. The corresponding Ni(II) and Zn(II) complexes showed significant reactivity toward the hydrolysis of PNPA and PNPH [32]. Metallomicellar aggregates composed of **74** and CTAB are effective in promoting the cleavage of substrate and the rate acceleration depends strongly upon pH. The second-order rate constants showed that the enhanced reactivity of the metallomicellar system was due to higher local substrate concentration and microenvironmental pH effects. Notably the system showed truly catalytic hydrolytic behavior with a turnover rate approaching that of the cleavage.

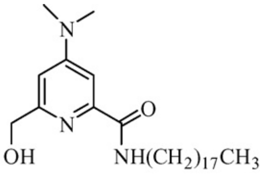


**74**

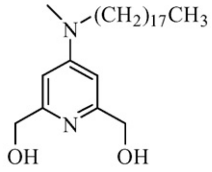
Bhattacharya et al. reported three 4,4′-(dialkylamino)pyridine (DAAP)-based ligand amphiphiles **75**–**77** [72]. These ligands showed modest rate acceleration at pH 7.6 in CTAB comicellar medium toward the hydrolysis of PNPH and PNPDPP when compared to rates in CTAB micelles only without ligands. But introduction of Cu(II) in the micellar medium made these ligands effective catalysts for the hydrolysis of both PNPH and PNPDPP. For each ligand a 2:1 complex ligand/Cu(II) afforded the most kinetically competent species. All the Cu(II) complexes demonstrate catalytic turnover in the hydrolysis of both PNPH and PNPDPP at pH 7.6 in CTAB micelles. Interestingly however, while **75** and **76** showed 'Burst' type kinetics in the presence of excess substrates, **77** manifested a fast turnover.



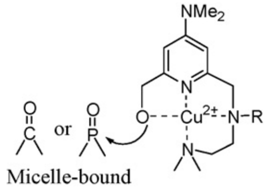
**75**



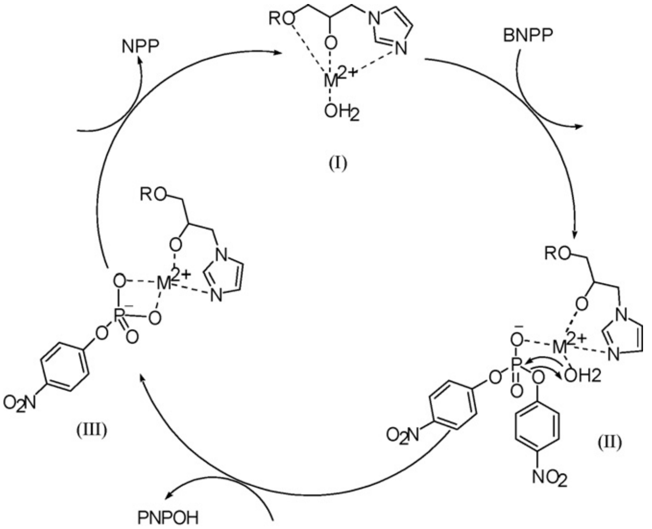
**76**



**77**

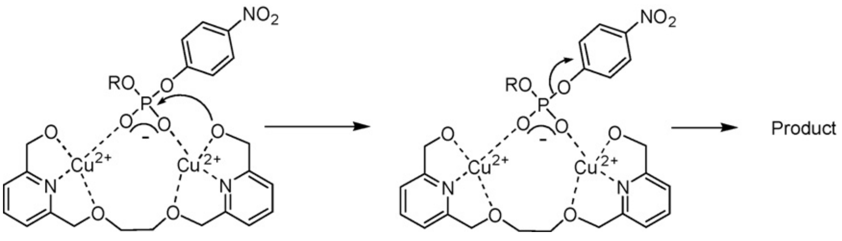


**Scheme 12.** Active species formed by the tetradentate ligand.

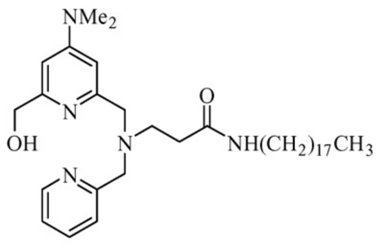


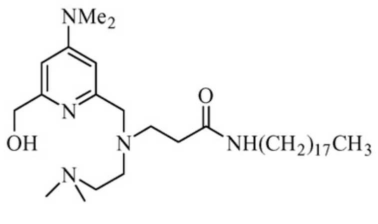
**Scheme 13.** Proposed mechanism of the BNPP hydrolysis by metallomicelles of **82** and **83**.

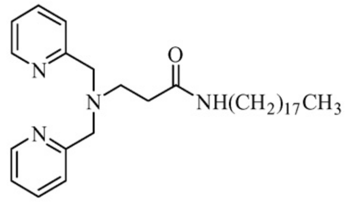
These authors then developed tetradentate ligands, **78** and **79** and compared the catalytic activity against their analogous tridentate ligands, **80** and **81** [73]. In absence of a metal ion, ligand **79** alone in CTAB micelles showed moderate rate enhancements for the hydrolysis of PNPH or PNPDPP. Other ligands showed moderate rate enhancements only for the hydrolysis of PNPDPP and not for PNPH in cationic micellar medium. This could be due to the involvement of 'supernucleophilic' DMAP moiety, although the reason for ligand **78** not showing esterolytic activity was not apparent. The involvement of Cu(II) ion enhanced the catalytic activity of all the ligands, but the tetradentate ligands (**78**–**79**) were superior to those of the analogous tridentate ligands. All the ligands evidenced formation of complexes in 1:1 ligand to metal ion ratio (Scheme 12). These results indicate that the presence of a pendant –$CH_2OH$ moiety plays an important role in activating the hydrolyzing species. Notably these metallomicellar also displayed true catalytic turnover in the hydrolysis reactions in presence of excess substrates.

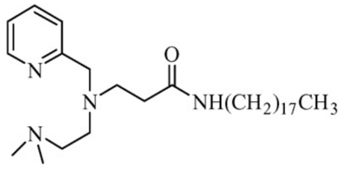


**Scheme 14.** Proposed mechanism of the phosphodiester hydrolysis.


**78**

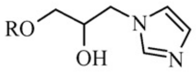

**79**

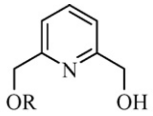

**80**


**81**

## 7. Phosphodiester and phosphomonoester hydrolysis

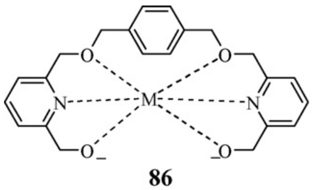
Jiang et al. developed various ligands based on long alkanol imidazole [74], or pyridine moiety [75,76]. Imidazole containing ligands **82** and **83** showed good hydrolyzing ability in presence of Cu(II), Zn(II) and Ni(II) toward bis (*p*-nitrophenyl) phosphate (BNPP) [75].

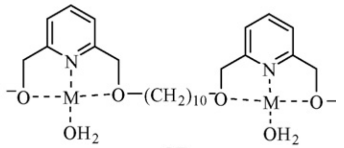

**82;** R = *n*-$C_4H_9$
**83;** R = *n*-$C_{12}H_{25}$

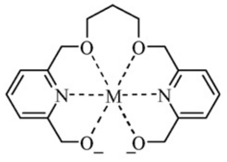

**84**; R = *n*-$C_{12}H_{25}$
**85**; R = $CH_3$

Ligand **83** showed higher rate than **82** toward the BNPP hydrolysis. The hydrophobic interactions between the substrate and the metallomicellar catalyst cause an increment in the local concentration of the catalyst which ultimately results into enhanced hydrolysis rate. A similar behavior was shown by pyridine-based ligands **84** and **85**, where **84** was more effective than **85** [75]. An increase in the hydrophobic chain length causes an increase in the hydrophobic interactions with the micellar assemblies which helps in decreasing the activation energy barrier of the hydrolysis reaction. The hydrolysis most probably follows a ternary complex pathway (Scheme 13). The metal complex adopts an octahedral geometry, in which the hydroxyl group is activated by coordination with the metal ion and the p*K*a is reduced to generate an effective nucleophile. This is followed by the displacement of RO coordination to the metal ion by the introduction of the phosphoryl anion of the substrate [37,77]. This finally results into the expulsion of *p*-nitrophenol (PNPOH) and release of *p*-nitrophenyl phosphate (NPP) to regenerate the catalyst.

The pyridine-based ligands form 2:1 complex of ligand with different metal ions, which produce esterolytically activated complex [75]. The catalytic activity follows the order, $Cu^{2+} \sim Zn^{2+} > Co^{2+} \sim Ni^{2+}$, which is consistent with the polarizability of the central metal ion. Thus the stronger is the polarization of the metal ion, the higher is the reactivity of the activated complex. Recently the catalytic effect of metallomicellar complex made up of ligands, **86**–**88** possessing hydrophobic methylene bridges embedded in CTAB medium was studied by Jiang et al. These catalysts induced the hydrolysis of both the monoester NPP and diester BNPP in micellar media [78].


**86**


**87**

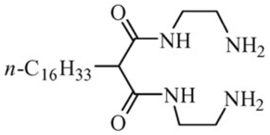

**88**

M = $Cu^{2+}$, $Zn^{2+}$

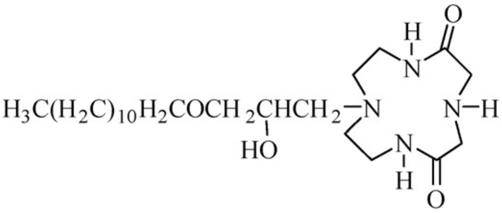
Among these ligands, **87** has shown the best activity and this can be attributed to two factors: (i) the ligand **87** possesses a lipophilic polymethylene chain which increases its hydrophobic interactions with the micelles and (ii) also **87** is prone to form dinuclear complex where the hydrolysis is considerably easier [79]. The mechanistic aspects with these complexes were examined. According to the authors, a higher p*K*a of the hydrated Zn(II) leads to the greater activity of its metallomicelles for hydrolysis than that of its counterpart based on Cu(II). However, at lower pH the Cu(II) metallomicelles are more active possibly because of easy deprotonation of the hydroxyl in ligands by Cu(II) at lower pH. Interestingly the catalytic efficiency of the Cu(II) and Zn(II) metallomicellar systems are higher for the hydrolysis of the monoester NPP than that of the diester BNPP. Also the Zn(II) metallomicellar system has shown better activity than the corresponding Cu(II) system for the hydrolysis of both NPP and BNPP. The reason could be due to the differences in the three-dimensional structure of the ligands. The ligands **84** and **86** both form mononuclear metallomicelle with metal ions giving rise to a tetrahedral geometry. According to coordination chemistry, Cu(II) easily forms quadrilateral complexes while, Zn(II) forms tetrahedral complexes because of its $d^{10}$ electronic configuration. In order to make a tetrahedral geometry, Cu(II) needs to change the steric structure, which in turn requires higher energy. Also the association constant of the complex with the metal ion and the substrate is highest for the ligand **87**. This association ability can be correlated to the noncovalent reciprocity of the metal complex with the substrate and also the flexibility of the ligand [80,81].

The phophodiester was the most stable kinetically among all the phosphate esters.

Cheng et al. studied the phosphodiester cleavage of BNPP using Cu(II) with the ligand **87** [82]. Examination of rate constants as a function of ligand to metal ion stoichiometry of the active complex shows the peak activity with a ligand/metal ratio of ~2:1 in CTAB micellar medium in the pH range of 7–8.5 (Scheme 14). The metallomicellar catalyst bound on Cu(II) complex of lipidated multiamine ligand **89** has been reported recently for the hydrolysis of BNPP [83]. The ligand forms a 1:1 complex with the Cu(II) ion. The analogous ligands having shorter alkyl chains of C-4, C-8 and the one without alkyl chain have been compared. The introduction of a long chain caused enhancement in the rate with the increase of the hydrocarbon chain length. Compared to the ligand having no lipophilic chain it was almost 100 times higher. The presence of a long hydrocarbon chain in such ligand changes the partitioning of the resulting system into micellar pseudophase and reduces the polarity and the local dielectric constant. The pendant-OH groups in the ligands of metallomicelles have shown remarkable effect in the hydrolysis of the activated esters and also on the amino acid esters as discussed earlier. Such a functional group also showed profound effect toward the hydrolysis of BNPP [84]. Toward this end, a long chain alkyl substituted 2,6-dioxo-1,4,7,10-tetraazacyclododecane **90** has been synthesized by Xie et al. and its hydrolyzing activity was investigated in presence of various metal ions, *e.g.* Zn(II), Cu(II), Ni(II), and Co(II) with which it forms a 1:1 penta-coordinate complex. In co-micellar medium, these complexes showed good catalytic ability for the hydrolysis of BNPP. Also the temperature effect has been studied and upon increase in temperature the rates of the hydrolysis reactions increase [84].



**89**

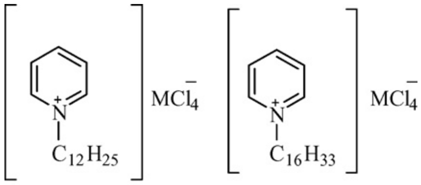


**90**

## 8. Decontamination of organophosphate toxins

Metallomicelles play catalytic role in a variety of chemical reactions. One of the important roles played by the metallomicelles is in the catalytic decomposition of the analogs of toxic organophosphorous agents [85,86]. Badawi et al. reported metallo-surfactants **91** and **92** comprising long chain incorporated pyridinium salt along with transition metal ions such as Cu(II), Fe(III), Co(II) and Cr(III). These authors investigated the catalytic destruction of Malathion [85] and Paraoxan [86] using such catalytic systems.

The metallomicelles made of **91** have shown good catalytic activity for the cleavage of Malathion. Thus the half-life of degradation of Malathion using **91**a proceeds ~158 times faster while the same is ~260 times faster with **91**b than that in the absence of the catalyst. The differences arise because of Fe(III) complex (cmc = $2.983 \times 10^{-2}$ M) is more surface active than the Cu(II) complex (cmc = $2.508 \times 10^{-4}$ mol $L^{-1}$). The half lives of the Paraoxan degradation have been ~16.5 and ~28.9 min, respectively in presence of Co(II) and Cr(III) complexes. For the hydrolysis of Paraoxon, the Co(II) complex **92**a showed greater activity than that of Cr(III) complex **92**b. This is because of the higher $K_{stab}$ value for the Cr(III) complex which leads to greater stability of the intermediate complex. The authors conclude that the catalytic activity in all such hydrolysis reactions arise due to the polarization of the P = S group by metal ions and due to micellization which is known to facilitate reduction [86].



**91**a M = $Cu^{2+}$ **92**a M = $Co^{2+}$
b M = $Fe^{3+}$ b M = $Cr^{3+}$

## 9. Concluding remarks

Although numerous natural hydrolytic enzymes have been isolated and a few of them have been characterized by single crystal X-ray diffraction, the design and synthesis of hydrolases based on metallomicellar ensembles are of significant utility and importance. The rationale for the design of such hydrolases is to create a system or a reagent that can be used in aqueous media for application in molecular biology and also for practical purposes such as organophosphate decontamination or enantioselective catalyses. The other important objective is to adequately understand the functioning of active sites of natural hydrolases from the principles of coordination chemistry. Although a substantial body of literature has been developed as presented in this review dealing with such design and synthesis and alternative strategies, there is a great deal of work that still needs to be done. For instance the role of host surfactants, such as the influence of host micelles and other aggregates, in terms of the molecular architectures [87] of the host amphiphiles or the role of other media such as microemulsion or vesicles [88] need to be probed for the elucidation of optimum conditions of achieving catalysis.

The present review confines itself to handful of examples, which demonstrate the ingenious exploitation of metallomicellar systems for specific hydrolysis reactions. Future design of more sophisticated metallomicellar systems holds the key to improve our understanding on the role of metal ions in natural hydrolase enzymes and to apply them for various practical purposes.

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