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REVIEW COMMENTARY

SUPRAMOLECULAR METALLOCATALYSTS FOR THE CLEAVAGE OF AMINO ACID ESTERS

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Transition metal ions are effective catalysts of the hydrolytic cleavage of amino acid esters and their effects can be enhanced and properly directed when they are chelated to functionalized ligands. The resulting metallocatalysts are attracting increasing attention and the systems so far investigated are briefly reviewed. Particular emphasis is given to supramolecular systems which may add to the metallocatalysts the benefits of the cooperativity, set upon convergent non-covalent interactions of their components, needed for substrate recognition. The results obtained with metallomicellar aggregates and molecular metalloreceptors, with particular reference to those studied in the authors' laboratory, are reported in more detail. In the case of loosely structured metallomicelles, remarkable accelerations and, generally, modest selectivities have been observed; less spectacular kinetic effects, but promising substrate selectivity, have been obtained with structurally well defined metalloreceptors.

INTRODUCTION

The hydrolytic cleavage of amino acid esters, to say nothing of peptides, has been extensively investigated owing to the relevance of this class of compounds in biological systems. Metal ions may be effective catalysts of the hydrolytic process and many studies have been devoted to the understanding of their role and of the mode of action of hydrolytic enzymes (metalloenzymes) which chelate metal ions, notably Zn(II), at their active site.

This paper addresses the issue of metal ion catalysis of the hydrolysis of amino acid esters, with particular reference to supramolecular metallocatalysts in which the cooperation of several molecules is involved in the process.

The examples discussed are largely taken from our research work in Padova. An exhaustive coverage of the matter is beyond the scope of this paper; the reader interested in a broader knowledge of selected topics is referred to the original literature, of which key references are given.

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TRANSITION ION CATALYSIS IN THE CLEAVAGE OF AMINO ACID ESTERS

Following early evidence of metal ion effects in hydrolysis reactions of amino acid esters published by Kroll[1] in 1952, many investigations, mainly focused on the mechanism of catalysis, have been reported.[2] Remarkable rate enhancements for the cleavage of complexed esters over that of uncomplexed species were observed. For instance, in the hydrolysis of glycine methyl ester, the accelerations are as large as 10^5 with Cu(II)[3] and 10^7 with Co(III)[4]. Most of the rate benefits were shown to result from positive entropic contributions. More recently, owing also to a better definition of the structure of some metalloenzymes such as carboxypeptidase A[5a] (CPA), simple models have been designed and investigated[5b] to mimic at least some features of the much more complex biological systems.

Key issues concerning the catalytic role of metal ions in hydrolytic systems include (see Scheme 1) (i) the direct coordination of the ester (or amide) carbonyl group to the metal ion (Lewis acid-type catalysis), (ii) the activation of the nucleophile due to possible coordination and (iii) the geometry of the complex (for instance, α-amino acid esters are more sensitive to metal ion catalysis than those of β-amino acids).

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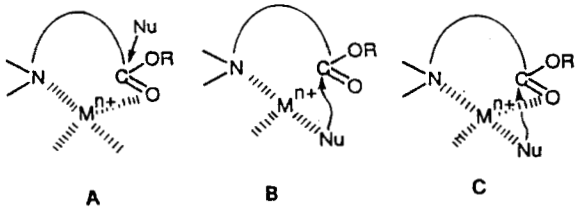
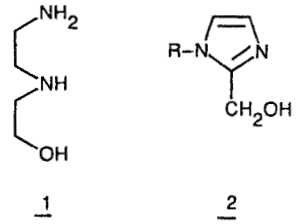


Scheme 1

Convincing evidence for the coordination of the carbonyl in the case of α-amino acid esters[6-8] and not in that of β-amino acid esters[9,12] has been reported. Whether the effective nucleophile, such as HO^-, is coordinated to the metal ion is still an open question. From a study of the hydrolysis of an α-amino acid amide coordinated to Co(III), Schepartz and Breslow[10] suggested that Lewis acid catalysis is the main source of the rate enhancements in the case of CPA and related metalloenzymes (A in Scheme 1). On the other hand, Groves and Baron[11] pointed to the key role of the metal ion-coordinated HO^- (B in Scheme 1) in the cleavage of a β-amino acid amide containing a pendant ligand subunit. A similar conclusion was also reached by Wells and Bruice[12] from a kinetic study of particular β-amino acid esters employing Co(II) and Ni(II). The leaving group effect in the metal ion-catalysed hydrolysis was also investigated. Interestingly, in the case of the hydrolysis of the esters of picolinic acid (an α-amino acid) in the presence of transition metal ions, Fife and Przystas[6] reported that the leaving group effect is virtually negligible up to the case where the pK_a of the leaving alcohol is *ca* 12·5; with esters made of alcohols of higher pK_a (and, by inference, in the case of amides), the rate-determining step changes from the formation (HO^- attack) to the breakdown of the tetrahedral intermediate.

Metalloenzymes bind substrates at their active site where the metal ion and nucleophilic species are properly located for the catalysed process. Using such a scheme as a guide, ligand molecules containing a nucleophilic function, mainly an alcoholic group in the proximity to the chelating subunit, have been designed and investigated. This is the case of ligand **1**,[13] which, when coordinated to Zn(II), is a very effective catalyst of the cleavage of the *p*-nitrophenyl ester of picolinic acid (PNPP) to give the transacylation product resulting from the nucleophilic attack of the activated hydroxyl at the carbonyl group of the ester. Remarkable results were also obtained using 2-hydroxymethyl imidazole (**2**) or pyridine (**3**) derivatives[14] complexed with transition metal ions. In all these cases, the formation of a ternary complex, shown schematically as **4**, has been suggested as the key step, preliminary to the nucleophilic attack of the (activated) hydroxy function in a pseudo-intramolecular process.



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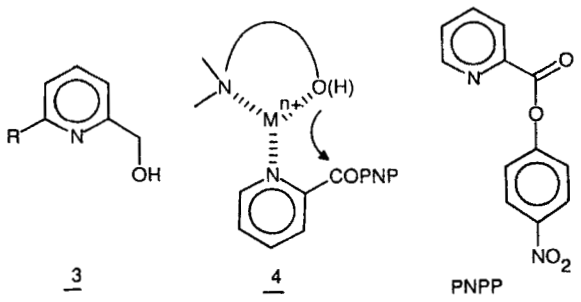

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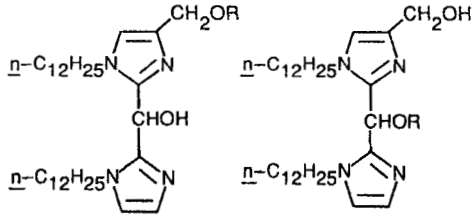
The geometry of the ligand and the nature of the metal ion were shown to be critical for the activation of the alcoholic function. Thus, Tagaki *et al.*[15] reported that the reactivity of the two ligands **5** and **6** is substantially dependent on the metal ion used: **5** is a better catalyst using Zn(II) which may be coordinated in a tetrahedral geometry in such a way that the hydroxyl (the nucleophilic species) is involved in the coordination sphere. This is not the case for **6**, which is reactive only using Cu(II). This latter ion may be chelated in a planar coordination arrangement with participation of the free hydroxyl. The geometry of the complexes thus plays a crucial role in these simple catalysts and in biological systems. In the case of metalloenzymes and related systems, the complex structure of the protein may constrain the complexes in less predictable geometries, the so-called entatic state,[16] with unexpected consequences.



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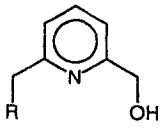
SUPRAMOLECULAR METALLOCATALYSTS

A supramolecular system is made of two or more molecules held together by non-covalent binding interactions. Following Lehn,[17] these systems comprise

supermolecules, i.e. oligomolecular species such as complexes of a receptor and its substrate(s), and molecular assemblies, i.e. polymolecular systems, such as micelles, vesicles and other aggregates, resulting from spontaneous association of surfactant molecules. The chemistry of supramolecular systems usually differs from that of the isolated components. In the case of metallocatalysts, new properties not already observed in the ligand systems may result from supramolecular association.

Metallomicelles

Micelles and other aggregates resulting from the association of functionalized surfactants are systems which operate collectively and may show interdependency and 'group behaviour'.[18] Functional micelles[19] have been extensively investigated in this[20] and in several other[18,19] laboratories. More recently, our[21,22] and other[23,24] research groups have synthesized and investigated the catalytic properties of transition metal ions ligand surfactants which are effective catalysts of the hydrolytic cleavage of α-amino acid and other esters. In our early studies,[22] we focused our attention on amphiphilic molecules, such as **7a–c**



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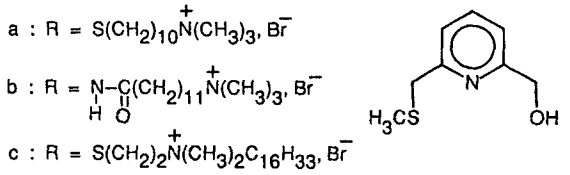

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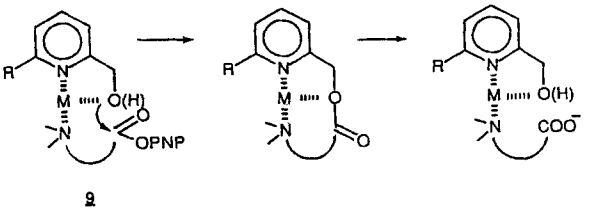
featuring a 2-hydroxymethylpyridine subunit and a hydrocarbon chain bearing, at the opposite end, a quaternary ammonium group.

In the presence of Cu(II), metallomicelles made of these surfactants in buffered (pH ≈ 6·3) aqueous solutions and using PNPP as a substrate, a 10^6 rate enhancement over hydrolysis in the absence of the metal ion was observed (Table 1). As for the mode of action of these aggregates, we showed that the reaction proceeds via the formation of a ternary complex (see **9**, Scheme 2), followed by a template-directed transacylation process and a subsequent metal ion-promoted hydrolysis of the transacylation intermediate. Hence the process proved to be a really catalytic one with fast turnover of the ligand.

Table 1. Observed rate constants,[a] k_ψ (s^{-1}), for the cleavage of PNPP by ligand surfactants **7a–c** in the presence of Cu(II) ions[b]

Ligand	k_ψ (s^{-1})	k_ψ/k_0
None[c]	$9{\cdot}7 \times 10^{-6}$	1
None	0·14	14,433
7a	15·5	1,597,938
7b	7·4	762,886
7c	0·76	78,350

[a] At 25 °C and in MES buffer (pH 6·3).
[b] [Ligand] = $2{\cdot}0 \times 10^{-3}$ M; [Cu(II)] = $4{\cdot}6 \times 10^{-4}$ M.
[c] Without Cu(II) ions.



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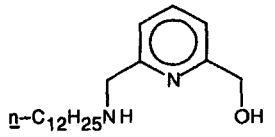
Scheme 2

Ligand **10** proved[25] to be even better and more flexible than **7**. Micelles made of **10** and Cu(II) are effective catalysts of the hydrolysis of PNPP and other α-amino acid esters through the same mechanistic pathway. The very large binding constant of **10** for Cu(II) allowed us to explore several facets of its metallomicelles. Thus, from kinetic experiments carried out at relatively high pHs, the pK_a of the Cu(II)-bound hydroxy group was estimated as *ca* 7·7 in micelles and a 1 : 1 substrate-to-ligand stoichiometry for the kinetically most reactive species could be clearly established in the case of PNPP and other α-amino acid esters. Micelles of **10** and Cu(II) are also effective catalysts of the hydrolysis of non-ligand esters such as activated alkanoates or phosphates; with these substrates, however, the hydrolytic cleavage was shown to occur via a different mechanism. Recently, the leaving group effect in the cleavage of picolinic acid esters by metallomicelles of **10**·Cu(II) was also investigated.[26] Disappointingly, we observed that the dependence of the rate on the pK_a is negligible for alcoholic leaving groups having a pK_a only up to 8–9 (down from 12·5 as observed in the simple metal ion-catalyzed hydrolysis, see above); further experiments are under way to provide a mechanistic explanation.

The key role of the ternary complex ligand–metal ion–substrate involving a tight interaction between ligand and substrate in the cleavage process, stimulated the investigation of chiral ligands as components for



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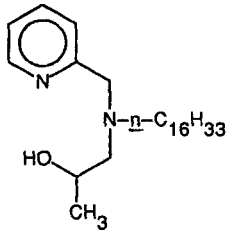
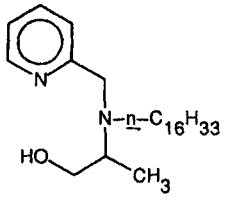


(R) or (S) – 11



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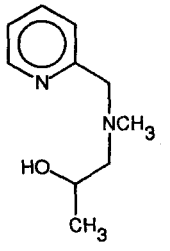
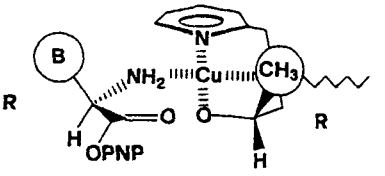


(R) or (S) – 13

enantioselective processes using chiral α-amino acid esters. We synthesized the lipophilic ligand **11** and metallomicelles made of (*R*)- and (*S*)-**11**·Cu(II). Enantioselectivity[27,28] was indeed observed in the hydrolysis of a variety of *p*-nitrophenyl esters of α-amino acids. Enantioselectivity factors ranging from 8 to 15, among the largest ever reported for chiral functionalized micellar aggregates, were observed in the case of the esters of phenylalanine and phenylglycine, being $[Cu(II)] = 8 \times 10^{-5}$ M and $[\mathbf{11}] = 2 \times 10^{-4}$ M. Smaller factors, ranging from 4 to 7, were observed under similar conditions in the process catalysed by metallomicelles of **12**, which features the hydroxy group not directly bound to the chiral centre as in the case of **11**. This can be taken as evidence that the hydroxyl is the actual nucleophile in the cleavage of the ester. This is further confirmed by the results of two sets of experiments. First, metallomicelles made of ligand **11** where the hydroxyl was methylated were shown to be virtually ineffective in promoting the hydrolysis of the *p*-nitrophenyl ester of α-phenylalanine (PhePNP); second, experiments performed using a large excess of substrate over ligand **11** resulted in the rapid release of *p*-nitrophenol in an amount equivalent to that of the ligand, followed by a slower process, i.e. the typical behaviour of turn-over experiments[29] which involve the formation of a transient intermediate, as illustrated in Scheme 2.

For all the substrates investigated, the highest acceleration was observed using the (*R*)-ester and the (*S*)-ligand (and *vice versa*): such enantiorecognition is likely to be the result of negative steric interactions between the two substituents bound to the chiral centres when they are on the same side of the coordination plane of the Cu(II) ion, as indicated schematically in **14** for the case of (*R*)–(*R*) or (*S*)–(*S*) ligand–substrate systems.



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Most interestingly, experiments carried out using Cu(II) and micellar **11** or its analogue **13**, which does not form micelles, showed that only metallomicelles accelerate the hydrolysis of PNPP[30] and other α-amino acid esters, as shown in Figure 1, and that the enantioselectivity effects are much larger in the case of metallomicelles. In the case of (*S*)-**11** and (*R*)-PhePNP, the difference in reactivity at the highest ligand concentration explored amounts to *ca* 10^3, an impressive kinetic effect on going from non-micellar to micellar metallocatalysts.

The effectiveness of micellar over non-micellar ligands may be attributed to higher concentration of the ternary complex due to the favourable partitioning of the substrate in the micellar pseudo-phase, to a higher pH at the micellar interface due to the electrostatic effects of the cationic headgroups of the aggregates and to an enhanced electrophilicity of the metal ion bound to the ligand.[24] The inventory is likely to be extended. In fact, there are indications that the geometry of the complex may assume a distorted geometry in the aggregate with possibly favourable effects in the catalytic action. Thus, from a comparative study of the hydroxy functionalized micellar ligands and of their *O*-methylated siblings, it appears that the hydroxyl acts as a nucleophile in the case of micellar **11**·Cu(II) and not in that of (non-micellar) **13**·Cu(II). Such a behaviour is specific for Cu(II) complexes and not for those with Zn(II), which do not show relevant differences between aggregate and non aggregate systems. From preliminary ESR measurements, it appears that in the micellar assembly the complex **11**·Cu(II) is forced in a distorted, non-planar geometry (leaning to a tetrahedral one which is preferred in the case of Zn^{2+} complexes). Such an effect is clearly reminiscent of the above-mentioned 'entatic state'[16] invoked for the mode of action of some metalloenzymes.

Metalloreceptors

Although micelles presents interesting features as supramolecular metallocatalysts, their rather loose structure

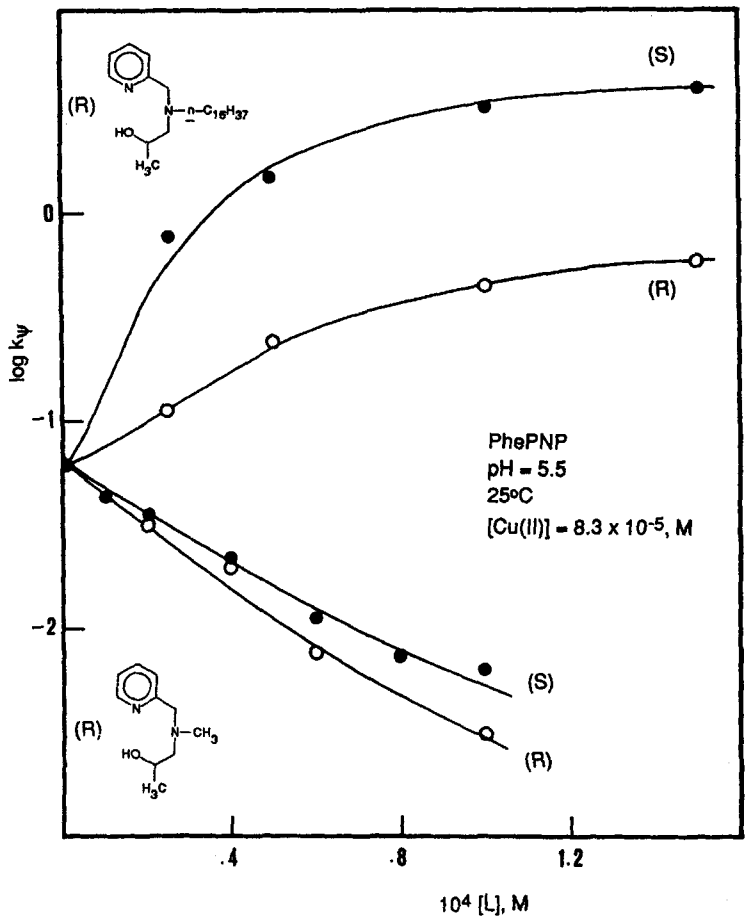
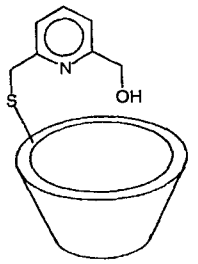


Figure 1. Dependence of the observed rate constant (k_ψ) for the release of *p*-nitrophenol in the cleavage of the enantiomers of the *p*-nitrophenyl ester of phenylglycine on the concentration of ligands (*S*)-**11** and (*S*)-**13**. pH = 5·5; 25 °C; [Cu(II)] = 8·3 × 10^{-5} M

can hardly provide rigid complexation sites needed for binding selectivity. Vesicles[31] are much more ordered systems than micelles and metallovesicles[32] are also being investigated in our laboratory. So far the investigations have been mainly focused on their morphology and on metal ion permeation through the bilayer membrane of the aggregate. Their behaviour as metallocatalysts of the hydrolysis of amino acid esters is also under study;[32b] it appears interesting although complicated by a variety of phenomena not yet fully understood. The search for selective metallocatalysts led us to the design and study of molecular receptors containing ligand subunits and capable of binding metal ions in addition to a proper substrate.

Functionalized cyclodextrins[33] (CDs) are increasingly attractive receptors owing to their ability to bind hydrophobic substrates into their (chiral) cavity with remarkable selectivity and good rate accelerations have been reported in the cleavage of esters.[33b] Further, several ligand-functionalized CDs have been synthesized[34] and some of them have been used as catalysts of the hydrolysis of esters,[34a,35] although not of amino acid esters. Recently, we have synthesized[36] the 2-hydroxymethylpyridine-functionalized β-CD **15**, featuring the same ligand subunit of surfactant **7** linked to the 3-position of one of the glucopyranose rings of the macrocycle via a thioether bond. The receptor binds Cu(II) and the complex was investigated as a catalyst of the hydrolytic cleavage of the *p*-nitrophenyl esters, PNPP, PNPQ and PNPQPh, i.e. of α-amino acids differing for the size of their hydrophobic portion. Such a metalloreceptor provides two distinct sites (the CD cavity and the metal ion) which may compete for substrate binding and, therefore, influence the reactivity depending on the structure of the substrate and on the mode of insertion.



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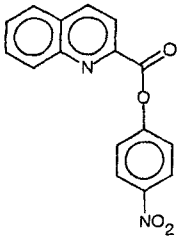
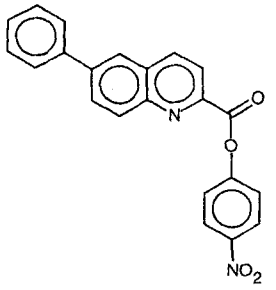


PNPQ

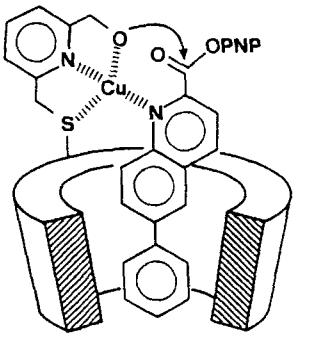


PNPQPh

Comparative kinetic experiments were performed using **15** and the simple ligand **8** in the presence of Cu(II) ions and using native β-CD in the absence of the metal ion. The cleavage of all esters is accelerated by the Cu(II) complexes of **15** and **8**, the latter being more effective than the modified CD. At pH 6·3, under the conditions $[Cu(II)] = 1{\cdot}4 \times 10^{-4}$ M and [ligand] = 8×10^{-4} M, the relative rates (**15**/**8**) are PNPQPh 0·85, PNPP 0·3 and PNPQ 0·26. At pH 9·8 using native β-CD, the rate benefits relative to the hydrolysis in pure buffer follow the reverse order, namely PNPQ > PNPP > PNPQPh.

^{1}HNMR studies indicate that in the case of PNPQPh, the substrate is associated to **15** with the phenyl group fully included inside the cavity and the carbonyl group forced outside towards the metal ion bound to the hydroxy functionalized ligand subunit, as indicated in **16**. Such a productive geometry apparently cannot be reached with the other two substrates featuring a less extended hydrophobic portion. In the case of native β-CD, the nucleophile is one of the secondary hydroxyls of the upper rim[37] and the best geometry for transacylation is achieved with PNPQ. The fact that **8**·Cu(II) is still a better metallocatalyst than **15**·Cu(II) indicates that we have not yet reached the optimum complexation geometry to capitalize on both the CD cavity and Cu(II) complexation sites.

For a receptor to be really selective as a metallocatalyst of the cleavage of amino acid esters, the following different functions should be effective: organization,



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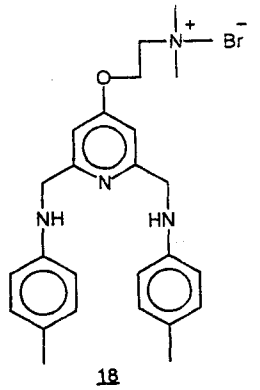
recognition and catalysis. Efforts to synthesize a suitable metalloreceptor have been pursued in our laboratory and, recently, we prepared[38] compound **17**. Such a molecule contains a pyridine subunit and two pairs of different amino groups which may provide two different chelating subunits; it also features three quaternary ammonium groups, which ensure solubility in neutral aqueous solutions, and two diphenylmethane hydrophobic spacers. Ligand **18**, a reduced model of **17**, was also synthesized and investigated for comparison purposes. On addition of two Cu(II) ions which are chelated to the binding sites of the receptor, **17** is forced to organize itself into a pseudomacrocyclic structure, **19**, which may provide a cavity suitable for the inclusion of low-polarity substrates. We thought that an amino acid ester of proper size could be accommodated within the cavity of the metalloreceptor in such a way that when its amino group is coordinated to one resident Cu(II) ion, the carbonyl group interacts with the other one.

The idea was apparently confirmed by experiments performed employing the *p*-nitrophenyl esters of α- and β-amino acid as substrates. The results reported in the rate–concentration plot in Figure 2 were obtained in the case of esters of β-alanine at fixed [Cu(II)] (4×10^{-4} M), pH = 6·3 and 25 °C. Taking as a reference the rate of the Cu(II)-catalysed process, i.e. when the ligand is absent, the hydrolysis of the β-alanine ester is accelerated by addition of **17** and, on the contrary, retarded by **18**, which can bind only one Cu(II) ion. The kinetic version of a Job plot[39] (see Figure 2, inset) clearly indicates that the maximum acceleration is obtained for the complex **17**·2Cu(II). Moreover, under the conditions used in the above experiments, both ligands decrease the hydrolysis rate of the ester of α-leucine to virtually the same extent.

Inspection of molecular model indicates that the β-amino acid ester is of the right size to be included between the two metal ions in **19** and take advantage of the interactions with both of them. In contrast the α-amino acid ester is too short for the inclusion to be



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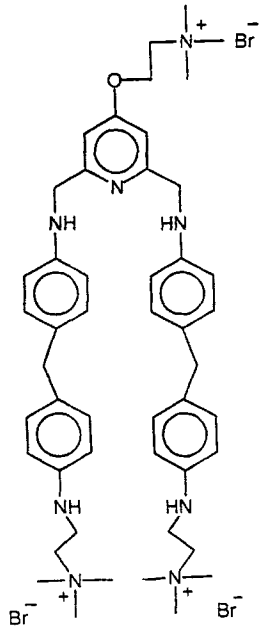

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effective and the ligand competes with the substrate for the metal ion; as a result, an overall retardation of the rate of hydrolytic cleavage is observed. Thus, although the catalytic effects are far from impressive, the polytopic receptor **17** behaves as a selective catalyst and the results obtained so far stimulate structural refinements to improve both catalytic efficiency and selectivity.

CONCLUSION

Transition metal ions are powerful catalysts or, in many cases, promoters of the cleavage of amino acid esters. The association to ligands with built-in nucleophilic functions may further improve the effect. Metallomicelles and other aggregates constitute organized systems able to magnify the effects of the interactions between the substrate and the catalytic site and provide a different environment for the occurrence of the process. In spite of the loose structure of the metalloaggregates, relatively high enantioselectivities have been observed and some unique properties connected with their reactivity have been revealed. However, selectivity based on the structural geometry of the substrate is out of reach for these systems. More rigidly structured metalloreceptors look more promising in this regard.

In spite of the many efforts to obtain hydrolytic metallocatalysts for esters of amino acids which may be both effective and selective, the goal still appears far away. However, some of the basic elements of the systems investigated so far and outlined here look promising and we believe that simple supramolecular systems able to rival natural metalloenzymes can be synthesized in near future. As recently stated by Knowles,[40] enzyme catalysis is 'not different, just better'. Nature, in refining the systems, has been working much longer than we have.

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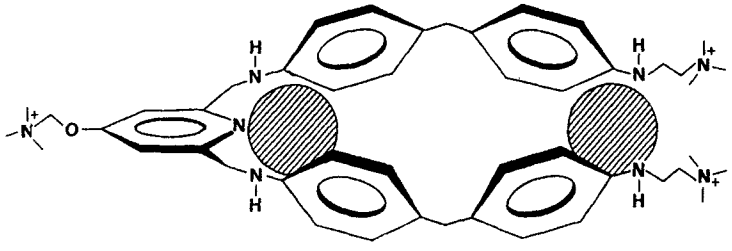

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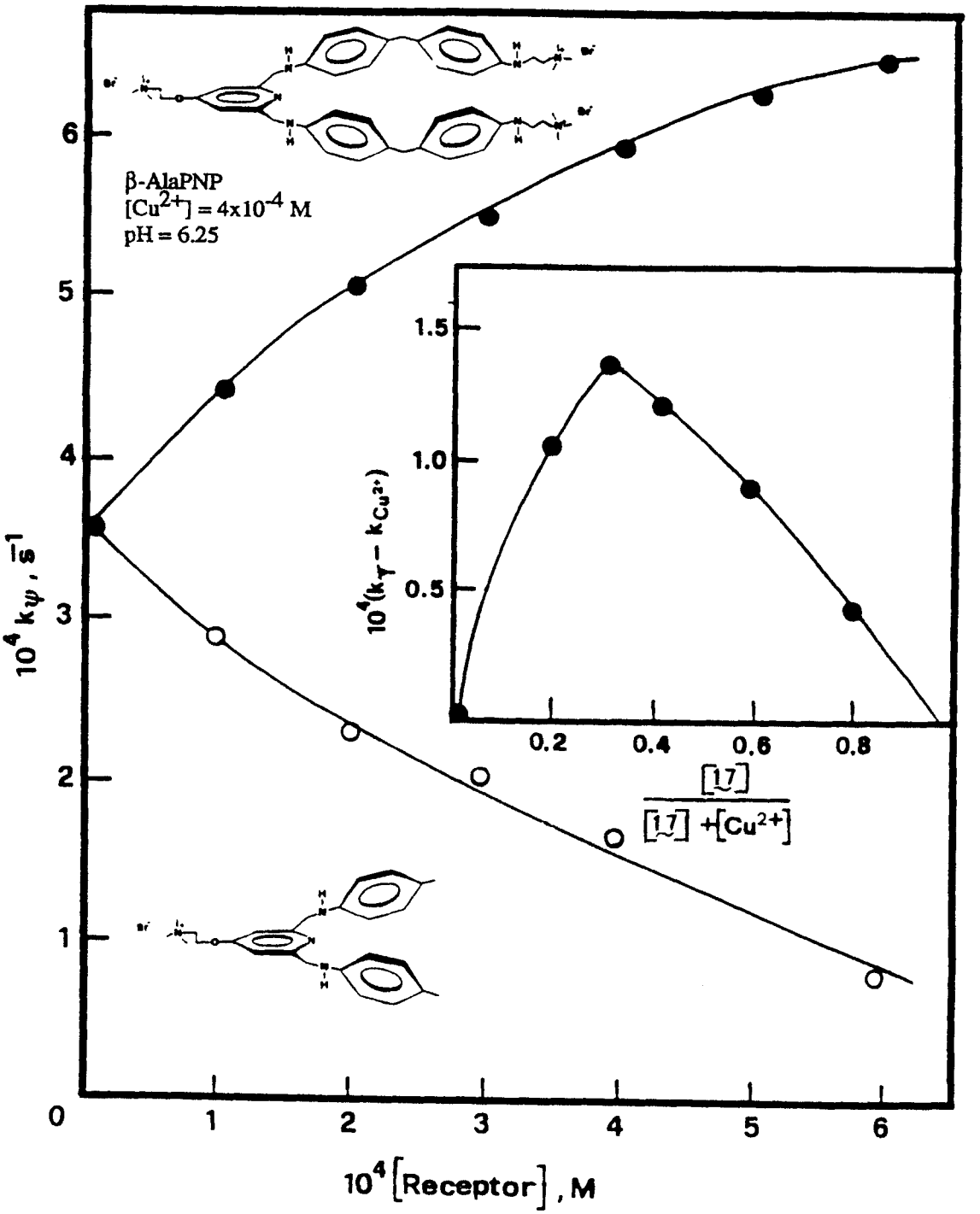

Figure 2. Dependence of the observed rate of cleavage, k_ψ, of the *p*-nitrophenyl ester of β-alanine on the concentration of ligands **17** and **18**. pH = 6·25; [Cu(II)] = 4×10^{-4} M. Inset: kinetic version of the Job plot for ligand **17**

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