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Recueil Review

Enzyme models

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Introduction [a]

The ability of enzymes to catalyze a large variety of reactions in aqueous solution under mild conditions (37°C, pH 7, 1 atm) has attracted the attention of many chemists. There have been numerous attempts both to explain the enormous rate accelerations achieved by enzymes and to reproduce them by designing more or less sophisticated enzyme models.

Catalysis in general means reduction of the free energy of activation, $\Delta G^{\neq}$. It has been pointed out by *Czarnik*[1] that "enzymes do not formally catalyze reactions, but rather catalyze state changes that can be described as processes, conversions, transformations, etc.". Most often, enzymes offer an alternative pathway[2] with a lower activation barrier from reactants to products. As $\Delta G^{\neq} = \Delta H^{\neq} - T \cdot \Delta S^{\neq}$, enzymes can catalyze a state change by affecting either one or both of the enthalpic and entropic terms.

Many hypotheses have been put forward to explain the large rate accelerations achieved by enzymes. Some examples are entropy[3], electrostatic stabilization[4], desolvation[5], orbital steering[6], and the spatio-temporal hypothesis[7]. Although enzymes probably use a combination of these strategies to catalyze reactions, there is much debate about the relative contribution of the different factors involved in reactivity.

In this review we will discuss enzyme models which try to mimic the strategy used by enzymes rather than the active site of the enzyme itself. The models have been divided into *supramolecular enzyme models*, which use a special binding site to position the substrate close to the catalytically active groups, *hydrolytic metalloenzyme models*, which use a metal ion for their catalytic activity, and *hydrolytic-supramolecular-metalloenzyme models*, which combine both features in the same model system.

Supramolecular-enzyme models

Regardless of which single factor is most important for achieving large rate accelerations in enzymatic catalysis, the complexation of the substrate molecule in the active site of the enzyme is of prime importance. Complexation of guest molecules by synthetic receptor molecules is the central theme of supramolecular chemistry[8]. Therefore, the development of enzyme models is one of the challenging applications of supramolecular chemistry, because it opens the possibility of examining systematically which factors contribute to enzymatic catalysis. Some typical examples of supramolecular-enzyme models based on crown ethers, cyclophanes, and cyclodextrins will be discussed below.

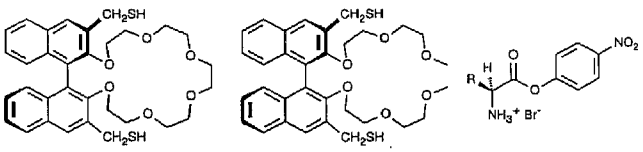
Acyl-transfer reactions

Functionalized binaphthyl crown ether **1** was reported[9] to accelerate the transacylation of the hydrobromide salts of α-amino acid 4-nitrophenyl esters **3** by a factor of 10^2–10^3 as compared to the linear polyether **2**. Due to the chirality of the binaphthyl unit, crown ether **1** shows enantiomeric discrimination ranging from a factor ~ 1 for R=CH_3 to 9.2 for R=$CH(CH_3)_2$. Although thiolysis (ester cleavage by thiols) of the ester **3** is accelerated considerably in the presence of crown ether **1**, the subsequent hydrolysis of the thiol ester is rather slow, thereby preventing any turnover.

Enhanced rates of thiolysis with high structural and chiral recognition were observed for the hydrobromide salts of dipeptide 4-nitrophenyl esters in the presence of 18-crown-6 derivative **4**[10]. The preference for dipeptide substrates results from the increased distance between the crown-ether ring and the nucleophilic thiol groups in this enzyme model. Compared to Pro-Gly-OPNP, the thiolysis of Gly-Gly-OPNP was accelerated $1.9 \cdot 10^3$–$1.5 \cdot 10^4$-fold, depending on the solvent. The L species of Gly-Phe-OPNP reacted 50–90 times faster with **4** than did the D enantiomer.

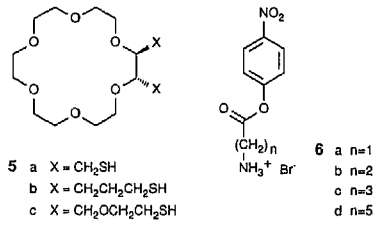
Crown ethers **5** show regioselective thiolysis of the amino acid 4-nitrophenyl ester salts **6**[11]. Crown ether **5a**, having the thiol groups close to the crown ether ring, showed a preference for the short-amino-acid ester **6a**. Increasing the distance between the nucleophilic thiol group and the crown ether ring changed the preference of **5b** to the longer-amino-acid esters **6b** and **6c**. The ester functionality of **6d** in the complex is too far from the crown-ether ring to be thiolyzed efficiently by any of the enzyme models **5**. Interestingly, crown ether **5c**, which has an ether oxygen atom in the side-chain, reacted comparatively quickly with substrates **6a-c**, presumably because the attractive interactions between the ether oxygen atom and the ammonium ion reduce the flexibility of the side-arm.

[a] **Abbreviations** Cyclen = 1,4,7,10-tetraazacyclododecane DMSO = dimethyl sulfoxide tren = tris(2-aminoethyl)amine trien = triethylenetetramine trpn = tris(3-aminopropyl)amine ZCl = benzyloxycarbonyl



1 2 3

Chart 1



5 a X = CH_2SH
b X = $CH_2CH_2CH_2SH$
c X = $CH_2OCH_2CH_2SH$

6 a n=1
b n=2
c n=3
d n=5

Chart 3

Realizing that the thiol esters can transfer the acyl groups to amines, *Koga* et al. developed the 18-crown-6-based enzyme model **7a**[12a,b] for the synthesis of peptides. Acylation of one thiol group with the hydrobromide salt of an α-amino acid 4-nitrophenyl ester, followed by protection of the amino group with benzyloxycarbonyl chloride (ZCl) gave enzyme model **8**, having one thiol ester and one nucleophilic thiol group.

The peptide synthesis consisted of the steps shown in Scheme 1. Crown ether **8**, complexed with another α-amino acid 4-nitrophenyl ester salt, was converted by intracomplex thiolysis to **10**, having two thiol esters and one ammonium group, which is complexed by the crown-ether ring. After addition of base, the free amine group reacted with the thiol ester to give **12**, which contains the thiol ester of a protected dipeptide and a nucleophilic thiol group, and which is therefore equivalent to **8**. Repetition of the reaction sequence resulted in elongation of the polypeptide chain. In this way, di-, tri-, and tetrapeptides have been synthesized[12a,b].

Although the intracomplex thiolysis reaction was quite rapid, the intramolecular aminolysis was rather slow. Therefore, *Koga* et al. introduced functional groups in the enzyme models **7** to catalyze the rate-determining proton transfer[12c].

Introduction of carboxylic acid groups (**7b**) quenched the aminolysis, probably by protonation of the nucleophilic amine group. The amide substituents of **7d** retarded the reaction. Presumably, these groups slow down the rate-determining proton transfer by over-stabilizing the dipolar reaction intermediate. A slightly accelerated reaction was observed, however, in the presence of the ester groups (**7c**).

In an incremental approach to host molecules that mimic serine proteases, *Cram* et al. synthesized enzyme models **13**[13] and **14**[14], which have either a nucleophilic benzylic alcohol (**13**) or a benzylic alcohol and an imidazole group (**14**) for catalyzing the acyl transfer of α-amino-acid 4-nitrophenyl ester salts.

Compared to the non-complexing model compound 3-phenylbenzyl alcohol (**15**) enzyme model **13** accelerated[13] the transacylation of the perchlorate salt of Ala-OPNP in the presence of base by a factor of 10^{11}, taking the solutions of Ala-OPNP, **13**, and **15** as the standard states for the reaction, although the correctness of this approach has been questioned[15].

Reaction of enzyme model **14a** with the perchlorate salt of Ala-OPNP in the absence of added base[14] gave a rapid initial acyl transfer to the N-3 nitrogen atom of the imidazole ring, followed by a much slower transfer to the benzylic alcohol group. Enzyme model **14b** showed catalytic turnover, eventually hydrolyzing 25 equiv of Ala-OPNP in about five days. The initial rate produced by **14b** was about three times that of 4-phenylimidazole, but product inhibition of **14b** occurred, slowing down the catalytic rate.

Phenol-capped cyclophanes **16** were synthesized by *Diederich* et al.[16] and both were shown by ^{1}H-NMR spectroscopy to form complexes of high stability with naphthalene guests in aqueous solution. Acylation of **16b** with 4-nitro-1-naphthyl acetate (**17**) was much faster than of **16a**, which was explained in terms of productive *versus* non-productive binding[16b]. As a result, intracomplex acylation of the phenolic group was only observed in the **16b** · **17** complex.

Hydride transfer reactions

Based on the fact that protons and metal ions (*e.g.* Zn^{2+} and Mg^{2+}) can catalyze hydride transfers from 1,4-dihydropyridine to carbonyl groups that are easily reducible[17a], *Kellogg* et al. developed enzyme model **18**[17], which combines a 1,4-dihydropyridine residue with a crown ether capable of complexing with a metal ion. In the ternary complex of crown ether, metal ion, and substrate, the carbonyl group of the substrate is activated towards hydride attack by its coordination to the metal ion.

Using the chiral enzyme model **18**[17d-g] in the presence of Mg^{2+} ions, alcohols were obtained from the corresponding ketones with enantiomeric excesses of 64–86%[17d].

Host molecule **19** was observed[18] to display enhanced rates of hydride transfer to pyridinium salts containing a

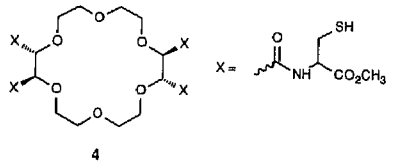


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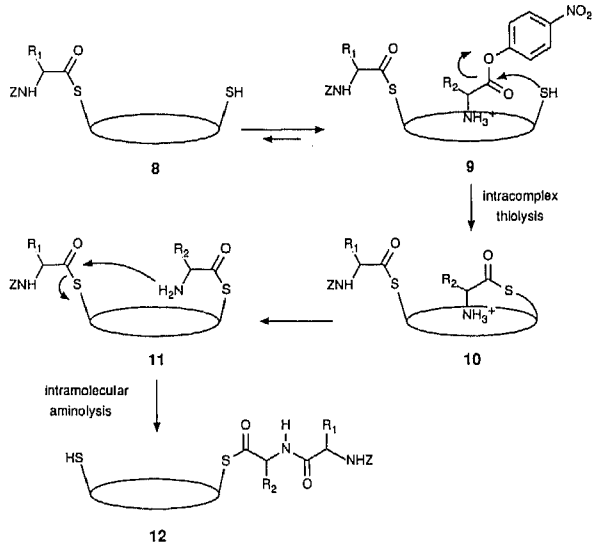
Chart 2



8 9 10 11 12

Scheme 1

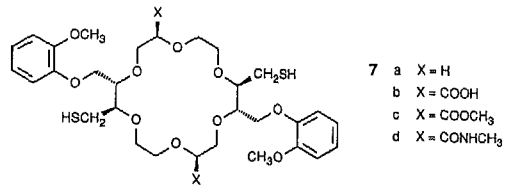


Chart 4

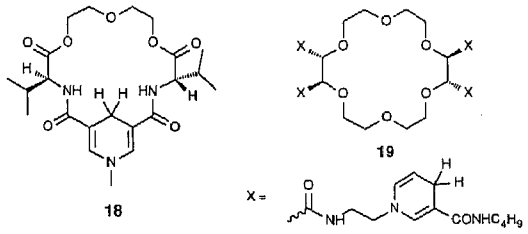


Chart 7

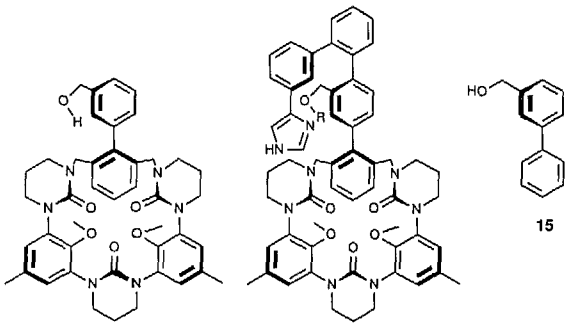


Chart 5

primary ammonium group that is complexed by the crown-ether ring.

Thiazolium-containing enzyme models

The coenzyme thiamine pyrophosphate is used in many enzymatic reactions in which carbon–carbon bonds are either formed or broken[19], the catalytic action depending on the presence of the thiazolium group.

Incorporation of a thiazolium ring in 18-crown-6 gave enzyme model **20**[20], which in a ternary complex of **20**, metal ion (K^+ or Na^+) and pyruvic acid showed a 10-fold increase in the oxidative decarboxylation of pyruvic acid, using flavin–oxidation of the active aldehyde intermediate.

Using cyclophane **21**, which has a thiazolium group close to its cavity, *Diederich* et al. were able to oxidize aromatic aldehydes[21] (*e.g.* 2-naphthaldehyde) in aqueous DMSO solutions using either $K_3Fe(CN)_6$[21a] or a flavin that was regenerated electrochemically[21b] as the oxidizing agent.

Positioning of thiazolium groups close to the cavity of a cyclophane (**22**)[22] or of γ-cyclodextrin (**23**)[23] gave enzyme models which increased the rate of the benzoin condensation by collecting two benzaldehyde molecules in close proximity to the catalytic thiazolium groups.

Although the supramolecular systems discussed above resemble real enzymes in their ability to complex with their substrates, thereby converting an inter- into an intramolecular reaction, they do not resemble them at all in catalytic activity. Most of the supramolecular hydrolytic enzyme models use activated substrates (4-nitrophenyl esters) instead of the amides that are hydrolyzed by real enzymes. Furthermore, most hydrolytic enzyme models show no catalytic turnover, accelerating only the first step of the hydrolysis reaction in which the acyl group is transferred from the substrate molecule to the enzyme model.

Hydrolytic metalloenzyme models

Some enzymes use metal ions as cofactors for their catalytic activity either for redox reactions or for hydrolytic reactions (*e.g.* Zn^{2+} in carboxypeptidase A, Ni^{2+} in urease). A large number of metal-ion-catalyzed hydrolytic reactions has been investigated in order to determine the mechanisms involved in this kind of catalysis.

Four different mechanisms have been proposed to explain the effect of metal ions on the rate of hydrolysis reactions.

- the *Lewis-acid mechanism:* the electrophilicity of the substrate molecule is enhanced by its coordination to the metal ion;
- the *metal-hydroxide mechanism:* coordination of the nucleophile to the metal ion increases its acidity to such an extent that deprotonation of the nucleophile occurs at physiological pH;
- the *bifunctional mechanism:* a combination of the Lewis acid and the metal hydroxide mechanisms, resulting in a four-membered-ring transition state;
- the *leaving-group mechanism:* coordination of the metal ion to the leaving group increases its leaving ability.

Some examples of systems using the different mechanisms and some indications of the rate accelerations that were achieved will be presented below.

Lewis-acid mechanism

Accelerations of 10^6 were observed for the hydrolysis of esters that are coordinated to Co^{3+} through the carbonyl oxygen atom (**24**)[24], which result largely from an increase in $\Delta S^{\neq}$. These activated esters also react with other nucleophiles such as acetate[25] and amines[26].

Smaller rate enhancements[27] (10^4) were observed during the hydrolysis of Co^{3+}-chelated glycine amide derivatives (**25**)[27a,c] and *O*-coordinated DMF (**26**)[27b].

The rate of hydrolysis of glycine amide in the presence of Cu^{2+}, Ni^{2+}, and Co^{2+} was much less enhanced[28] ($< 10^2$) and for **27** and **28** these metal ions were even reported[29] to have an inhibitory effect. Very recently, however, it was

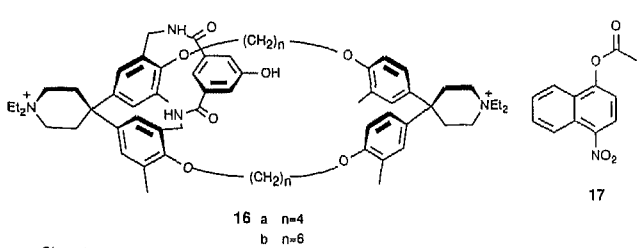


Chart 6

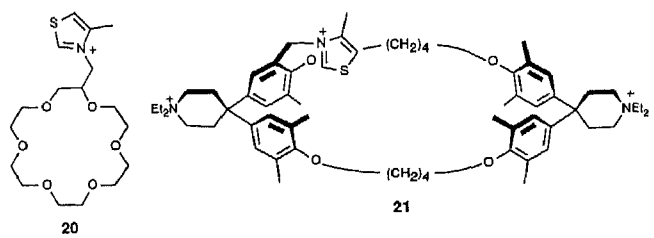
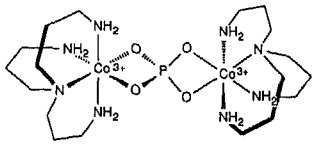


Chart 8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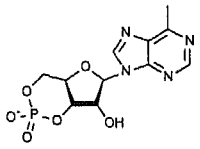
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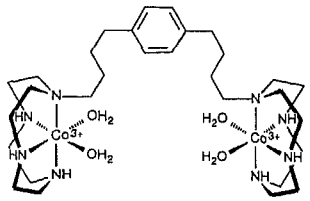
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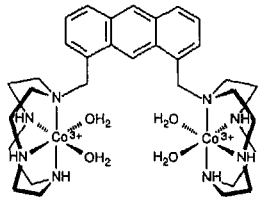
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Chart 13

In the hydrolysis of the *N*-acylbenzimidazole **40**[51], a large rate acceleration (10^{11}) was observed in the presence of Cu^{2+}. Furthermore, the value of the rate constant ($5 \cdot 10^{11}$ $M^{-1} \cdot s^{-1}$) is above the diffusion limit, indicating that an intramolecular reaction takes place.

Unactivated amides (formamide, *N*-methylformamide, and *N*,*N*-dimethylformamide) have been hydrolyzed with the Cu^{2+} complex **36**[43] at neutral pH and 100°C. Although only a moderate acceleration[43] of the hydrolysis rate was observed (10^2), this is one of the few examples in which the hydrolysis of an unactivated amide is accelerated by a metal ion without enforced proximity.

The *cis*-diaqua Co^{3+} complexes have also been applied to the hydrolysis of phosphate esters, which are important structural elements of DNA and RNA and which are extremely resistant to hydrolysis.

Stirring 2 equiv of $[(trpn)Co(OH_2)_2]^{3+}$ (**38**) with adenosine monophosphate (AMP) at 25°C for about 6 h gave free adenosine and the dinuclear Co^{3+} complex **41**[45]. The first equivalent of $[(trpn)Co(OH_2)_2]^{3+}$ was shown to give a four-membered chelate ring with the substrate molecule without ester hydrolysis. Only the second equivalent of $[(trpn)Co(OH_2)_2]^{3+}$ accelerated the hydrolysis of the phosphate ester.

The hydrolysis of adenosine 3′,5′-monophosphate (cAMP, **42**)[46] was shown to occur 10^8 times faster in the presence of $[(trien)Co(OH_2)_2]^{3+}$)[52] at 50°C.

Large ligand effects on the Co^{3+}-complex-promoted hydrolysis of bis(4-nitrophenyl) phosphate were observed[47], resulting in $[(trpn)Co(OH_2)_2]^{3+}$ being some 300 times more reactive than $[(tren)Co(OH_2)_2]^{3+}$, which indicates the important role of the tetraamine ligand in stabilizing the four-membered chelate ring formed in the transition state.

As two equiv of Co^{3+} complex are required for the complete hydrolysis of phosphate esters, *Czarnik* et al. prepared binuclear Co^{3+} complex **43**[53], which hydrolyzes bis(4-nitrophenyl) phosphate 3.2 times faster than an equivalent amount of $[(cyclen)Co(OH_2)_2]^{3+}$ (**39**)[54]. The effect was attributed to the highly effective concentration of a second Co^{3+} complex once coordination to the first has occurred. The moderate size of the effect can be explained by the many degrees of freedom in **43**. Therefore, binuclear Co^{3+} complex **44** was prepared[55], which has two convergent Co^{3+} centers, rigidly kept at a distance that can be bridged by a phosphate ion. Binuclear complex **44** hydrolyzes 4-nitrophenyl phosphate 10 times faster than an equivalent amount of $[(cyclen)Co(OH_2)_2]^{3+}$ (**39**).

A *cis*-hydroxo Ir^{3+} complex was reported[56] to hydrolyze a bound phosphate ester more slowly than Co^{3+}, despite the more basic coordinated OH^- on the Ir^{3+} ion. This

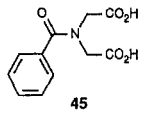
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Chart 14

effect was attributed to the Ir^{3+} ion being larger than Co^{3+}, which makes formation of the four-membered chelate ring more difficult. Therefore, the biological relevance of four-membered chelate rings in biological systems was questioned[56], because these often use Mg^{2+} and Zn^{2+}, which are larger than Ir^{3+}.

Very recently[48], an enhanced reaction rate (10^{10}) was also observed in the hydrolysis of the unactivated phosphate diester, dimethyl phosphate, by $[(cyclen)Co(OH_2)_2]^{3+}$ (**39**) at neutral pH.

Leaving-group mechanism

As described above, the $7 \cdot 10^4$ rate acceleration that was observed in the Ni^{2+}-catalyzed ethanolysis of **31**[32] was attributed to the Lewis-acid mechanism. Very recently, however, it was shown[57] that the metal ion in the Cu^{2+} complex of **31**, which showed a comparable rate acceleration, is coordinated to the urea nitrogen atom and the pyridine nitrogen atom, forming a five-membered chelate ring, instead of to the urea oxygen atom.

Complexes of urea derivatives (*N*-methylurea[58a] and *N*-phenylurea[58b]) with Co^{3+} were reported to be reactive when the metal ion was coordinated to the nitrogen atom[58], but not to the oxygen atom[33]. The *N*-bonded urea molecules showed no enhanced hydrolysis, however. An isomerization reaction, giving the *O*-bonded urea complex, and an elimination reaction, giving a coordinated cyanate ion, were observed.

Recently, *Czarnik* et al.[59] tried to determine the importance of leaving-group activation by investigating the metal-catalyzed hydrolysis of **45**. Although a considerable rate acceleration was observed in the presence of Cu^{2+}, no definite evidence of *N*-coordination was obtained.

Hydrolytic supramolecular-metalloenzyme models

From the results described above, it is clear that metal ions can achieve large rate accelerations in the hydrolysis of both activated and unactivated substrates. Moreover, catalytic turnover has been observed in many cases. Therefore, it would be very attractive to incorporate metal ions as catalytic centers in supramolecular enzyme models.

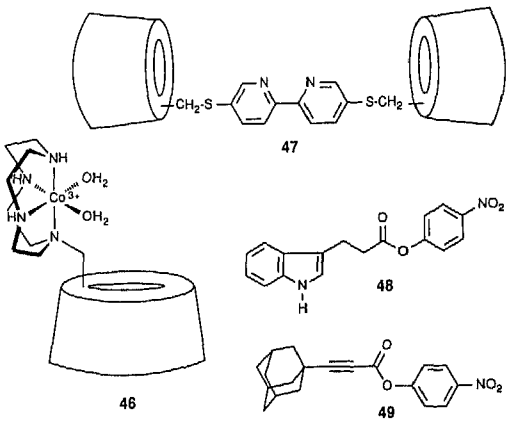

46 47 48 49

Chart 15

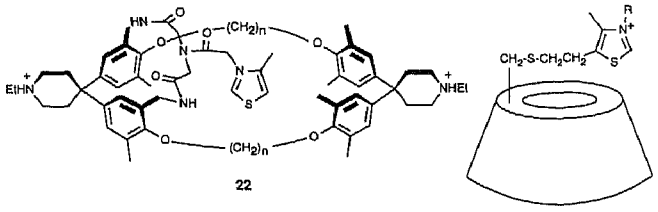


Chart 9

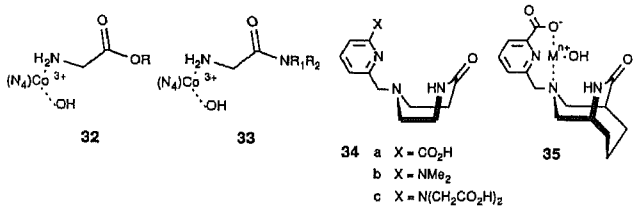


Chart 11

shown[30] that Cu^{2+} greatly enhanced the rate of hydrolysis of amides (10^6–10^8), provided that the metal-ion-coordination-induced amide NH deprotonation was prevented by the use of tertiary amides. No evidence is available, unfortunately, as to whether the Lewis-acid or the metal-hydroxide mechanism is operative in this case.

The observation that bifunctional buffer species (*e.g.* AcOH and $H_2PO_4^-$) accelerated the hydrolysis of Co^{3+}-chelated glycine amide derivatives resulted in the development of models **29** and **30**[31], which have either a bifunctional phenolic OH group or a carboxylic acid close to the amide bond. Only in the case of the phenolic group was an additional rate enhancement (10^2) observed[31b].

A rate enhancement of $7 \cdot 10^4$ has been reported for the Ni^{2+}-catalyzed ethanolysis of *N*-[(2-pyridyl)methyl]urea **31**[32], which was attributed to coordination of the metal ion to the carbonyl oxygen atom, although no evidence for this mode of complexation was given. Urea, coordinated to Co^{3+} via the carbonyl oxygen, did not show accelerated hydrolysis[33], only replacement of urea by a solvent molecule being observed.

Metal-hydroxide mechanism

A metal-coordinated hydroxide ion is believed[34] to be a good nucleophile in a bimolecular sense only when the substrate is very electrophilic (*e.g.* SO_2, CO_2) or when a good leaving group is involved (*e.g.* acid chlorides, anhydrides, or reactive esters)[35]. In intramolecular reactions, however, when the metal-coordinated hydroxide ion and the electrophile are held in close proximity, the behavior is very different.

Tracer studies have shown this mechanism to be active in Co^{3+}-coordinated glycine ester **32**[36] and glycine amide **33**[37]. In the case of **33**, an acceleration between 10^7 and 10^{11} has been estimated, indicating that, in this system, the metal-hydroxide mechanism is much more efficient than the Lewis acid mechanism.

Groves et al.[38] designed special ligands (**34** and **35**), in which the metal ion was forced to lie perpendicular to the amide plane[39]. Metal complexes (Cu^{2+}, Zn^{2+}, $Co^{2+/3+}$, Ni^{2+}) of these ligands were shown to contain a very acidic metal-bound water molecule[38]. Titrations revealed pK_a values close to physiological pH (7.6 [**34a** · Cu^{2+}-OH_2][38a], 7.2 [**34b** · Cu^{2+}-OH_2][38b], ≈ 7.1 [**35** · Zn^{2+}-OH_2][38c], and 6.6 [**35** · Cu^{2+}-OH_2][38c]).

Large rate accelerations for the hydrolysis of the amide bonds were observed, *viz.* $1.6 \cdot 10^6$ (**34a** · Cu^{2+})[38a], $1.9 \cdot 10^5$ (**34a** · Zn^{2+})[38a], $1.0 \cdot 10^3$ (**34c** · Zn^{2+})[38b], $1.4 \cdot 10^7$ (**35** · Zn^{2+})[38c], $1.7 \cdot 10^7$ (**34b** · Co^{3+})[38d], and $5.3 \cdot 10^8$ (**34c** · Zn^{2+})[38d]. From these results it is clear that large rate enhancements can be obtained by positioning a metal-bound hydroxide ion close to the carbonyl carbon atom. The rate of hydrolysis can be further increased by forcing the amide group closer to the metal-bound hydroxide ion (**35** · Zn^{2+}/**34c** · Zn^{2+} = $1.4 \cdot 10^4$). Interestingly, the pending carboxyl group in **34c** · Co^{3+} was observed to increase the rate of hydrolysis, although coordination of the ionized second carboxyl group reduced the electrophilicity of the metal ion.

Bifunctional mechanism

Although examples of the simultaneous operation of the Lewis acid and the metal hydroxide mechanism were already known, *Chin* et al.[40] were the first to use this approach for the hydrolysis of esters[41,42], amides[43], nitriles[44], and phosphate monoesters[45] and diesters[46,47,48]. In contrast to monoaqua complexes, *cis*-diaqua Cu^{2+} complex **36** was able to catalyze the hydrolysis of methyl acetate[41] at pH 7.0 and 25°C. Catalytic hydrolysis was also observed with *cis*-[(trpn)$Co(OH_2)_2$]$^{3+}$ (**38**)[42,49] at neutral pH and 25°C and evidence was presented that the complexation of the ester to the cobalt complex is the rate-determining step[42].

Interestingly, *cis*-[(tren)$Co(OH_2)_2$]$^{3+}$ (**37**)[50] did not show any catalytic activity, indicating the importance of the tetraamine ligand structure in stabilizing the four-membered chelate ring which is formed during the transition state.

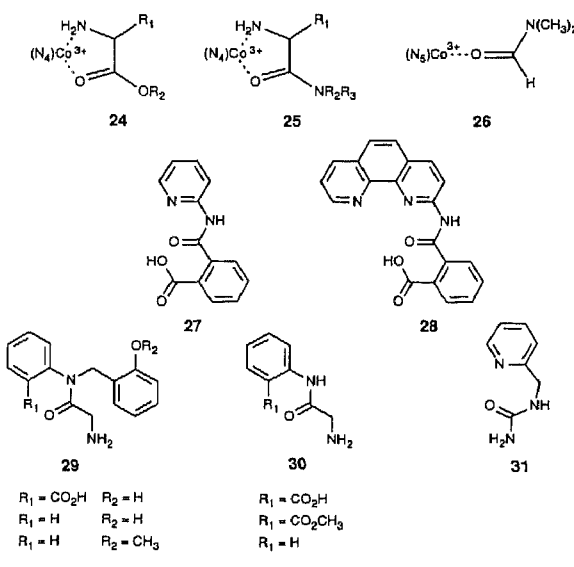


Chart 10

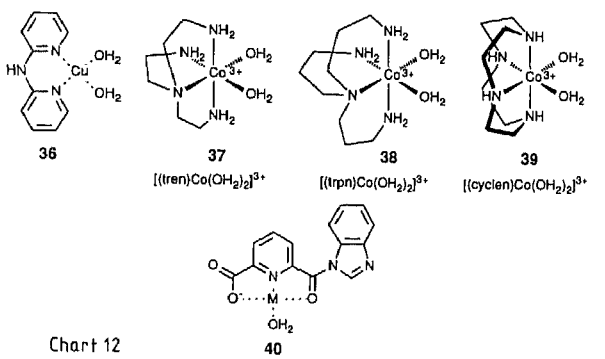


Chart 12

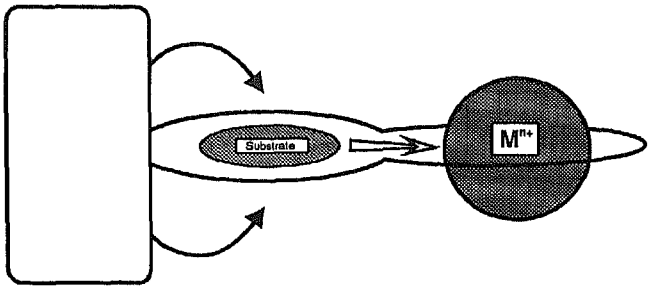


Figure 1. Schematic representation of a functionalized metallomacrocycle.

Incorporation of a $[(cyclen)Co(OH_2)_2]^{3+}$ moiety in a β-cyclodextrin molecule[60], either on the primary side (**46**) or on the secondary side, gave a metalloenzyme model that accelerated the hydrolysis of 4-nitrophenyl acetate 900-fold and of 4-nitrophenyl phosphate 2900-fold.

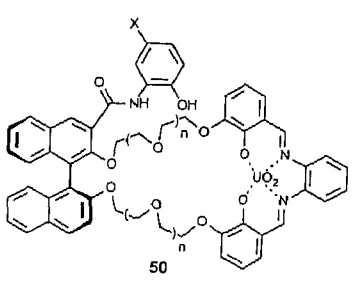
Connection of a β-cyclodextrin molecule to both sides of a bipyridine unit gave metalloenzyme model **47**[61], which showed enhanced hydrolysis rates (10^4–10^5) for substrates **48** and **49** in the presence of Cu^{2+} ions.

Previously, we have shown that incorporating a coordinatively unsaturated metal ion in a crown ether results in a receptor molecule that can complex with substrates containing both electrophilic and nucleophilic sites, such as formamide, acetamide, urea, DMSO, etc[62]. Furthermore, because the substrate molecule is coordinated to the electrophilic metal ion via the carbonyl oxygen atom, the metal ion may accelerate the formation of the tetrahedral intermediate and catalyze the hydrolysis of the substrate molecule by the Lewis-acid mechanism described above. Therefore, we incorporated building blocks in these metalloreceptors such as functionalized binaphthyl units[63a,b] (**50**) or a calix[4]arene moiety[63c] (**51**), that contain catalytic (acidic) groups for accelerating the productive breakdown of the tetrahedral intermediate (the expulsion of NH_3). A schematic representation of such a functionalized metalloreceptor is shown in Figure 1.

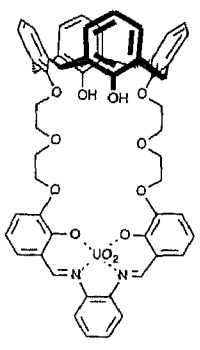
Preliminary experiments showed no catalytic activity for the decomposition of urea under the conditions investigated (4:1 dioxane/water mixture, 80°C) in the presence of **50**[63b] or **51**[64].

Conclusions

Despite the limited number of examples of supramolecular-metalloenzyme models to date, the combination of supramolecular-binding sites with the high catalytic activity of metal ions promises to become a fruitful approach to highly active enzyme models.



50



51

Chart 16

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