DALTON PERSPECTIVE

Metal complexes of azacrown ethers in molecular recognition and catalysis

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Reversible coordination of ligands or substrates with Lewis-basic groups to Lewis-acidic metal ion binding sites can provide the binding enthalpy and selectivity necessary for molecular recognition or catalysis. Metal complexes of functionalised azamacrocycles have proven to be particularly useful for this purpose. This review summarises the properties and applications of some recently published compounds of this kind, giving typical examples, but no comprehensive coverage of the field. With focus on molecular recognition, the binding of inorganic and organic anions to metal complex binding sites, changes of anion properties induced by the binding and the interaction of metal complexes with the polyanion DNA are discussed. The second part of the review focuses on catalysis mediated by azamacrocyclic Lewis-acidic metal binding sites leading to ester hydrolysis, redox catalysis or polymerisation.

1 Introduction

Intermolecular interactions are essential for the function of enzymes, proteins and catalysts. Over the last decades chemists have developed model systems, which are able to mimic some of such functions by providing suitable binding sites.[1] Hydrogen bonds, salt bridges and hydrophobic interactions are the typical intermolecular interactions found in receptor–ligand or substrate interaction in biological systems. However, reversible coordinative interactions may fulfill the task of reversible and selective binding of a guest or substrate equally well. The coordination must be kinetically labile with an exchange rate in the order of milliseconds or faster to be practically useful for binding and assembly. The provided binding enthalpy by formation of a coordinative bond is in many cases much higher than enthalpies found for hydrogen bonds or salt bridges. This is of particular advantage if binding in solvents which strongly compete for the intermolecular interaction, such as DMSO or water, is anticipated. A single ligand to metal ion coordination may provide sufficient binding enthalpy to obtain stable aggregates with millimolar or higher affinities. To achieve this by hydrogen bonding or salt bridges multiple binding interactions are required, which calls for receptors of complex molecular structure. In nature reversible coordinative substrate binding is observed in some metalloenzymes possessing the zinc-finger motif[2,3] and as a general principle for binding of small neutral molecules, such as oxygen, carbon dioxide or carbon monoxide.[4,5]

In this review we will focus on the chemistry of one class of model compounds, which has been widely used to study reversible coordinative interactions for molecular recognition and supramolecular catalysis: metal complexes of azamacrocyclic ligands. The azacrown ligand is known for its high affinity towards transition metal ions and—if further functionalised—high affinity for lanthanide ions. The metal ions are usually bound thermodynamically strongly by the ligand, but additionally, unoccupied coordination sites of the Lewis-acidic metal ion allow reversible coordination of Lewis-basic binding partners. Research in this area has been very active in the last few years and it would be beyond the scope of this paper to provide a comprehensive overview of all reported results. We will rather focus on some instructive and typical examples and apologise that not all scientifically interesting results of the last few years can be discussed.

2 Molecular recognition

2.1 Zn(II) complexes of 1,5,9-triazacyclododecane in anion recognition

One of the characteristic properties of Zn(II) complexes of 1,5,9-triazacyclododecane **1** is their Lewis acidity, illustrated by a pK_a value of 7.30[6] (at 25 °C, $I = 0.1$) for deprotonation of the water molecule occupying the vacant coordination site at the zinc ion (Scheme 1). This value is nearly two orders of magnitude lower than the pK_a value of 9.0 for free solvated zinc(II) ions in aqueous solution.

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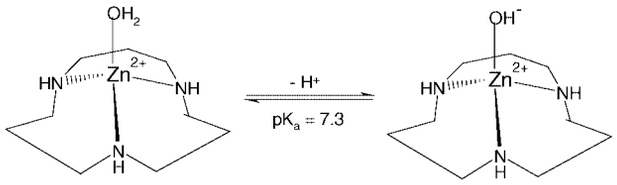

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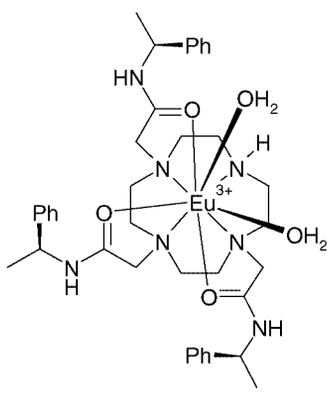
Scheme 1 Deprotonation of the Zn^{2+}-[12]aneN$_3$ complex.

Zn(II)-1,5,9-triazacyclododecane binds hydroxide anions very strongly with an affinity constant of 6.4[6] as determined by potentiometric pH titration at 25 °C. Other anions like acetate, HCO_3^-, SCN^-, halides and deprotonated sulfonamides can interact with **1** as well. By displacement of the coordinated water molecules a variety of anions coordinate to the Zn(II) ion. In Table 1 the 1 : 1 affinity constants of anion binding to **1** are summarised. As expected, the anion affinity constants correlate with the pK_a values of the corresponding conjugated acids of the anions. More basic anions show a higher binding affinity to the Lewis-acidic zinc binding site of **1**.

These anion recognition properties make **1** a suitable model system for the enzyme carbonic anhydrase (see section 3.1).

2.2 Anion binding at heptacoordinated lanthanide centres

Parker and coworkers explored another example suitable for anion recognition.[8,9] They used 1,4,7,10-tetraazacyclododecane (cyclen) derivatives with chiral amide side chains and Eu^{3+} or Tb^{3+} ions to assemble a binding site as shown in Scheme 2.



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Scheme 2 Structure of the chiral Eu^{3+} complex.

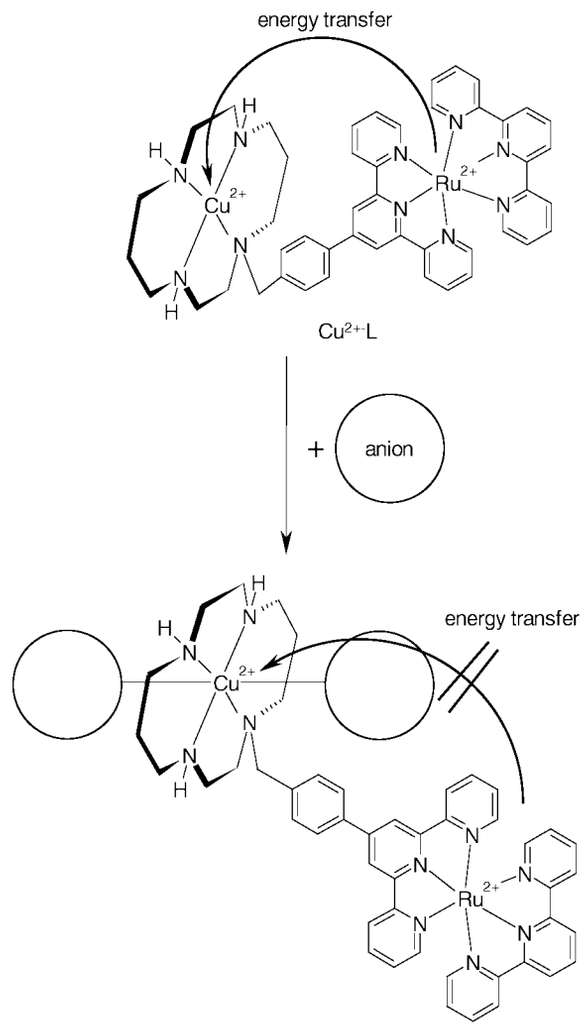
The lanthanide centre is coordinated by the four nitrogen atoms of the azamacrocycle and the three amide oxygen atoms of the side arms. To complete its coordination sphere the metal centre further binds two water molecules. It is possible to displace one or both of these water molecules by various anions. This binding event can easily be monitored by the lanthanide luminescence. A stepwise displacement of quenching metal-bound water results in an increase in the lifetime of the excited state and the emission intensity.

While halides and nitrate did not significantly bind to **2** and the corresponding Tb^{3+} complex in water at pH 7.4, an affinity for CO_3^{2-}/HCO_3^-, phosphate, lactate, citrate, acetate and malonate ions was found. Citrate and malonate ions bound most strongly with a binding constant of $K \geq 40\ 000\ M^{-1}$. In general, the affinity was found to decrease as a function of the overall negative charge on the complex. All anions with the exception of phosphate ions form chelated ternary 1 : 1 complexes in which displacement of both metal-bound water molecules occurs.

2.3 Anion recognition at a cyclam-Cu^{2+} complex[10]

The Cu^{2+} complex of the ligand L (L = [Ru(tpycyclam)-mtpy)]$^{2+}$, tpycyclam = 1-[4′-*p*-tolyl-(2,2′ : 6′,2″-terpyridyl)]-1,4,8,11-tetraazacyclotetradecane, mtpy = 4′-methyl-2,2′ : 6′2″-terpyridine) consists of a binding unit—the Cu^{2+}-1,4,8,11-tetraazacyclotetradecane (cyclam) moiety—and a sensing unit—the Ru^{2+}-terpyridyl complex.

In the presence of Cu^{2+} the characteristic emission of the Ru(tpy)$_2^{2+}$ centre in L is quenched through energy transfer to the copper ion (Scheme 3). This quenching effect is observed in acetonitrile–water solutions in a pH range of 4–7. While in a more acidic or basic environment, the quenching mechanism is hindered due to formation of protonated species or hydroxo complexes ([Cu(L)(OH)]$^{3+}$ or [Cu(L)(OH)$_2$]$^{2+}$). By addition of



Scheme 3 Sensing of anions by Cu^{2+}-L.

Table 1 Anion affinity constants

Anion (A^-)	log K (A^-)[a]
OH^-	6.4[b]
p-toluenesulfonamide	5.7[c]
acetazolamide	4.9[c]
4-nitrobenzenesulfonamide	4.8[c]
HCO_3^-	4.0[c]
CH_3COO^-	2.6[b]
SCN^-	2.4[b]
I^-	1.6[b]
Br^-	1.5[b]
Cl^-	1.3[b]
F^-	0.8[b]

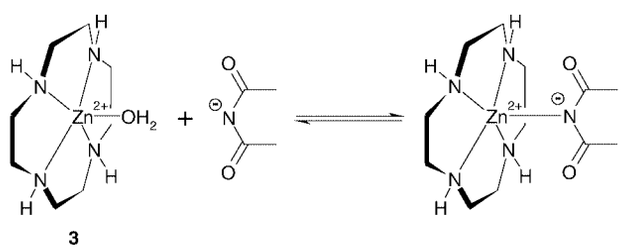
[a] log K (A^-) = [complex-A^-]/[complex][A^-] (M^{-1}). [b] Determined by potentiometric pH titration at 25 °C and I = 0.10.[6] [c] Determined by inhibition kinetics at pH 8.4 (50 mM TAPS buffer), I = 0.10 and 25 °C.[7]

anions like chloride, bromide or OH^- that can coordinate at the free axial positions of the square-planar cyclam-Cu^{2+} unit an enhancement of the fluorescence is observed. Other anions such as sulfate, phosphate and ADP interact with Cu^{2+}-L mainly in an electrostatic manner but the emission is also increased. A unique selectivity is achieved in the binding of ATP by Cu^{2+}-L. Hereby the fluorescence intensity is not restored but the quenching is induced in a different pH range. The minimum emission is measured at pH 9.2 where none of the other anions studied is able to produce any significant quenching effect.

2.4 Imide coordination by Zn^{2+}-cyclen

Similarly to Zn^{2+}-1,5,9-triazacyclododecane **1**, Zn^{2+}-cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) **3** completes its coordination sphere in aqueous media with one water molecule. The resulting geometry is distorted square-pyramidal with the zinc ion facing out of the plane that is formed by the four azamacrocyclic nitrogens. The pK_a of the coordinated water is 7.9[6] as determined by potentiometric pH titration at 25 °C. This value is slightly more basic than in **1**, but significantly lower than zinc(II) ions in aqueous solution.

The coordinated water can be replaced by a deprotonated imide moiety as shown in Scheme 4. The Lewis-acidic zinc



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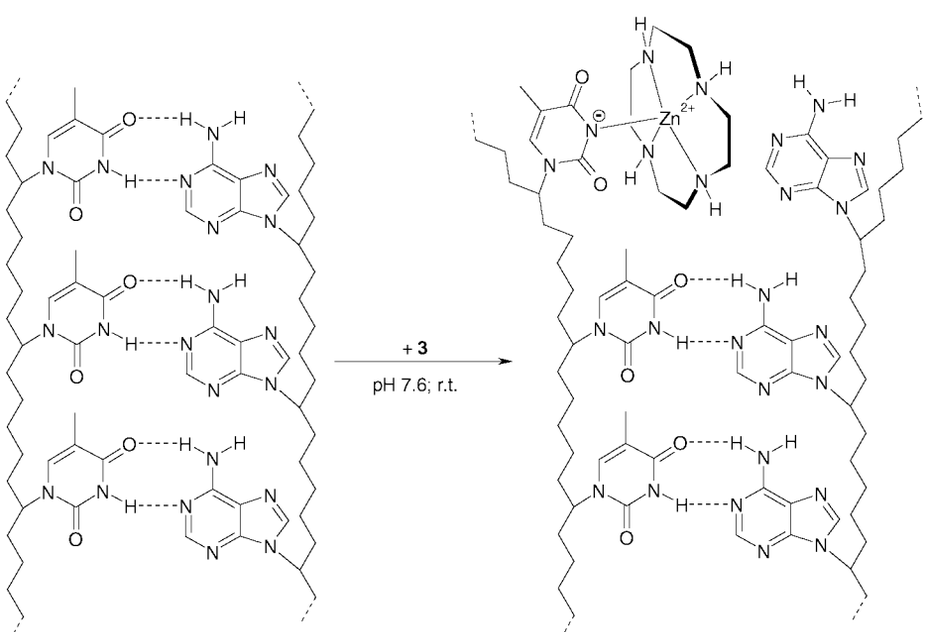
Scheme 4 Imide coordination by Zn^{2+}-1,4,7,10-tetraazacyclododecane.

coordinates to the negatively charged nitrogen atom of the imide unit. The binding is probably enhanced by hydrogen bonds between the carbonyl oxygen atoms and the NH groups of the cyclen. This Zn^{2+}-cyclen imide coordination was explored by Kimura and coworkers by the reaction of **3** with thymidine and related nucleosides.[11] The anion affinity constants of a series of imide-containing molecules were determined by potentiometric titration in aqueous solution. Thymidine (dT), 3′-azido-3′-deoxythymidine (AZT) and riboflavin showed the highest affinity constant of log $K = 5.6$. The log K values of other imide derivatives like uridine (log $K = 5.2$) or 5-fluoro-1-(tetrahydro-2-furyl)uracil (log $K = 4.6$) were slightly smaller. The anion affinity constants correlate with the pK_a value for deprotonation of the imide NH.

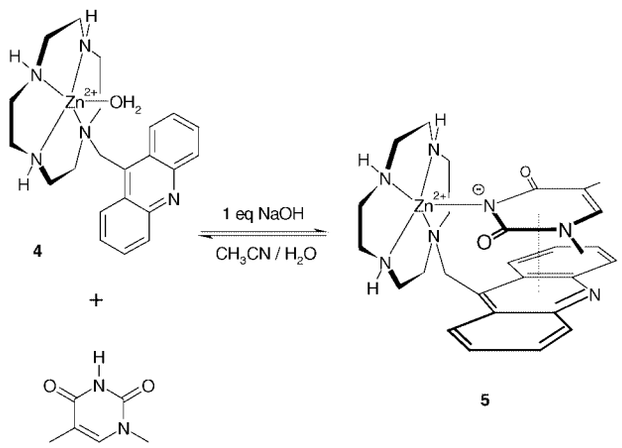
This strong affinity of Zn^{2+}-cyclen to imide containing nucleosides was also studied by reaction with different polynucleotides.[12–14] As shown in Scheme 5, Zn^{2+}-cyclen (**3**) disrupts double-stranded polyT–polyA at room temperature and pH 7.6 by invasion into the two complementary hydrogen-bonding sites in T–A pairs. The same effect was observed by reaction of **3** with double-stranded polyA–polyU. By addition of **3** the melting temperature of the double-stranded polynucleotide was significantly lowered. As the ratio of **3** to uracil bases in polyU reached 3.0, which corresponds to a three-fold excess of **3** over uracil, the double strand was already completely dissociated at room temperature.

The selective coordination of thymidine and uridine against the other nucleosides adenine, cytosine and guanine was used in transport experiments through a lipophilic liquid membrane.[15] For this purpose 1-alkyl derivatives of **3** were synthesised to make azamacrocyclic zinc(II) complexes soluble in chloroform. To detect binding events more comfortably by UV spectroscopy, cyclen was derivatised with a 2,4-dinitrophenyl chromophore.[16] The resulting Zn^{2+}-1-(2,4-dinitrophenyl)-1,4,7,10-tetraazacyclododecane has an even stronger anion affinity for thymidine than **3**. The log K was determined to be 6.9 by potentiometric pH titration. This enhanced stability was explained by an additional π–π stacking interaction between the 2,4-dinitrophenyl group and the pyrimidine ring.

Another example[17] of multipoint molecular recognition is shown in Scheme 6. Here the cyclen was selectively functionalised at one nitrogen with an acridine group. The resulting Zn^{2+} complex **4** binds to a variety of nucleosides by Zn^{2+}-cyclen imide coordination and an additional π–π stacking between the acridine moiety and the pyrimidine ring of the nucleoside. This two-point molecular recognition results in an enhanced affinity compared to the unsubstituted Zn^{2+}-cyclen. For example, the complexation constant with thymidine in water under physiological conditions increased from log $K = 5.6$ for Zn^{2+}-cyclen to log $K = 7.2$ for **4**. The interaction of **4** with different single- and double-stranded oligonucleotides was also studied.[14,18]



Scheme 5 Denaturation of polyT–polyA by Zn^{2+}-cyclen.

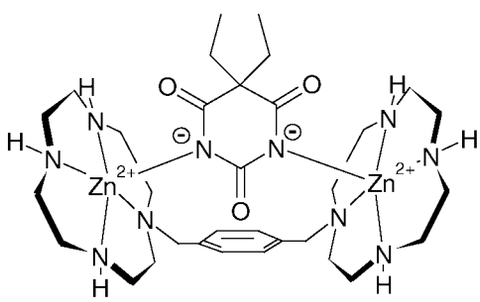


Scheme 6 Reaction of 1-methylthymine with Zn^{2+}-(9-acridinyl)-methyl-1,4,7,10-tetraazacyclododecane **4**.

This binding motif was extended to other aromatic side groups at the azamacrocycle.[19] In addition to acridine, cyclen was substituted with quinoline and naphthalene. Either one or two aromatic groups of the same kind were attached to the macrocycle. The resulting Zn^{2+} complexes selectively bind to AT-rich regions of native double-stranded DNA. The binding affinities and specificities varied with the kind and number of aromatic rings appended to the cyclen. The complexes bearing two aromatic side groups showed the highest affinities.[20]

In order to have two imide recognition sites a bis(Zn^{2+}-cyclen) complex was synthesized by Kimura *et al.*[21] In this receptor two Zn^{2+}-cyclen complexes are connected through a *para*-xylene bridge. The pK_a values of the two coordinated water molecules at the Zn^{2+} centres were measured to be 7.2 and 7.9 by potentiometric titration.

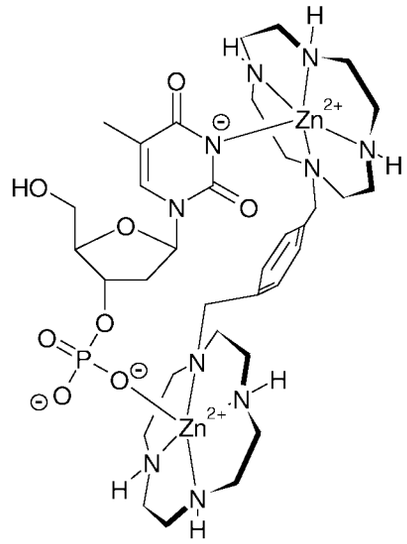
The bis(Zn^{2+}-cyclen) **6** is a good host for barbital in aqueous solution (Scheme 7). The binding constant was determined by



Scheme 7 Binding of barbital to bis(Zn^{2+}-cyclen).

pH titration as log $K = 5.8$ at pH = 8. This is nearly two orders of magnitude better than the affinity of barbital for Zn^{2+}-cyclen (log $K = 4.2$). It was also found that **6** is a more powerful disruptor of polyA–polyU than **3**.[13] At a ratio of **6**/uracil bases = 0.4 the double-strand was already completely dissociated at room temperature and pH = 7.6.

A slightly different binding motif of the bis(Zn^{2+}-cyclen) was found in the interaction with thymidine and uridine nucleotides.[22] As can be seen in Scheme 8, thymidine 3′-monophosphate (3′-dTMP) and related nucleotides can bind to **6** through two different modes of interaction. One Zn^{2+}-cyclen moiety coordinates to the deprotonated imide functionality and the other one binds to the terminal phosphate dianion. This was confirmed by spectrophotometric UV titration and ^1H NMR measurements. The potentiometric pH titration of **6** with 3′-dTMP and other related nucleosides gave high complexation constants with a log K value in the range of 5.5 to 6.4 at pH 7.6 and 25 °C. These values are about double the log K of 3.2 for a thymidine complex with a monomeric Zn^{2+}-benzylcyclen.



Scheme 8 Interaction of bis(Zn^{2+}-cyclen) with thymidine 3′-monophosphate.

Based on these promising results with **6**, studies were extended to a linear tris(Zn^{2+}-cyclen) complex.[23] In this tris-(Zn^{2+}-cyclen), three Zn^{2+}-cyclen moieties were connected by two *para*-xylene bridges similar to the arrangement found in **6**. Recently it was reported that the tris(Zn^{2+}-cyclen) complex is the most potent inhibitor of HIV-1 TAR RNA-Tat peptide binding due to its strong binding to the UUU bulge.[24]

A different C_3-symmetric tris(Zn^{2+}-cyclen) complex was also synthesised.[25] Here the three Zn^{2+}-cyclens were connected through only one 1,3,5-trimethylbenzene spacer. The resulting complex is a good receptor for organic phosphate dianions in aqueous solution.

The molecular recognition of flavins by Zn^{2+}-cyclen imide coordination has already been mentioned. Recently it was found that the coordination of riboflavintetraacetate **7** to tetraalkylated Zn^{2+}-cyclen derivatives like 1,4,7,10-tetrabutyl-1,4,7,10-tetraazacyclododecane zinc(II) bisperchlorate and 1,4,7,10-tetradodecyl-1,4,7,10-tetraazacyclododecane zinc(II) bisperchlorate **8** significantly changes the redox properties of the flavin.[26a]

The cyclic voltammogram of **7** (see Fig. 1) shows a reversible

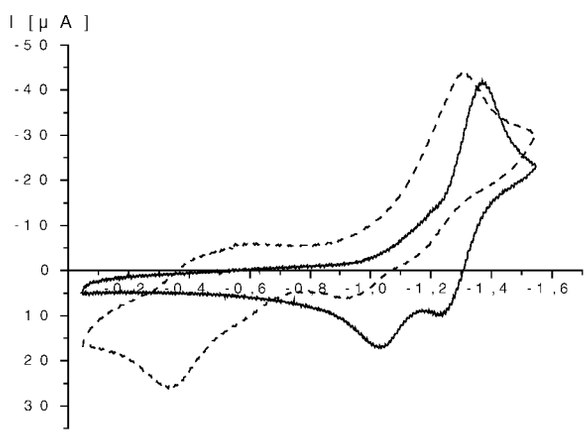
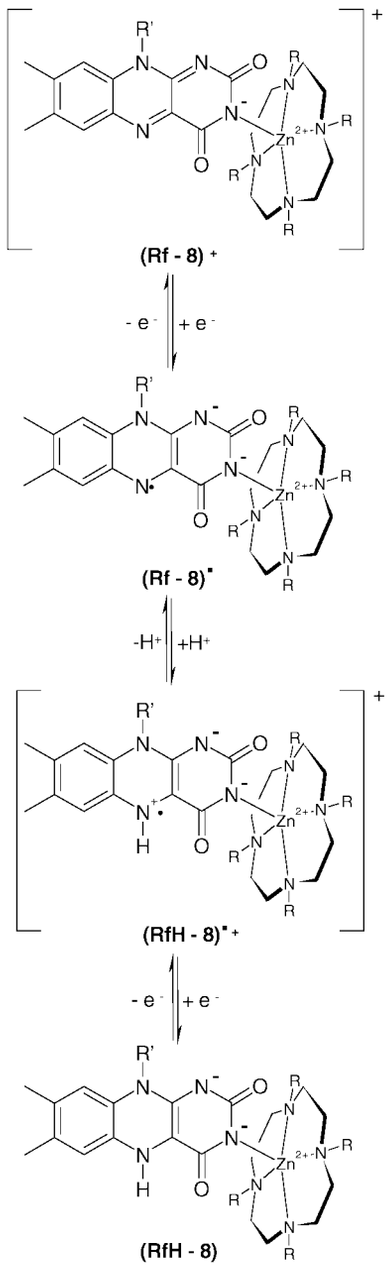


Fig. 1 Cyclic voltammogram of **7** ($c = 10^{-3}$ mol l^{-1}) (straight line) and **7** + 3 equiv. **8** (dashed line). 0.5 V s^{-1} in 0.1 mol l^{-1} $NBu_4^+BF_4^+$ in CH_2Cl_2 *vs.* Fc/Fc^+.

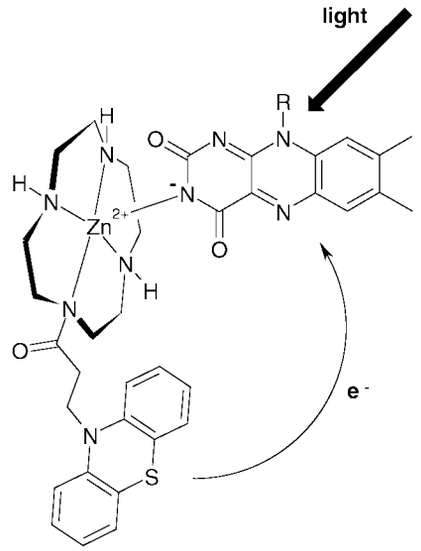
two-electron reduction which is explained perfectly by the ECE mechanism proposed by Rotello *et al.*[26b] First an electron is transferred to the oxidised flavin to give a radical anion. In the following steps the flavin radical anion is rapidly protonated and a second electron is taken up immediately to give the flavohydroquinone anion (see Scheme 9). By addition of 3 equiv.



Scheme 9 Possible chemical and electrochemical steps in the reduction of riboflavintetraacetate in the presence of **8**.

8 the reduction peak potential is shifted by approximately 100 mV. More significantly the first oxidation wave, which is assigned to the reoxidation of the flavin radical anion, nearly disappears and the second oxidation peak belonging to the oxidation of RfH^- is shifted by more than 600 mV to positive potential. This means that the coordination of the riboflavintetraacetate to the zinc complex **8** stabilises the fully reduced form of the flavin significantly. Similar results were obtained by studying the electrochemistry in polar solvents like methanol. In conclusion, **8** serves as a simple model for a so far unknown metalloprotein binding site that modulates the redox properties of a flavin cofactor.

The zinc(II)-cyclen imide coordination was also used to study photoinduced electron transfer in aqueous media under physiological conditions.[27] For this purpose cyclen was functionalised with a redox active phenothiazine group. The resulting zinc(II) complex was then assembled with riboflavintetraacetate to give an electron donor–acceptor dyad as shown in Scheme 10. Under excitation with light the riboflavintetraacetate becomes a stronger oxidising reagent and an electron from the phenothiazine is transferred to the flavin.



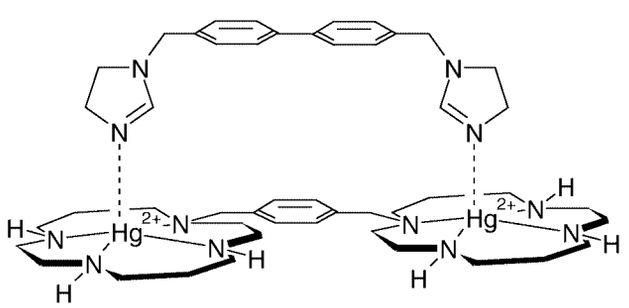
Scheme 10 Photoinduced electron transfer between phenothiazine and riboflavin mediated by a Zn^{2+}-cyclen coordination site.

This charge separated state was observed by transient spectroscopy.

Moieties which are structurally related to imides can also reversibly bind to zinc(II)-cyclen. A recently obtained X-ray structure analysis proved the coordination of creatinine, an important biodegradation product in the human body, to zinc(II)-cyclen after deprotonation of N^1.[28]

2.5 Recognition of imidazole

Another example of molecular recognition through a metal-to-ligand interaction is the binding of bis-imidazoles by bis-Hg^{2+}-cyclams[29,30] as outlined in Scheme 11.



Scheme 11 Coordination of 4,4″-bis(imidazol-1-ylmethyl)-*p*-biphenyl by 1,4-bis(1′,4′,8′11′-tetraazacyclotetradecan-1′-ylmethyl)benzene bis-(Hg^{2+}) tetraperchlorate **9**.

Three different bis-imidazole derivatives containing phenyl, biphenyl and terphenyl spacers were synthesised. The spacers of the corresponding bis-metal receptors were designed by computer modelling to position the metal ions to match the coordinating nitrogen atoms of the target imidazole molecules. The crystal structure parameters of the Hg^{2+}-cyclam binding site are quite similar to Zn^{2+}-cyclen. The geometry is square pyramidal with the four nitrogen atoms in one plane and the Hg^{2+}-ion displaced from the plane by 0.80 Å.[31] The large ionic radius of Hg^{2+} prevents it from remaining in plane with the four nitrogen atoms of the macrocycle. So one side of the mercury is blocked by the azamacrocycle and the other side is open for further coordination of only one additional ligand.

Binding studies were performed in DMSO by competitive NMR titration experiments between the bis-imidazoles and 1-benzylimidazole. The system outlined in Scheme 11 showed the highest binding constant of 3.1×10^6 M^{-1}. Selectivities were also examined. For example receptor **9** (Scheme 11) preferred

binding of 4,4″-bis(imidazol-1-ylmethyl)-*p*-biphenyl **10** over 1-benzylimidazole by a factor of 140 and **10** over the shorter and longer bis-imidazoles by a selectivity factor of about 11. This binding motif was extended to the recognition of a tris-(histidine) ligand by a tris(Hg^{2+}-cyclam).[32]

A different receptor that can bind imidazole in histidine and histamine was developed by Inoue and coworkers.[33] This receptor is a copper(II) complex of the 13-membered macrocycle 2,9-dioxo-1,4,7,10-tetraaza-4,7-cyclotridecanediacetic acid, **11** (Scheme 12). In complex **11** copper(II) is six-coordinated. The water molecule that usually occupies the sixth coordination site can be replaced by one imidazole nitrogen. The binding of histidine and histamine to **11** was studied by potentiometric pH titration and changes in the d–d band absorption of the Cu^{2+} centre. The association constant between **11** and histidine was determined in aqueous solution to be log $K = 2.8$ by potentiometric pH titration and a value of log $K = 2.5$ was derived from changes in absorption.

Scheme 12 Binding of histidine (R = H) or histamine (R = COO^-) to 2,9-dioxo-1,4,7,10-tetraaza-4,7-cyclotridecanediacetate Cu^{2+} complex **11**.

3 Catalysis

3.1 Various enzyme mimics

The already mentioned Zn^{2+} complexes of 1,5,9-triazacyclododecane **1** and 1,4,7,10-tetraazacyclododecane **3** were also studied as catalysts and enzyme mimics. In this context Zn^{2+}-cyclen was used in the cleavage of the β-lactam ring of benzylpenicillin as a functional model of the zinc-containing hydrolytic enzyme β-lactamase II.[34]

On the other hand **1** serves as a model for carbonic anhydrase.[6,7,35–37] Carbonic anhydrase is a zinc(II)-containing enzyme that catalyses the reversible hydration of carbon dioxide to bicarbonate. In **1** the geometry around the zinc(II) centre is quite similar to the ligand field surrounding Zn^{2+} in carbonic anhydrase. Moreover the pK_a of the coordinated water in **1** (see section 2.1) has almost the same value as reported for the Zn(II)-enzyme. The activity of **1** was studied in the hydrolysis of methyl acetate and the hydration of acetaldehyde, where the Zn^{2+}-bound OH^- commonly acted as a nucleophile to the carbonyl carbons.

Zn^{2+}-cyclen is an even better functional model system for carbonic anhydrase. The hydration of CO_2 and the dehydration of HCO_3^- catalysed by **3** and **1** were studied in aqueous solution.[38,39] The second-order rate constants for the two reactions were measured and it was shown that **3** is 5 and 11 times more reactive in the hydration and dehydration reactions, respectively, if compared with **1**.

The two complexes **1** and **3** were also studied as catalysts in hydride transfer reactions from alcohols to *p*-nitrobenzaldehyde and *N*-benzylnicotinamide chloride.[40]

3.2 Ester hydrolysis

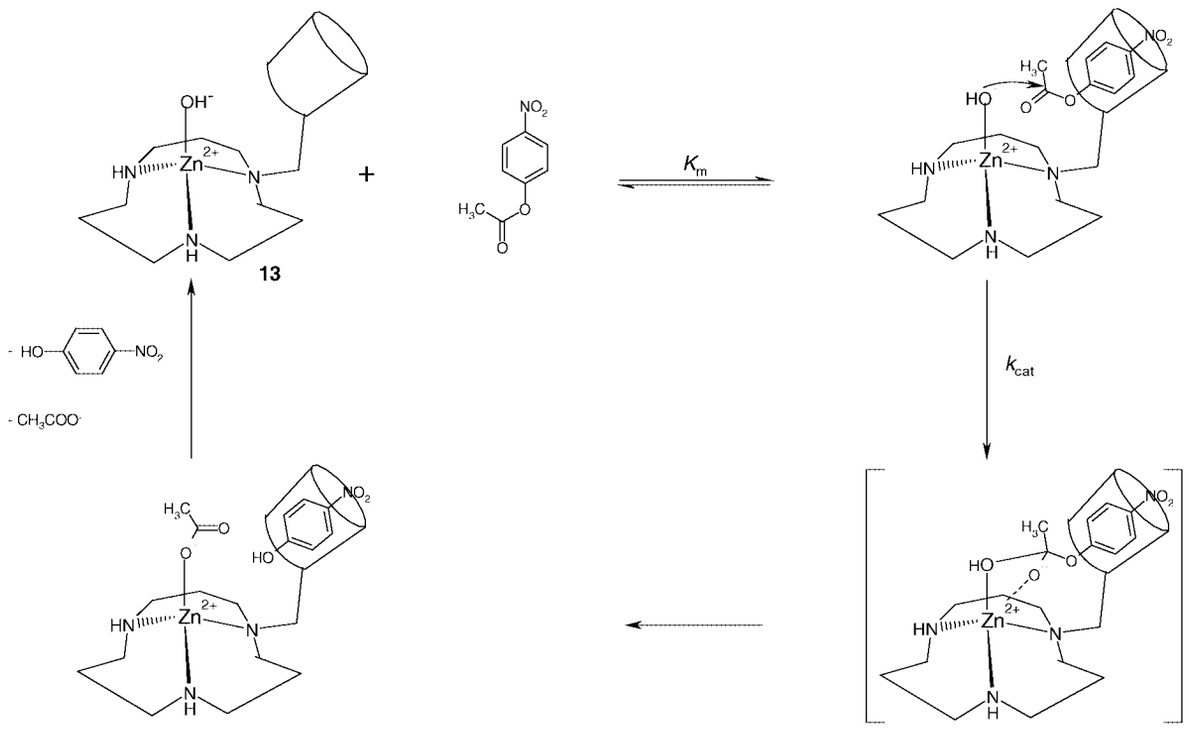
3.2.1 Zn(II) complexes. One of the most interesting applications of metal complexes of azacrown ethers is the catalytic hydrolysis of ester groups. In particular, the hydrolysis of phosphate esters as found in DNA or RNA has attracted a lot of attention during recent years. For this purpose a new alcohol functionalised cyclen derivative 1-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane was synthesised by Kimura and coworkers and the corresponding Zn^{2+} complex **12** was studied in catalytic ester hydrolysis.[41] The kinetics of the hydrolysis of 4-nitrophenyl acetate (NA) were measured in aqueous solution with 10% CH_3CN as cosolvent at a pH between 6.4 and 9.5. The reaction mechanism is outlined in Scheme 13. **12** is in equilibrium with its monoaquo complex and the coordinated water molecule is deprotonated at a pK_a of 7.6. The pendant alcohol is activated by the Zn(II)-bound hydroxy group and becomes a strong nucleophile towards NA. In the rate-determining step NA is cleaved with a second-order rate constant of $k_{NA} = 0.46\ M^{-1}\ s^{-1}$. This is about ten times faster than the comparable reaction rate reached with Zn^{2+}-*N*-methylcyclen having no alcohol group. In neutral or alkaline solution the resulting acyl intermediate is deprotonated and acetate is hydrolysed immediately to give the final products CH_3COO^- and starting material **12**.

Scheme 13 Reaction mechanism for 4-nitrophenyl acetate hydrolysis catalysed by Zn^{2+}-1-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane bisperchlorate.

A similar hydroxyl containing complex (*S*)-1-(2-hydroxy-2-phenylethyl)-1,4,7,10-tetraazacyclododecane zinc(II) bisperchlorate was used in the hydrolysis of the phosphodiester bis(4-nitrophenyl)phosphate.[42] But this reaction gave no catalytic turnover because the cleaved phosphomonoester stayed tightly bound to the Zn(II) complex.

Besides Zn(II) complexes of cyclam, derivatives having strategically appended phenolic groups were examined in the hydrolysis of 4-nitrophenyl acetate.[43] But all these complexes showed lower rate constants than complex **12**. Moreover, dimeric Zn^{2+} complexes derived from 1,4,7-triazacyclododecane and 1,5,9-triazacyclotetradecane were studied as catalysts for the hydrolyses of *p*-nitrophenyl phosphate and bis(4-nitrophenyl)phosphate.[44] These dimeric complexes with 1,4-phenyl and 1,3-phenyl linkers were more effective in phosphate cleavage than the corresponding monomers.

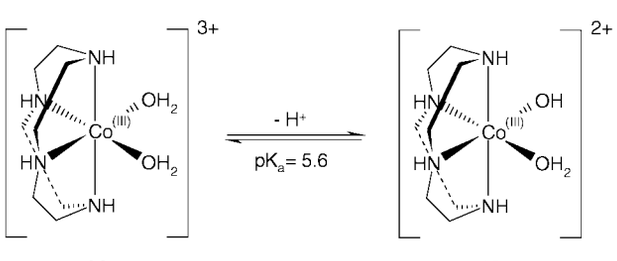
New derivatives of [12]aneN_3, cyclen ([12]aneN_4) and cyclam ([14]aneN_4) bearing a hydrophobic β-cyclodextrin (β-CD) were explored by Kim and Lee.[45] These compounds were prepared by reaction of 6-deoxy-*O*-tosyl-β-CD with one of the macrocyclic nitrogens and subsequent complexation with Zn(II).



Scheme 14 Schematic representation of the hydrolysis of 4-nitrophenyl acetate catalysed by Zn^{2+} complex **13**.

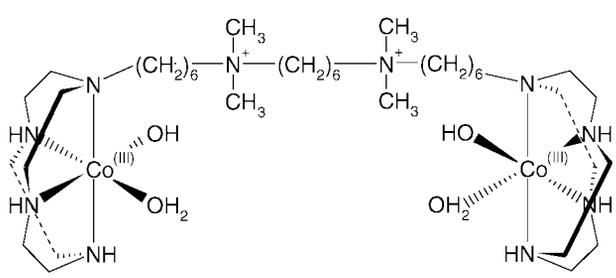
Kinetic studies in the hydrolysis of NA were carried out in aqueous solution at pH 7.0 and 25 °C. The catalytic cycle is outlined in Scheme 14: NA is able to bind into the hydrophobic β-CD pocket with dissociation constants K_M of around 3.5 mM. When the NA is bound the Zn^{2+}-coordinated hydroxy group can attack the ester. The reactivity increased with the basicity of the zinc bound OH^-. The highest rate constant of $k_{cat} = 7.72 \times 10^{-4}$ s^{-1} was observed with complex **13**. This corresponds to a 291-fold acceleration of hydrolysis compared with the unsubstituted complex **1**.

3.2.2 Co(III) complexes. The hydrolysis of phosphate esters by the Co(III) complex of cyclen **14** was studied extensively.[46–52] In **14** (see Scheme 15) the Co(III) centre is six coordinated with



Scheme 15 Deprotonation of $[Co(cyclen)(OH_2)_2]^{3+}$ to $[Co(cyclen)(OH)(OH_2)]^{2+}$.

an octahedral geometry. Two kinetically labile water molecules occupy the *cis* coordination sites. The pK_a values for deprotonation of the two water molecules are 5.6 and 8.0 as determined by potentiometric titration.[52] So at neutral pH compound **14** is present in its deprotonated form as the hydroxoaqua complex **15**. This is also the active species in the hydrolysis of phosphoesters. By adding a phosphate ester like 2,4-dinitrophenylphosphate (DNPP) to an aqueous solution of **15** the labile water molecule at the Co(III) centre is substituted by the ester that coordinates with one of the phosphate oxygens to the Co^{3+}. In the next, rate-determining step the neighbouring *cis*-coordinated hydroxide attacks the phosphorus(V) centre and the BNPP is cleaved to orthophosphate and 2,4-dinitrophenolate.



Scheme 16 Dinuclear Co(III)-cyclen complex.

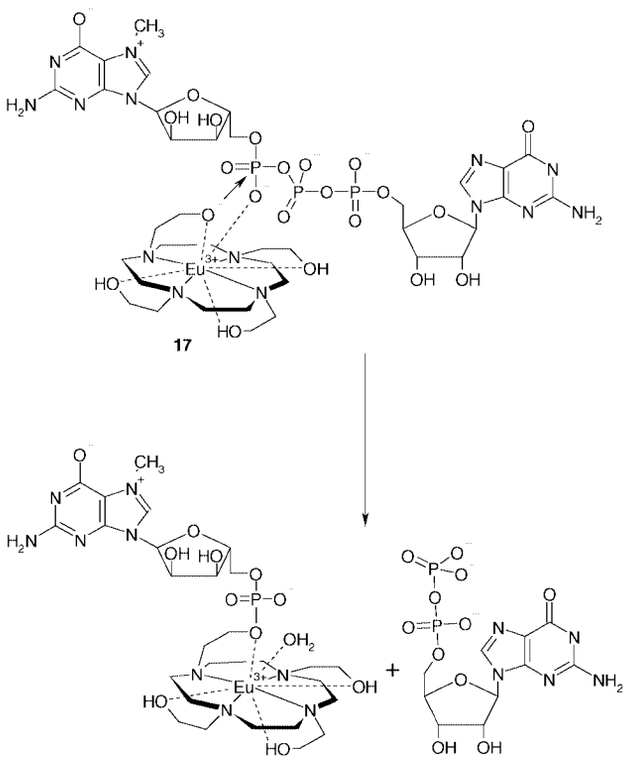
Recently the dimeric complex **16** (see Scheme 16) with two Co^{3+}-cyclen centres separated by a charged spacer was studied in the hydrolysis of phosphate esters and plasmid DNA.[53] The positively charged tetraalkylammonia spacer had only small effects on the hydrolysis of NA and BNPP but led to an enhanced cleavage of plasmid DNA. As shown by an ethidium bromide displacement assay the additional positive charges result in a stronger binding to the negatively charged DNA. Mainly this enhanced affinity is the reason for the efficient hydrolysis of DNA by **16**. Incubation of DNA with 0.05 mM **16** at 37 °C and pH 7.0 lead to almost complete cleavage within 2 hours and an observed rate constant of $k_{obs} = 1.1 \times 10^5$ s^{-1}. This corresponds to a rate enhancement factor of 1.6×10^7 and is the largest value measured in the hydrolysis of DNA so far.

3.2.3 Complexes with Eu(III), La(III) and Th(IV). Lanthanide(III) complexes of the tetraamide cyclen 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane were studied in the cleavage of RNA. While the La^{3+} complex[54] promoted rapid RNA hydrolysis the corresponding Eu^{3+} complex[55] showed no activity. The La^{3+} ion has ten coordination sites to fill: four are occupied by the cyclen-nitrogen atoms and another four are coordinated to the amide carbonyl moieties. Two additional sites are available for binding and catalysis. On the other hand the Eu^{3+} ion can bind only nine ligands (see Scheme 2) and so just one site is provided for further interactions. This led to the conclusion that the number of available coordination sites correlates with the RNA-cleavage activity. This was confirmed by the synthesis of a different Eu^{3+} complex where one of the coordinating amide groups was replaced

by a non-binding 4-nitrobenzyl residue.[56] Hereby the catalytic activity was restored.

Morrow *et al.* also studied a thorium(IV) complex of the above mentioned tetraamide cyclen.[57] The Th^{4+} complex showed 40-times higher activity in phosphate diester cleavage than the corresponding La^{3+} macrocycle. This greater reactivity of the Th(IV) centre can be attributed to its higher Lewis acidity as compared to La^{3+}.

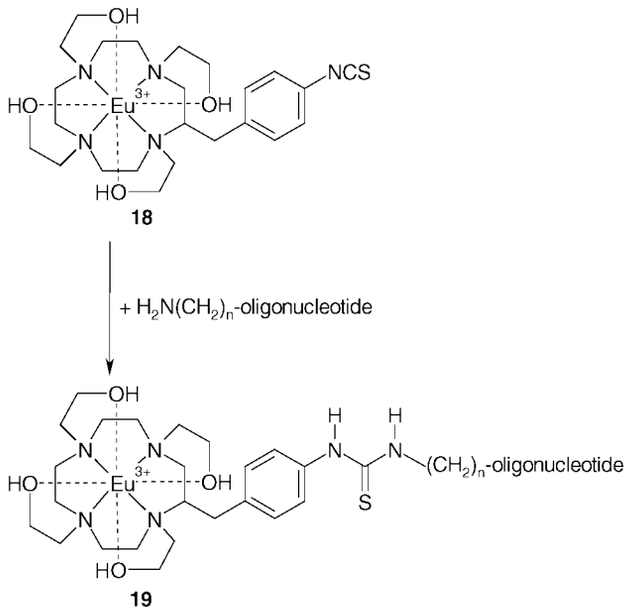
Another Eu^{3+} complex **17** with a 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane ligand was explored in hydrolytic cleavage of phosphate diesters[58] and the 5′-cap structure of mRNA.[59] The reaction mechanism is outlined in Scheme 17. The 5′ capped RNA model substance m^7GpppG



Scheme 17 Cleavage of m^7GpppG by **17**.

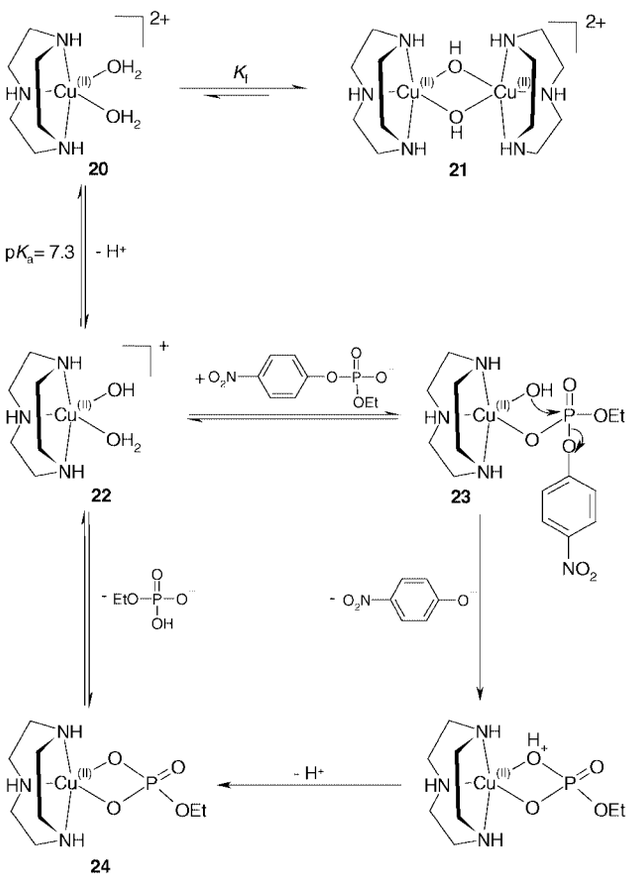
binds to the Eu^{3+} complex **17** through the triphosphate linkage with a binding constant of 5.9×10^3 M^{-1}.[60] Simultaneously one of the metal activated hydroxyethyl groups in **17** is deprotonated with a pK_a = 7.4 and acts as a nucleophile at a phosphorus(V) centre in the coordinated phosphate bridge. In the following step m^7GpppG is cleaved by a nucleophilic displacement reaction into a nucleotide diphosphate and a nucleotide monophosphate adduct of **17**. This proposed mechanism is supported by the kinetic data where a first-order dependence on both **17** and m^7GpppG was observed. **17** also showed reactivity upon a oligoribonucleotide. After 4 h incubation with **17** at 37 °C and pH 7.1, 86% of the RNA was cleaved. Because of the formation of covalent adducts the hydrolysis requires stoichiometric amounts of complex **17** and is not a catalytic process. But the reaction rate is enhanced 15-fold by addition of stoichiometric amounts of $Zn(NO_3)_2$.[60] This indicates that Zn^{2+} may bind to and activate the phosphate linkage acting as a Lewis acid. Compared to Eu^{3+}-cyclen complexes with mixed alcohol and amide groups **17** showed the highest reactivity.[61]

The ability of **17** to hydrolyse phosphate esters was used in sequence-specific RNA cleavage.[62] For this purpose a new Eu^{3+} complex **18** with an isothiocyanate functionality was reacted with oligonucleotides containing 2′-*O*-propylamine linkers to give oligonucleotide conjugate **19** (see Scheme 18). Sequence specific cleavage of a 25-mer oligoribonucleotide was achieved in the presence of **19** at pH 7.5 and 37 °C.



Scheme 18 Synthesis of oligonucleotide conjugate **19**.

3.2.4 Cu^{2+} complexes. The mechanism of phosphate diester hydrolysis catalysed by dichloro(1,4,7-triazacyclononane)-copper(II) Cu[9]aneN_3Cl_2 was investigated by Burstyn and co-workers in detail.[63–65] As shown in Scheme 19 Cu[9]aneN_3Cl_2



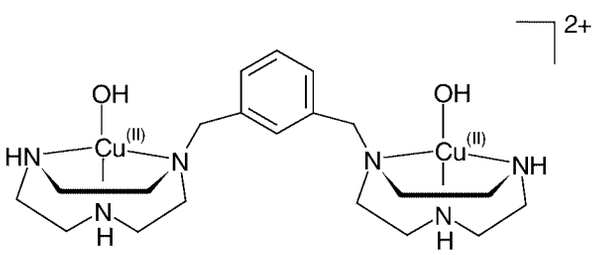
Scheme 19 Mechanism of ethyl-4-nitrophenyl phosphate hydrolysis catalysed by the Cu^{2+}-1,4,7-triazacyclononane complex.

forms in aqueous solution a diaquo complex **20**, which is in equilibrium with its dimeric form **21**. Compound **21** is the thermodynamically more stable species as shown by the large K_f of 1220 M^{-1} favouring the dimer. The catalytically active species **22** is obtained by deprotonation of one coordinated water with a pK_a of 7.3 as determined by potentiometric titra-

tion. This species is in the presence of ethyl-4-nitrophenyl phosphate in rapid equilibrium with the catalyst-phosphate complex **23**, which is formed by the exchange of a labile Cu(II)-coordinated water molecule for the phosphate diester substrate. In **23** the coordinated hydroxide is positioned closely to the phosphorus centre favouring an intramolecular nucleophilic attack. In the next rate-determining step nucleophilic attack and departure of the leaving group *p*-nitrophenolate take place simultaneously in a concerted mechanism as proven by isotope effect studies. A rapid deprotonation follows to generate the phosphate complex **24** which dissociates to regenerate the catalyst **22** and to release the phosphate monoester. At a reaction temperature of 50 °C a 2000-fold rate enhancement was observed compared to hydroxide ion mediated hydrolysis. Moreover, Cu[9]aneN_3Cl_2 was used in the hydrolysis of single-stranded and double-stranded DNA[66] and RNA.[67] Even for the cleavage of amide bonds of dipeptides and proteins Cu[9]ane-N_3Cl_2 showed catalytic activity.[68]

Recently 1,4,7-triazacyclononane has been covalently immobilised onto a silica surface by a rhodium-catalysed hydrosilation reaction between *N*-(4-but-1-enyl)-1,4,7-triazacyclononane and hydride-modified silica.[69] Subsequent reaction with copper(II) nitrate generated a silica-bound Cu(II)-triazacyclononane complex which is an active catalyst in the heterogeneous hydrolysis of the phosphodiester bis(4-nitrophenyl)phosphate.

Dimeric Cu^{2+} complexes with two different bis(triazacyclononane) ligands, 1,3-bis(1,4,7-triaza-1-cyclononyl)-*p*-xylene and 1,3-bis(1,4,7-triaza-1-cyclononyl)-*m*-xylene were studied in the hydrolysis of GpppG and m^7GpppG, two models for the 5′-cap of mRNA.[70] At pH 7.3 the predominant species are the bis(hydroxide) complexes as shown in Scheme 20. These dimeric

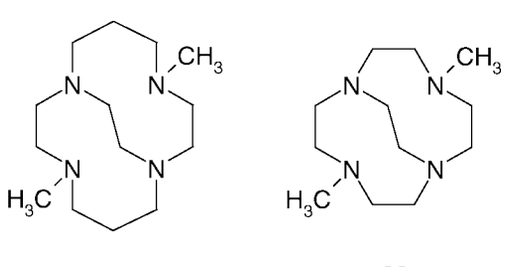


Scheme 20 Dinuclear Cu(II) complex of 1,3-bis(1,4,7-triaza-1-cyclononyl)-*m*-xylene.

complexes cleaved GpppG about a hundred times faster than the monomeric Cu(II)-1,4,7-triazacyclononane complex.

3.3 Redox catalysts

Recently Busch and coworkers prepared the Mn(II) and Fe(II) complexes of the cross-bridged tetraazamacrocycles 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane **25** and 4,10-dimethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane **26** (Scheme 21).[71] The X-ray crystal structures of all of these complexes showed a distorted octahedral geometry around the



25 **26**

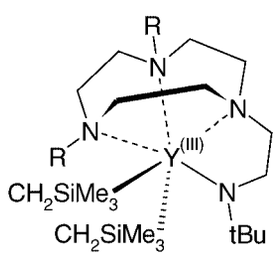
Scheme 21 Ligands 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane and 4,10-dimethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

metal centres with the two *cis* coordination sites occupied by labile chloride ligands. These two chlorides are replaced by water molecules in aqueous solution. Because of the cross-bridging the ligands **25** and **26** are extremely rigid, which enables them to stabilise the Mn^{2+} and Fe^{2+} oxidation state in aqueous solution. In the case of the manganese complexes even the oxidation states +3 and +4 are stabilised significantly by the ligand as determined by cyclic voltammetry. Such stabilisation of multiple oxidation states together with two labile *cis* coordination sites is quite useful for various catalytic cycles. In this context the manganese complexes were studied in the catalytic oxidation of 1,4-cyclohexadiene in MeOH–H_2O (1 : 1 v/v) with H_2O_2 as the terminal oxidant. Quantitative formation of benzene with a first-order rate constant of 4×10^{-4} s^{-1} was achieved.

Another manganese complex Mn^{4+}-*N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane was explored as catalyst in olefin oxidation with hydrogen peroxide in aqueous media.[72] The catalysed rates of oxidation of water-soluble olefins showed a 12-fold increase compared to the nocatalysed reaction.

3.4 Polymerisation catalyst

An interesting new aspect in metallaazamacrocyclic chemistry is their potential for catalytic ethene polymerisation. For this purpose yttrium complexes of new 1,4,7-triazacyclononane-amine ligands as shown in Scheme 22 were synthesised.[73]



27 R = ^{i}Pr

28 R = Me

Scheme 22 Yttrium complexes.

The X-ray structure of **27** confirmed that the three nitrogens of the triazacyclononane moiety are bound in *fac* arrangement to the metal centre. For ethene polymerisation experiments the complexes **27** and **28** were activated with the Brønsted acid $[PhNMe_2H][B(C_6F_5)_4]$ to produce the ionic species {[*N*,*N*′-R_2-1,4,7-triazacyclononane-*N*″-$(CH_2CH_2)N^t$-Bu]$Y(CH_2SiMe_3)$}$[C(C_6F_5)_4]$, which is the active polymerisation catalyst. Productivities in ethene polymerisation of up to 1.79×10^3 kg(PE) mol(Y)$^{-1}$ h^{-1} bar^{-1} were obtained with these catalysts.

4 Summary and outlook

Metal complexes of functionalized azamacrocyclic ligands are suitable binding sites for a variety of anionic guest molecules and some even catalyse reactions of their coordinated substrates. However, from the large number of coordination compounds with kinetically labile ligands only a small fraction has been investigated in this context so far. This leaves many opportunities for new discoveries in the future. Combination of guest or substrate binding by reversible coordination with molecular imprinting techniques or selection from combinatorial compound libraries may yield hosts or catalysts with improved selectivities. The high association constants observed for ligand binding with azamacrocyclic coordination compounds in water clearly make them appropriate binding sites in the design of artificial receptors for binding of biological structures.

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