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Metal ion effect on reactivity of pendant groups in functionalized macrocyclic complexes

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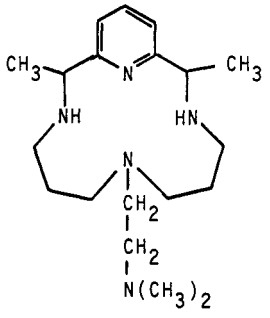
Abstract- As donor groups of functionalized tetraaza-macrocycles change the properties of the metal ion when they coordinate, so the metal ion can modify the reactivity of the functional group.
Examples of Cu(II) promoted ester and nitrile hydrolysis in the complexes **2** - **5** have been studied kinetically. The mechanisms of the two reactions are probably different, the nitrile being hydrolyzed to the amide by an internal, the esters probably by an external OH^- attack. The X-ray structure of the Cu(II) complex with **5** clearly shows that the ester group is coordinated through its carbonyl oxygen to the metal ion, thus supporting the proposed external OH^--attack.
The second series of examples show that in the symmetrical Cu(II) complexes **6** and **9** only one group can selectively be modified. These reactions are possible because of the special structure these macrocycles adopt in the trans-I (RSRS) configuration and because of the coordination of only one of the two groups.

INTRODUCTION

After the discovery of the complexation ability and selectivity of macrocycles (ref. 1), these compounds have been modified in several ways in order to obtain ligands with new properties. One direction of this development has been the introduction of functionalized side chains, attached to the macrocycle either at a carbon or a nitrogen atom, to increase the stability, to change the selectivity or modify the solubility of their complexes (ref. 2).

In other cases the functional group of the side chain has been introduced to tune the properties of the metal ion to which it coordinates. So, for example, one can shift in the Ni(II) complex of **1** from a square planar, diamagnetic yellow species to an octahedral, paramagnetic blue one just by controlling the coordination of the amino side chain group through protonation or deprotonation of it (ref. 3).



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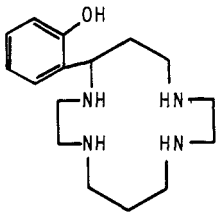

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For the Ni(II) complex with **2** it has been shown that the redox potential Ni(II)/Ni(III) is greatly affected by the coordination or non-coordination of the chain functional group (ref. 4).

Beside these interesting aspects, there is an additional one, which, however, has only little been studied up to now. As the functional group of the side chain can modify the properties of the metal ion through coordination, one

would expect that the opposite also would take place: by binding of the functional group to the metal ion it should be possible to change its reactivity. This would allow to study metal ion promoted or induced reactions under a strict control of the geometrical or sterical situation, since the macrocycle will hold the metal ion in a kinetically inert environment.

HYDROLYSIS REACTIONS

Many cases (ref. 5) of metal ion promoted hydrolysis reactions have been described in the literature. One of the first examples was the observation of Kroll (ref. 6) that amino acid esters are hydrolyzed in their Cu(II) complexes at a much faster rate as the non-complexed ones. For the discussion of the hydrolytic mechanism studies of kinetically inert Co(III) complexes have played an important role. Buckingham and Sargeson (ref. 7) have clearly shown that there are mainly two types of reaction paths: either attack of free OH^- onto the coordinated ester group (external OH^- attack) or intramolecular nucleophilic attack of coordinated OH^- onto the dangling ester group (external OH^- attack). If we apply these results to monofunctional tetraazamacrocycles with an hydrolyzable group, we expect the situation given in Figure 1. The metal ion is coordinated by the four nitrogens of the macrocycle, an apical position can either bind the dangling group, as has been shown for typical ligating functions X, or an OH^-. In the first case we would expect external, in the second internal OH^- attack.

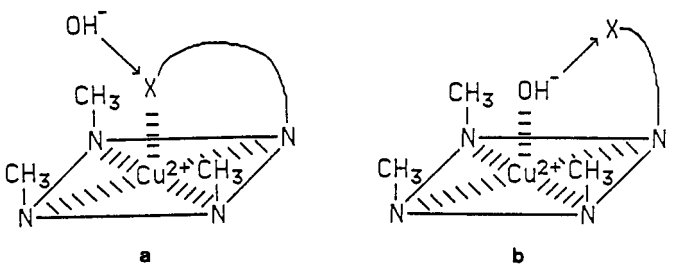


Figure 1. External (a) and internal (b) OH^- attack in a monofunctionalized macrocyclic complex.

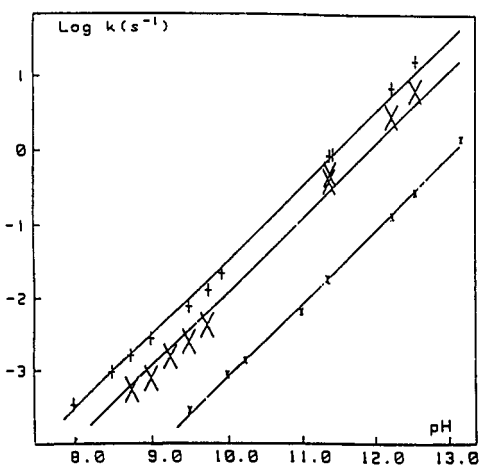
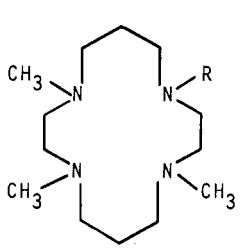


Figure 2. pH profiles of the hydrolysis of the Cu^{2+} complex with **2** (+), **3** (×) and **4** (✱).

To study such reactions we have prepared a series of macrocycles with -CN and -COOR groups at the end of the side chain and have investigated whether Cu(II) will promote their hydrolysis (ref. 8). In these cases hydrolysis was observed, whereas for amide functions $-CONH_2$ and $-CONR_2$ no such reaction takes place.

HYDROLYSIS OF ESTERS

To study this type of reaction the Cu^{2+} complexes with **2** - **4** were prepared



1 R = H
2 R = CH_2-$COOCH_3$
3 R = CH_2-$COOC_2H_5$
4 R = CH_2-CH_2-$COOC_2H_5$
5 R = CH_2-CN

by alkylation of 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane (**1**) with bromoacetic acid esters or acrylic ester. The hydrolysis (1) can be studied

$$Cu(L\text{-}COOR)^{2+} + OH^- \longrightarrow Cu(L\text{-}COO)^{+} + ROH \qquad (1)$$

either by pH-stat technique, titrating the OH^- consumed during the process as a function of time, or by stopped-flow measurements following the colour change from the ester to the carboxylate complex. In the pH region between 8 and 13 the rate (2) is first order in complex concentration and first order in $[OH^-]$ (Figure 2).

$$v = k_1[Cu(L\text{-}COOR)^{2+}]\cdot[OH^-] \qquad (2)$$

The bimolecular rate constants k_1 are comparable to those of the hydrolysis of glycine methyl, glycine ethyl and β-alanine ethyl ester (3). The rate enhancement through the metal ion is relatively small and perhaps dissappointing (Table 1).

$$OH^- + H_2N\text{-}(CH_2)_n\text{-}COOR \xrightarrow{k_1} H_2N\text{-}(CH_2)_n\text{-}COO^- + ROH \qquad (3)$$

Table 1. Bimolecular rate constants for the hydrolysis of the ester group in the Cu(II) complexes and in free amino acid esters at 30°.

Compound	$k_1(M^{-1}s^{-1})$	enhancement
$Cu(2)^{2+}$	231	137
$H_2N\text{-}CH_2\text{-}COOCH_3$	1.69[a]	
$Cu(3)^{2+}$	84	109
$H_2N\text{-}CH_2\text{-}COOC_2H_5$	0.82[b]	
$Cu(4)^{2+}$	5.9	87
$H_2N\text{-}CH_2\text{-}CH_2\text{-}COOC_2H_5$	0.068[c]	

a) From ref.9; b) From ref.10; c) From ref.11. All values extrapolated to 30°

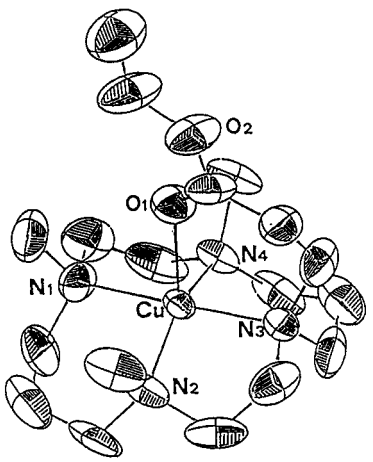


Figure 3. Structure of the Cu^{2+} complex with **4**

For the Cu(II) complex with **4** the X-ray structure analysis (Figure 3) shows a pentacoordinated Cu(II) surrounded by the four nitrogens of the macrocycle and the carbonyl oxygen of the pendant ester group in a distorted square pyramidal geometry. Since the absorption spectrum in the solid and in solution are very similar to each other, one can expect that the geometry observed in the solid will also be present in solution.

HYDROLYSIS OF THE NITRILE GROUP

The Cu(II) complex with a pendant nitrile group (**5**) reacts according to (4),

$$Cu(L\text{-}CH_2CN)^{2+} + OH^- \longrightarrow Cu(L\text{-}CH_2CONH)^+ \qquad (4)$$

whereby the amide formed by hydrolysis deprotonates and coordinates to the Cu(II) ion. The kinetics monitored by stopped-flow measurements gives the rate law (5), which is first order in the complex concentration and shows a pH-dependence with a plateau at high pH values (Figure 4).

$$v = K_{OH}\cdot k_2[Cu(L\text{-}CH_2CN)^{2+}]\cdot[OH^-]/(1 + K_{OH}\cdot[OH^-]) \qquad (5)$$

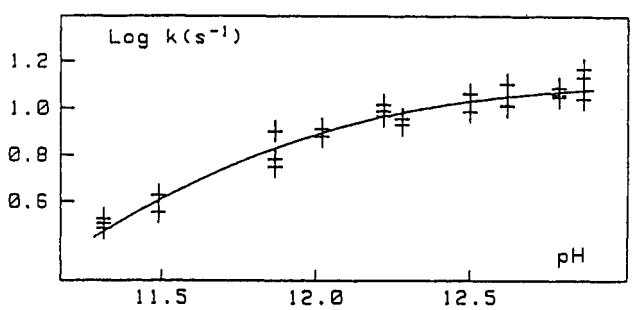


Figure 4. pH profile of the hydrolysis of the Cu^{2+} complex with **5**

This can be explained by assuming a rapid pre-equilibrium (6) in which a hydroxo complex is formed, followed by the rate determining step (7) (ref. 12).

$$Cu(L\text{-}CH_2CN)^{2+} + OH^- \longrightarrow Cu(L\text{-}CH_2CN)(OH)^+ \quad : \quad K_{OH} \qquad (6)$$

$$Cu(L\text{-}CH_2CN)OH^+ \longrightarrow Cu(L\text{-}CH_2CONH)^+ \quad : \quad k_1 \qquad (7)$$

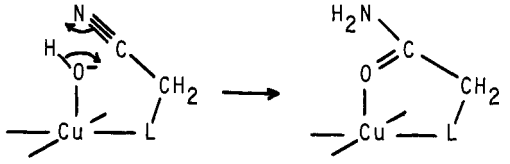
That a pre-equilibrium (6) is present can be seen at high pH by the sudden change in the absorbance, when the complex and NaOH are mixed in the stopped-flow instrument. It has also been observed that SCN^- inhibits the hydrolysis by coordinating to the Cu(II) complex.

MECHANISM OF THE Cu^{2+} PROMOTED HYDROLYSIS

The two examples described above show very different behaviour in their hydrolysis reactions. For the esters **2** - **4** a bimolecular reaction with OH^- is observed up to pH 13, whereas for the nitrile **5** a plateau at high pH is found. These two different pH-dependences could, but do not necessarily indicate different mechanisms.

Let us now discuss the two possibilities of external and internal OH^- attack (Figure 1). For external OH^- attack one expects a bimolecular rate constant with OH^- at any pH. For internal OH^- attack, the hydroxo complex has first to form and only then the coordinated OH^- can react with the group to be hydrolyzed. This would lead to a rate law similar to (5) and a plateau at high pH values. So the observation of a plateau is a strong indication for internal OH^- attack, but the opposite is not equally true, since the plateau could come at pH values outside the pH range accessible to measurements and then the rate would also be first order in $[OH^-]$.

For the nitrile hydrolysis all experimental facts speak for an internal OH^- attack: the pH dependence, the observation of a rapid pre-equilibrium step and the SCN^- inhibition can only be interpreted, if the hydroxo complex is the reactive species. In this compound an intramolecular attack by OH^- can then take place, whereby a five-membered transition state is formed (8).



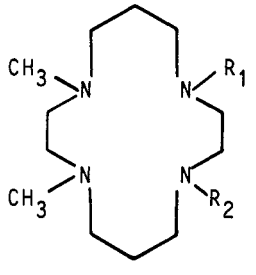
(8)

The ester hydrolysis mechanism on the other side is not as easy to discuss. Although we observe a linear pH dependence up to pH 13, although the rate constants are similar to those of free amino acid esters and although we find a coordinated ester group in the complex, it still could be that a small quantity of the hydroxo complex is present in an equilibrium with the other species and that the hydrolysis path goes through it.

Cu^{2+} INDUCED SELECTIVITY

Since the metal ion in a macrocyclic complex with a pendant chain can coordinate the functional group, it should be possible to selectively react this group, depending on whether it is coordinated or not.

A first example of a selective reaction was observed for the hydrolysis of the dinitrile **6**. If one reacts the Cu(II) complex of **6** with 0.1 M NaOH one



6 R_1, R_2 = CH_2CN
7 R_1 = CH_2CN, R_2 = CH_2CONH_2
8 R_1 = R_2 = CH_2CONH_2
9 R_1 = R_2 = $CH_2CH_2NH_2$
10 R_1 $CH_2CH_2NH_2$, R_2 = $CH_2CH_2NHCOC_5H_6$
11 R_1 = R_2 = $CH_2CH_2NHCOC_5H_6$

obtains after a few seconds the monoamide **7**. Longer reaction time at alkaline pH does not produce the expected bis-amide **8**.
How can the large difference in reactivity between the two nitrile groups be explained? As discussed before the hydrolysis of such nitriles goes through a hydroxo species (8). In the first step an analogous hydroxo species is formed in the dinitrile complex **6**, hydrolysis then takes place and

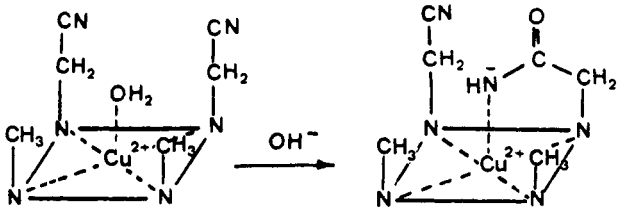


Figure 5. Hydrolysis of the Cu^{2+} complex with **6** to the monoamide **7**

gives the monoamide 7. The deprotonated amide group blocks the axial position and prevents the binding of a second OH^- (Figure 5). Thus further hydrolysis is inhibited. From a symmetrical compound with two chemically equivalent nitrile groups we have obtained a product in which only one function has been hydrolyzed.

A second example of differential reactivity was found in the Cu(II) complex of **9**. A study of the properties of this complex clearly shows that at high pH the two amino groups are not equivalent any more. Potentiometric and spectrophotometric measurements indicate that one amino group is

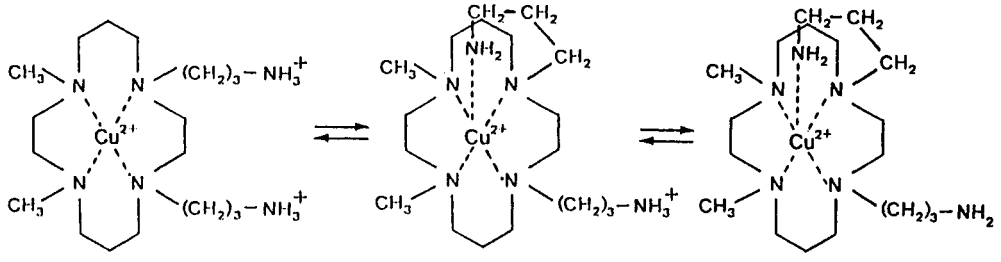


Figure 6. Different protonated species of the Cu^{2+} complex with **9**

coordinated to the axial position of the metal ion, whereas the second is not (Figure 6). This comes from the fact that macrocycles with tertiary nitrogens very often adopt the trans-I (RSRS) configuration, in which all nitrogen substituents are on the same side of the N_4-plane. Thus only one of the two side chain amino groups can coordinate.

We have made use of this observation and reacted the Cu(II) complex of **9** at alkaline pH with benzoyl chloride. The product is the monoamide **10**, whereas the acylation of the free ligand gives as expected the bis-product **11** (Figure 7).

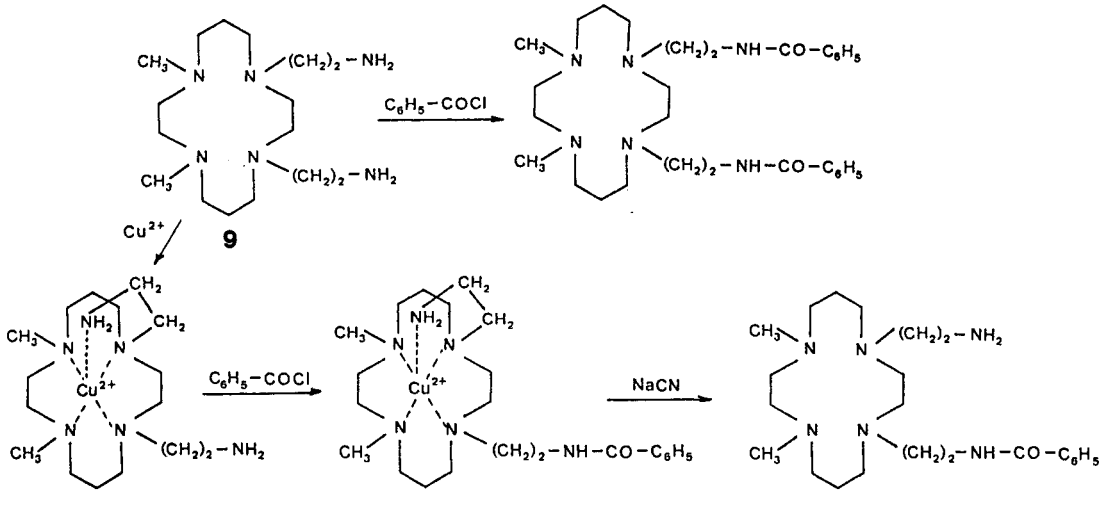


Figure 7. Products of the benzoylation of the free ligand **9** and its Cu(II) complex

So through selective coordination and protection of one amino group the other can be reacted and starting from a symmetrical product it is possible to prepare a monobenzoylated derivative.

CONCLUSION

The examples of metal ion promoted hydrolysis of esters and nitrile as well as those of metal ion induced selective reactions show that the metal ion plays an important role, dictating the reactivity of the functional groups in the side chains.

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