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Metal Complexes of Macrocyclic Ligands

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Abstract. Metal complexes of macrocyclic ligands are studied with a view to understanding aspects of metalloprotein structure and function.

Thomas Kaden studied chemistry at the University of Basel, where he received his Ph.D. in 1965 with *S. Fallab* and completed his habilitation in 1966. From 1970 to 1971, he worked as a research associate with *B.L. Vallee* at Harvard. He then returned to the University of Basel and was promoted to Professor in 1975. Amongst his many duties, he is a member of the executive committee of the *NSCS* and is president of Section II of the Swiss Academy of Sciences.

For many years, we have been involved in the study of metal complexes with functionalized macrocyclic ligands with three main aims:

1) *Fundamental aspects.* The introduction of side chains containing coordinating groups allows new multidentate ligands to be prepared, metal complexes might be more stable or formed more selectively. The structural aspects of these compounds are especially interesting.

2) *Modelling metalloenzymes.* If a carefully designed reactive group is introduced in a side chain of a functionalized macrocycle such that the functionality is close to the metal centre, then biomimetic metal-induced or -promoted reactions can be studied.

3) *Applications in nuclear medicine.* Functional side chains can also be used to covalently attach macrocyclic ligands to monoclonal antibodies, so that they can be labelled by complexing them with radionuclides.

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1. Fundamental Aspects

The structural study of metal complexes with tetra *N*-substituted tetraazamacrocycles (**1**–**3**) has shown that very different species are formed depending on the size of the ring and on the nature of the metal ion [1]. In 1:1 complexes, the metal ion is bound by the four nitrogens of the macrocycle and by either two or four carboxylate side chains, depending whether 3d- or 4f-centres are bound. In the case of Ni^{2+} and Cu^{2+}, both *cis*- and *trans*-octahedral arrangements have been observed (*Fig. 1*). This seems to be controlled by the ring size. The 12-membered ring is too small to encompass the metal ion and assumes a folded structure leaving two *cis*-positions open for the carboxylate groups, whereas the 14-membered ring can bind the metal ion in its centre and forms *trans*-octahedral species.

For the 2:1 species, two different structures have been observed. In the first type, one metal ion is bound as in the 1:1 species, and the carboxylate groups which are pointing away are used to coordinate the second metal ion, thus giving a polymeric

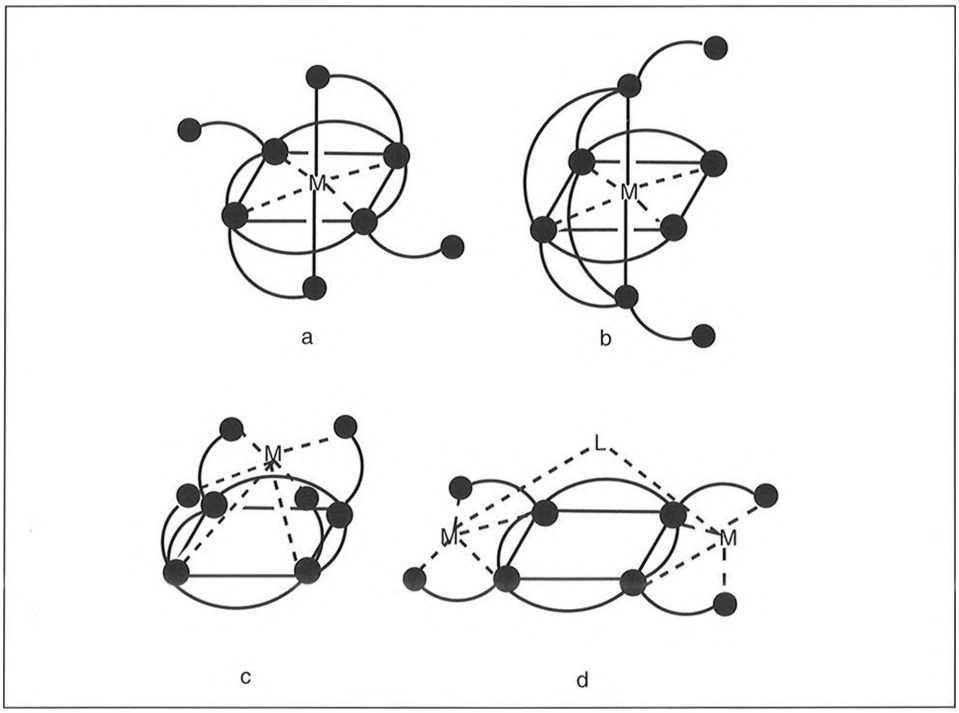


Fig. 1. Structures of the 1:1 (a: *trans*-, b: *cis*-octahedral, c: octacoordinated)) *and 2:1* (d) *metal complexes with ligands* **1**–**3**

CHIMIA 1999, *53*, No. 5

structure. The other structure consists of a more symmetrical arrangement in which the two metal ions are bound by two nitrogen atoms and two acetates of the same macrocycle (*Fig. 1d*).

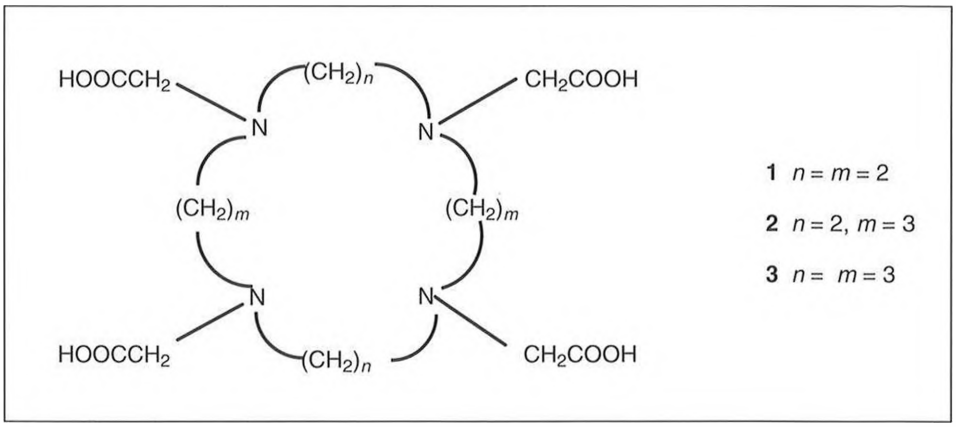
Another interesting aspect of the coordination chemistry of functionalized azamacrocycles is the possibility of controlling the binding of the side chain through the pH of the solution (*Fig. 2*). In several cases, we have observed that a reversible pH-dependent equilibrium exists in which the metal ion changes its structure from square-planar in acidic solution to penta- or hexacoordinated in alkaline solution [2]. In acidic solution the protonation of the side chain prevents the binding of the donor group to the metal centre, whereas in alkaline solution a deprotonaed group may coordinate to the metal centre. The effects of the nature of the donor group as well as of the length of the chain have been determined.

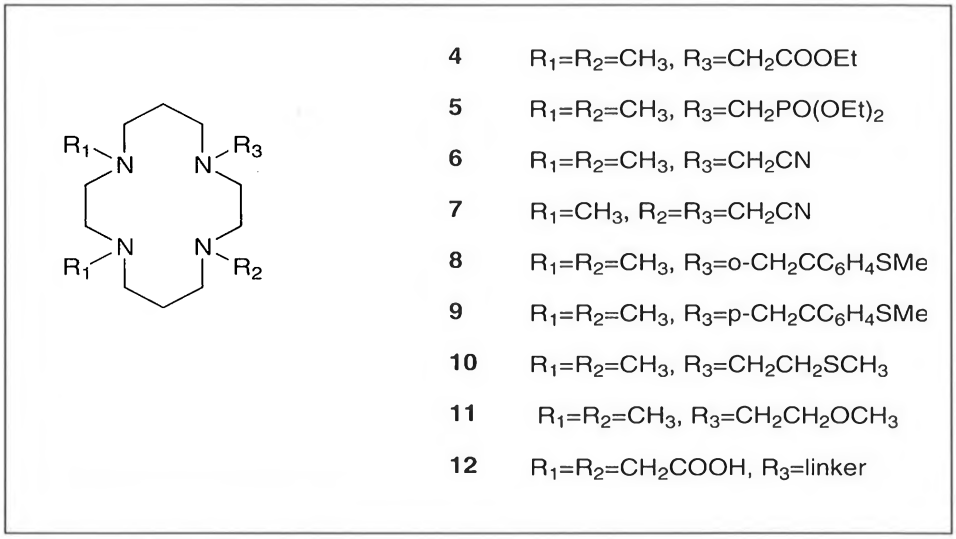
2. Modelling Metalloenzymes

Functionalized macrocycles can be used to mimic enzyme-substrate complexes, if a reactive side chain is introduced in such a way that a functional group can come close enough to the metal ion to be activated.

We have prepared a series of compounds of type **4**–**6** which bear functionality capable of hydrolysis. We have studied the hydrolysis of esters, phosphonate esters, and nitriles as models for hydrolases [3]. Whereas the Cu^{2+}-induced ester hydrolyses were not very efficient, hydrolysis of the nitrile groups was very fast. The mechanism of this reaction indicates that the reactive species is a hydroxo complex, and that an intramolecular nucleophilic attack of a coordinated hydroxo group onto the nitrile function takes place in a five-centred transition state (*Fig. 3*). It was interesting to note that in the dinitrile derivative **7** only one of the two functional groups is hydrolysed. This is because the amide hydrolysis product of the first nitrile is deprotonated and binds to the axial position of the metal ion (*Fig. 3*) preventing the formation of a second hydroxo species for attack onto the second nitrile group. This means that, using a symmetrical compound such as **7**, we can selectively hydrolyse one of the two chemically equivalent nitrile groups.

A second reaction we have studied in detail is the reductive cleavage of methyl thioethers to methane and a thiolate as a model for methyl-coenzyme M, an enzyme which requires F_{430}, a Ni^{2+} complex,





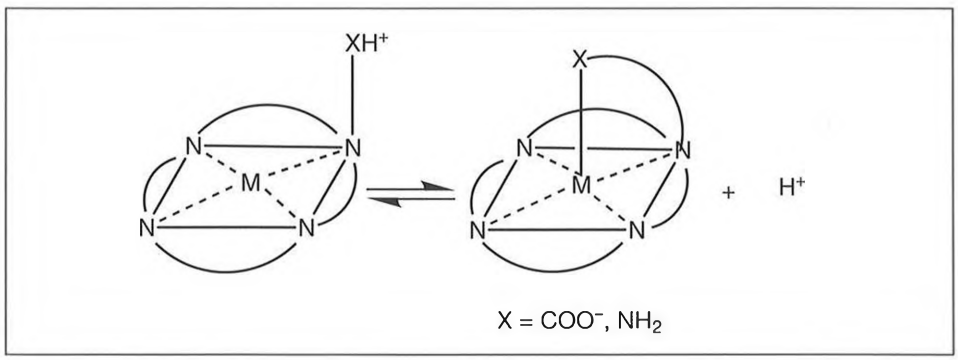


Fig. 2. *pH-Dependent geometry change in mono-N-functionalized macrocyclic complexes*

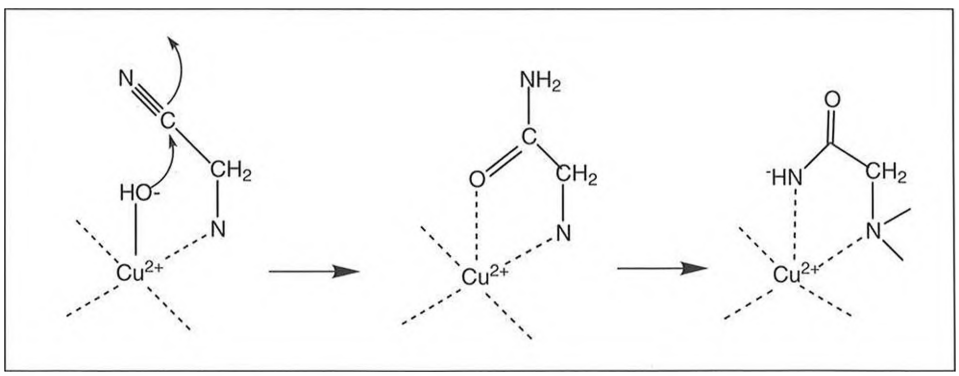


Fig. 3. *Transition state of the nitrile hydrolysis in the Cu^{2+} complex with* **6**

as cofactor. As model compounds, Ni^{2+} complexes of thioether-functionalized macrocycles **8**–**10** were studied [4]. Under reductive conditions, the Ni^{2+} species are rapidly reduced to the Ni^{+} complexes, as confirmed by EPR and VIS-spectroscopy. In the cases of the *ortho*-derivative **8** and of the aliphatic thioether **10**, small amounts (*ca.* 5%) of methane were detected as reaction products, whereas the corresponding *para*-derivative **9** and the methoxy compounds **11** did not produce any methane under similar conditions.

3. Applications in Nuclear Medicine

The side chain of a functionalized macrocycle can be used to attach its complex with a radioactive metal to a monoclonal antibody specific for receptors expressed by tumor cells. Such conjugate antibodies labelled with γ- or β-emitters can be used for diagnostic and therapeutic purposes, respectively. Studies with $^{111}In^{3+}$ (γ-emitter) and $^{90}Y^{3+}$ (β-emitter) have shown that in a series of bifunctional tetraazamacrocycles of type **12**, the best compound is a derivative of the 12-membered ring which is able to form complexes which are stable enough for a physiological application.

A simple mono-functionalized macrocycle attached to monoclonal antibodies has been shown to be an ideal chelating group for $^{64/67}Cu^{2+}$ [6]. The stability of the complex is high enough that no transchelation takes place in the blood; the ligand can be easily attached to monoclonal antibodies specific for tumors by synthetic methods typical for peptide-bond formation.

4. Conclusions

The field of functionalized macrocycles has many challenging points. It offers the possibility of synthesizing specific ligands, it is interesting because of the structures of the metal complexes, allows one to correlate structure and reactivity in model compounds for metalloproteins, and, finally, has practical applications in the field of medicine [7].

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