Journal of Inclusion Phenomena and Macrocyclic Chemistry **49**: 3–9, 2004.

Metal Complexes of Ditopic and Polytopic Macrocyclic Ligands

THOMAS A. KADEN
Department of Chemistry, Spitalstr. 51, CH-4056 Basel, Switzerland; E-mail: th.kaden@unibas.ch

(Received: 15 July 2003; in final form: 20 October 2003)

Key words: heteronuclear complexes, polytopic ligands, potentiometry, spectrophotometry, synthesis

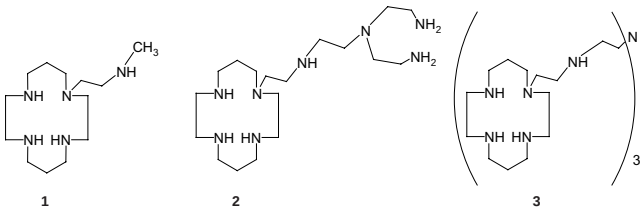
Abstract

Using 1,4,8,11-tetraazacyclotetradecane (cyclam) and tris(2-aminoethyl)amine (tren) as building blocks a ditopic (**2**) and a polytopic (**3**) ligand were prepared. Their complexation potential towards Cu^{2+} and Ni^{2+} was studied by potentiometric and spectrophotometric techniques. The results show that in the case of **2** the first metal ion and in the case of **3** the first three metal ions added bind at the macrocyclic unit, whereas the metal ion added afterwards is coordinated by the tren unit. This allows to selectively prepare heteronuclear metal complexes.

Introduction

There are several examples of ditopic ligands based on macrocycles in the literature. So large rings have been synthesized in which two metal ions can be accommodated (Figure 1) sometimes with additional exogenous bridging ligands [1]. Bis-macrocycles are another way to build ditopic ligands (Figure 1). The two rings can be connected either by a bridge starting from the carbon backbone [2] or from a nitrogen donor [3]. The properties of the metal complexes formed by these bis-macrocycles strongly depend on the length of the bridging chain, which modulates the metal–metal interaction, and by the nature of the two rings. Symmetrical bis-macrocycles give homoditopic ligands, whereas bis-macrocycles having different rings are examples for heteroditopic chelators [4]. In addition there are also a few compounds with a macrocycle combined with a noncyclic ligand [5] (Figure 1).

The combination of macrocyclic and open chain structural elements is especially interesting since it produces ligands with very different properties in regard to their complexation with metal ions. The macrocyclic unit, mainly characterized by a relatively rigid backbone of the molecule, imposes onto the metal ion a coordination geometry, forms metal complexes with relatively high thermodynamical stability and high kinetical inertness against acid dissociation or transmetallation [6]. In contrast the open chain unit of such a ligand being more flexible can adapt itself to the geometrical requirements of the metal ion and form metal complexes of somewhat lower thermodynamical stability and higher kinetical lability than those of macrocycles.



1 2 3

Based on these ideas we have prepared two new ligands **2** and **3**, which contain the macrocycle 1,4,8,11-tetraazacyclotetradecane (cyclam) and the open chain ligand tris(2-aminoethyl)amine (tren). For comparison we also have prepared the pendant arm macrocycle **1**, which has part of the structure of **2** and **3**, and resembles the scorpiand previously described [7].

Discussion

Synthesis of the ligands

The synthesis of **1** is straightforward. Tritosyl-cyclam **4** [8] was reacted with ditosyl-*N*-methylethanolamine in the presence of *N*-ethyldiisopropylamine and the product **5** was then deprotected with CF_3SO_3H in the presence of anisole (Figure 2) [9].

Ligand **2** was prepared starting from the triply boc-protected cyclam **6** [10], which was alkylated with iodoacetic acid. The carboxylic group of **7** was then activated with NHS and reacted with a 10-fold excess of tren, so that statistically the mono *N*-substituted tren-derivative **8** resulted. For purification purpose we

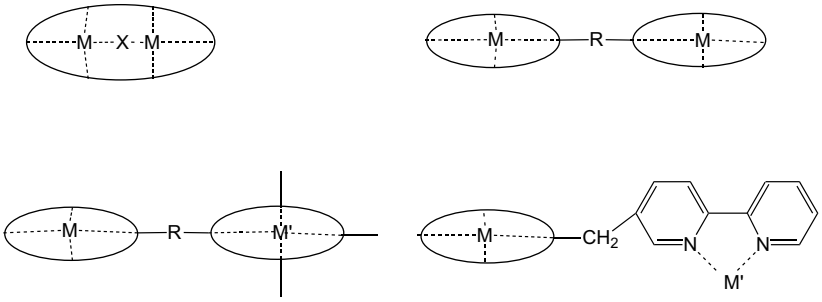


Figure 1. Examples of ditopic macrocyclic ligands.

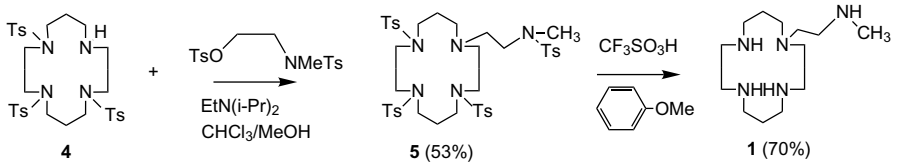


Figure 2. Synthesis of ligand **1**.

substituted the free amino groups of **8** with additional boc-groups, which gave us the completely protected product **9**. This allowed us to run for **9** a flash-chromatogram and thus to purify the product, whereas **8** being to polar did not move on silica gel. The boc-groups were then removed with CF_3COOH (**10**) and the amide group reduced with $LiAlH_4$ to give the final product **2** (Figure 3) [11].

Finally ligand **3** was prepared in an analogous way as **2**, but the activated carboxylic group of **7** was reacted with 1/3 equivalent of tren so that all three amino groups formed amide bonds (**11**). The amide was deprotected (**12**) and then reduced to give **3** (Figure 4) (L. Siegfried *et al.*, in preparation).

Metal complexes of **1**

Ligand **1** reacts with one equivalent of Cu^{2+} or Ni^{2+} to give a complex in which at low pH the metal ion is bound only by the macrocycle. This is confirmed by the typical absorption spectra of these species with λ_{max} values (Table 1) comparable to those of the unsubstituted cyclam, for which $\lambda_{max} = 520$ nm for Cu^{2+} and $\lambda_{max} = 460$ nm for Ni^{2+} are reported [12].

At higher pH a colour change is observed which is coupled with an acid-base equilibrium. The shift of λ_{max} to 621 nm for the Cu^{2+} complex is indicative for an axial binding of the *N*-methyl amino group of the side chain. At low pH this group is protonated and thus

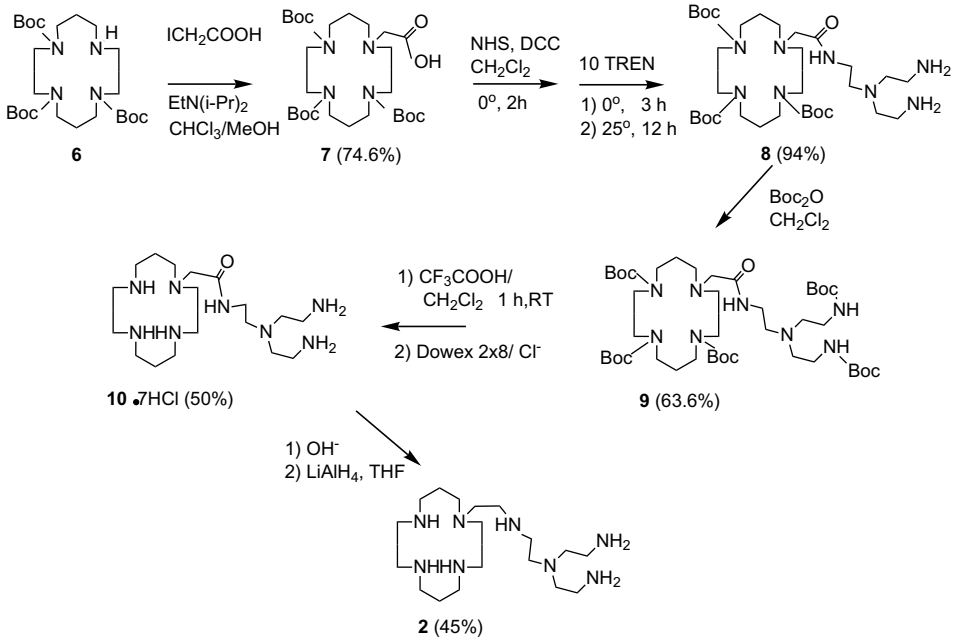


Figure 3. Synthesis of ligand **2**.

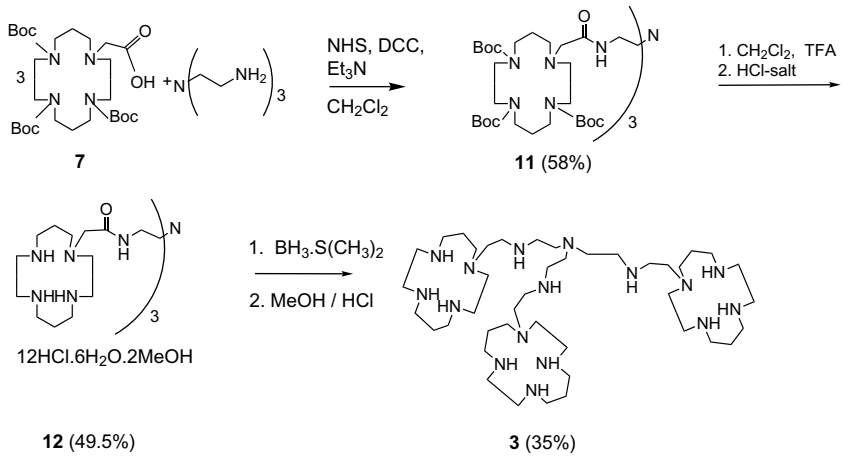


Figure 4. Synthesis of ligand **3**.

Table 1. Absorption maxima (nm) and molar absorptivities (M^{-1} cm^{-1}) of the mono-, dinuclear and polynuclear complexes of **1**, **2**, and **3**

Metal ion	pH	**1**	**2**	**3**
Cu^{2+}	2	530 (151)	524 (187)	535 (437)
	5	621 (142)	582 (129)	588 (448)
Ni^{2+}	2	463 (29)	456 (25), 350 (sh)	470 (110)
	7	345 (20), 525 (12)	359 (sh), 528 (19)	475 (66), 583 (sh) 836 (20)
Cu^{2+}/Cu^{2+}	5		525 (165), 680 (150) 833 (188)	550 (400), 620 (sh), 820 (330)
Ni^{2+}/Ni^{2+}	8		330 (sh), 452 (55), 570 (28), 850 (23)	470 (146), 580 (sh), 880 (23)
Ni^{2+}/Cu^{2+}	8		469 (55), 680 (80), 834 (120)	473 (127), 680 (129), 814 (129)
Cu^{2+}/Ni^{2+}	8		548 (152), 800(sh)	541 (389)

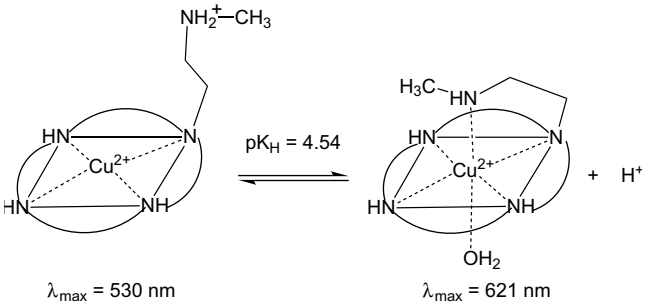


Figure 5. pH-dependent coordination of the methyl amino group in the Cu^{2+} complex with **1**.

cannot coordinate to the metal ion, whereas at higher pH the ammonium group is neutralized and axial coordination can take place (Figure 5). The quantitative analysis of the acid base equilibrium by potentiometry and spectrophotometry gives log $K_H = 4.54$ [11].

The change in coordination geometry is also confirmed for the Cu^{2+} complex by a change of the EPR spectrum on going from pH below 4 to a higher value. At low pH the complex has an exact square planar geometry ($g_1 = g_2 = 2.044$, $g_3 = 2.157$, $A_1 = A_2 = 28$G, $A_3 = 197$G), whereas at higher pH a tetragonally distorted geometry results ($g_1 = 2.033$, $g_2 = 2.059$, $g_3 = 2.193$, $A_1 = 18$G, $A_2 = 28$G, $A_3 = 185$G).

Similarly the Ni^{2+} complex of **1** shows at low pH the typical spectrum (Table 1) of a square planar NiN_4-chromophore [13]. At higher pH, however, the band at 463 nm disappears and new weak bands at 345 and 525 nm are formed, giving a spectrum, which is typical for a pseudo-octahedral Ni^{2+} ion [13]. Here too the pH increase results in an additional amino donor group, which can axially bind (at the same time as an axial water molecule) to the Ni^{2+}.

Metal complexes of **2**

If one equivalent of a metal ion is added to ligand **2**, it reacts to give the 1:1 species in which the metal ion is selectively bound by the macrocyclic unit. The higher stability of the macrocyclic complex compared to that of the complex with the tren unit is responsible for the thermodynamical outcome of the reaction. The 1:1 species with Cu^{2+} has properties very similar to those of the Cu^{2+} complex with **1**. It shows a shift of the absorption maximum from 524 nm to longer wavelengths at 582 nm when the pH is raised (Table 1). The EPR spectrum also changes from a square planar geometry to a tetragonally distorted one as described for the Cu^{2+} complex of **1**. This all shows that the amino group of tren, which is part of the bridge linking the macrocycle with the open chain amine, can axially bind to the metal ion in the macrocycle as shown for **1** in Figure 5.

However, if two equivalents of Cu^{2+} are added to **2** a dinuclear complex with new properties results. This can

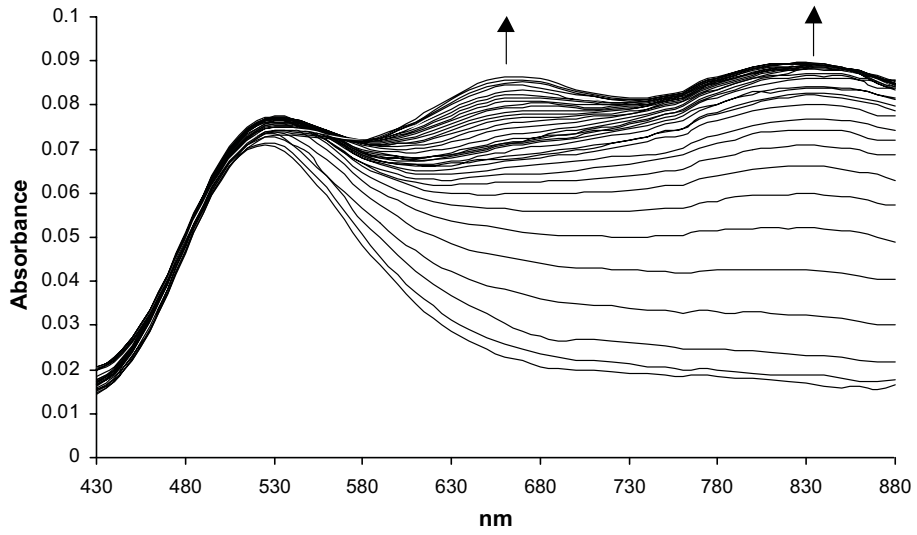


Figure 6. Spectrophotometric titration of the 2:1 complex of **2.** $[Cu_2(\mathbf{2})] = 5\ 10^{-4}$ M, titrated with increments of NaOH (0.4 M) up to a total volume of 0.28 ml, I = 0.5 (KNO_3), 25 °C.

be seen from the spectra when a solution of ligand **2** with two equivalents Cu^{2+} is titrated (Figure 6). At low pH the Cu^{2+} macrocyclic complex is already formed ($\lambda_{max} = 524$ nm). Increasing the pH (pH > 5) produces new bands in the long wavelength region resulting in a spectrum, which very closely is the sum of the $[Cucyclam]^{2+}$ and $[Cutren]^{2+}$ spectra. This clearly shows that the second metal ion binds to the tren unit. At even higher pH a series of hydrolysis reactions takes place [11], which, however, will not be discussed here.

Because of the differential stability of the two binding sites in **2** it is possible to selectively prepare heterodinuclear species. So for example the addition of one equivalent Cu^{2+} first and then one equivalent of Ni^{2+} gives a 2:1 complex with an absorption band at 548 nm typical for Cu^{2+} in the macrocycle. The contributions of the Ni^{2+} chromophore in the tren unit are relatively weak and cannot be seen (Table 1). The reverse sequence of additions, first Ni^{2+} and then Cu^{2+}, gives an isomeric compound with the typical absorption properties of $[Nicyclam]^{2+}$ and $[Cutren]^{2+}$ (Table 1).

Kinetics of the Cu^{2+} binding

Equilibrium studies described above show that the first metal ion added to ligand **2** binds to the macrocyclic unit, which gives the thermodynamically most stable complex. It was therefore interesting to investigate the kinetics of this reaction, in particular to find out how mechanistically the Cu^{2+} binding takes place.

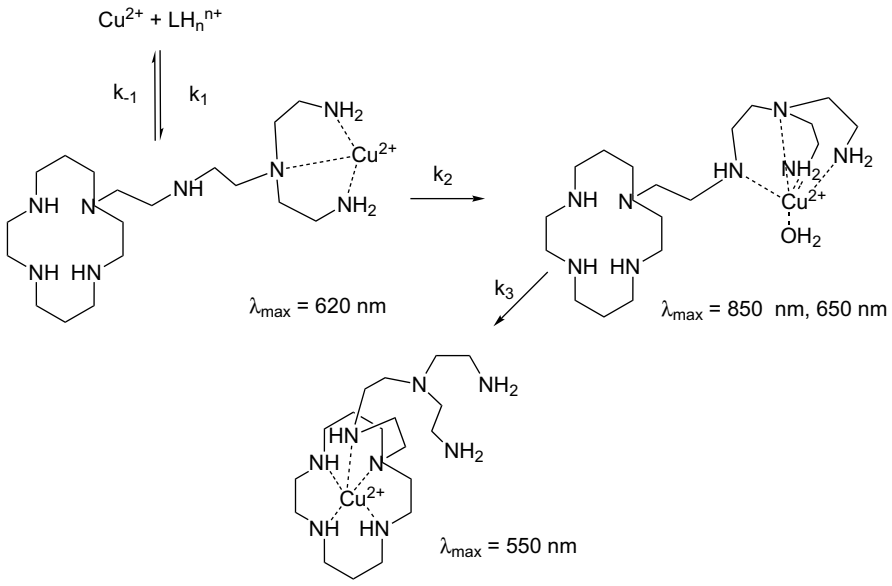


Figure 7. Reaction sequence and mechanism of the complexation of Cu^{2+} by ligand **2**.

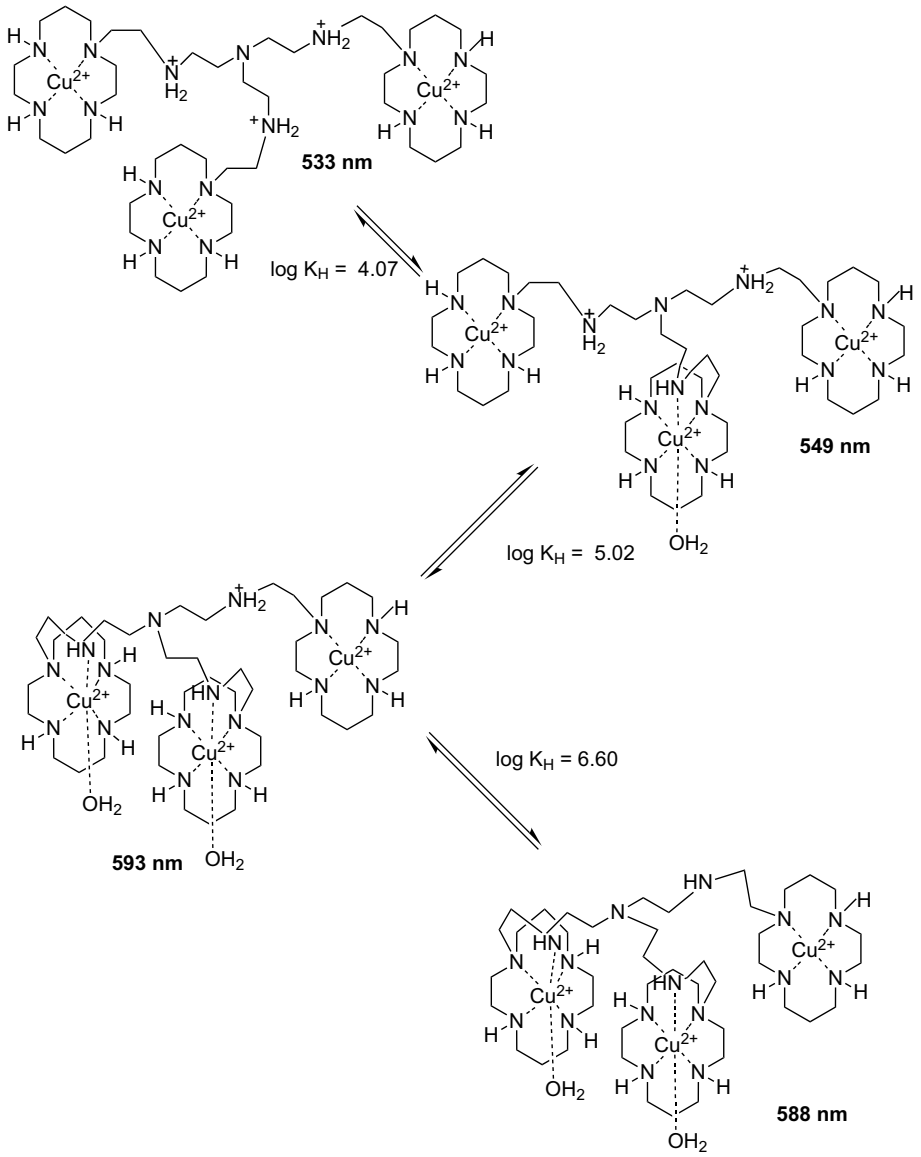


Figure 8. Deprotonaton and axial coordination sequence in the 3:1 Cu^{2+} complex of **3.**

For this we have studied the kinetics of complex formation of **2** with Cu^{2+} using the stopped-flow photodiode array technique, which allows to rapidly mix the reactants and to follow the spectral changes of the reaction as a function of time [11]. Reacting **2** with one equivalent of Cu^{2+} at pH = 4.96 gives a complicated sequence of reaction steps. In a relatively fast bimolecular reaction between Cu^{2+} and the ligand (L = **2**) a first intermediate CuL′, which has a spectrum typical for a CuN_3-chromophore, is formed. Thereafter CuL′ interconverts to a second intermediate CuL″, with an absorption spectrum very similar to that of $[Cutren]^{2+}$. Finally CuL″ reacts to give the end product with an absorption maximum at 524 nm, corresponding to a Cu^{2+} in the macrocyclic unit. The reaction sequence can thus be written as Equation (1), whereby the protonation degree of CuL″, CuL and CuL^{2+} is not specified.

$$Cu^{2+} + LH_n^{n+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CuL' \xrightarrow{k_2} CuL \xrightarrow{k_3} CuL^{2+} \qquad (1)$$

Mechanistically the reaction proceeds in such a way that the Cu^{2+} ion is rapidly complexed by three nitrogens of the ligand. We can assume that the less sterically hindered two primary amines and the tertiary nitrogen of tren are probably involved, whereby an intermediate with a structure similar to $[Cudien]^{2+}$ is formed (Figure 7). This species interconverts to a second intermediate with Cu^{2+} coordinated by the tren unit, which then slowly transfers the Cu^{2+} to the macrocyclic ring thus giving the thermodynamically most stable species. The here observed interesting sequence of reactions in the complexation process is a direct consequence of the higher reactivity of the open chain part of the ligand (tren unit) compared to the well-known lower reactivity of the tetraaza macrocycle towards metal ions and of the

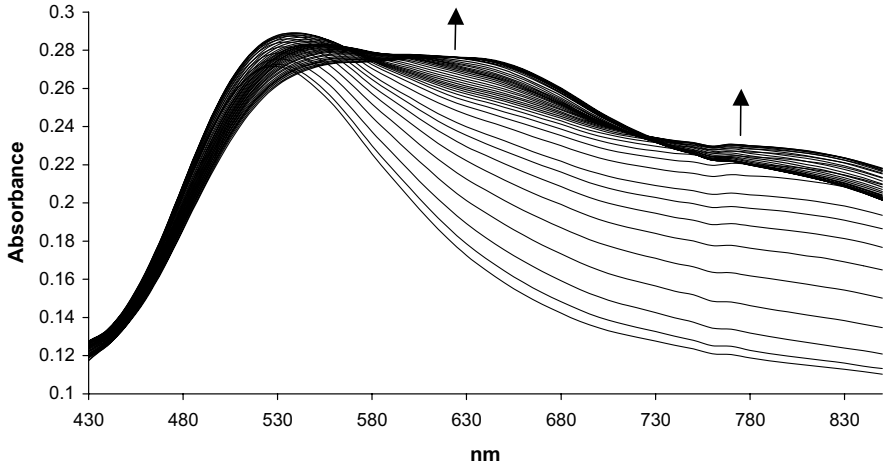


Figure 9. Spectrophotometric titration of the 4:1 complex of **3**. $[Cu_4(\mathbf{3})] = 7\ \ 10^{-4}$ M, titrated with increments of NaOH (0.4 M) up to a total volume of 0.41 ml, I = 0.5 (KNO_3), 25 °C.

different thermodynamical stabilities of the macrocyclic and open chain units.

Metal complexes of **3**

The complexation of **3** with metal ions is even more complicated, since we have three macrocyclic binding sites and a tren unit. Here also we observe that the first three equivalents of metal ion are bound by the macrocycles, again due to the higher thermodynamic stability of these binding sites compared to that of tren (L. Siegfried *et al*., in preparation).

At acidic pH we find for the 3:1 species $\lambda_{max} = 530$ nm and this value gradually moves to longer wavelengths, when the protons of the tren unit are neutralized to give amino group as additional ligands. The process is spread out to nearly four pH units indicating that the deprotonation and coordination of side chains takes place in discrete steps. Whereas for the first (549 nm) and second (593 nm) deprotonation there is a distinct shift in λ_{max}, the last deprotonation (588 nm) has practically no influence on the absorption spectrum. We therefore propose a reaction sequence as shown in Figure 8.

The coordination of the third side chain does not take place probably because of steric reasons. Reaction of an additional Cu^{2+} to the 3:1 species of **3** results in the coordination of Cu^{2+} by the tren unit. This is clearly seen in a spectrophotometric titration (Figure 9). Beside the band at 524 nm stemming from the Cu^{2+} in the three cyclam units additional bands at 830 and 660 nm can be observed, which are similar to those of the 2:1 complex of **2**. With **3** heteronuclear complexes can also be prepared, since addition of the first three equivalents always gives the complex with the three cyclam units and the fourth then binds to the tren moiety.

Conclusions

The two ligands **2** and **3** were designed to coordinate metal ions in different environments thus to produce complexes with different properties. The absorption spectra of the Cu^{2+} and Ni^{2+} complexes very clearly show that both binding sites are taking up metal ions, not in a statistical way, but selectively. Thereby the high thermodynamic stability of the cyclam unit is responsible for the binding of the first metal ion, although the kinetics shows that the more flexible tren unit first interacts with the metal ion, but then rearranges itself to the more stable species.

The different properties of metal ions bound by the cyclam and tren units are revealed by their different spectral properties and also by their differential reactivity against acid. If one acidifies a solution of the 2:1 Cu^{2+} complex with **2** or the 4:1 Cu^{2+} complex with **3**, only the metal ion bound by the tren units dissociates, so that the 1:1 species of **2** and the 3:1 species of **3** with the remaining metal ion(s) in the macrocyclic ring(s) are formed.

Acknowledgements

This work was supported by the *Swiss National Science Foundation* (Project N. 2000-66826) and this is gratefully acknowledged.

References

1. D.E. Fenton, M. Mercer, N.S. Poonia, and M.R. Truter: *J. Chem. Soc., Chem. Commun*. 66 (1972); S.M. Nelson: *Inorg. Chim. Acta* **62**, 39 (1982); K. Travis and D.H. Busch: *J. Chem. Soc., Chem. Commun*. 1041 (1970); J. Comarmond, P. Plumere, J.-M. Lehn,Y. Agnus, R. Louis, R. Weiss, O. Kahn, and I. Morgenstern-Badarau: *J. Am. Chem. Soc*. **104**, 6330 (1982).

2. J.A. Cunningham, and R.E. Sievers: *J. Am. Chem. Soc.* **95**, 7183 (1973); E.K. Barefield, D. Chueng, D.G. van Derveer, F. and Wagner, *J. Chem. Soc., Chem. Commun.* 302 (1981); L. Fabbrizzi, F. Forlini, A. Perotti, B. Seghi, *Inorg. Chem.* **23**, 807 (1984); L. Fabbrizzi, L. Montagna, A. Poggi, L. Siegfried, and Th.A. Kaden, *J. Chem. Soc.*, *Dalton Trans.* 2681 (1987).
3. I. Murase, K. Hamada, and S. Kida: *Inorg. Chim. Acta* **54**, L171 (1981); P.L. Burk, J.A. Osborn, M.-T. Youinou, Y. Agnus, and R. Louis, *J. Am. Chem. Soc.* **103**, 1273 (1981); S.V. Rosokha, Y.D. Lampeka, *J. Chem. Soc.*, *Chem. Commun.* 1077 (1991); S.V. Rosokha, Y.D. Lampeka, *J. Chem. Soc. Dalton Trans.* 631 (1993); S. Brudenell, L. Spiccia, and E.R. Tiekink, *Inorg. Chem.* **35**, 1974 (1996); R. Schneider, A. Riesen, M. Zehnder, and Th.A. Kaden, *Helv. Chim. Acta* **69**, 53 (1986).
4. A. Urfer, Th.A. Kaden: *Helv. Chim. Acta* **77**, 23 (1994).
5. N.W. Alcock, A.J. Clarke, W. Errington, A.M. Josceanu, P. Moore, S.C. Rawle, P. Sheldon, S.M. Smith, and M.L. Turonek: *Supramol. Chem.* **6**, 281 (1996).
6. See for ex. L.F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge (1989); B. Dietrich, P. Viout, and J.-M. Lehn: *Macrocyclic Chemistry*, VCH, Weinheim, (1993).
7. P.S. Pallavicini, A. Perotti, A. Poggi, B. Seghi, and L. Fabbrizzi: *J. Am. Chem. Soc.* **109**, 5139 (1987).
8. M. Ciampolini, L. Fabbrizzi, A. Perotti, A. Poggi, B. Seghi, and F. Zanobini: *Inorg. Chem.* **26**, 3527 (1987).
9. A. Schlageter, Ph.D. Thesis (1996).
10. S. Brandes, G. Gros, F. Denat, P. Pullumbi, and R. Guilard: *Bull. Soc. Chim. Fr.* **133**, 65 (1996).
11. L. Siegfried, M. Honecker, A. Schlageter and Th.A. Kaden, *J. Chem. Soc. Dalton Trans.* 3939 (2003).
12. F.L. Urbach: In *Coordination Chemistry of Macrocyclic Compounds* (Ed. G.A. Melson), Plenum Press, New York (1979).
13. A.P.B. Lever: *Inorganic Spectroscopy*, Elsevier, Amsterdam (1968).