262. Metal Complexes with Macrocyclic Ligands. XIV[1]). Formation, Dissociation and Metal Exchange with an N_2S_2-macrocycle

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Summary

10,10,12-Trimethyl-3,4-benzo-1,6-dithia-9,13-diazacyclopentadecen-dihydrochloride (LH_2^{2+}, **2**) and its Ni^{2+} complex were synthesized and their reactivity studied. The formation kinetics of **2** with Cu^{2+} were found to be a second order reaction between Cu^{2+} or $CuACO^+$ and the monoprotonated form of the ligand LH^+. The rate constant $k_{Cu}^{LH} = 29$ $M^{-1}s^{-1}$ is 10^5-10^6 times smaller than those of monoprotonated tetraazamacrocycles either because of second bond formation or because of a strong electrostatic interaction between the positive charges of the Cu^{2+} and the ammonium group. The metal-metal exchange between NiL^+ and Cu^{2+} was also investigated. The reaction is independent of $[Cu^{2+}]$ and has the same rate and activation parameters as the dissociation of NiL^{2+}. In contrast to open chain ligands, no mixed complex $CuNiL^{4+}$ as intermediate was observed.

The kinetics of complex formation with macrocyclic ligands is well documented in the literature. The compounds studied are cyclic polyethers [2], polythiaethers [3], polyamines [4] and a series of N_2O_2-macrocycles [5]. Whereas in the case of polyethers and polythiaether no protonation equilibria are involved, the cyclic amines are generally protonated in the pH-region in which the complexation kinetics with transition metal ions can be studied. This makes a mechanistic interpretation of the complexation more difficult and several authors have tried to avoid this difficulty by working in organic solvents [5] or at strongly alkaline pH [6].

However, if one is interested in the reactivity of cyclic polyamines and wants to understand why their protonated forms react at slower rates than those of analogous open chain ligands, the protonation and its effects on the ring conformation, on hydrogen bonding and on electrostatic interactions must be studied.

One way to investigate this last point is to use mixed donor macrocycles, for example with N- and S-atoms, for which the relative position of the protonated

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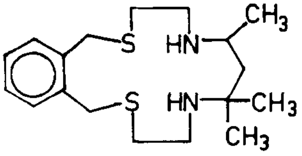
center and that where first bond formation occurs are known. *N, S*-macrocycles might also be interesting in other regards. The acid induced dissociation, which for tetraazacycloalkanes is generally very slow, can eventually be measured like that of the tetrathiamacrocycles [3]. Only a few examples of complex dissociation have been studied up to now [7] and their mechanism is not yet clear. Finally with an *N, S*-macrocycle one expects less stable complexes so that metal-metal exchange can become accessible to a study and then can be compared with the reactivity of open chain systems, which have been described in detail [8].



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With this in mind we have prepared **2**, a ligand with a *cis* N_2S_2-arrangement of the donor atoms, and have investigated the complexation, dissociation and metal-metal exchange using Ni^{2+} and Cu^{2+} as typical examples.

Experimental Part. - *10,10,12-Trimethyl-3,4-benzo-1,6-dithiadiazacyclopentadecen*-N,N′,S,S′-*nickel(II)-dibromide* (**1**). The suspension of 5,0 g (8,9 mmol) 10,10,12-trimethyl-3,4-benzo-1,6-dithia-9,13-diazacyclopentadeca-3,12-diene-*N,N′,S,S′*-nickel(II)-dibromide [9] in 10 ml glacial acetic acid was treated with 0.65 g (11 mmol) dimethylaminoborane in 10 ml glacial acetic acid keeping the temperature below 25°. The mixture was then heated for 5 h at 45°. After cooling the blue cristals were collected, washed with abs. EtOH and dried i.V. Yield 2.5 g (50%). - IR. (KBr): no 1680 cm^{-1} band (C=N).

$C_{18}H_{30}Br_2N_2NiS_2$	Calc.	C 38.81	H 5.43	N 5.03	S 11.51%
(557.09)	Found	„ 38.70	„ 5.40	„ 5.10	„ 11.70%

10,10,12-Trimethyl-3,4-benzo-1,6-dithia-9,13-diazacyclopentadecendihydrochloride (**2**). The solution of 1.2 g (18,5 mmol) KCN in 10 ml water was added to that of 2,0 g (3.6 mmol) **1** in 25 ml water. With gentle heating, the complex dissolves to give $Ni(CN)_4^{2-}$ and the free ligand, which was extracted with ether in a *Kutscher-Steudel*-apparatus. The oil left after the evaporation of the ether was dissolved in abs. EtOH and treated with ethanolic HCl-solution. The white precipitate was recristallized from abs. EtOH giving 1.25 g (84%) of **2**, mp. 199-201°. - NMR. ($CDCl_3$): 1.44, 1.60 and 1.64 (1*s* and 1*d*, 9 H, 3 CH_3); 2.35 (*d*, 2 H, CH_2); 3.11 (*m*, 8 H, 2 CH_2–N and 2 CH_2S); 4.04 (4 H, Ar–CH_2–S); 7.45 (*m*, 4 H, arom. H).

$C_{18}H_{32}Cl_2N_2S_2$	Calc.	C 52.54	H 7.84	Cl 17.23	N 6.81%
(411.49)	Found	„ 52.56	„ 8.14	„ 17.04	„ 6.82%

Measurements. All chemicals were of analytical grade. I=0.5 (KNO_3). IR.-spectra were run on a *Beckman IR-8*, NMR.-spectra on a *Brucker WH-90* and the visible absorption spectra of the Ni^{2+} and Cu^{2+} complex on a *Varian Techtron 635* with a *Honeywell* recorder. The Ni^{2+} complex (**1**) absorbs at 365 nm (35 $M^{-1}cm^{-1}$) and 575 nm (13.7 $M^{-1}cm^{-1}$), the Cu^{2+} complex at 575 nm (488 $M^{-1}cm^{-1}$).

The pK^H-values of **2** were obtained from pH-titrations with 0.1M NaOH under N_2 and computed with the program VARIAT [10]. The kinetics of formation, dissociation and metal-metal exchange were followed spectrophotometrically for Cu^{2+} at 575 nm and for Ni^{2+} at 365 nm. The formation of the Cu^{2+} complex was measured at 25° using a mixing device mounted on the spectrophotometer which allows the two reactants to mix in less than 0.5 s. Typical concentrations were $8 \cdot 10^{-4}$M **2**, $5 \cdot 10^{-3}$-$5 \cdot 10^{-2}$M $CuSO_4$, 0.02-0.1M acetate buffer of different pH-values (3.3-5.2) and KNO_3 to obtain I = 0.5. The temperature dependence was obtained at pH = 3.8 between 25° and 50°. All reactions were computed as second order processes. The dissociation of the Cu^{2+} complex was followed at 75° between pH = 0.09 and 1.32 with 10^{-3}M Cu^{2+} complex in HNO_3/KNO_3 mixtures of I = 0.5M. The temperature dependence was measured at pH = 0.09 between 60° and 75°. The concentration-time curves were calculated as first order processes. The dissociation of **1** was studied at 61° in 0.025M acetate buffer between pH = 4.5 and 6.8 using $3.6 \cdot 10^{-3}$M NiL^{2+}. The temperature dependence was run at pH = 4.89 between 55° and 70°. All reactions were first order processes. The metal-metal exchange between $9.5 \cdot 10^{-4}$M NiL^{2+} and $5 \cdot 10^{-3}$–$5 \cdot 10^{-2}$M $CuSO_4$ was followed at 61° at pH = 3.8–5.0 in 0.025M acetate buffers. The temperature dependence was measured at pH 4.83 between 50° and 70°. The kinetics was first order in $[NiL^{2+}]$ and independent of $[Cu^{2+}]$ so that first order rate constants were calculated.

Results and discussion. – The cyclic *Schiff* base obtained by *Urbach & Busch* [9] through template reaction can be reduced to **1** by dimethylaminoborane, but not by the generally used reducing reagents such as $NaBH_4$ or *Raney*-Ni and H_2 [11]. The demetallation with KCN gives as usual the free ligand.

The pK^H-values of **2** were determined as $pK_1^H = 11.03$ and $pK_2^H = 5.09$. They differ considerably from those of tetraazacycloalkanes, for which the first two protonation constants are above 9.5 [4]. The large difference between the two protonation steps of **2** must result from the close proximity of the two basic centers. While in the tetraazamacrocycles the second proton can bind to a N-atom *trans* to the one already protonated, in **2** the second protonation must occur at the N-atom in *cis* position. This results in a strong electrostatic interaction which lowers the second pK^H-value.

The Ni^{2+} complex **1** dissolves in water with a bluish colour, however upon heating it reversibly changes to red. The absorption spectrum of the blue form shows the typical bands for a high spin octahedral complex with ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ at 27400 cm^{-1} and ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ at 17390 cm^{-1} [12]. The Cu^{2+} complex absorbs at 17390 cm^{-1} with a relatively high molar absorbtivity of 488 $M^{-1}cm^{-1}$.

Kinetics. The formation of the Cu^{2+} complex is a first order process in C_{Cu}, C_L and is dependent on the pH and the total acetate concentration C_{ACO}. From the acetate dependence one can guess that beside Cu^{2+} also $CuACO^+$ is a reactive species. In addition the pH-dependence indicates that the complexation takes place with the monoprotonated form of the ligand LH^+. The kinetics can therefore be described by (1) and (2),

$$Cu^{2+} + LH^+ \xrightarrow{k_{Cu}^{LH}} CuL^{2+} + H^+ \qquad (1)$$

$$CuACO^+ + LH^+ \xrightarrow{k_{CuACO}^{LH}} CuL^{2+} + H^+ + ACO^- \qquad (2)$$

from which the law (3) can be derived.

$$v_f = (k_{Cu}^{LH}[Cu^{2+}] + k_{CuACO}^{LH}[CuACO^+])[LH^+] = k_{obs} \cdot C_{Cu} \cdot C_L \qquad (3)$$

Using the stability of $CuACO^+$ ($pK_{CuACO} = 1.65$ [1]), the second protonation constant of the ligand (K_2^H) and the stoichiometric equation for the total concentrations of the metal ion (C_{Cu}), acetate (C_{ACO}) and ligand (C_L) one obtains (4), which can be rewritten as (5)

$$k_{obs}=\left(k_{Cu}^{LH}+\frac{k_{CuACO}^{LH}[ACO^-]}{K_{CuACO}}\right)\cdot\frac{K_{CuACO}\cdot K_2^H}{(K_{CuACO}+[ACO^-])\cdot([H^+]+K_2^H)} \qquad (4)$$

$$Y=\frac{k_{obs}([H^+]+K_2^H)}{K_2^H}=\frac{k_{Cu}^{LH}K_{CuACO}+k_{CuACO}^{LH}[ACO^-]}{K_{CuACO}+[ACO^-]} \qquad (5)$$

We have plotted for all measurements at different pH and C_{ACO} the value of Y against $[ACO^-]=X$ and fitted the data points with (5) using k_{Cu}^{LH} and k_{CuACO}^{LH} as parameters. The results are given in the *Table* and the fit is shown in *Figure 1*. The bimolecular rate constant k_{Cu}^{LH} is smaller by a factor of 10^5-10^6 than the values found for the 12 to 15-membered tetraazamacrocycles, which range from $1.8\cdot10^6$ to $36\cdot10^6$ $M^{-1}s^{-1}$ [4]. One can think of two main reasons to explain the large difference in reactivity. First bond formation with the monoprotonated form of the N_2S_2-macrocycle can occur either at a S- or at a N-atom. From the electrostatic point of view the most favourable attack should take place at a S-atom *trans* to the positive charge of the ammonium group. However, if first bond formation with the thioether is rate determining, one would expect a formation rate similar to those observed for the tetraazacycloalkanes. Since this is not so, one could argue that second bond formation becomes rate determining. This would be consistent with the fact that Cu^{2+}–S-bonds are relatively weak [3]. Thus $k_2 \ll k_{-1}$ and for $k_{obs}=K_0\cdot k_1k_2/k_{-1}$ or $k_{obs}=K_0K_1k_2$ [8]. Since it is difficult to guess the value of K_1

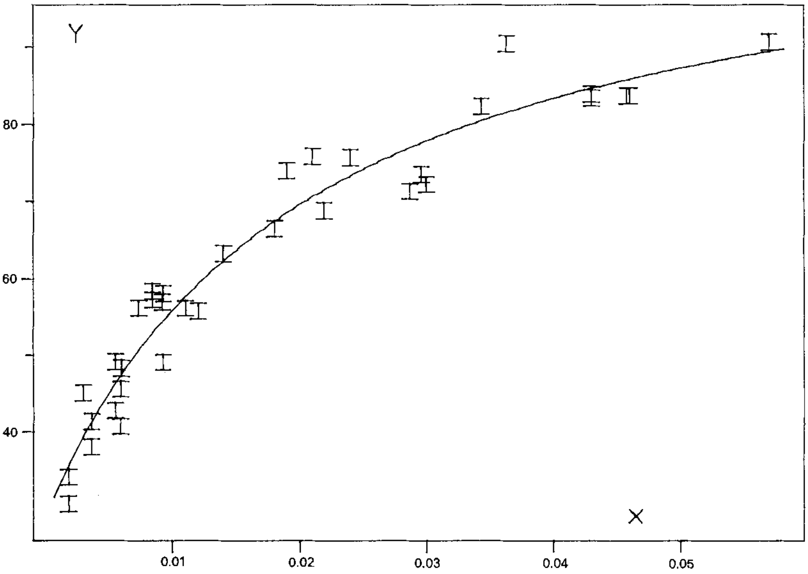

Figure 1. *Formation of the Cu^{2+} complex with* **2**, *at 25°*. Experimental points plotted according to (5) and curve fit with k_{Cu}^{LH} and k_{CuACO}^{LH} given in the *Table* ($\sigma_Y=4.0$)

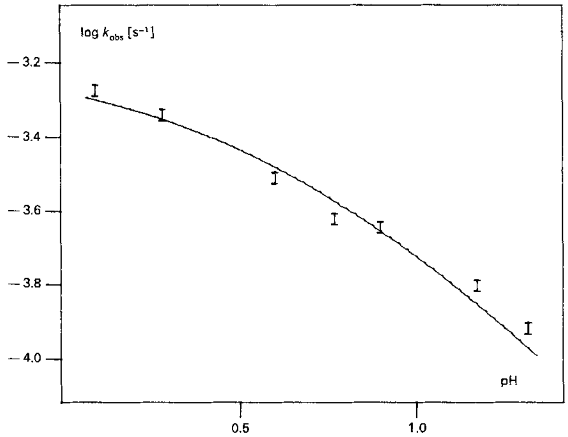

Figure 2. *pH-Dependence of the dissociation of CuL^{2+} at 75°.* The curve is calculated with (9) and rate constants given in the *Table* ($\sigma_y = 0.04$)

one is not able to definitively predict whether second bond formation could fully explain the lower reactivity of the N_2S_2-ligand.

The other possibility of a rate determining first bond formation with N-atom of the amino group *cis* to the ammonium group must also be considered. It is evident that the electrostatic repulsion between the positive charges in such an intermediate is extremely high and unfavourable. Example of this type of interaction are well known. So the complexation rate of Cu^{2+} with ethylenediamine is $3.4 \cdot 10^9$ $M^{-1}s^{-1}$ whereas that with the monoprotonated form is $2.2 \cdot 10^5$ $M^{-1}s^{-1}$ [13]. Similarly 2-aminomethylpyridine and the monoprotonated species react with Cu^{2+} with rate constants of 10^8–10^9 $M^{-1}s^{-1}$ and $7.6 \cdot 10^3$ $M^{-1}s^{-1}$, respectively [13]. Thus the positive charge of an ammonium group which is two or three carbon atoms away from the donor at which the coordinative bond is formed reduces the reactivity by a factor of 10^4–10^5, which is in the same order of magnitude as the one found for **2**.

The dissociation of the Cu^{2+}-complex, measured in acidic solution, is first order in $[CuL^{2+}]$ and pH-dependent *(Fig. 2)*. At low pH a limiting value is reached. This can be explained by assuming a rapid preequilibrium in which the complex is protonated followed by the rate determining step of the ligand dissociation (6).

$$CuL^{2+} + H^{+} \overset{K_{CuLH}}{\rightleftharpoons} CuLH^{3+} \xrightarrow{k_H} Cu^{2+} + LH^{+} \tag{6}$$

$$v_d = k_H[CuLH^{3+}] = k_H \frac{C_{Cu} \cdot [H^+]}{[H^+] + K_{CuLH}} \tag{7}$$

The rate is then given by (7), whereby C_{Cu} is the total concentration of Cu^{2+}-complex. The reaction pathway (6) implies that at low pH the protonation equilibrium is shifted to $CuLH^{3+}$ for which a slightly different spectrum than that of CuL^{2+} would be expected. However, no spectral difference was detected between CuL^{2+} at pH 5 and in 0.5 M HNO_3 at 25°. Another possible explanation for the pH dependence of the dissociation is given by (8). The complex CuL′ present in steady state concentration could be a species with a Cu^{2+} coordinated to only three donor atoms of the ligand, which then dissociates under H^+ assistance. The rate equation is given by (9). At low acid concentration the second step of the dissociation is rate determining and $k_{obs}=k_{+1}^{H} \cdot k_{+2}^{H}[H^+]/k_{-1}^{H}$, whereas at high acid concentration the first step becomes rate determining and $k_{obs}=k_{+1}^{H}$. The values of k_{+1}^{H} and $k_{+1}^{H} \cdot k_{+2}^{H}/k_{-1}^{H}$ are given in the *Table* and the the curve fit is shown in *Figure 2*. From the formation and dissociation the stability of CuL^{2+} can be determined (10). The value of K_{CuL} lies between those of the more stable tetraazaligands (10^{24}–10^{30} M^{-1} [14]), and those of the less stable tetrathiamacrocycles (10^{2}–10^{4} M^{-1} [3]). The dissociation of NiL^{2+} takes place already at neutral pH and is pH independent. It is interesting that the complex is thermodynamically unstable and the equilibrium (11)

$$CuL^{2+} \underset{k_{-1}^{H}}{\overset{k_{+1}^{H}}{\rightleftharpoons}} CuL' \xrightarrow[H^+]{k_{+2}^{H}} Cu^{2+}+LH^{+} \qquad (8)$$

$$v_d=\frac{k_{+1}^{H}\,k_{+2}^{H}[CuL^{2+}][H^+]}{k_{-1}^{H}+k_{2}^{H}[H^+]} \qquad (9)$$

$$K_{CuL}=\frac{[CuL^{2+}]}{[Cu^{2+}][L]}=\frac{k_{LH}^{Cu}}{K_{1}^{H}\cdot k_{+1}^{H}}=2.6\cdot 10^{18} \qquad (10)$$

$$Ni^{2+}+LH^{+} \overset{k_{Ni}}{\rightleftharpoons} NiL^{2+}+H^{+} \qquad (11)$$

lies in water on the left side. In this regard, the Ni^{2+} complex resembles those of the cyclic polythiaethers for which the hydration energy is also higher than the complexation [15]. Because of this low stability, it was possible to study the metal exchange reaction with Cu^{2+}. Such reactions are, in the case of macrocyclic ligands, extremely slow. So a mixture of the Ni^{2+} complex of 1, 4, 8, 11 tetraazacyclotetradecane and Cu^{2+} is stable over months with no sign of metal exchange.

In our case, the exchange was measured between pH 3.8 and 5. It is pH-, buffer- and $[Cu^{2+}]$-independent. In addition, it was found that the metal-metal exchange proceeds at the same rate and has the same activation parameters as the NiL^{2+}-

Table. *Formation, dissociation and metal-metal exchange rate constants for the Cu^{2+} and Ni^{2+} complexes with* **2**. All values for 25° and I = 0.5.

Rate constant		ΔE^* (Kjoule/mol)	logA
k_{Cu}^{LH} ($M^{-1}s^{-1}$)	29 ± 1	69 ± 2	11.4 ± 0.3
k_{CuACO}^{LH} ($M^{-1}s^{-1}$)	111 ± 3		
k_{1}^{H} (s^{-1})	$(4.7 \pm 0.4)\ 10^{-6}$[b]	85 ± 4	9.5 ± 0.6
k_{2}^{H}/k_{-1}^{H} (M^{-1})	4.11 ± 0.08[a]	–	–
k_{NiL} (s^{-1})	$(2.78 \pm 0.08)\ 10^{-5}$[b]	84 ± 4	10.2 ± 0.5
k_{NiL}^{Cu} (s^{-1})	$(2.53 \pm 0.08)\ 10^{-5}$[b]	82 ± 7	9.8 ± 1.3

[a] At 75°.

[b] Extrapolated to 25° for measurements at higher temperature by use of activation parameters.

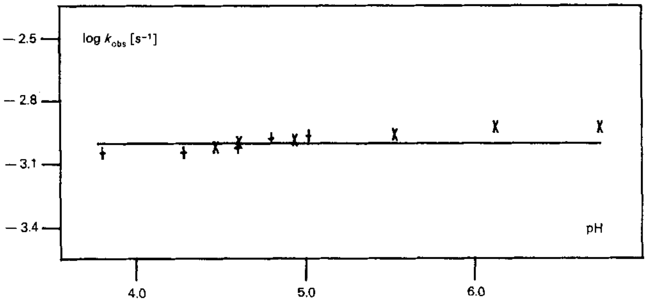

Figure 3. *pH-Dependence of the dissociation of* NiL^{2+} (X) *and of the exchange reaction between* NiL^{2+} *and* Cu^{2+} (+) *at 61°* ($\sigma_y = 0.05$)

dissociation (see *Table* and *Fig. 3*). The reaction can therefore be described by (12) in which, after the slow dissociation of NiL^{2+}, the Cu^{2+} rapidly reacts with the

$$NiL^{2+} \xrightarrow{\text{slow}} Ni^{2+} + L \xrightarrow[\text{fast}]{Cu^{2+}} CuL^{2+} + Ni^{2+} \qquad (12)$$

ligand. In metal-metal exchange processes, the independence from [Cu^{2+}] is uncommon. It occurs for open chain ligands at acidic pH, where the proton can compete with Cu^{2+}. At higher pH the exchange becomes Cu^{2+} dependent and it is assumed that a binuclear mixed complex is formed as an intermediate [8]. This is only possible when the ligand can dissociate stepwise from one metal ion and stepwise bind to the other. For macrocyclic ligands this seems difficult. Firstly, it is not possible to dissociate only one coordinative bond, and additionally, the electrostatic repulsion between the two metal ions, which in a macrocyclic ligand are much closer, makes such an intermediate unfavourable.

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