71. Metal Complexes of Macrocyclic Ligands. XII¹). A Complexone-like Tetraazamacrocycle

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Summary

The complexone-like tetraazamacrocycle **1** (LH_4) forms a series of metal complexes with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} (M^{2+}) of the type MLH_2, ML^{2-} and M_2L, which have been isolated and characterized by VIS., IR. and NMR. spectroscopy. Based on these results tentative structures for the different species are proposed.

Polyazamacrocycles with secondary as well as with tertiary amino groups are known. Those of the latter type can be obtained either by cyclisation of the corresponding alkylated amines [2] [3], by reductive methylation of the cyclic polyamines with formaldehyde and formic acid [2] [4], or by alkylation of the macrocyclic Ni^{2+}-complexes after deprotonation with KOH in DMSO [5]. Of all the *N*-alkylated compounds the persubstituted ones are by far the most interesting, since they form pentacoordinated metal complexes [2] [4] [6-8], which in some cases, maintain their structures even in good donor solvents such as water [8, 9]. It has also been shown that the geometry of these complexes is kinetically determined, since the tetraalkylated macrocycles cannot form the conjugate base necessary to reach the thermodynamically more stable planar or *trans* octahedral structure [10].

In addition to the *N*-alkylated compounds just mentioned a few examples of functionalized tetraazamacrocycles have recently been described. Two derivatives of CRH³) having a hydroxoethyl or a dimethylaminoethyl tail attached to one of the nitrogen atoms as well as their metal complexes have been studied [11] and in the case of one of the Ni^{2+}-complexes a pH induced change of coordination geometry has been observed [12]. A general synthesis for mono-*N*-substituted tetraazacyclotetradecanes describing the preparation of two key intermediates with three protected nitrogen atoms has also appeared [13]. During the present investigation *Stetter et al.* [14] published a communication on the stability of metal complexes with a series of tetraazamacrocycles bearing four acetate groups.

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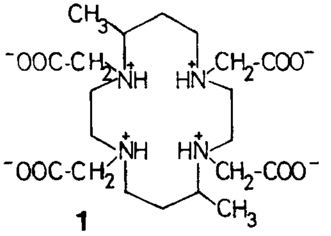
³) CRH = 2,12-dimethyl-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene.

In this paper we describe the synthesis of the macrocycle **1** as well as the preparation and properties of its metal complexes with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}.



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Experimental Part. - Melting points are uncorrected. IR. spectra (bands in cm^{-1}) were obtained as KBr discs on a *Perkin-Elmer* 157G or a *Beckman* 4240 spectrophotometer. ^{1}H-NMR. spectra were recorded on a *Varian* EM360 using 3-(trimethylsilyl)propane-sulfonate as internal standard. ^{13}C-NMR. were run on a WH90 *Bruker* FT-instrument. VIS. spectra of the solid compounds were obtained by the nujol technique [15] on a *Cary* 118 spectrophotometer. Conductivity data were measured on a *Metrohm* E365B conductometer at two different concentrations. Magnetic moments were determined by the *Faraday* method[4]). Cu^{2+} was analyzed by atomic absorption on a *Unicam* SP90 instrument.

meso-5, 12-Dimethyl-1, 4, 8, 11-tetraazacyclotetradecane-N, N', N'', N'''-tetraacetic acid (**1**). To 24.2 g (0.175 mol) bromoacetic acid in 50 ml water 14.0 g (0.375 mol) NaOH in 70 ml cold water were added in such a way that the temperature remained below 5°. Then 8.0 g (0.0353 mol) *meso*-5, 12-dimethyl-1,4,8,11-tetraazacyclotetradecane [16] in 50 ml EtOH were given at once and the temperature was raised to 70° for 1.5 h. The solution was then acidified to pH 3.44 with hydrochloric acid, whereby a white precipitate was formed overnight. It was filtered off and recrystallized from water. The product was first dried at 13 Torr, then left in contact with air until no further change in its weight was observed. Yield 9.08 g (51%), m.p. (dec.) 258-262°. - IR.: 3400 (NH), 2500-2300 (NH^+), 1610 (COO^-).

$C_{20}H_{36}N_4O_8 \cdot 2\,H_2O$ (496.56) Calc. C 48.38 H 8.12 N 11.28% Found C 48.23 H 8.18 N 11.19%

1-*Tetrahydrochloride pentahydrate* (**2**). 1.0 g (2 mmol) **1** was dissolved in 5 ml water and 5 ml conc. hydrochloric acid. Addition of acetone gave the crystalline product which was equilibrated in contact with air until no further weight change occurred. Yield 1.1 g (80%), m.p. 234-236°. - IR.: 3400 (NH), 2500-2400 (NH^+), 1730 (COOH). - ^{1}H-NMR. (D_2O): 1.33 (*d*, 6 H, 2 CH_3); 2.24 (*m*, 4 H, 2 $C-CH_2-C$); 3.49 (*m*, 14 H, 6 $N-CH_2$ and 2 N-CH); 3.98 (*d*, 8 H, 4 CH_2-COOH). - ^{13}C-NMR. (D_2O): 13.84 (*qa*, CH_3); 27.30 (*t*, $-CH_2-$); 47.63, 50.11, 52.24 and 55.82 (*t*, $N-CH_2-$); 58.75 (*d*, =CH-); 170.52 and 171.50 (*s*, COOH).

$C_{20}H_{40}Cl_4N_4O_8 \cdot 5\,H_2O$	Calc.	C 34.49	H 7.24	Cl 20.36	N 8.04%
(696.45)	Found	„ 34.84	„ 7.10	„ 20.40	„ 7.85%

Metal complexes. - *$CuLH_2 \cdot 2.5\,H_2O$* (**3**). To 348 mg (0.5 mmol) **2** dissolved in 75 ml water 100 mg (0.4 mmol) $CuSO_4 \cdot 5\,H_2O$ in 75 ml water were added. The intensive blue colour which was rapidly formed, slowly changed to a light blue nuance. From this solution light blue crystals precipitated upon standing. These were collected, dried and equilibrated at room temperature to give 153 mg (54%) product. - IR.: see *Table 1.*

$C_{20}H_{34}CuN_4O_8 \cdot 2.5\,H_2O$	Calc.	C 42.43	H 6.89	Cu 11.58	N 9.90%
(565.54)	Found	„ 42.41	„ 6.95	„ 11.30	„ 9.80%

$NiLH_2 \cdot 3\,H_2O$ (**4**). 70 mg (0.1 mmol) **2** and 300 mg (1.3 mmol) $NiCl_2 \cdot 6\,H_2O$ were dissolved in 5 ml water and the pH was adjusted to 2.6 with NaOH. After heating for 2 h violet crystals were formed, which were filtered off, dried and equilibrated in contact with air. Yield 32 mg (56%). - IR.: see *Table 1.*

$C_{20}H_{34}N_4NiO_8 \cdot 3\,H_2O$ (571.27) Calc. C 42.05 H 7.06 N 9.81% Found C 42.32 H 6.94 N 9.87%

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[4]) We thank Prof. *H. Güntherodt* (Institute of Physics, Univ. of Basle) for allowing us to use his *Faraday* set up.

$ZnLH_2 \cdot 4 H_2O$ (**5**). The compound was prepared in a similar way as **4**. Yield 72%. - IR.: see *Table 1.*

$C_{20}H_{34}N_4O_8Zn \cdot 4 H_2O$ (595.37) Calc. C 40.27 H 7.04 N 9.39% Found C 40.37 H 6.68 N 9.33%

$CoLH_2 \cdot 2.5 H_2O$ (**6**). 70 mg (0.1 mmol) **2** and 237 mg (1 mmol) $CoCl_2 \cdot 6 H_2O$ were dissolved in 5 ml water and the pH was adjusted to 6 with NaOH. After heating for 2 h light orange crystals separated. They were filtered off, dried and equilibrated with air. Yield 44 mg (79%). - IR.: see *Table 1.*

$C_{20}H_{34}CoN_4O_8 \cdot 2.5 H_2O$ (562.45) Calc. C 42.67 H 6.93 N 9.95% Found C 42.96 H 7.04 N 10.14%

$Cu_2L \cdot 5 H_2O$ (**7**). To 384 mg (0.5 mmol) **2** in 75 ml water 312 mg (1.2 mmol) $CuSO \cdot 5 H_2O$ in 75 ml water were added. The solution turned intensively blue and dark blue crystals were obtained upon standing. These were filtered off, dried and equilibrated with air to give 250 mg (74%) product. - IR.: see *Table 1.*

$C_{20}H_{32}Cu_2N_4O_8 \cdot 5 H_2O$ Calc. C 35.66 H 6.28 Cu 18.87 N 8.32%
(673.67) Found „ 36.08 „ 6.45 „ 18.44 „ 8.15%

$Ni_2L \cdot 6 H_2O$ (**8**). The solution of 50 mg (0.1 mmol) **1** and 300 mg (1.3 mmol) $NiCl_2 \cdot 6 H_2O$ in 8 ml water was heated after adjusting the pH to 2.6 with NaOH. Light violet crystals were formed and filtered off, dried and equilibrated with air to give 34 mg (50%) product. - IR.: see *Table 1.*

$C_{20}H_{32}N_4Ni_2O_8 \cdot 6 H_2O$ (681.62) Calc. C 35.19 H 6.45 N 8.21% Found C 35.12 H 6.28 N 8.30%

$Ba[CuL] \cdot 7 H_2O$ (**9**). The solution of 315 mg (1 mmol) $Ba(OH)_2 \cdot 8 H_2O$ and 275 mg (0.5 mmol) **1** in 30 ml water was gentle heated under nitrogen. After addition of 125 mg (0.5 mmol) $CuSO_4 \cdot 5 H_2O$ in 10 ml water the solution turned green and $BaSO_4$ precipitated. The latter was filtered off and acetone was added until the green complex crystallized. After filtration the product was dried and equilibrated in contact with air to give 239 mg (60%) product. - IR.: see *Table 1.*

$C_{20}H_{32}BaCuN_4O_8 \cdot 7 H_2O$ (783.45) Calc. C 30.63 H 5.87 N 7.15% Found C 30.57 H 5.64 N 7.20%

Results and discussion. - The synthesis of the new complexone-like macrocycle **1** (LH_4) by aklylation of the cyclic tetraamine with bromoacetic acid is straightforward. The IR.-, ^1H- and ^{13}C-NMR.-spectra are fully consistent with the *trans*-C-*meso* structure.

The complexes of **1**, which has eight potential coordinating atoms, were studied in part in solution but mainly by preparing several crystalline compounds. According to the elemental analysis, **1** forms with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} either complexes with a metal to ligand ration of 1:1 or 2:1. The 1:1 complexes were obtained from acidic solutions by mixing aqueous solutions of the corresponding metal ion with the ligand hydrochloride. They are only slightly soluble in most solvents except DMSO. Their elementary analyses fit to the formula $MLH_2 \cdot nH_2O$, thus indicating a 1:1 ratio of metal to ligand and the presence of two protons which are not displaced by the metal ion upon complexation. More information about the structure of these complexes can be obtained from their IR. and VIS. spectra (*Table 1* and *2*).

At about 2500 cm^{-1} one finds the typical intercombination bands for the NH^+ group and at 1610 and 1705-1710 cm^{-1} two bands for the carboxylic function. The detailed study of the IR. spectra of amino carboxylic acid complexes has shown that the absorption of the carboxylic group (COOH) comes at 1750-1700 cm^{-1}, that of the coordinated carboxylate ($COO^- \ldots M^{2+}$) at 1650-1590 cm^{-1} and that of the free carboxylate (COO^-) at 1630-1575 cm^{-1} [17]. In addition it was also shown that for Cu^{2+} it is generally not possible to differentiate between the coordinated and free carboxylate group. The IR. results of *Table 1* indicate that at least one amino group of the ring must be protonated and that the carboxylic functions are in the COOH as well as in the COO^- or $COO^- \ldots M^{2+}$ form. Because protonation of one amino group excludes coordination of the metal ion by the complete tetraazacycloalkane unit, we must consider as donor both nitrogen and oxygen atoms.

The VIS. spectrum of $CuLH_2$ in the solid state has one band at 660 nm. This is comparable to the 671 nm absorption of Cu(EDDA) [18], in which the chromophore is $CuN_2O_2(H_2O)_2$. Similarly the VIS. spectra of $CoLH_2$ and $NiLH_2$ closely resemble those of Co(EDDA) (502 nm) [18] and Ni(EDDA) (757, 609 and 367 nm) [18], which both exhibit octahedral geometry with a $MN_2O_2(H_2O)_2$ chromophore. We suggest therefore that in the 1:1 complexes of the type MLH_2 the metal ion is not incorporated into the macrocyclic ring, but is coordinated by two amino-nitrogen atoms and two carboxylate groups.

Deprotonated 1:1 complexes can be obtained by addition of NaOH to the complexes MLH_2. This allows to study their absorption spectra in aqueous solution *(Table 2)*. The results show that only a little change has occurred on going from the spectra of MLH_2 in the solid state to those of ML^{2-} in solution, indicating only minor alteration of the coordination sphere. Both Ni^{2+} and Co^{2+} experience an octahedral ligand field in these compounds.

In addition to the solution studies we were able to isolate the Cu^{2+} complex as $Ba[CuL] \cdot 7\,H_2O$. The two protons present in $CuLH_2$ have been neutralized by the base and the two positive charges are now compensated by a Ba^{2+}. The VIS. spectrum in the solid state exhibits a band at 660 nm and the IR. spectrum shows no NH^+ intercombination bands and only one band for the asymmetric streching of the

Table 1. *IR. absorption bands (in cm^{-1}) of LH_4 (**1**) and its metal complexes*

Compound	NH^+ intercombination bands	Carboxyl streching modes	
LH_4 (**1**)	2600 br.	1600 br.	1695
$LH_4 \cdot 4\,HCl$ (**2**)	2600 br.		1725
$CuLH_2$ (**3**)	2500 br.	1610	1705
$NiLH_2$ (**4**)	2500 br.	1610	1710
$ZnLH_2$ (**5**)	2500 br.	1610	1705
$CoLH_2$ (**6**)	2500 br.	1610	1710
Cu_2L (**7**)		1610 br.	
Ni_2L (**8**)		1600 br.	
Ba[CuL] (**9**)		1590	

br. = broad.

Table 2. *VIS. spectra (λ_{max} in nm) of the Cu^{2+}, Ni^{2+} and Co^{2+} complexes of **1** (ε in M^{-1} cm^{-1})*

Compound	Solid state[a])	In H_2O (pH = 11)
$CuLH_2$ (**3**)	660	653 (40)
$NiLH_2$ (**4**)	550, 600 (sh)	342 (9), 554 (6.2), 580 (sh), 868 (4.3)
$CoLH_2$ (**6**)	480	504 (4.5)
Cu_2L (**7**)	610	
Ni_2L (**8**)	500, 570	
Ba[CuL] (**9**)	670	

[a]) Using the nujol-mull technique [15].

carboxyl group. The water soluble complex **9** gives upon acidification the light blue crystals of $CuLH_2$ (**3**). Since the colour change of this reaction is fast, it seems improbable that the metal ion could change from a coordination by four nitrogen atoms to one by two nitrogen atoms and two oxygen atoms as in the case of $CuLH_2$ (see above). For ZnL^{2-}, obtained by dissolving $ZnLH_2$ in D_2O at *pD* = 7, we have studied the ^{13}C-NMR. spectrum and have compared it with that of the free ligand *(Table 3)*. In a first experiment with a mixture of ligand and Zn^{2+}-complex we noticed that the metal ion exchange is slow, since we observe both the resonances of the complex and those of the ligand. Further it is interesting to note that the Zn^{2+}-complex and the free ligand have the same number of resonances, which is only possible when coordination of the Zn^{2+} does not alter the symmetry of the molecule. The observation that one carboxylate resonance does not change whereas the other one is distinctly shifted by coordination could indicate that one sort of carboxylate is coordinated to the metal ion while the other is free.

All the results concerning the species ML^{2-} seem to infer that the metal ions are in a pseudo-octahedral environment coordinated to two nitrogen and two oxygen atoms in a way similar to that proposed for the MLH_2 compounds.

The 2:1 complexes were obtained when two or more equivalent of metal ion were added to the ligand. They are insoluble in most solvents except DMSO. Their IR. spectra *(Table 1)* exhibit one band at 1600-1610 cm^{-1} for the carboxylic group. Conductivity measurements of Cu_2L in DMSO show that the compound is a non-electrolyte. Therefore the two Cu^{2+} must be equally coordinated to the macrocycle. That the two Cu^{2+} are close to each other is indicated by the lower magnetic moment of Cu_2L (1.33 B.M.) compared to those of $CuLH_2$ (1.96 B.M.) and Ba[CuL] (1.98 B.M.). Due to the proximity of the two paramagnetic centers antiferromagnetic coupling results, which is responsible for the lower value of the magnetic moment. The VIS. spectrum of Cu_2L has one symmetrical band at 605 nm. A suggestion for the coordination sites and geometry of this complex is more difficult than for the other ones discussed above, since it is conceivable that Cu_2L could be polymeric. The low solubility of it prevents the determination of the molecular weight. On the other side, however, the presence of only one symmetrical band in the VIS. spectrum

Table 3. *Comparison of the* ^{13}*C-NMR. resonances* (in ppm) *of* **1** *and its* Zn^{2+}*-complex in* D_2O *at* pD = 7

Carbon atom[a])	LH_4 (**1**)	ZnL^{2-}
COO^-	179.1	179.05
	176.0	173.1
=CH– (C(5) and C(12))	63.19	56.91
N–CH_2[b])	57.40	55.59
	54.44	53.34
	53.12	52.76
	52.36	50.86
	51.83	48.87
CH_2 (C(6) and C(13))	30.53	29.61
CH_3	14.94	13.65

[a]) Identified by off-resonance coupling.

[b]) The single resonances could not be attributed to single carbon atoms.

suggests that both Cu^{2+} must experience a similar ligand field. Thus it seems improbable that one of the two Cu^{2+} is bound in the center of the macrocyclic ring coordinated to four nitrogen atoms and the second one is ligated by the four carboxylate groups.

Ni_2L was also isolated, whereas the corresponding Co^{2+} and Zn^{2+} complexes could not be prepared.

In conclusion it seems that **1** forms a series of metal complexes in which the metal ion is bound by two amino nitrogen atoms and two carboxylates and not as one would expect by the four nitrogen atoms of the macrocycle.

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