220. Metal Complexes with Macrocyclic Ligands

Part XXV[1])

One-Step Synthesis of Mono-*N*-substituted Azamacrocycles with a Carboxylic Group in the Side-Chain and their Complexes with Cu^{2+} and Ni^{2+}

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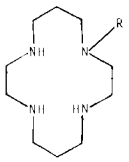
Mono-*N*-substituted azamacrocycles **2**–**7**, containing a carboxyalkyl or carboxyaryl side-chain, are obtained by reacting a five-fold excess of the macrocycle with 1 equiv. of a suitable halogenocarboxylic acid in alkaline aqueous EtOH. For halogenocarboxylic acids, which easily lactonize under alkaline conditions, a variant with the corresponding ester or nitrile as alkylating agent is also described. The salient point of this synthesis lies in the use of an excess of the macrocycle over the alkylating agent, thus reducing the amount of polyalkylation to a minimum, and in the easy separation of the excess of unreacted educt from the aminocarboxylic acid. These new ligands form Ni^{2+} and Cu^{2+} complexes, the spectral properties of which have been studied. In the case of the Cu^{2+} complexes with ligand **2**, **3**, and **6**, a pH-dependent color change is observed. This is explained with an equilibrium between a species, in which the carboxylate group is bound to the metal, and one, in which it is protonated and non-coordinated. In the case of the Ni^{2+} complexes with the same ligands, only the species with a coordinated carboxylate was observed. In the Cu^{2+} and Ni^{2+} complexes with ligands **4** and **5**, however, the carboxylate group does not coordinate at all, because of the length or the special structure of the chain.

Introduction. – *N*-Functionalized tetraazamacrocycles have been described in the literature [2]. It is especially easy to prepare tetraderivatives of these macrocycles by reacting the cyclic tetraamines with an excess of alkylating agent. Such reactions have been described with halogenocarboxylic acids [3], with acrylonitrile [4], and with ethyleneoxide [5]. The complexing properties of these compounds are relatively complicated, as has been shown by the structures of the Ni^{2+} and Cu^{2+} complexes with two tetraazacycloalkanetetraacetic acids [1] [6]. This is a consequence of the large number of donor groups in these chelators.

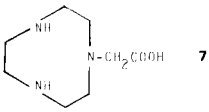
The *mono*-substituted macrocycles are simpler from the point of view of their complexing properties. However, their synthesis is more complicated and necessitates several steps. The introduction of the side-chain before cyclisation [7] is time-consuming and labour-intensive, since the synthesis of the starting compound as well as the cyclisation procedure must be repeated for each new derivative. Another synthetic route consists of the preparation of a selectively protected tetraazamacrocycle, in which three N-atoms are tosylated and, thus, the side-chain can be introduced at the fourth N-atom [8]. This synthesis offers the advantage of being flexible, since different pendant groups can be attached to the same cyclic key compound. However, this route is also a multistep synthesis, which requires relatively much time.

[1]) Part XXIV: [1].

We have previously suggested that selective monoalkylation of a tetraazamacrocycle could be a further possibility, provided that the separation and purification of the product is easy enough, since, in general, one expects that beside the mono-derivative, polyalkylated products will also be formed [2]. We present here a single-step synthesis of a series of 1,4,8,11-tetraazacyclotetradecanes having a pendant carboxylic group (see **2–6**), and we discuss their metal complexes. To show, that this method works well also for other macrocycles, we have prepared a *mono-N*-substituted derivative **7** of 1,4,7-triazacyclononane.



1 R = H
2 R = CH_2COOH
3 R = $(CH_2)_2COOH$
4 R = $(CH_2)_3COOH$
5 R = *o*-CH_2–Ph–COOH
6 R = *p*-CH_2–Ph–COOH



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Experimental. – *1,4,8,11-Tetraazacyclotetradecane* (**1**) was synthesized according to [9], *1,4,7-triazacyclononane* following the procedure described in [10]. *2-(Bromomethyl)benzoic acid* was prepared in analogy to [11] by reacting ethyl *o*-toluate in CCl_4 with Br_2.

Procedure 1. To 10 g (50 mmol) **1**, dissolved in 150 ml of EtOH and 30 ml of H_2O, 480 mg (20 mmol) of LiOH and 10 mmol of alkylating agent, dissolved in 40 ml of H_2O at 5°, were added and the mixture was refluxed for several h. The EtOH was then evaporated, and the alkaline aq. soln. was treated with $CHCl_3$ (7 × 50 ml) to extract the excess of **1**. The aq. soln. was concentrated to about 10 ml. After addition of 10 ml of conc. HCl and abs. EtOH, the tetrahydrochloride of the product precipitated. It was recrystallized from EtOH/H_2O/HCl or acetone/H_2O/HCl. From the $CHCl_3$ phase, dried over Na_2SO_4, the unreacted educt **1** can be recovered by evaporation of the solvent (yield: 70–75%, compared to the theoretical 80%).

1,4,8,11-Tetraazacyclotetradecane-1-acetic Acid Tetrahydrochloride (**2**). Alkylating agent: ICH_2COOOH, refluxing: 3 h. Yield: 69%. IR (KBr): 1730 (COOH). ^{1}H-NMR (D_2O): 2.10 (*quint.* 2 C–CH_2–C); 3.1–3.7 (*m*, 8 CH_2N); 3.80 (*s*, CH_2COOH). Anal. calc. for $C_{12}H_{30}Cl_4N_4O_2 \cdot H_2O$ (422.21): C 34.13, H 7.58, Cl 33.58, N 13.27; found: C 34.32, H 8.03, Cl 33.94, N 13.42.

3-(1,4,8,11-Tetraazacyclotetradec-1-yl)propionic Acid Tetrahydrochloride (**3**). Alkylating agent: $Br(CH_2)_2COOH$, refluxing: 8 h. Yield 59%. IR (KBr): 1720 (COOH). ^{1}H-NMR (D_2O): 2.25 (*quint.*, 2 C–CH_2–C); 2.90 (*t*, CH_2COOH); 3.2–3.6 (*m*, 9 CH_2N). Anal. calc. for $C_{13}H_{32}Cl_4N_4O_2 \cdot 2.75\ H_2O$ (467.96): C 33.36, H 8.09, Cl 30.30, N 11.97, O 16.27, H_2O 10.63; found: C 33.60, H 7.77, Cl 29.96, N 12.01, O 16.18, H_2O 10.63.

4-(1,4,8,11-Tetraazacyclotetradec-1-yl)methylbenzoic Acid Tetrahydrochloride (**6**). Alkylating agent: 4-(bromomethyl)benzoic acid, refluxing: 3 h. Yield 70%. IR (KBr): 1700 (COOH). ^{1}H-NMR (D_2O): 2.20 (*quint.*, 2 C–CH_2–C); 3.2–3.6 (*m*, 8 CH_2N); 4.50 (*s*, $PhCH_2$); 7.85 (*m*, 4 arom. H). Anal. calc. for $C_{18}H_{34}Cl_4N_4O_2 \cdot 0.5H_2O$ (489.32): C 44.18, H 7.21, Cl 28.98, N 11.45, O 8.17, H_2O 1.84; found: C 44.09, H 7.37, Cl 28.61, N 11.54, O 8.25, H_2O 1.84.

1,4,7-Triazacyclononane-1-acetic Acid Dihydrochloride (**7**). Alkylating agent: $ClCH_2COOH$, refluxing: 6 h. The unreacted educt was extracted using a continuous extraction apparatus with $CHCl_3$ over night. Yield 35%. IR (KBr): 1730 (COOH). ^{1}H-NMR (D_2O): 3.2 (*m*, 8 H, CH_2(2), CH_2(3), CH_2(8), CH_2(9)); 3.6 (*s*, CH_2COOH); 3.7 (*s*, CH_2(5), CH_2(6)). Anal. calc. for $C_8H_{19}Cl_2N_3O_2$ (260.17): C 36.93, H 7.36, Cl 27.25, N 16.15, O 12.30; found: C 36.94, H 7.38, Cl 27.27, N 16.15, O 12.24.

The cupric complex was synthesized with $CuCl_2$ at pH 7. It was purified by gel filtration over *Sephadex G 10* and isolated as its perchlorate salt by addition of $NaClO_4$. IR (KBr): 1600, 1550 (COO^-). Anal. calc. for $C_8H_{16}ClCuN_3O_6$ (349.22): C 27.51, H 4.62, Cl 10.15, Cu 18.19, N 12,03; found: C 27.55, H 4.51, Cl 10.11, Cu 18.0, N 12.02.

Procedure 2. A mixture of 10 g (50 mml) of **1** and 10 mmol of alkylating agent dissolved in $CHCl_3$ or EtOH were reacted for 1 d. The solvent was then evaporated and the product hydrolyzed. The workup followed that of *Procedure 1.*

4-(1,4,8,11-Tetraazacyclotetradec-1-yl)butyric Acid Tetrahydrobromide (**4**). Alkylating agent: $Br(CH_2)_3CN$, refluxing: over night in EtOH with 10 mmol of LiOH. Hydrolysis of the nitrile: refluxing over night in 24% HBr.

Yield: 40%. IR (KBr): 1720 (COOH). ^{1}H-NMR (D_2O): 2.15 (*quint.* 3 C–CH_2–C); 2.50 (*t*, CH_2COOH); 3.2–3.6 (*m*, 8 CH_2N). Anal. calc. for $C_{14}H_{34}Br_{3.94}N_4O_2 \cdot H_2O$ (623.29): C 26.98, H 5.78, Br 50.51, N 8.99, O 7.70, H_2O 2.89; found: C 27.26, H 5.90, Br 50.56, N 8.99, O 7.39, H_2O 3.02.

The cupric complex was prepared with $Cu(ClO_4)_2$ at pH 7 and isolated as mixed bromide and perchlorate salt by addition of $NaClO_4$ at pH 1. Anal. calc. for $C_{14}H_{32}BrClCuN_4O_7$ (547.33): C 30.72, H 5.89, Br 14.60, Cl 6.48, Cu 11.61, N 10.24, H_2O 3.29; found: C 30.78, H 5.65, Br 14.09, Cl 6.44, Cu 11.60, N 10.04, H_2O 3.47.

2-(1,4,8,11-Tetraazacyclotetradec-1-yl)methylbenzoic Acid Tetrahydrochloride (**5**). Alkylating agent: ethyl 2-(bromomethyl)benzoate, the mixture is stirred over night in $CHCl_3$. Hydrolysis: refluxing 2 h in aq. EtOH with 10 mmol of LiOH. Yield: 16%. IR (KBr): 1700 (COOH). ^{1}H-NMR (D_2O): 2.20 (*quint.* 2 C–CH_2–C); 3.2–3.6 (*m*, 8 CH_2N); 4.45 (*s*, PhCH_2); 7.60 (*m*, 4 arom. H). Anal. calc. for $C_{18}H_{34}Cl_4N_4O_2 \cdot O \cdot 3\,H_2O$ (485.71): C 44.51, H 7.12, Cl 29.19, N 11.53, O 7.58, H_2O 1.11; found: C 44.78, H 7.30, Cl 28.75, N 11.53, O 7.58, H_2O 1.26.

Measurements. IR spectra were obtained on a *Perkin Elmer 157G* in KBr pellets. ^{1}H-NMR spectra were run on a *Varian EM 360*, using sodium 3-(trimethylsilyl)propanesulfonate as internal standard. Absorption spectra of the Cu^{2+} ($2 \cdot 10^{-3}$–5.10^{-3} M) and Ni^{2+} complexes ($2 \cdot 10^{-3}$–6.10^{-3} M) were measured in 1-cm and 4-cm cuvettes, using a *Cary 118 C* spectrophotometer. pH-Titrations were run on the fully automatic pH-titration apparatus described in [12] and the calculations were done with the program TITFIT [13]. Typical concentrations were $4–8 \cdot 10^{-3}$ M ligand tetrahydrochloride or tetrahydrobromide, titrated with 0.4–0.5M NaOH. All measurements were done at 25 ± 0.1° and I = 0.5M KNO_3.

Results and Discussion. – Functionalized macrocycles have attracted the interest for their many possibilities, as described by *Pilichowski et al.* [14]. However, in general the synthesis of these compounds, especially of the mono-functionalized ones, is not simple [2]. This, because the introduction of a substituent requires either protection of the N-atoms [8], which should not be substituted, or cyclisation with a precursor of the pendant group [7]. To simplify the synthesis, we have looked for other possibilities and present here a one-step preparation of tetraazamacrocycles, bearing a carboxylic function (see **2**–**6**). The synthesis consists in the alkylation of a five-fold excess of **1** with an alkylating carboxylic acid or a corresponding nitrile in EtOH with LiOH as base, or with a corresponding ester in $CHCl_3$. Due to the large excess of the macrocycle, the *mono-N*-alkylated derivative becomes statistically the main product of the reaction, beside unreacted starting material. The workup procedure must be such, that the cyclic polyamine and the product can be separated. In case of the ester or the nitrile, the products are, therefore, hydrolized before the isolation step. In case of the ester, this is done with LiOH in aq. EtOH, in case of the nitrile with 24% HBr. After the hydrolysis step, the separation is then the same for both procedures and consists in the extraction of the unreacted cyclic polyamine from alkaline solution by $CHCl_3$. About 70–75% of **1** can be recovered this way, and of course, it can be reused. The last traces of **1** can be eliminated, if necessary, by running the product over an anion-exchanger column (OH^- form) and eluting the compound with 0.1M HCl. This extra purification was only necessary for **3**, whereas the other aminocarboxylic acids could be purified by crystallization of their tetrahydrochlorides or tetrahydrobromides. The salient point of this synthesis lies in the use of an excess of macrocycle over the alkylating agent, thus reducing the amount of polyalkylation to a minimum, and in the easy separation of the unreacted macrocycle from the monosubstituted product. This procedure should be applicable to any other macrocycle, which is extractable from alkaline solution and available in large amounts. To exemplify this, we have reacted 1,4,7-triazacyclononane with $ClCH_2COOH$ under the same conditions as described above and obtained the monoalkylated product **7**.

The pK_H values of the new ligands **2**–**6**, determined by pH titrations, are given in *Table 1*.

Table 1. *pK_H Values and the Standard Deviations* (in brackets) *of* **1-6** *at 25° and* I = *0.5* M (KNO_3)

	1[a])	2	3	4	5	6
pK_{H1}	11.83	12.18 (2)	11.45 (3)	11.58 (3)	11.44 (2)	11.69 (3)
pK_{H2}	10.76	10.87 (3)	10.11 (2)	9.93 (9)	9.94 (4)	9.91 (3)
pK_{H3}	–	3.01 (3)	3.66 (3)	4.30 (5)	3.85 (6)	3.84 (3)
pK_{H4}	< 2	< 2	< 2	< 2	< 2	< 2
pK_{H5}	< 2	< 2	< 2	< 2	< 2	< 2

[a]) From [15].

All these compounds have, as **1** [15], two high pK_H values, which are due to the protonation of two N-atoms *trans* to each other. The third pK_H, not found for **1**, is probably that of the additional carboxylate group. This value increases in the series **2**, **3**, and **4**, since the electrostatic interaction with the ammonium group in the ring decreases, the longer the chain is. The last two pK_H values are low and similar to those of **1**.

We have prepared the Cu^{2+} and Ni^{2+} complexes of **2–6** and studied their spectral properties in acidic and alkaline solution. The results are given in *Table 2*. In the case of Cu^{2+}, there is a clear spectral change on going from acidic to alkaline solution for the complexes with **2**, **3**, and **5**. No shift of the maximum, however, is observed for the complexes with **4** and **6**. The absorption maxima of the species in acidic solution and for **4** and **6** also in alkaline solution are practically identical with that of the Cu^{2+} complex with **1**. This indicates that, under these conditions, the carboxylic group is not involved in coordination to the metal ion.

Table 2. *Spectral Properties* (λ_{max} in nm and molar absorbitivities in $M^{-1}cm^{-1}$) *of the Cu^{2+} and Ni^{2+} Complexes with* **1-6**

Ligand	Cu^{2+} Complex		Ni^{2+} Complex
	Acidic[a])	Alkaline[b])	Alkaline[b])
1	510 (125)	510 (123)	460 (68)[c])
2	514 (97)	547 (98)	518 (4), 325 (11)[d])
3	512 (113)	533 (123)	536 (11), 450 (15)[d])
4	506 (119)	508 (124)	455 (13), 550 sh
5	516 (80)	544 (123)	550 (6), 340 (60)
6	516 (98)	514 (94)	460 (31), 560 sh

[a]) pH < 1. [b]) pH 10–11. [c]) From [17]. [d]) Additional broad band at ~ 800 nm.

In analogy to similar reactions of complexes with mono-*N*-substituted macrocycles [7], we propose here also *Equilibrium 1*, in which

$$Cu(L{-}COOH) \rightleftarrows Cu(L{-}COO^-) + H^+ \qquad (1)$$

the proton and the metal ion compete for the carboxylate group *(Fig. 1)*.

Based on this proposed equilibrium, the pH-dependent colour change and the shift of the maximum to longer wavelengths through axial coordination of the carboxylate group can be explained [16].

The ease, with which different carboxylic acids can be prepared, allowed us to study the effect of chain length and structure on *Equilibrium 1*. The results of *Table 2* show, that,

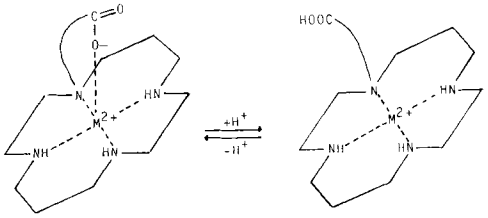

Fig. 1. *pH-Dependent equilibrium involving the carboxylate side-chain in the Cu^{2+} complex with* **2**, **3**, *and* **5**

with aliphatic chains, a coordination of the carboxylate group is only possible with **2** and **3**, where a five- or six-membered chelate ring is formed, whereas, with **4**, the carboxylate group remains free and dangling. With the aryl substituents, only the *ortho*-derivative **5**, but not the *para*-derivative **6** is able to bind the metal ion through its carboxylate ion because on their specific structures.

In addition to the spectral measurements, we have also titrated the Cu^{2+} complexes of **5** and **6**. The calculations show that for both complexes there is only one proton to titrate *(Fig. 2)* and that the pK_H value of this proton is 2.93 for **5** and 3.80 for **6**. The value 3.80 for **6** is practically identical with those of the carboxylic group in the free ligands: $pK_{H3} = 3.85$ and 3.84 for **5** and **6**, respectively. This seems to indicate, that the two positive charges of the two ammonium groups in the free ligands and the charge of the Cu^{2+} in the complex, exert the same effect on the pK_H value of the carboxylic group.

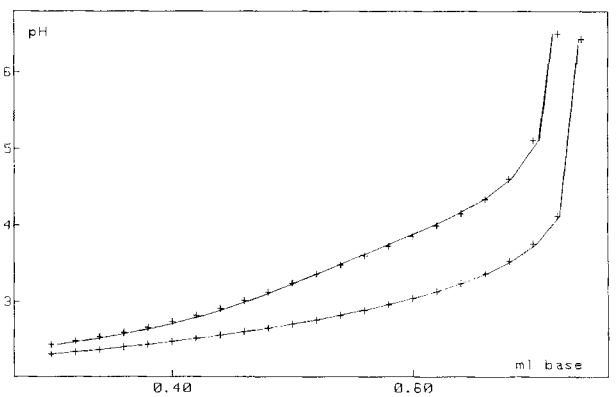

Fig. 2. *pH-Titrations of the Cu^{2+} complexes* ($3 \cdot 10^{-3}$ M) *of* **5** (bottom) *and* **6** (top) *with NaOH at 25° and* I = 0.5 M (KNO_3)

However, the value of 2.93 for the Cu^{2+} complex with **5** clearly indicates, together with the spectral change, an interaction of the carboxylate with Cu^{2+} and suggests an axial coordination of the group.

The results with the Ni^{2+} complexes in alkaline solution (*Table 2*) show that with **4** and **6**, as in the case of Cu^{2+}, there is no or only little interaction between the carboxylate group and the axial position of the metal ion, the spectra of these complexes being very similar to that of the Ni^{2+} complex with **1**, except for a small shoulder around 550 nm. The

complexes with **2**, **3**, and **5** are definitively not square-planar any more, since they exhibit the typical spectral characteristics of hexacoordinate high spin Ni^{2+}. The spectra in acidic solution could not be measured, since, by acidifying the solutions, a side reaction takes place, which produces intensively yellow compounds, whose nature is not yet known.

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