73. Metal Complexes of Macrocyclic Ligands

Part XXXIII[1])

Effect of the Side-Chain Length on the On/Off Equilibrium in the Ni^{2+} and Cu^{2+} Complexes of 11-(2-Aminoethyl)- and 11-(3-Aminopropyl)-1,4,7,11-tetraazacyclotetradecane

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Alkylation of 1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane with CH_2O/KCN or acrylonitrile gave the corresponding cyanomethyl or 2-cyanoethyl derivatives, which, by treatment with Na in BuOH, were detosylated and reduced to the macrocyclic pentaamines **1** and **2**. The Ni^{2+} and Cu^{2+} complexes with **1** and **2** show a reversible pH-dependent change in geometry, in which the side-chain amino group is either coordinated to the metal ion (basic form) or protonated and, thus, non-coordinated (acidic form). The length of the side chain determines the log K_a values of these protonation/deprotonation equilibria: 1.89 and ~ 2.0 for the Cu^{2+} and Ni^{2+} complexes of ligand **1** with the 2-aminoethyl side chain, and 6.17 and 7.43 for the Cu^{2+} and Ni^{2+} complexes of ligand **2** with the 3-aminopropyl side chain.

Introduction. – Tetraazamacrocycles carrying a side chain with a functional group capable to coordinate to the metal ion represent an interesting class of ligands [2]. Since the first example [3], a large number of such compounds with a variety of donor groups have been described [2–8]. The synthetic approach has been also developed from metal-template reactions [3][4] to non-template condensation of tosylated fragments [4], following the *Richman-Atkins* method [9], to condensations of amines with α,β-unsaturated esters [5], to *N*-alkylation of selectively protected macrocycles [6][7], and to the non-selective alkylation followed by a purification step [8]. In the case of 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane, a large number of functionalized side chains have been introduced, and the effect of the coordinating group on the metal-ion properties has been studied [10].

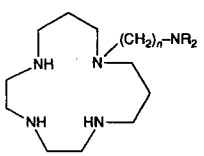
In many cases, a pH-dependent equilibrium between the coordinated and non-coordinated side chain has been observed [3][4][6][7]. This behaviour is a consequence of the differential reactivity of the kinetically stable macrocyclic unit, which is not displaced from the metal ion by acid addition, and of the kinetically labile side-chain donor group, which can be protonated and dissociated from the metal ion. The quantitative description of this equilibrium (*1*) is given by the log K_a value.

$$MLH^{3+} \rightleftarrows ML^{2+} + H^+: K_a = [MLH^{3+}]/[ML^{2+}][H^+] \quad (1)$$

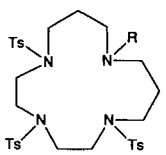
[1]) Part XXXII: [1].

The higher the tendency to form a coordinative bond the lower log K_a compared to the protonation constant of the side chain.

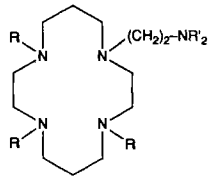
In this paper, we present quantitative data on the effect of the side-chain length on the complexation properties of the amino group in the Cu^{2+} and Ni^{2+} complexes with **1** and **2**.



1 $n = 2$, R = H
2 $n = 3$, R = H
6 $n = 2$, R = CH_3



3 R = H
4 R = CH_2CN
5 R = CH_2CH_2CN



7 R = CH_3, R' = H
8 R = R' = H

Experimental. – *General.* IR spectra [cm^{-1}]: *Perkin Elmer 157G*; KBr pills. ^{1}H-NMR spectra: *Varian EM 360* using TMS or sodium 3-(trimethylsilyl)propanesulfonate as internal standard.

1,4,7-Tritosyl-1,4,7,11-tetraazacyclotetradecane (= *1,4,7,11-Tetraazacyclodecane-1,4,7-triyl tri*(p-*toluenesulfonate*); **3**) was prepared as described in [6].

11-(Cyanomethyl)-1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (= *11-(Cyanomethyl)-1,4,7,11-tetraazacyclotetradecane-1,4,7-triyl Tri*(p-*toluenesulfonate*); **4**). To a soln. of **3** (26.5 g, 40 mmol) in 200 ml CH_2Cl_2 and 100 ml MeOH, a 37% HCHO soln. (3.3 ml, 45 mmol), then after cooling to 5°, a soln. of KCN (3.0 g, 46 mmol) in H_2O (12 ml), and finally AcOH (10 ml) were added. After stirring for 4 h, the mixture was extracted with 2.5M NaOH (100 ml) and H_2O (100 ml). The aq. phases were extracted with CH_2Cl_2 (150 ml). The combined org. phases dried (Na_2SO_4) were evaporated. The residue was taken up with CH_2Cl_2 (80 ml), and Et_2O (140 ml) was added in small portions. After 1 h, the product was filtered, washed with Et_2O, and dried: 28 g (99%) of **4**. M.p. 160–160.5°. IR (KBr): 2240 (CN), 1340, 1160 (SO_2N). ^{1}H-NMR ($CDCl_3$): 1.75 (*m*, 2 C–CH_2–C); 2.40 (*s*, 3 CH_3); 2.50 (*m*, 2 CH_2N); 3.1–3.4 (*m*, 8 CH_2NSO_2); 3.50 (*s*, CH_2CN); 7.4 (*m*, 12 arom. H). Anal. calc. for $C_{33}H_{43}N_5O_6S_3$ (701.92): C 56.47, H 6.18, N 9.98, S 13.70; found: C 56.27, H 6.23, N 9.72, S 13.41.

11-(2-Cyanoethyl)-1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (= *11-(2-Cyanoethyl)-1,4,7,11-tetraazacyclotetradecane-1,4,7-triyl Tri*(p-*toluenesulfonate*); **5**). A suspension of **3** (36.5 g, 55 mmol) in freshly distilled acrylonitrile (100 ml) was refluxed for 3 d. Thereafter, the soln. was filtered and evaporated. The residue was taken up with CH_2Cl_2 (100 ml), to which Et_2O (*ca.* 100 ml) was added. The crystals were filtered and washed with Et_2O: 39.1 g (99%) of **5**. M.p. 159–160° (156–159° [6]). IR (KBr): 2250 (CN), 1340, 1160 (SO_2N). ^{1}H-NMR ($CDCl_3$): 1.75 (*m*, 2 C–CH_2–C); 2.35 (*s*, 3 CH_3); 2.4–2.7 (*m*, 3 CH_2N, CH_2CN); 3.1–3.4 (*m*, 6 CH_2NSO_2); 7.40 (*m*, 12 arom. H).

11-(2-Aminoethyl)-1,4,7,11-tetraazacyclotetradecane Penta(hydrochloride) (= *2-(1,4,7,11-Tetraazacyclotetradec-11-yl)ethylamine Penta(hydrochloride)*; **1**). To a suspension of **4** (1.40 g, 2 mmol) in BuOH (100 ml), Na (1.5 g) cut in small pieces was added under stirring at r. t. during 2 h. Then, the soln. was heated to reflux, and more Na (5 g) was added. When the reaction was finished and cooled down to r. t., the mixture was treated with H_2O (3 × 60 ml). The aq. phases were extracted with BuOH (75 ml). The combined org. phases were evaporated, and the residue was dissolved in $H_2O/CHCl_3$ (80 ml/80 ml). The aq. phase made acidic with conc. HCl soln. was then separated from the $CHCl_3$ phase, concentrated, and the residue crystallized from 6N HCl soln. (18 ml) EtOH (*ca.* 50 ml), with so much Et_2O that crystallization was induced. The product was filtered and washed with EtOH. M.p. 279–283° (dec.). (IR (KBr): 2300–2500 (NH^+). ^{1}H-NMR (D_2O): 1.55 (*m*, 2 C–CH_2–C); 2.2–2.7 (*m*, 10 CH_2N). Anal. calc. for $C_{12}H_{34}Cl_5N_5 \cdot H_2O$ (443.72): C 32.48, H 8.17, N 15.78, Cl 40.01; found: C 32.45, H 8.10, N 15.89, Cl 40.33.

11-(3-Aminopropyl)-1,4,7,11-tetraazacyclotetradecane Penta(hydrochloride) (= *3-(1,4,7,11-Tetraazacyclotetradec-11-yl)propylamine Penta(hydrochloride)*; **2**). Following the above procedure, **5** (7.16 g, 10 mmol) was suspended in BuOH (600 ml) and reacted with Na (8.5 g) at r. t. Thereafter, more Na (26 g) was added in small portions under reflux. The workup similar to that for **1** gave **2** (3.65 g, 83%). M.p. 277–281° (dec.). IR (KBr): 2300–2500 (NH^+). ^{1}H-NMR (D_2O): 1.75 (*m*, 3 C–CH_2–C); 2.3–2.9 (*m*, 10 CH_2N). Anal. calc. for $C_{13}H_{36}Cl_5N_5$ (439.73): C 35.51, H 8.25, Cl 40.31, N 15.95; found: C 35.36, H 8.10, Cl 39.96, N 15.85.

Metal Complexes. To prepare the free ligand **1** or **2**, the pentahydrochloride (1 mmol) was dissolved in 6M NaOH (1 ml) and extracted with $CHCl_3$ (6 × 20 ml). The org. phase was evaporated and the residue taken up with

EtOH (10 ml); $Cu(ClO_4)_2$ or $Ni(ClO_4)_2$ (1 mmol) dissolved in EtOH (5 ml) was added and heated for 15 min, whereupon the precipitate formed. The product was recrystallized from MeOH.

[11-(2-Aminoethyl)-1,4,7,11-tetraazacyclotetradecane]copper(II) Diperchlorate. Blue crystals (91%). Anal. calc. for $C_{12}H_{29}Cl_2CuN_5O_8$ (505.84): C 28.49, H 5.87, Cl 14.02, Cu 12.56, N 13.85; found: C 28.59, H 5.81, Cl 13.46, Cu 12.4, N 13.71.

[11-(2-Aminoethyl)-1,4,7,11-tetraazacyclotetradecane]nickel(II) Diperchlorate. Mauve crystals (82%). Anal. calc. for $C_{12}H_{29}Cl_2N_5NiO_8$ (501.01): C 28.59, H 5.89, Cl 14.06, N 13.89; found: C 28.53, H 5.90, Cl 14.01, N 13.98.

[11-(3-Aminopropyl)-1,4,7,11-tetraazacyclotetradecane]copper(II) Diperchlorate. Blue crystals (96%). Anal. calc. for $C_{13}H_{31}Cl_2CuN_5O_8$ (519.87): C 30.04, H 6.01, Cl 13.64, Cu 12.22, N 13.47; found: C 30.25, H 5.92, Cl 12.89, Cu 12.2, N 13.62.

[11-(3-Aminopropyl)-1,4,7,11-tetraazacyclotetradecane]nickel(II) Diperchlorate. Blue crystals (89%). Anal. calc. for $C_{13}H_{31}Cl_2N_5NiO_8$ (515.04): C 30.29, H 6.02, Cl 13.77, N 13.59, Ni 11.40; found: C 30.35, H 6.00, Cl 13.71, N 13.57, Ni 11.4.

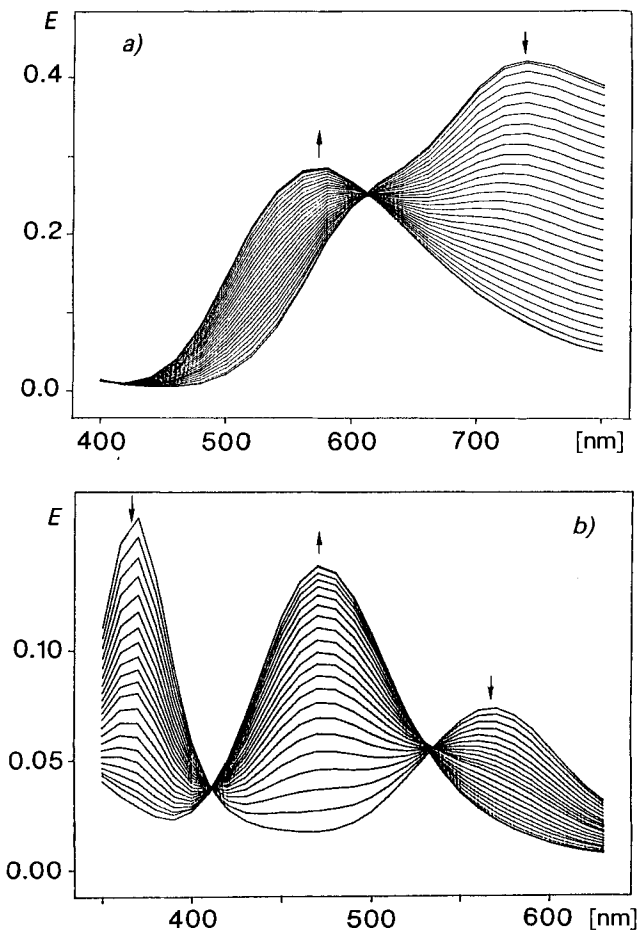


Figure. *Spectrophotometric titrations of Cu* (**2**) (a) *and Ni* (**2**) (b) *with 0.5* M HNO_3 *at 25°*. The arrows indicate the change of the absorption maxima with decreasing pH. Conditions: *a*) $[Cu(\mathbf{2})] = 1.4 \cdot 10^{-3}$ M, [2-picoline] $= 6 \cdot 10^{-2}$ M, $[KNO_3] = 0.5$ M; *b*) $[Ni(\mathbf{2})] = 1.4 \cdot 10^{-3}$ M, [2,4,6-collidine] $= 6 \cdot 10^{-2}$ M, $[KNO_3] = 0.5$ M.

Measurements. Potentiometric titrations were performed under N_2 with 0.4M NaOH at 25° and $I = 0.5$ (KNO_3) using the automatic titrator described in [11]. The protonation constants were obtained by titrating 10 ml of $6 \cdot 10^{-3}$ M ligand pentahydrochloride **1** or **2**.

The determination of the log $K_b^{'}$ value of the amino side chain was run with an out of cell titration. 19 solns. containing $2.2 \cdot 10^{-3}$ M Ni^{2+} complex of **1** or **2** were treated with increasing amounts of 0.08M NaOH, whereby the ionic strength was kept constant with 0.5M KSCN. After equilibration of the solns. in a thermostat at 25°, the pH values were measured. The calculation was performed using the program TITFIT [12].

The spectrophotometric titrations were run on the set up described in [13]. The titrations *(Fig.)* were done directly in the cell by titrating 2 ml of the reaction soln. with 0.5M HNO_3. Typical concentrations: $1.3 \cdot 10^{-3}$–$2 \cdot 10^{-3}$M metal complex, $6 \cdot 10^{-2}$ M base (acetate for Cu(**1**), 2-picoline for Cu(**2**), and 2,4,6-collidine for Ni(**2**)) and so much KNO_3 to obtain $I = 0.5$M. The choice of the base was done so that a reasonable number of measurements in the pH region of the colour change could be obtained. The titrations were calculated using the program SPECFIT [14].

Discussion. – *Ligands.* Starting from the tritosyl derivative **3**, which is an ideal compound for the preparation of mono-*N*-substituted tetraazamacrocycles [6], the introduction of a side chain with a CN function is easy and gives excellent yields. The reduction of the CN to NH_2 as well as the detosylation were achieved in a single step using Na in BuOH [15]. Thereby, it is very important that the first part of the reaction is done at room temperature (probably reduction of the CN), before refluxing and addition of the second portion of Na (detosylation).

Table 1. *Protonation Constants of the Ligands* **1**, **2**, *and Isocyclam at 25° and* I = 0.5 M

	log $K_{H,1}$	log $K_{H,2}$	log $K_{H,3}$	log $K_{H,4}$	log $K_{H,5}$	Ref.
1	11.07 (1)	9.94 (1)	8.76 (1)	2.02	< 2	
2	11.22 (1)	10.13 (1)	9.32 (1)	3.79	< 2	
Isocyclam	11.29	10.19	4.52	< 2		[6]

The protonation constants of the ligands **1** and **2** obtained by fitting the titration curves with the program TITFIT [12] are given in *Table 1*. Compared to the values of the parent compound 1,4,7,11-tetraazacyclotetradecane (isocyclam), we find three relatively high log K_H values instead of only two. We, thus, infer that the protonation of the side-chain NH_2 group must correspond to one of these. It is worth pointing out that the fourth log K_H value depends on the length of the side chain, which is obvious because of the electrostatic repulsion of the positive charges.

Metal Complexes. The spectra of the Cu^{2+} and Ni^{2+} complexes with **1** and **2** depend on the pH and, in the case of Cu^{2+}, also on the age of the solutions *(Table 2)*. The pH effect can be explained by the protonation of the side-chain NH_2 group to give a square-planar complex $[MLH]^{3+}$ and the deprotonation of it with concomitant apical coordination of the NH_2 group to form $[ML]^{2+}$ *(Eqn. 1)*. Similar behaviour has been observed in other *N*-(aminoethyl)-substituted macrocycles [4][16].

The absorption bands of the two Ni^{2+} complexes under acidic conditions at $\sim$ 460 nm are comparable to that of the Ni^{2+} complex with the parent compound isocyclam and can be assigned to the square-planar NiN_4 chromophore. When the side-chain NH_2 group is coordinated, a colour change to blue is observed. In the case of **6** [4] and **7** [16], this has been interpreted as a geometry change to penta-coordination, whereas for **8** [7] an octahedral microsymmetry was postulated, in which an additional solvent molecule is also

Table 2. *Spectral Properties of the Ni^{2+} and Cu^{2+} Complexes with Isocyclam and with Macrocycles Bearing an Aminoalkyl Side Chain*

	λ_{max} [nm] ($\varepsilon \cdot M^{-1} \cdot cm^{-1}$)		Ref.
	Acidic solution	Alkaline solution	
Ni (isocyclam)	460 (58)	460 (58)	[6]
Ni (**1**)	460[a])	353 (29), 539 (15)	
Ni (**2**)	457 (53)	366 (81), 564 (39)	
Ni (**6**)	464 (122)[b])	375 (78), 584 (36), 1240 (14)	[4]
Ni (**7**)	[a])	379 (114), 588 (46)	[16]
Ni (**8**)	464 (45)	350 (20), 508 (11)	[7]
Cu (isocyclam)	551 (154)	551 (154)	[6]
Cu (**1**)	598 (140)[c]), 557 (145)[d])	615 (sh), 731 (199)	
Cu (**2**)	574 (175)[c]), 547 (175)[d])	618 (sh), 733 (238)	
Cu (**6**)	541 (158)[b])	625 (sh), 772 (262)[b])	[4]
Cu (**7**)	[a])	684 (205)	[16]

[a]) Dissociation in acidic solution prevents the determination of λ_{max} and/or ε.
[b]) In CH_3NO_2.
[c]) Fresh solution.
[d]) Old solution.

coordinated. Both seem plausible, especially if one takes into account the values of the molar absorptivities. If we compare the spectra of our two Ni^{2+} complexes with those given in the literature, we see that the complex with **1** resembles that of **8** with relatively low ε and somewhat lower λ_{max} values, whereas the complex with **2** has absorption characteristics more similar to those of the pentacoordinated species **6** and **7**. It is very possible that in our case the side-chain length affects the geometry of these species.

The spectra of the Cu^{2+} complexes depend on the pH, but moreover also on the age of the solution. Old solutions (*ca.* 2 weeks) of the complexes with **1** and **2** exhibit absorption maxima at shorter wavelenghts than the corresponding complexes in fresh solutions and compare well with the spectral properties of the Cu^{2+} complex of the parent compound isocyclam [6]. The absorption maxima of fresh solutions, however, indicate a weaker ligand field, which can be due to a macrocycle configuration, which is not the thermodynamically most stable one. The slow interconversion of the Cu^{2+} complexes and the shift of the absorption maxima seems, therefore, due to *N*-isomerization.

In alkaline solutions, the spectra of the Cu^{2+} complexes are shifted to longer wavelengths as expected for axial coordination of the fifth amino group and are comparable with those of a pentacoordinated CuN_5 chromophore [17]. Similar results were obtained with the ligands **6** [4] and **7** [16].

The new ligands **1** and **2** allow to discuss the effect of the side-chain length on the properties of the *Equilibrium 1*, since the spectrophotometric titrations allow to determine the log K_a value for the deprotonation of the ammonium group and its subsequent coordination. The results, given in *Table 3*, show that the Ni^{2+} and Cu^{2+} complexes with **1** have lower log K_a values than those with **2**.

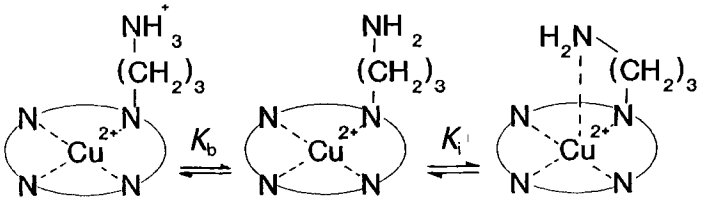
Since log K_a value is determined by the basicity of the amino group (K_b) as well as by its tendency to coordinate (K_i) to the metal ion, a discussion of both aspects is necessary (*Scheme*). To get an idea of the basicity of the side-chain group, we have titrated the

Table 3. *log* K_a *and log* K'_b *Values for the* Ni^{2+} *and* Cu^{2+} *Complexes with* **1** *and* **2** *at 25° and* I = 0.5 M *(*KNO_3 *or KSCN)*

	$\log K_{a,Cu}$	$\log K_{a,Ni}$	$\log K'_{b,Ni}$	$\log K_{i,Ni}$ [a])
1	1.89 (2)	~ 2.0 [b])	5.23 (2)	−3.23
2	6.17 (1)	7.43 (1)	9.10 (2)	−1.67

[a]) Calculated from $\log K_i = \log K_a - \log K'_b$. [b]) Because of the dissociation of the complexes, only an approximate value can be determined.

Scheme. *Separation of the On/Off Reaction Described by* K_a *into a Deprotonation* (K_b) *and a Complexation* (K_i) *Step*



Ni^{2+} complexes in the presence of 0.5M SCN^-, which blocks the apical position of the metal ion and prevents coordination of the amino group *(Eqn. 2)*.

$$NiLH(SCN)_2^+ \leftrightarrows NiL(SCN)_2 + H^+ : K'_b \qquad (2)$$

The log K'_b values are 5.23(2) and 9.10(2) for the ligands with the 2-aminoethyl and 3-aminopropyl side chain, respectively. The large difference in basicity is due to the electrostatic interaction between the Ni^{2+} in the macrocycle and the ammonium group of the side chain with different lengths. If we assume that log K'_b is approximately equal to log K_b, we can calculate log K_i = log K_a − log K_b to − 3.23 and − 1.67 for the Ni^{2+} complexes with **1** and **2**, respectively. This indicates that the NH_2 group of ligand **1** has a higher complexation tendency than that of ligand **2**, which is probably due to the more favourable entropic contribution for the shorter chain compared to the longer one.

These quantitative results are in complete agreement with the more qualitative ones obtained for the Cu^{2+} complexes of tetraazamacrocycles substituted with carboxyalkyl side chains ($(CH_2)_n$ – COOH, n = 1 to 3) [8].

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