205. Metal Complexes with Macrocyclic Ligands, XVIII[1])

A Study of Steric Effects in the Co^{2+}-, Ni^{2+}- and Cu^{2+}-Complexes with 1-(2-Aminoethyl)- and 1-(2-Dimethylaminoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane

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Summary

The two macrocycles 1-(2-aminoethyl)- and 1-[2-(dimethylamino)ethyl]-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane, **1** and **2**, respectively, and their metal complexes with Co^{2+}, Ni^{2+} and Cu^{2+} were prepared. The different spectral properties of the complexes with these two ligands can be rationalized by assuming that, in the case of **1**, the amino group of the pendant arm is axially coordinated to the metal ion giving a pentacoordinate structure, whereas the dimethylamino group of **2** cannot bind because of sterical hindrance. This is also corroborated by the observation that the complexes of **2** react with unidentate ligands such as N_3^- and SCN^- to give ternary species MLX^+, whereas those of **1** do not. This indicates that the complexes of **1** have no free coordination site, their coordination sphere being completely saturated by the five N-atoms of the macrocycle, whereas the complexes of **2** having a vacant site still can add an unidentate ligand.

Mono-*N*-functionalized tetraazamacrocycles with coordinating groups in their side chain show interesting properties as ligands in metal complexes [2]. Depending on whether the ligating group of the side chain does or does not bind to the metal ion, different structures and properties are expected. The equilibrium between the open and the chelated structure *(Fig. 1)* has been observed in the case of the Ni^{2+}-complex of **4** [3]. At $pH < 6.3$ the dimethylamino group is protonated and the Ni^{2+}-complex is square planar. At $pH > 6.3$ deprotonation occurs and the dimethylamino group binds to the metal ion changing the geometry to pseudo-octahedral.

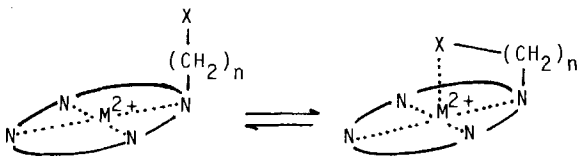

Fig. 1. *Equilibrium between the open and the chelated form of the pendant side chain*

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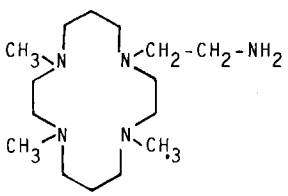
The acid-base equilibrium and the concomitant geometry change show that by designing a side chain of the right length and with a good ligating group at the end of it one can reversibly change and influence the properties of the metal ion. Similar equilibria with a pendant acetamido group have been observed in two macrocyclic Cu^{2+}-complexes [1] [4] [5]. At low pH the amide group probably is not coordinated, whereas at high pH the group binds through the deprotonated N-atom.

In continuation of our studies on this aspect we have chosen, as an additional model, macrocycles with tertiary amino groups, to which we have attached a 2-aminoethyl- (**1**) and a 2-(dimethylamino)ethyl (**2**) side chain.



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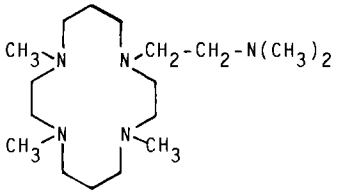

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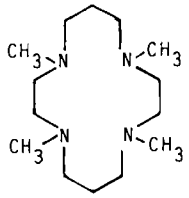

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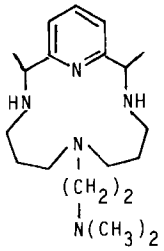

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Macrocycles with tertiary amino groups such as **3** have been shown to give metal complexes with different geometry than those of analogous macrocycles with secondary amines [6] [7] [8]. The complexes of **3** exhibit either square pyramidal or trigonal bipyramidal structures in which the macrocycle occupies four coordination sites and the solvent or an unidentate ligand the fifth [6] [8]. With **1** and **2** we expected that all five coordination positions would be taken up by the macrocyclic ligand and that equilibria of the type shown in *Figure 1* would take place.

Experimental. – Melting points determined on a *Büchi* apparatus are uncorrected. IR spectra were run in KBr pills on a *Perkin-Elmer 157G* spectrophotometer. ^{1}H-NMR spectra were obtained on a *Varian EM 360* instrument using TMS as internal standard.

1-(2-Aminoethyl)4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (**1**). To 3.2 g (13 mmol) of (4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradec-1-yl)acetonitrile [5] dissolved in 125 ml abs. EtOH and cooled with acetone/dry-ice, 100 ml liq. NH_3 and 5–6 g *Raney*-Ni *(Fluka)* were added. The nitrile was hydrogenated at 30° and 60 atm H_2 for 72 h. After decompression and removal of NH_3 the catalyst was filtered off, the solvent evaporated and the residual oil distilled at 140°/0.35 Torr. Yield 2.1 g (65%). ^{1}H-NMR ($CDCl_3$): 1.61 (*quint.*, 4 H, 2 C–CH_2–C); 2.18 and 2.20 (2 *s*, 9 H, 3 CH_3N); 2.3–2.7 (*m*, 22 H, 10 CH_2N and 2 NH).

Amine **1** was converted to the pentahydrochloride dihydrate by addition of HCl in abs. EtOH. Cooling to 0° gave white crystals which were washed with EtOH and Et_2O. M.p. 253–254°. IR (KBr): 3430 (H_2O), 2950 (NH), 2600–2450 br. (NH^+), 1605 (H_2O), 1480–1460 (CH).

$C_{15}H_{40}N_5Cl_5 \cdot 2\,H_2O$	Calc.	C 35.76	H 8.80	N 13.90	Cl 35.18%
(503.82)	Found	„ 36.07	„ 8.71	„ 13.80	„ 34.79%

1-[2-(Dimethylamino)ethyl]-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane (**2**). A mixture of 1.7 g (6 mmol) **1**, 10 ml HCOOH, 9 ml 37% HCOH solution and 5 ml H_2O were refluxed for 24 h. After cooling to 5° conc. NaOH was added and the alkaline solution was extracted five times with 40 ml $CHCl_3$. The org. phase was dried over Na_2SO_4, filtered and evaporated. The residual oil was distilled at 120–125°/0.2 Torr to give 0.9 g (52%) of **2**. ^{1}H-NMR ($CDCl_3$): 1.65 (*quint.*, 4 H, 2 $C-CH_2-C$); 2.25 (*s*, 15 H, 5 CH_3N); 2.4–2.6 (*m*, 20 H, 10 CH_2N).

The pentahydrochloride dihydrate of **2** was prepared by treatment with ethanolic HCl. M.p. 257–258°. IR (KBr): 3450 (H_2O), 2960 (CH), 2450–2700 (NH^+), 1620 (H_2O), 1460, 1480 (CH).

$C_{17}H_{44}N_5Cl_5 \cdot 2\,H_2O$	Calc.	C 38.38	H 9.10	N 13.17	Cl 33.32%
(531.86)	Found	„ 38.45	„ 9.05	„ 13.16	„ 33.43%

Metal Complexes. The metal complexes of **1** and **2** were prepared by reacting 1 mmol ligand in 5 ml EtOH with 1 mmol $M(ClO_4)_2 \cdot 6\,H_2O$ also in 5 ml abs. EtOH. After waiting or gently heating to allow the formation of the complex the product was filtered off, washed with abs. EtOH and dried. Recrystallization from $EtOH/CH_3CN$ gave the pure compounds.

The IR spectra of the complexes are very similar to each other showing bands at 3470 br. (H_2O) when hydrated, 2920–2930 (CH), 2890–2870 ($N-CH_3$), 1480–1430 (CH) and 1095–1090 (ClO_4).

Cu(**1**)*(ClO$_4$)$_2$:* blue crystals (85%).

$C_{15}H_{35}Cl_2CuN_5O_8$	Calc.	C 32.88	H 6.44	N 12.78	Cl 12.94%
(547.92)	Found	„ 32.91	„ 6.51	„ 12.86	„ 12.86%

Ni(**1**)*(ClO$_4$)$_2 \cdot 0.5\,H_2O$:* blue crystals (80%).

$C_{15}H_{35}Cl_2N_5NiO_8 \cdot 0.5\,H_2O$	Calc.	C 32.63	H 6.57	N 12.68	Cl 12.84%
(552.10)	Found	„ 33.06	„ 6.89	„ 12.70	„ 12.58%

Co(**1**)*(ClO$_4$)$_2$:* violet crystals (62%).

$C_{15}H_{35}Cl_2CoN_5O_8$	Calc.	C 33.16	H 6.49	N 12.89	Cl 13.05%
(543.31)	Found	„ 33.06	„ 6.77	„ 12.66	„ 12.23%

Cu(**2**)*(ClO$_4$)$_2$:* blue crystals (75%).

$C_{17}H_{39}Cl_2CuN_5O_8$	Calc.	C 35.45	H 6.82	N 12.16	Cl 12.31%
(575.98)	Found	„ 35.32	„ 6.79	„ 12.25	„ 12.28%

Ni(**2**)*(ClO$_4$)$_2$:* dark green crystals (65%).

$C_{17}H_{39}Cl_2NiN_5O_8$	Calc.	C 35.75	H 6.88	N 12.26	Cl 12.42%
(571.14)	Found	„ 35.65	„ 6.85	„ 12.29	„ 12.75%

Co(**2**)*(ClO$_4$)$_2$:* violet crystals (55%).

$C_{17}H_{39}Cl_2CoN_5O_8$	Calc.	C 35.74	H 6.88	N 12.26	Cl 12.41%
(571.37)	Found	„ 35.53	„ 6.89	„ 12.11	„ 12.69%

Measurements. All experiments were run at 25°±0.1° and I = 0.5 M (KNO_3). Except the buffer bases 2,6-lutidine and 2,4,6-colidine, which were distilled, all other chemicals were of analytical grade and were used without purification.

Potentiometric titrations were carried out using the automatic titration unit described in [9] and the calculations were performed by the computer program TITFIT [10]. The pK_H-values of the ligands **1** and **2** were obtained by titrating 25 ml $3 \cdot 10^{-3}$ M amine pentahydrochloride in 0.5 M KNO_3 with 0.4 M NaOH.

The protonation of the Cu^{2+}-complexes of **1** and **2** was studied by titrating 25 ml $1.4 \cdot 10^{-3}$M $ML(H_2O)^{2+}$ in 0.5M KNO_3 with 0.1M HNO_3. The curves were fitted with the computer program TITFIT to give a $pK^H_{ML} = 7.28 \pm 0.02$ for L = **2**.

VIS spectra were obtained on a *Perkin-Elmer 402* and *550* spectrophotometer fitted with a *Perkin-Elmer 56* recorder in 1-cm cells. Nujol spectra [11] were run on a *Cary 118*.

The stabilities of the ternary complexes MLX^+ (L = **2**, X = SCN^- or N_3^-) were measured by spectrophotometric titrations using the automatic titration set up for a *Cary 118* spectrophotometer interfaced with an *Apple II* [12]. All solutions were filtered through *Swinnex SX 100* units with *RAWP 1300* filters (Millipore). The titrations were performed by addition of 0.01-ml portions of the ligand X^- from a *Metrohm* motor burette to 2.5 ml of the complex $M(\mathbf{2})^{2+}$ in the cell. Generally up to 0.2–0.3 ml of X^- were added to ensure the complete formation of the ternary complex MLX^+. The exact experimental conditions are given in *Table 1*.

Table 1. *Experimental Conditions for the Spectrophotometric Titrations of the Complexes with* **2** *at 25° and I = 0.5 (KNO_3)*

Complex[a])	Ligand X[b])	Buffer[a])	pH	Spectral range [nm][c])
$Cu(\mathbf{2})^{2+}$	SCN^- (0.1M)	0.1M 2,6-lutidine	6.8	440–780
$(1.5 \cdot 10^{-3}$M)	N_3^- (0.98M)	0.1M 2,4,6-collidine	7.8	440–700
$Ni(\mathbf{2})^{2+}$	SCN^- (0.1M)	0.1M 2,4,6-collidine	7.9	380–720
$(3 \cdot 10^{-3}$M)	N_3^- (0.51M)	0.1M 2,4,6-collidine	7.5	440–700
$Co(\mathbf{2})^{2+}$	SCN^- (0.15M)	0.1M 2,6-lutidine	7.4	460–760
$(5 \cdot 10^{-3}$M)	N_3^- (0.25M)	0.1M 2,4,6-collidine	7.5	460–620

[a]) Concentration in the cell. [b]) Concentration in the burette. [c]) The spectra were measured every 20 nm.

The equilibrium constants were calculated using the information from all wavelengths at once with a program based on the *Golub* algorithm, which was written to run on a *Hewlett Packard HP9835* desk top computer [13].

Results and Discussion. – The synthesis of the ligands consists in the reduction of the nitrile group to give **1** and in the subsequent reductive methylation to produce **2**. The protonation constants obtained by titration of the corresponding pentahydrochlorides are given in *Table 2* whereby the pK^H_5 was to low (< 2) to be determined.

Table 2. *pK_H-Values[a]) of* **1** *and* **2** *at 25° and I = 0.5 (KNO_3)*

Ligand	pK^H_4	pK^H_3	pK^H_2	pK^H_1
1	3.16 ± 0.02	8.10 ± 0.02	9.63 ± 0.01	10.39 ± 0.01
2	3.17 ± 0.03	8.00 ± 0.02	9.49 ± 0.01	9.92 ± 0.03

[a]) All values are the mean of 5 or 6 titrations.

By analogy to the parent compound 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (**3**), which has two high and two low pK_H-values [14], the three high pK_H-values of **1** and **2** correspond to the protonation of the side chain and of two N-atoms of the macrocycle, whereas the two lower ones are due to the protonation of the remaining two N-atoms of the ring.

Both ligands react with Co^{2+}, Ni^{2+} and Cu^{2+} to give complexes which were characterized as solids and in solution. Their VIS spectra are given in *Table 3*

Table 3. *VIS Spectra of the Co^{2+}-, Ni^{2+}- and Cu^{2+}-Complexes of* **1–3** *in Aqueous Solution and in the Solid State*

L	λ_{max} in nm (ε in M^{-1} cm^{-1})		
	Co^{2+}	Ni^{2+}	Cu^{2+}
1	H_2O 464 (29), 516 (25), 580 (21), 660 (13)	379 (114), 588 (46)	684 (205)
	sol. 458, 513, 576, 650	388, 588	638
2	H_2O 488 (22), 542 (23), 730 (10)	395 (75), 517 (61), 657 (24)	642 (240)
	sol. 477, 527, 610, 730	407, 493 (sh), 673	658
3[a])	H_2O 472 (20), 543 (21), 725 (12)	394 (95), 512 (82), 650 (33)	640 (257)
	sol. 472, 545, 703	520	580

[a]) From [6] and [7a].

together with those of **3**, which can be used as references, since the geometries of its complexes have been studied before [6]. Except for small differences in the position of the maxima the spectra in the solid state and in aqueous solution are similar to each other. Comparing the spectral properties of the complexes of the three macrocycles one finds a close resemblance between those of **3** and **2**, whereas those of **1** are distinctly different. As an example the spectra of the Ni^{2+}-complexes with the three ligands **1**, **2** and **3** are shown in *Figure 2.*

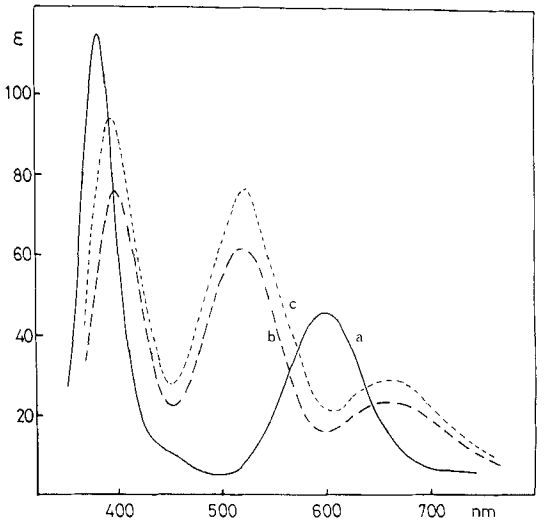

Fig. 2. *Spectra of the Ni^{2+}-complexes of* **1** *(a),* **2** *(b) and* **3** *(c)*

For the Co^{2+}- and Cu^{2+}-complexes of **3** it has been proposed that they are pentacoordinated in aqueous solution [6], whereas for the Ni^{2+}-complex an equilibrium between a pentacoordinate and a square-planar species was suggested [6] [7]. Thus, we assume that the same geometries are also present in the complexes of **2**. This implies that the dimethylamino group at the end of the side chain is not involved in the coordination to the metal ion.

As the complexes of **3** add unidentate ligands X^- such as N_3^-, SCN^- and OCN^- to give pentacoordinate species MLX^+ [6] so the complexes of **2** bind unidentate

Table 4. *Stability Constants* ($\log K^X_{ML}$) *for the Ternary Complexes of* **2** *and* **3** *According to* Equation 1 *at 25° and I = 0.5 (KNO_3)*

M^{2+}	$\log K^X_{ML}$ [a])		
	X^-	L = **2**	L = **3** [b])
Co^{2+}	SCN^-	2.67 ± 0.02	3.07 ± 0.04
	N_3^-	2.19 ± 0.02	2.57 ± 0.03
Ni^{2+}	SCN^-	≈ 3	[c])
	N_3^-	2.16 ± 0.05	2.50 ± 0.05
Cu^{2+}	SCN^-	2.12 ± 0.04	2.14 ± 0.03
	N_3^-	1.20 ± 0.02	1.29 ± 0.03

[a]) Mean values of three determinations. [b]) From [6]. [c]) Precipitation of Ni(**3**)$(SCN)_2$.

ligands X^-. The reaction which can quantitatively be described by K^X_{ML} *(Eqn. 1)* can be followed by the spectral changes on going from ML^{2+} to MLX^+. The $\log K^X_{ML}$-

$$ML^{2+} + X^- \rightleftharpoons MLX^+ : K^X_{ML} \quad (1)$$

values obtained from spectrophotometric titrations *(Table 4)* are very similar to those previously measured for the complexes of **3** [6]. Thus the two ligands **2** and **3** give complexes which, compared by their spectral properties and chemical reactivities, are very similar to each other. This clearly indicates that the dimethylamino group of **2** is not involved in binding. This is additionally shown by the reaction of Cu(**2**)$^{2+}$ with 0.1 M HNO_3. The titration shows that 1 H^+ for Cu(**2**)$^{2+}$ is taken up with a pK_H 7.28. Since this is not accompanied by a change in the spectrum of the complex we ascribed the reaction to the protonation of the non-coordinated dimethylamino group in the Cu(**2**)$^{2+}$-complex.

The structures of the complexes with **1**, however, must differ from those of **2** and **3**. Their VIS spectra can be understood by assuming that the amino group in the side chain of **1** interacts and binds to the metal ion. Thereby pentacoordinate complexes with five N-donors are formed. So the absorption maximum of Cu(**1**)$^{2+}$ at longer wavelength than those of the complexes Cu(**2**)$^{2+}$ and Cu(**3**)$^{2+}$ indicates axial coordination of the amino group [15]. Similarly the spectra of the Ni^{2+}- and Co^{2+}-complexes of **1** are typical for pentacoordinate high-spin species [16] and resemble the spectra of the ternary complexes MLX^+ found for **2** and **3**.

In addition one finds that there is no spectral change in the complexes with **1** when unidentate ligands X^- are added. The metal ions seem to be completely masked, which is compatible with the proposed structure in which the amino group of the side chain binds to the metal ion and thus prevents unidentate ligands to coordinate. Finally there is no indication of protonation of Cu(**1**)$^{2+}$ even at pH as low as 3, in contrast to the finding that Cu(**2**)$^{2+}$ is protonated at pH < 7.

The different structures of the complexes with **1** and **2** must be related to steric factors, since the basicity of the primary and tertiary amino group of the side chain are not so different (see pK_H-values). We have previously shown that in the Ni^{2+}-complex of **4** the dimethylamino group of the side chain can bind in an axial position [3]. So the steric effect of the two methyl groups *per se* cannot be responsible for the differences observed for the complexes of **1** and **2**. To fully understand the

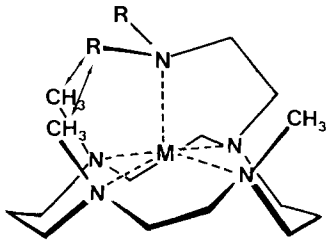

Fig. 3. *Steric interactions between the* N-*methyl groups of the macrocycle and the substituents R of the side chain.* When R = H (ligand **1**) the interaction is small enough so that coordination of the side chain amino group takes place. When $R = CH_3$ (ligand **2**) the steric repulsion is such that the side chain amino group does not bind.

effects observed, we must recall the structures of the complexes of **3**. The complex $NiLN_3^+$ with L = **3** has a square pyramidal structure with the four N-atoms at the base and the N_3^- axially bound [8]. The macrocycle is in the *trans*-I-(*RSRS*)-configuration *(Fig. 3)*, in which all four methyl groups are on the same side as the one to which the azide binds. If we assume that in the complexes of **1** and **2** the same *trans*-I-(*RSRS*)-configuration of the macrocycle is present and that the amino group of the side chain binds axially at the same side as the methyl groups are located, one can easily see from space filling models that with the dimethylamino group of **2** strong steric interaction occurs thus preventing the binding of this group whereas the primary amino group of **1** can coordinate without steric hindrance.

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