38. Metal Complexes with Macrocyclic Ligands

Part XXIX[1])

Structural and Kinetic Studies of Two Isomeric Cu^{2+} Complexes with 1,4-Dimethyl-8-[2-(2-pyridyl)ethyl]-1,4,8,11-tetraazacyclotetradecane

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The synthesis and complexation properties of 1,4-dimethyl-8-[2-(2-pyridyl)ethyl]-1,4,8,11-tetraazacyclotetradecane (**2**) are described. This ligand forms with Cu^{2+} two complexes, one of which has been characterized by X-ray structure analysis. The structural, spectral, and kinetic studies indicate that the two Cu^{2+} complexes are isomers with the macrocycle in the *trans-III* and *trans-I* configuration. The rate of the interconversion of the *trans-I* isomer to the thermodynamically more stable *trans-III* species is proportional to $[OH^-]$. A mechanism for this reaction is proposed.

Introduction. – In metal complexes of 1,4,8,11-tetraazacyclotetradecanes, the macrocycle can adopt five different configurations, which have been called *trans I–V* [2]. So far, three of them have been characterized by X-ray structure analysis [3]. In general, the *trans-III (RRSS)* arrangement has been found, in agreement with calculations which show it to be the thermodynamically most stable form [4]. However, in complexes with tertiary N-atoms, the *trans-I (RSRS)* form is often observed [5]. It is interesting to note that the reaction of 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane with Ni^{2+} and Cu^{2+} gives complexes with the *trans-I* configuration, whereas alkylation of the Ni^{2+} complex of 1,4-dimethyl-1,4,8,11-tetraazacyclotetradecane with MeI in DMSO leads to the *trans-III* isomer [6]. This has been explained by the fact that the bimolecular reaction between the metal ion and the macrocycle first produces the *trans-I* isomer, which then rearranges itself to the thermodynamically more stable *trans-III* form through N inversion [7]. In the case of the tetramethyl derivative, no N inversion through an internal conjugate-base mechanism is possible, so that the kinetically determined species *(trans I)* becomes the end product. When one, however, alkylates the already formed Ni^{2+} complex, the product is *trans-III*-configurated. Interconversion of the two forms seems possible in nonaqueous solvents with strong donor properties or in the presence of a ligand with a strong donor [8].

During our studies on functionalized tetraazamacrocycles, we were able to prepare the monofunctionalized ligand **2** which reacts with Cu^{2+} to give a mixture of a blue and a

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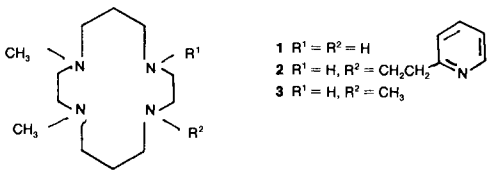
violet complex. The study of these species showed that they are isomers, and that the blue form interconverts to the violet one in a base-catalyzed reaction. This allowed us to study configurations of a macrocycle with three tertiary N-atoms and their relative stabilities.



Experimental. – IR spectra (KBr pellets) were run on a *Perkin Elmer 157G* spectrometer, VIS spectra (either using the nujol mull technique [9] or in solution) on a *Cary 118C* instrument. The ^{1}H-NMR spectra were obtained on a *Bruker C60* spectrometer using sodium 3-(trimethylsilyl)propanesulfonate as internal standard.

1,4-Dimethyl-8-[2-(2-pyridyl)ethyl]-1,4,8,11-tetraazacyclotetradecane Penta(hydrobromide) (**2**·5 HBr). *1,4-Dimethyl-1,4,8,11-tetraazacyclotetradecane* (**1**) [10] (2 g, 8.8 mmol), 2-vinylpyridine (1.1 g, 10.5 mmol), and glacial AcOH (1.1 g, 21 mmol) were refluxed overnight in 30 ml of abs. MeOH. TLC (*Alox E60*; abs. EtOH/H_2O/25% NH_3 10:5:1) of the mixture showed one main product. After removal of the solvent and the excess of 2-vinylpyridine as an azeotrope with H_2O, the residual oil was dissolved in abs. MeOH (50 ml) and conc. HBr (2 ml) from which the product crystallized. Recrystallization from H_2O/EtOH gave colorless crystals (4.8 g, 70%). ^{1}H-NMR (D_2O): 1.90–2.55 (*m*, 2 H–C(6), 2 H–C(13)); 3.04 (*s*, 2 CH_3); 3.20–4.00 (*m*, 8 CH_2–N, CH_2CH_2–py); 7.77–8.74 (*m*, 4 arom. H). Anal. calc. for $C_{19}H_{40}Br_5N_5 \cdot 2H_2O$ (774.11): C 29.48, H 5.73, Br 51.61, N 9.05, H_2O 4.65; found: C 29.52, H 5.64, Br 51.07, N 9.29, H_2O 4.64.

Cu^{2+} Complexes. The crude yellow oil of the reaction mixture described above dissolved in 20 ml of i-PrOH was reacted with $Cu(ClO_4)_2 \cdot 5\,H_2O$ (3.73 g, 10.6 mmol) in i-PrOH, whereupon a purple precipitate was formed. It consisted of a mixture of two isomeric Cu^{2+} complexes with **2**, as well as of the Cu^{2+} complex of the unreacted macrocycle **1**. Separation of the mixture was carried out on a *Sephadex G10* column (25 × 2 cm) with 10^{-3} M $HClO_4$ as eluent. Three main fractions were collected. From the first one, 1.65 g of the blue isomer were obtained, by evaporation, washing the crystals with abs. EtOH, and recrystallizing from 5 ml of H_2O. Similar treatment of fraction 3 yielded, on standing overnight, 0.98 g of the violet isomer.

Blue Isomer (*trans I, RSRS*). Anal. calc. for $C_{19}H_{36}Cl_3CuN_5O_{12} \cdot 1.5\,H_2O$ (723.45): C 31.54, H 5.43, Cl 14.70, Cu 8.78, N 9.68, H_2O 3.73; found: C 31.71, H 5.43, Cl 14.48, Cu 8.80, N 9.80, H_2O 3.85.

Violet Isomer (*trans III, RRSS*). Anal. calc. for $C_{19}H_{35}Cl_2CuN_5O_8 \cdot 0.5\,HClO_4 \cdot H_2O$ (664.21): C 34.25, H 5.69, Cl 13.34, Cu 9.56, N 10.54, H_2O 2.77; found: C 34.39, H 5.70, Cl 13.30, Cu 9.75, N 10.46, H_2O 3.11.

The kinetics of the blue-to-violet interconversion was studied spectrophotometrically at 620 nm using a *Varian Techtron* spectrophotometer with an automatic probe exchanger at 25°. Typical concentrations were $[CuL]_{blue} = 5 \cdot 10^{-3}$ M, *c* (buffer) (Et_3N, pyridin-2-ol) = 0.1 M, or NaOH of different concentrations were used to fix the pH between 9.9 and 13.1, and KNO_3 to adjust the ionic strength to 0.5 M.

Table 1 summarizes the crystal data, data collection details, and structure-determination parameters. Unit cell parameters were determined by accurate centering of 25 independent strong reflections by the least-squares method. Four standard reflections monitored every h during data collection showed no significant variation of the intensity. The raw data set was corrected for polarisation effects, but no correction for absorbance was applied. The structure was solved by *Patterson* techniques in the space group *C*2/*c* by the program SHELXS-86 [11]. The asymmetric unit contains one complex cation and three highly disordered perchlorates of which one is situated on a twofold axis of the unit cell. Also, 1 H_2O molecule in general position and one on a centre of symmetry could be localized. The crystal, thus, contains 0.5 H_2O more than found by elemental analysis. This probably comes from the fact that the crystals for the analysis were dried, whereas those for the X-ray diffraction study were used as obtained. Anisotropic least-squares refinements were carried out on all non-H-atoms of the ligand, the Cu^{2+} cation, and the Cl-atoms by the SHELX-76 program [11]. The pyridine ring was refined as a rigid group, and the H-atoms were in calculated positions. Scattering factors are from *Cromer et al.* [12] or given in the SHELX-76 program.

Table 1. *Crystal Data and Parameters of the Data Collection for the Violet Cu^{2+} Complex with* **2**

Formula	$C_{19}H_{35}Cl_2CuN_5O_8 \cdot 0.5\,HClO_4 \cdot 1.5\,H_2O$
Space group	monoclinic C 2/c
a [Å]	38.317(3)
b [Å]	9.701(2)
c [Å]	15.734(7)
α [°]	90
β [°]	97.81(2)
γ [°]	90
Z; V [Å^3]	8; 5794.2
θ_{max} [°]	25
Radiation	MoK_α ($\lambda = 0.71069$ Å)
Scan type	$\omega/2\theta$
Collected intensities	$\pm h, +k, +l$
μ[cm^{-1}]	4.91
F(000)	2576
No. of independent refl.	5431
No. of refl. used in ref.	1594 ($F > 4\sigma(F)$)
No. of variables	318
Observations/variables	5.0
Largest shift/esd	0.11
Largest peak on final ΔF[e/Å^3]	0.74
Final R	0.096
Final R_w	0.103
Weighting scheme	$1.84\,(\sigma^2(F) + 4.74 \cdot 10^{-3}F^2)^{-1}$

Results and Discussion. – The reaction of **1** with 2-vinylpyridine gives mainly the mono-product **2**, in contrast to other alkylation reactions of the same compound, which yield disubstituted products [13]. The macrocycle **2** reacts with Cu^{2+} to give a mixture of two isomers, one blue and the other violet, the properties of which are collected in *Table 2*.

Table 2. *Properties of the Blue and Violet Cu^{2+} Complexes with* **2**

		Blue isomer	Violet isomer
Formula		$[CuLH](ClO_4)_3$	$[CuLH_{0.5}](ClO_4)_{2.5}$
IR spectra		3260 (NH) cm^{-1}	3220 and 3080 (NH) cm^{-1}
VIS spectra	Solution	579 nm (262 M$^{-1}\cdot$cm^{-1})	540 nm (235 M$^{-1}\cdot$cm^{-1})
	Solid	580 nm	514 nm
pH Titration	$[H^+]/[CuL]$	0.998	0.507
	pK_H	4.40(1)	4.43(1)

In its IR spectrum, the violet isomer exhibits a band at 3080 cm^{-1}, which is not present in that of the blue isomer. The VIS spectra also differ significantly in the solid state and in solution. The absorption maximum at shorter wavelengths for the violet compound compared to that of the blue one indicates that the macrocycle exercises a stronger ligand field in the violet isomer than in the blue one. Most remarkable is the difference in composition, since the blue isomer crystallizes as a triperchlorate, whereas the violet species crystallizes with 2.5 ClO_4^- as anions. Consequently, if one titrates the two compounds with NaOH, one finds one or half a proton per molecule, respectively. The pK_H values so determined are typical for a protonated pyridine in the presence of the positive

charge of the Cu^{2+} ion. In contrast to many pH-dependent color changes previously observed in functionalized tetraaza-macrocycles [14] [15], no such color change is found either in the blue or violet isomer. This indicates that the pyridine group is not able to bind axially to the Cu^{2+} ion. It is probable but not proven that this is due to steric reasons, as observed in the case of a 2-(dimethylamino)ethyl derivative [15].

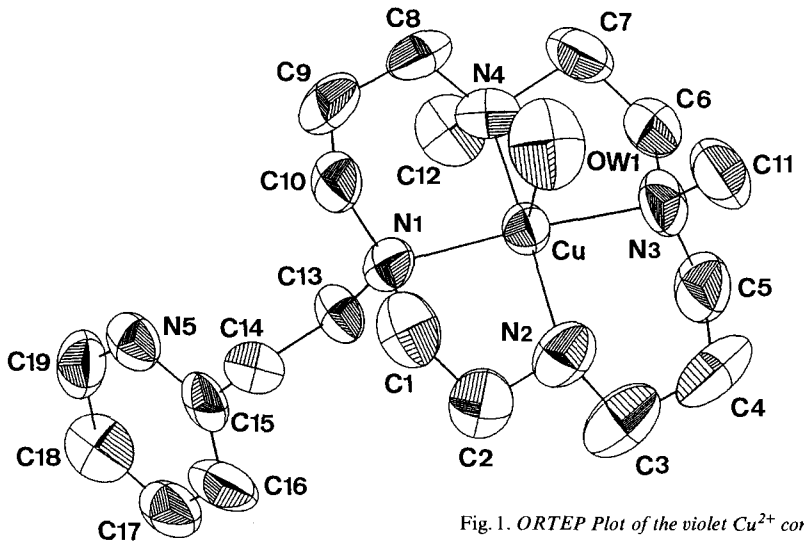


Fig. 1. *ORTEP Plot of the violet Cu^{2+} complex with* **2**

Since the analytical and spectral data were not sufficient to unequivocally describe the two compounds, the structure of the violet isomer was established by X-ray diffraction analysis. The X-ray structure of the Cu^{2+} complex *(Fig. 1)* shows that the pyridine N-atom does not coordinate to the metal ion. The four N-atoms of the macrocycle are in a nearly planar arrangement with a maximal deviation of ±0.02 Å from the best plane. The metal ion is displaced only by 0.07 Å out of the best plane towards the coordinated H_2O molecule O(W1). On the other side of the ring, the O-atom of a ClO_4^- ion is located at 3.50-Å distance from the Cu^{2+}. The Cu–N bond lengths *(Table 3)* of 2.00 to 2.09 Å are in the expected range. The longest bond is Cu–N(1), N(1) being the N-atom at which the

Table 3. *Selected Bond Lengths* [Å] *and Bond Angles* [°] *for the Violet Cu^{2+} Complex with* **2**

Cu – N(1)	2.091(14)	Cu – O(W1)	2.552(16)
Cu – N(2)	2.054(17)	Cu – O(7B)	3.505(18)
Cu – N(3)	2.077(16)		
Cu – N(4)	2.007(18)		
N(1) – Cu – N(3)	176.4(8)	N(1) – Cu – N(2)	85.6(7)
N(2) – Cu – N(4)	174.7(8)	N(2) – Cu – N(3)	92.0(8)
O(W1) – Cu – O(7B)	176.9(8)	N(3) – Cu – N(4)	87.5(8)
O(W1) – Cu – N(1)	89.5(6)	N(1) – Cu – N(4)	94.7(7)
O(W1) – Cu – N(2)	90.0(7)		
O(W1) – Cu – N(3)	93.2(6)		
O(W1) – Cu – N(4)	95.3(7)		

2-(2-pyridyl)ethyl side chain is attached. The macrocycle assumes the *trans-III* configuration with one Me group (C(11)) and the H-atom of the secondary amine (N(2)) on the same side of the macrocyclic ring as the coordinated H_2O molecule, whereas the second Me group (C(12)) and the 2-(2-pyridyl)ethyl side chain (C(13)) are located on the opposite side. The X-ray diffraction does not give any indications about the half proton per molecule as found analytically. In the asymmetric unit, there is only one type of molecule, although one would expect that half of the pyridine N-atoms should be protonated and the other half not. The bond lengths and angles found in our structure closely resembles those of other Cu^{2+} macrocycles such as $[Cu(Cyclam)](ClO_4)_2$ [16], $[Cu(Cyclam)(SC_6F_5)_2]$ [17] and $[Cu(Cyclam)(CH_3COO)](ClO_4)$ [18], which all have the macrocycle in the *trans-III* configuration and a planar CuN_4 unit. The structure of the blue isomer can be discussed by comparing its properties *(Table 2)* with those of the α-isomer of the trimethyl derivative **3** [19]. The complex $[Cu(\mathbf{3})]^{2+}$ has an absorption maximum at 567 nm, and it isomerizes to the β-isomer with λ_{max} of 532 nm, in close analogy to the blue and violet isomers of **2**. In agreement with *Barefield et al.* [19], we, thus, assign the *trans-I* structure to the blue isomer.

The purification of the blue isomer was difficult, since it slowly transforms to the more stable violet compound. This observation led us to study the kinetics of this reaction in which the macrocycle changes its configuration from *trans I* to *trans III*. The reaction rate, followed spectrophotometrically at 620 nm in the pH region of 9–13, is proportional to $[OH^-]$ (*1*), with $k_{obs} = 2.9 \cdot 10^{-2}\ M^{-1} \cdot s^{-1}$.

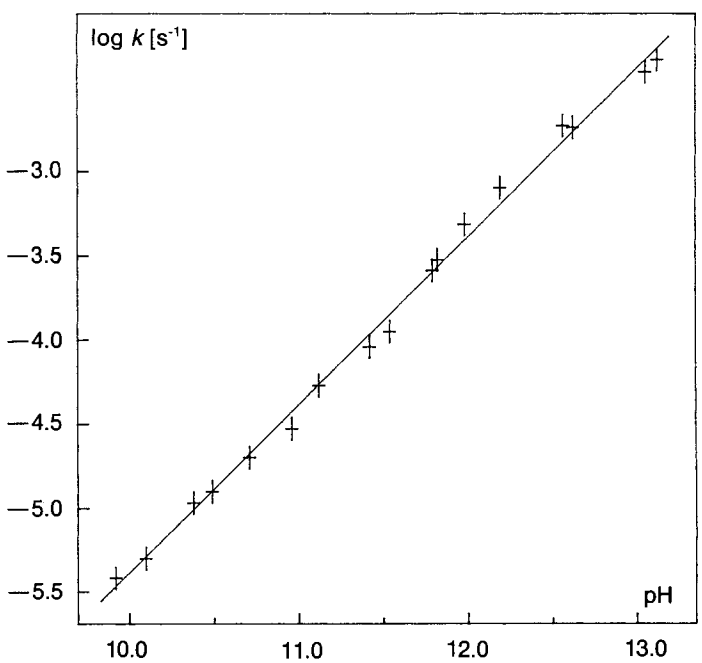


Fig. 2. *pH Dependence for the isomerization rate* k_{obs} *for the interconversion of the blue to the violet* Cu^{2+} *complex of* **2**

$$v = k_{obs} \cdot [CuL_{blue}] \cdot [OH^-] \quad (1)$$

The $[OH^-]$ dependence *(Fig. 2)* is indicative for a conjugate base mechanism in which the secondary N-atom is deprotonated and, thus, allows inversion at this centre. However, one must bear in mind that the interconversion from *trans-I* to *trans-III* configuration is coupled with an inversion of two adjacent N-centres, one of which is a tertiary amino group which cannot give a conjugate base. We, thus, propose mechanism (*2*), which leads to

$$\underset{trans\ I}{(CuL)_{blue}} \overset{K_{OH}}{\rightleftharpoons} \underset{trans\ I}{(CuLH_{-1})_{blue}} \overset{k}{\rightarrow} \underset{trans\ II\ or\ III}{(CuL)_{int}} \overset{fast}{\rightarrow} \underset{trans\ III}{(CuL)_{violet}} \quad (2)$$

the rate law (*3*).

$$v = \frac{k \cdot K_{OH} \cdot [OH^-] \cdot C_{tot}}{1 + K_{OH} \cdot [OH^-]} \quad (3)$$

Eqn. 3 can be simplified to *Eqn. 4*, when the acid-base equilibrium described by K_{OH} favors the left side ($1 \gg K_{OH} \cdot [OH^-]$).

$$v = k \cdot K_{OH} \cdot C_{tot} \cdot [OH^-] = k_{obs} \cdot C_{tot} \cdot [OH^-] \quad (4)$$

The rate law (*4*) for the isomer interconversion *trans-I* → *trans-III* does not resemble that found for the blue-to-violet rearrangement of the $[Cu(tet\ a)]^{2+}$ complex [20]. The rate of this last reaction reaches a plateau at high pH, which was explained by postulating a hydroxo complex as reactive species. In our case, no indication of such a plateau is found up to pH 13.

The final question about the rate-determining step in *Eqn. 2* is difficult to answer in regard to the inversion of the second centre which is a tertiary N-atom. It could be that the second centre is also inverted in the conjugate base $(CuLH_{-1})_{blue}$ to the *trans-III* arrangement, and, thus, the last fast step only consists of a proton addition, or that the intermediate $(CuL)_{int}$ has the *trans-II* configuration, which, being instable, rapidly rearranges to the final *trans-III* product.

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