110. Metal Complexes with Macrocyclic Ligands. XIII[1]). The Complexation of Cu^{2+} with Triazacycloalkanes

by **Theodor J. Riedo** and **Thomas A. Kaden**[2])

Institute of Inorganic Chemistry, Spitalstrasse 51, CH-4056 Basel, Switzerland

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Summary

The potentiometric study of the complexation of Cu^{2+} with 1,4,7-triazacyclononane (**1**), 1,4,8-triazacyclodecane (**2**) and 1,5,9-triazacyclododecane (**3**) has shown that CuL, CuL_2 and $(CuLOH)_2$ are the main species present in solution. Their stabilities *(Table 1)* and their absorption spectra *(Table 2)* indicate facial coordination of the cyclic triamines in a distorted octahedral geometry.

The formation and dissociation kinetics have been measured by stopped-flow techniques. The formation in acetate buffer can be described by the reaction of Cu^{2+} and $CuAcO^+$ with the monoprotonated species of the ligand. The bimolecular rate constants for these complexations *(Table 3)* decrease when the ring size increases. In contrast the dissociation induced by acid is only little affected by the ring size. Thus for these complexes the rate of formation and not that of the dissociation determines the overall stability.

The kinetics of complex formation of several macrocyclic ligands with 4 N- or 4 S-atoms as donors have been studied. Whereas the tetrathioethers [2] and the free tetraamines [3] react with transition metal ions at rates comparable to those of open chain ligands, the protonated species of the cyclic tetraamines are less reactive [4]. The complexation of the monoprotonated species is 10^2–10^3 times slower and that of the diprotonated species is – depending on the ring size – 10 to 10^5 times slower compared to that of open chain ligands. In most of the systems studied the metal ion is encompassed by the macrocycle, whereby *trans*-octahedral or square planar coordination geometries result [5]. For the 12-membered tetraazaring, however, a folding of the macrocycle is necessary to coordinate the metal ion through the 4N-atoms. Thus *cis*-octahedral complexes are formed [6]. Although the metal ion is not surrounded by the 4N-atoms of the tetraazacyclododecane the complexation

[1]) Part XII, see [1].

[2]) Author, to whom correspondance should be addressed.

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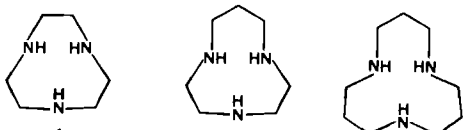
kinetics of this ligand is similar to those of the larger rings [4]. This observation has induced us to search for other cyclic ligands which do not bind the metal in their center and to investigate their complexation kinetics. The triazacycloalkanes **1–3** are of this type since their ring size is too small to accomodate a metal ion. In the case of Co(III) a facial coordination in octahedral geometry has been found for **1** and **2** [7]. In addition the smaller triaza ligands are interesting because, in their protonated forms, the positive charges are closer to each other than in those of the tetraaza macrocycles, thus allowing to study the effect of electrostatic interactions on the complexation kinetics. This paper describes the complexation properties of 1,4,7-triazacyclononane (**1**), 1,4,8-triazacyclodecane (**2**) and 1,5,9-triazacyclododecane (**3**) with Cu^{2+} as well as the formation and dissociation kinetics.



Experimental part. – The cyclic triamines **1**, **2** and **3** were synthesized by a combination of methods described previously [7–9] and were characterized by their melting points, NMR. spectra and analysis. **1** · 3 HBr m.p. 272–274° (274–275° [7]); **2** · 3 HBr m.p. 240–241° (242–243° [7]) and **3** · 3 HBr m.p. 266–267° (267.5–268.5° [7]).

Reagent of analytical grade were used without purification. $T = 25 \pm 0.05°$, $I = 0.5$ (KNO_3).

The equilibria were studied by pH titration and the pK_1^H values were determined by following the NMR. shift of the methylene groups as a function of the pH as described previously [9].

In addition, spectrophotometric titrations were run on a *Cary* 118, equipped with a microtitrating apparatus which allows to add NaOH and to measure the pH directly in the cell [10]. Ligand concentrations were 10^{-3}M with 0.45 and 0.9 equivalent Cu^{2+} and the pH was changed from 3 to 10 by addition of 0.1M NaOH. Spectra were run from 800 to 400 nm in a 1 cm cell.

The kinetics of the complex formation and dissociation were followed on a *Durrum* stopped flow spectrophotometer on line with a top desk computer HP 9821 [11]. All solutions were filtered through a *Swinnex*-unit (SXOOO 1300) with *Rawpo* 1300 filters. The transmission changes were recorded at the wavelength of the absorption maximum of the CuL^{2+} complex, *i.e.* at 637 nm for **1**, 664 nm for **2** and 689 nm for **3**. Typical concentrations for the formation reaction were [Ligand] = 0.5–1.6 · 10^{-3}M, [Cu^{2+}] = 0.5–2 · 10^{-2}M, [Acetate] = 0.02–0.14M and pH = 3.5–5.5. In general an excess of Cu^{2+} was used to assure only the formation of CuL^{2+}. These measurement were calculated as pseudo-first order reactions.

For each ligand several buffer dependences at different pH, at least two pH-dependences at two buffer concentrations as well as two [Cu^{2+}]-dependences at two pH values were measured. For the dissociation reactions 6 · 10^{-4} to 2 · 10^{-3}M CuL^{2+} at pH 5.8 for **1** and **2** and pH 7.4 for **3** were mixed with HNO_3 of different concentrations so that pH values of 0.5–2.5 resulted. In addition, the dissociation of CuL^{2+} with **3** was also measured in the presence of other acids (0.04–0.12M) such as acetic acid at pH 3.57 and 3.73, chloroacetic acid at pH 2.57 and 2.88 and formic acid at pH 3.22 and 3.46.

Results. – Except the pK_1^H all other equilibrium constants of *Table 1* were obtained from the titration curves by the computer program *Variat* [12] on an *Univac* 1108 or by a nonlinear least square regression based on *Marquardt*'s method [13] run on a HP 9821. For the calculation the reactions (1–5) were taken into account.

$$H^+ + L \overset{K_1^H}{\rightleftharpoons} HL^+ \quad (1)$$

$$H^+ + HL^+ \overset{K_2^H}{\rightleftharpoons} H_2L^{2+} \quad (2)$$

$$Cu^{2+} + L \overset{K_1}{\rightleftharpoons} CuL^{2+} \quad (3)$$

$$CuL^{2+} + L \overset{K_2}{\rightleftharpoons} CuL_2^{2+} \quad (4)$$

$$2\,CuL^{2+} + 2\,OH^- \overset{K_3}{\rightleftharpoons} (CuLOH)_2^{2+} \quad (5)$$

This scheme allows the fitting of all titration curves with different Cu^{2+}: L ratios obtained at different total concentrations. The introduction of $CuLOH^+$ instead of $(CuLOH)_2^{2+}$ as a species failed to satisfactory fit the titration curves in the region of 3–4 equivalent base and this complex was therefore rejected [9].

The pK of *Table 1* are weighted means values obtained from 4 to 7 curves with each about 30 points.

The pH dependence of the absorption spectra was used to check the potentiometric results. With the computer program *Spana* [12] the absorption characteristics of each species were obtained *(Table 2)*.

The formation kinetics were measured at different pH values and different acetate buffer concentrations. In the case of the ligands **1** and **2** the pH and buffer dependences of k_{obs} can be explained by assuming that both Cu^{2+} and $CuAcO^+$ react with LH^+ (6).

$$v_f = k_{obs} \cdot [L]_{tot} = (k_{Cu}^{LH} \cdot [Cu^{2+}] + k_{CuAcO}^{LH} \cdot [CuAcO^+]) \cdot [LH^+] \quad (6)$$

Taking into account the stoichiometric equations for $[Cu]_{tot}$, $[L]_{tot}$, $[AcO]_{tot}$ and K_{CuAcO}, the stability constant of $CuAcO^+$, one obtains (7):

$$y = \frac{k_{obs} \cdot [H^+]}{[Cu]_{tot} \cdot K_2^H} = \frac{k_{Cu}^{LH} \cdot K_{CuAcO} + k_{CuAcO}^{LH} \cdot [AcO^-]}{K_{CuAcO} + [AcO^-]} \quad (7)$$

Table 1. *Protonation and stability constants of the Cu^{2+} complexes with* **1**, **2** *and* **3** *at 25° and $I = 0.5$ (KNO_3)*

Ligand	pK_1^H[a])	pK_2^H	pK_1	pK_2	pK_3
1	12.6 ± 0.2	7.24 ± 0.02	17.50 ± 0.04	14.01 ± 0.05	15.04 ± 0.06
2 [9]	12.75 ± 0.2	6.86 ± 0.02	16.14 ± 0.09	10.26 ± 0.03	14.52 ± 0.09
3 [9]	13.15 ± 0.2	7.97 ± 0.03	13.16 ± 0.02	7.68 ± 0.04	13.23 ± 0.08

[a]) Determined by ^{1}H-NMR. technique (see text).

Table 2. *Absorption maxima* (nm) *and molar absorptivities* ($M^{-1}\,cm^{-1}$) *of the Cu^{2+} complexes of* **1**, **2** *and* **3**

	1	**2**	**3**
CuL^{2+}	637 (42)	664 (74)	689 (138)
CuL_2^{2+}	579 (37)	632 (44)	662 (185)
$(CuLOH)_2^{2+}$	620 (124)	631 (196)	649 (285)

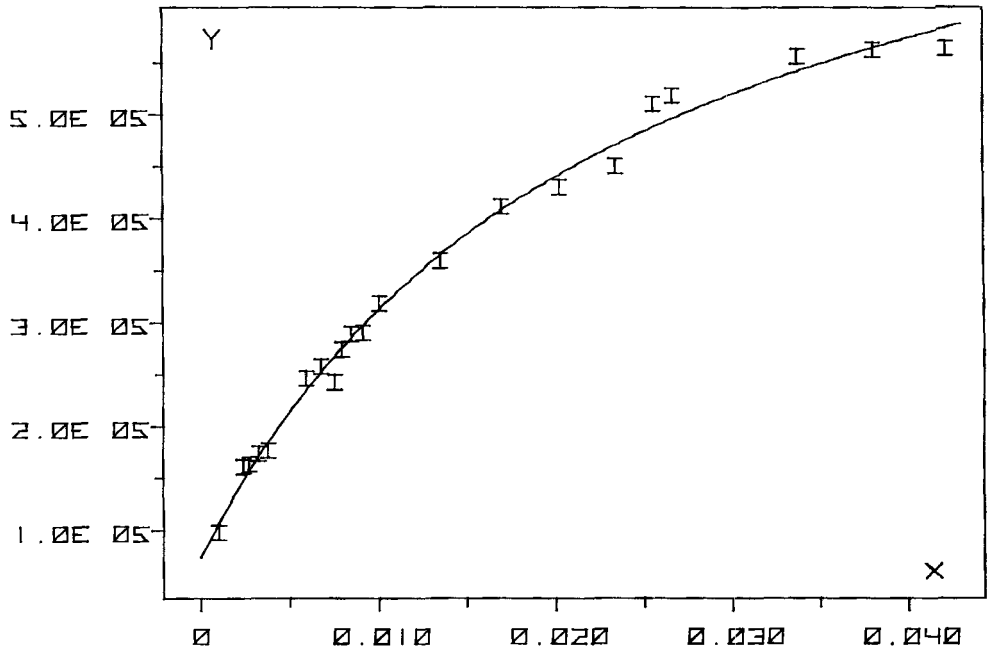


Fig. 1. *Plot of equation (7) for the complexation of Cu^{2+} with* **2** *in acetate buffer.* The curve is calculated with the values of k_{Cu}^{LH} and k_{CuAcO}^{LH} given in *Table 3*

Table 3. *Formation* ($M^{-1}s^{-1}$) *and dissociation* ($M^{-1}s^{-1}$) *rate constants for the Cu^{2+} complexes with* **1**, **2** *and* **3** *at 25° and $I = 0.5$ (KNO_3)*

	k_{Cu}^{LH}	k_{CuAcO}^{LH}	k_H	k_{ClAcOH}	k_{HCOOH}	k_{AcOH}
1	$(2.4 \pm 0.1)\ 10^6$ [a])	$(1.0 \pm 0.2)\ 10^7$ [a]) $6.8\ 10^6$ [22]	34 ± 2 [b])	–	–	–
2	$(7.4 \pm 1.1)\ 10^4$	$(8.6 \pm 0.4)\ 10^5$	13 ± 1 [b])	–	–	–
3	23 [c])	$(2.8 \pm 0.1)\ 10^3$	21 ± 1 [b])	6.2 ± 0.1 [d])	2.2 ± 0.04 [d])	0.74 ± 0.01 [d])

[a]) Calculated from 31 points. [b]) Calculated from 8–11 points. [c]) Calculated from K_1 and k_H of **3**. [d]) Calculated from 10 points.

For each measurement the left side of (7) and $[AcO^-]$ were computed and plotted. Then the function $y(AcO^-)$ was fitted by a nonlinear least square program with k_{Cu}^{LH} and k_{CuAcO}^{LH} as parameters. pK_{CuAcO} was taken as a parameter in the case of **2**. Its value of 1.65 nicely fits into those found in the literature (1.61–1.8) [14] and was therefore used for the other systems too. The rate constants and their standard deviations are given in *Table 3* and one example of curve fitting is shown in *Figure 1*.

In the case of **3** the kinetics is more complex since one has to work under pH conditions at which formation and dissociation overlap. Using a large excess of Cu^{2+} the equilibrium (8) is reached under pseudo-first order conditions. Then the reaction

$$Cu^{2+} + LH_2^{2+} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} CuL^{2+} + 2\,H^+ \qquad (8)$$

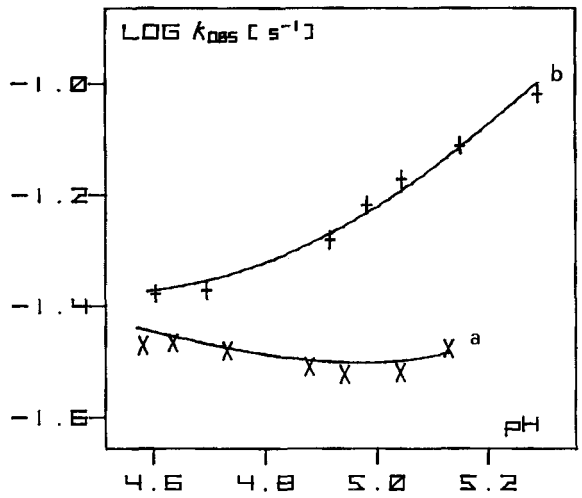


Fig. 2. *pH-Dependence of the observed rate constant for the reaction of* Cu^{2+} *(a)* $[Cu^{2+}] = 6.30 \cdot 10^{-3}$ M, *b)* $[Cu^{2+}] = 2.53 \cdot 10^{-2}$ M) *with* **3** *in 0.08*M *acetate buffer at 25°.* Curves calculated with (9) and *k*-values of *Table 3*

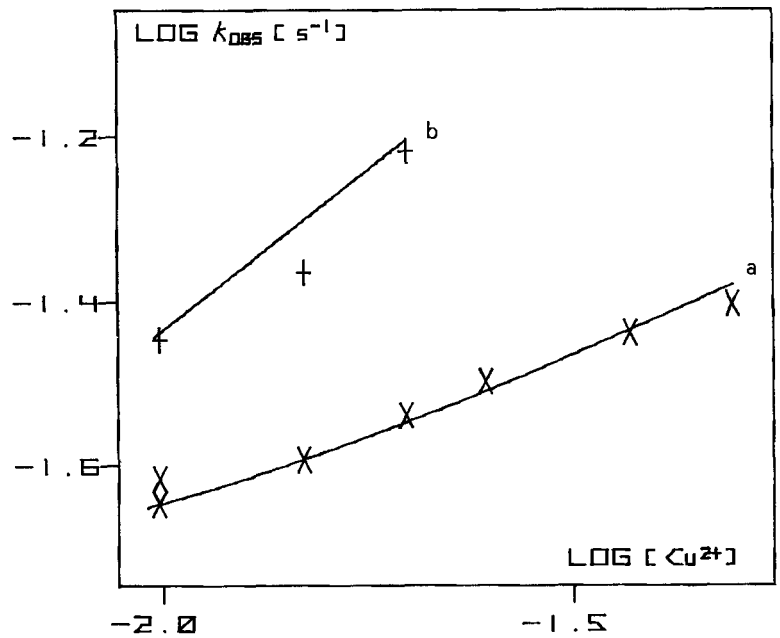


Fig. 3. *[*Cu^{2+}*]-Dependence of the observed rate constant with* **3** *in 0.04*M *acetate buffer and at a) pH = 4.78 and b) pH = 5.29.* Curves calculated with (9) and the rate constants of *Table 3*

rate is described by an exponential function with $k_{obs}=k_+ + k_-$ [15]. The best fit of k_{obs} resulted with (9)

$$k_+ = k^{LH}_{CuAcO}\,[CuAcO^+] \qquad k_- = k_{AcOH}\,[AcOH] + k_H\,[H^+] \tag{9}$$

k_H and k_{AcOH} were taken from the acid-catalyzed dissociations (see below) whereas k^{LH}_{CuAcO} was considered a parameter. The results are also given in *Table 3* and the different dependences are shown in *Figures 2* and *3*.

The dissociation kinetics, studied in HNO_3 of different concentration, gave the rate law (10).

$$v_d = k_H \cdot [CuL^{2+}] \cdot [H^+] \tag{10}$$

The k_H values determined by linear curve fitting are given in *Table 3*.

For **3** the dissociation was also studied in the presence of other acids such as CH_3COOH, $ClCH_2COOH$ and HCOOH. The rate law is given by (11) indicating a general acid catalyzed process. The rate constants for these acids are also included in *Table 3*.

$$v_d = [CuL] \cdot \sum_i k_i \cdot [HA]_i \tag{11}$$

Discussion. – The protonation and stability constants of the cyclic triamines **1**–**3** are interesting in many regards *(Table 1)*. The three compounds **1**, **2** and **3** have extremely high pK^H_1 values which are unusual for open chain polyamines [14]. This is probably due to intramolecular H-bonds resulting from a conformation which allows the interaction of the 3 N-atoms [9]. Such intramolecular hydrogen bonds can increase the basicity of a species as has been observed in the case of 1,8-bis(dimethylamino)-naphthalene [16]. The pK^H_1 for **1** nicely fits into the series of values found for **2** and **3** [9], but is in contrast to that of 10.42 reported in [17][3]). The second and third protonation constants are lower. This is mainly due to the electrostatic interaction between the positive charges, although conformational changes may also be important. For example the fact that the pK^H_2 of **2** is smaller than that of **1** is an indication for it. The pK^H_3 values are all below 2.5 and were not determined in this work.

All three compounds form complexes with similar stoichiometric composition, *i.e.* CuL^{2+}, CuL_2^{2+} and $(CuLOH)_2^{2+}$. These species are necessary to fully explain the titration curves with excess of ligand and at different total concentration. This contrasts to the results of *Zompa et al.* [17] [18], who find for **1**–**3** CuL^{2+} and for **1** and **3** $CuLOH^+$, but no CuL_2^{2+}. As discussed previously [9] we cannot explain the concentration dependences of the buffer region which corresponds to a hydrolyzed CuL-species without taking into account dimerisation to $(CuLOH)_2^{2+}$. It is however possible that in more dilute solution $CuLOH^+$ is also present.

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[3]) The value reported in [17] was obtained from a pH-titration, which however does not allow the determination of such high pK^H-values.

Because of the high basicity of the ligands the 1:1 complexes with Cu^{2+} belong to the strongest known for triamines which bind facially and are – in the case of **1** and **2** – also comparable to those of dien and dipren which preferably coordinate in a meridional arrangement [14]. The observation that strong 1:2 complexes are formed with the triazamacrocycles is also understandable when facial and not meridional coordination takes place. The absorption spectra of the Cu^{2+}-complexes *(Table 2)* are indicative for facial coordination since the absorption maxima for CuL^{2+} and CuL_2^{2+} are at higher wavelength than one would expect for a CuN_3- or CuN_4-chromophore and in accordance to systems which have additional axial ligands (pentaamineeffect) [19].

The complexation and dissociation kinetics of the CuL^{2+}-complexes with **1**–**3** are peculiar in many regards. First we find a strong dependence of k_{Cu}^{LH} and k_{CuAcO}^{LH} from the ring size *(Table 3)*. Secondly the dissociation rates are very similar for the three ligands although their stabilities are different. Thirdly we observe a general acid catalysis in the case of the dissociation of the CuL^{2+}-complex of **3**.

The first two points are unusual when compared to the results of the complexation and dissociation reactions with open chain ligands. There the formation rates are very similar to each other and generally determined by the rate of solvent exchange, whereas the dissociation rates differ and determine the stability of the complexes [20]. Thus closer examination at the mechanism of these reactions with the cyclic triamines seems appropriate.

If we assume that electrostatic factors play a role in the formation reaction, we would expect a change of k_{Cu}^{LH} and k_{CuAcO}^{LH} with ring size. For a protonated ligand the repulsion between the two positive charges of the ammonium group and the Cu^{2+} will decrease by increasing the ring size. Thus the complexation rate with the larger rings will be higher than that with the smaller rings. This was observed for the reaction of LH_2^{2+} and Cu^{2+} in the series of the tetraazamacrocycles [4]. For the cyclic triamines, however, the rate constants decrease by increasing the ring size. In other words these systems behave differently from the open chain systems and from the tetraazacycloalkanes.

On the other side the general acid catalysis in the dissociation of the CuL^{2+}-complex of **3** is indicative that the rate determing step for the dissociation must be the attack of the acid with a more or less concomitant breaking of the Cu^{2+}-N bond. In contrast the acid promoted dissociation of open chain ligands consists of a rapid protonation preequilibrium followed by the rate determing dissociation of the protonated ligand from the metal ion. This difference in reactivity could be a consequence of the more rigid structure of the cyclic ligands, which does not allow a rapid protonation of one of the nitrogens except when a conformational change takes place. Perhaps we have a situation similar to that described for *cis,cis*-1,3,5-triaminocyclohexane, for which a conformation change of the ligand becomes the slowest step [21]. As a consequence of the principle of microscopic reversibility we expect that the same step will be rate determing for the formation.

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111. The Absolute Configuration of Naturally Occurring (*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, a Constituent of Civet *(Viverra civetta)*[1])

by **Bruno Maurer** und **Walter Thommen**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

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Summary

The absolute configuration of the title compound, a minor constituent of civet, is shown to be *S,S*.

We recently reported the isolation of a new compound, (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1a**), from civet *(Viverra civetta)* [1]. Although the constitution

[1]) Supplement to [1].

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