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KINETICS AND MECHANISM OF FORMATION AND DECOMPOSITION OF COPPER(II) COMPLEXES WITH A BINUCLEATING HEXAAZAMACROCYCLE

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Abstract—The kinetics of formation and decomposition of mono- and binuclear copper(II) complexes of the macrocycle 3,6,9,17,20,23-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25(26),27-hexaene (L) has been studied at 25°C and 1.0 M ionic strength under a variety of conditions. All reactions occur in the stopped-flow time-scale and results indicate that upon addition of a large excess of H^+ binuclear complexes convert rapidly into mononuclear species in which some nitrogens of the ligand are uncoordinated. The kinetics of decomposition of the resulting mononuclear species is intermediate between that of complexes with linear polyamines and those with mononucleating macrocycles. On the other hand, the formation of Cu^{II} complexes at high concentrations of OH^- occurs essentially through reaction of $Cu(OH)_3^-$ with the unprotonated form of the ligand, at a rate similar to that observed for reactions with simpler ligands. Coordination of the second Cu^{II} is very rapid under these conditions. Copyright © 1996 Elsevier Science Ltd

The kinetics of formation of Cu^{II} complexes with polyamines and polyazamacrocycles is very complicated because of the inherent lability of the metal centre and of the many species that occur in equilibrium depending on the solvent, pH and buffer used. However, the results available point to several conclusions. (i) The formation of metal complexes in highly basic media from $Cu(OH)_3^-$ is usually faster than formation from $Cu(OH)_4^{2-}$. For $Cu(OH)_3^-$, the rate-determining step is Jahn–Teller inversion following the formation of the first metal–ligand bond, although bulky substituents in the ligand can cause the process to be kinetically controlled by the inversion following the formation of the second Cu—N bond.[1,2] (ii) The decomposition of Cu^{II}–macrocycle complexes in acid solutions is usually much slower than decomposition of the analogues with open-chain polyamines. The mechanism proposed by Margerum *et al.*[3] supposes the initial partial dissociation of one Cu—N bond to form an activated intermediate that can be attacked by the solvent or H^+. For complexes with macrocycles, the ligand makes the approach of a solvent molecule difficult and decomposition occurs preferentially by the proton-attack pathway. (iii) The kinetics of formation at intermediate pH is more complicated because the number of species under these conditions is usually very large. However, the results obtained suggest that the rate-determining step can be the formation of the first or second Cu—N bond,[4] with an internal conjugate base acceleration being operative in some cases. (iv) The use of a non-aqueous solvent such as dimethylformamide reduces the number of species to be considered and the analysis of the data results is simplified. Some kinetic studies in this solvent revealed that formation of Cu^{II}–macrocycle complexes occurs in two steps, with initial formation of

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an intermediate that rearranges to form the final product.[5,6]

We are interested in determining the kinetic effects associated with the formation of macrocyclic binuclear complexes and particularly their relevance to the behaviour of many metalloproteins that require two close metal ions to carry out their biological function. Binucleating macrocycles form a variety of complexes depending on the pH and the metal : ligand ratio,[7] although conditions can be selected in such a way that either mononuclear or binuclear species predominate. The formation and decomposition of mononuclear complexes is expected to show kinetics similar to that of complexes with polyamines or mononucleating macrocycles. However, to our knowledge, little is known about the kinetics associated with the coordination and release of the second Cu^{II} ion. For this reason, we decided to study the kinetics of formation and decomposition of Cu^{II} complexes with the macrocycle 3,6,9,17,20,23-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(2),1(30),12,14,25(26),27-hexaene[8] (Scheme 1) in aqueous solution. In this paper we report the results obtained at extreme pH values. Under these conditions, there are not many species in equilibrium and the analysis of the data is simplified.

EXPERIMENTAL

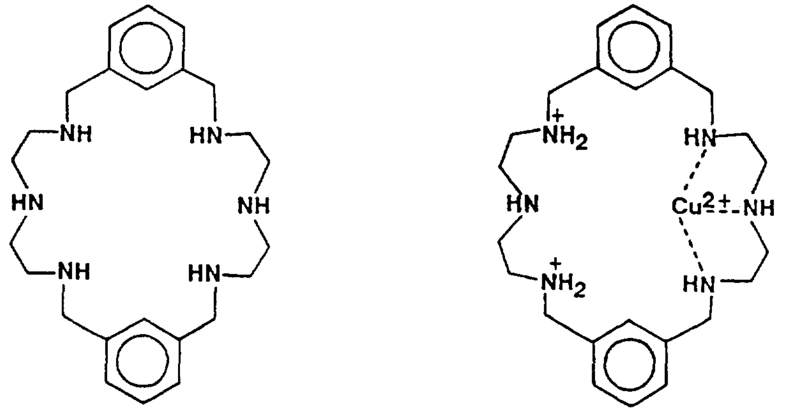
The ligand 3,6,9,17,20,23-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25(26),27-hexaene was synthesized as the hexabromohydrate following the procedure of Martell and coworkers.[8] All other reagents were obtained from Aldrich.

Kinetic experiments were carried out at 25°C with an Applied Photophysics DX17MV stopped-flow unit. The ionic strength was adjusted to 1.0 M by adding the amount of KNO_3 required in each case. The kinetics of decomposition in acid media was studied under pseudo-first-order conditions by using a large excess of H^+. The values of k_{obs} were obtained by conventional fitting of kinetic traces to a single exponential. The kinetics of complex formation in basic media was studied using OH^- in excess. However, in some cases the low solubility of the reagents precluded the use of a large excess of Cu^{II} or L and so, pseudo-first-order conditions cannot be considered to be valid. Although most kinetic curves obtained under these conditions could be fitted satisfactorily to single exponentials, the data were best fitted using eq. (1), where $z = [Cu]_0/[L]_0$ and $\beta = k[L]_0(1-z^{-1})$:[5]

$$D = D_\infty + \frac{(D_0 - D_\infty)(z-1)\,e^{-\beta t}}{z - e^{-\beta t}}. \qquad (1)$$

The wavelength selected for every type of experiment was that showing the maximum change of absorbance in preliminary spectrophotometric scanning experiments, and these were also used to check that the observed rate constants do not change when the concentration of the limiting reagent is changed. Reported values of the observed rate constants (k_{obs}) correspond to the mean value for at least five determinations showing a standard deviation lower than 10%. The analysis of the data was carried out with the standard software of the stopped-flow instrument.

KOH solutions were obtained from Aldrich and titrated with potassium hydrogenphthalate. These solutions were used to titrate the HNO_3 solutions required for the work. The pH readings were obtained with a Crison 2002 instrument provided with an Ingold combined electrode. Copper(II) solutions were prepared from $Cu(NO_3)_2 \cdot 2.5\ H_2O$ and titrated with EDTA using murexide as indicator.



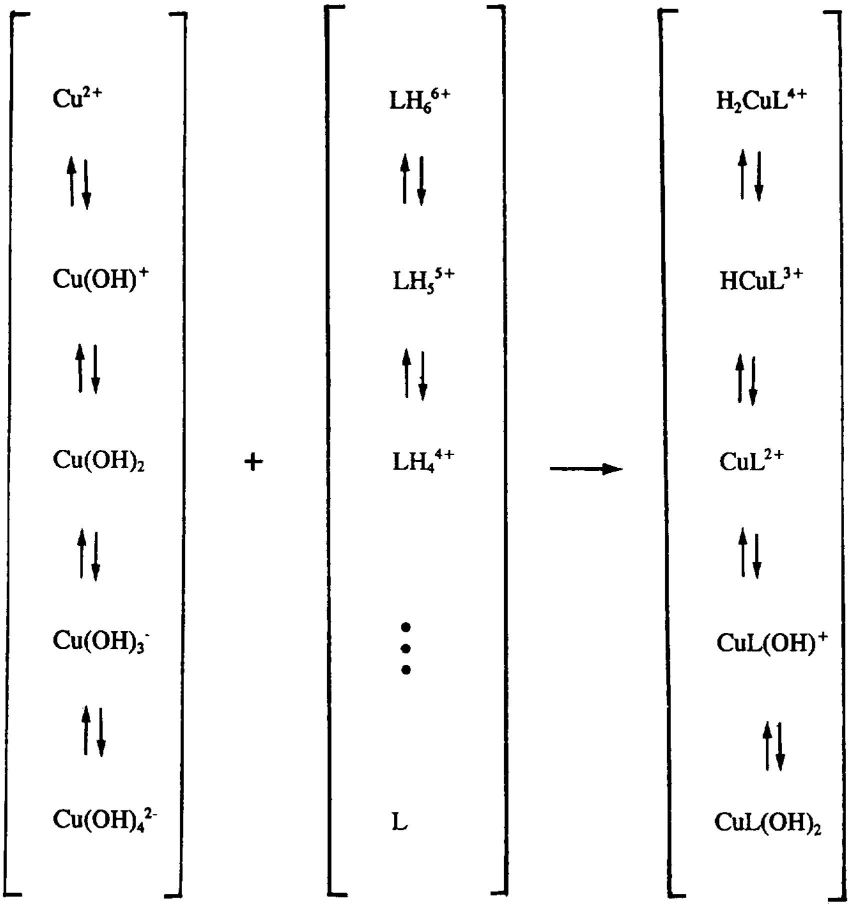
Scheme 1.

RESULTS AND DISCUSSION

The major problem in the study of the kinetics of formation of metal complexes with macrocyclic ligands is the exceedingly large number of species usually involved. Thus, the metal ion hydrolyses to give $M(OH)_x^{(2-x)+}$ species and the ligand protonates to give H_yL^{y+}. Moreover, the metal complex also participates in acid–base equilibria to form protonated species and hydroxo complexes. Scheme 2 illustrates the possibilities for the case of Cu^{II} and a hexaazamacrocycle. The situation is even more complicated when L is a binucleating macrocycle, because of the additional formation of M_2L and binuclear hydroxo complexes.[9] Fortunately, the selection of adequate pH ranges simplifies the problem and leads to valid, although partial, mechanistic conclusions. In this work, the complex formation was studied at high pH to avoid protonation of the ligand and the kinetics of decomposition of the metal complexes was studied using an excess of acid. The results obtained under these conditions are presented below.

Kinetics of decomposition in acid solutions

Equilibrium studies[8] show that Cu^{II}–L complexes are not formed at pH lower than *ca* 2, and so the complexes will decompose in solution when an excess of H^+ is added to decrease the pH to a low enough value. Kinetic studies of these decomposition processes are usually carried out by mixing strongly acidic solutions with a water solution of the solid complex containing the required ionic strength. However, in order to check the possibility of kinetic differences in the decomposition of mononuclear and binuclear complexes and their corresponding protonated and hydroxylated forms, solutions containing Cu^{II} and L with ratios 1 : 1 and 2 : 1 were prepared and the pH adjusted with KOH and HNO_3 to reach values corresponding to the formation of the different species involved in the equilibrium system. These solutions were mixed in the stopped-flow unit with solutions containing an excess of H^+. The kinetics of decomposition was monitored at 650 nm and the values of the rate constant obtained for the only kinetically dis-



Scheme 2.

Table 1. Observed rate constants for the decomposition of Cu–L complexes in acid media at 25 C and 1.0 M KNO_3[a]

M : L ratio	2 : 1				1 : 1	
Starting pH	4.03	6.01	8.08	10.35	5.83	11.70
$[H^+]$			k_{obs} (s^{-1})			
0.0125	20	19	17	14	16	17
0.0250	22	24	21	17	21	18
0.0500	33	30	26	28	26	34
0.1000	44	33	37	32	29	36
0.2000	58	52	46	52	48	56
0.4000	84	72	68	71	68	66
0.6000	100	84	75	80	77	76
0.8000	99	86	88	91	82	90
1.0000	103	92	89	96	93	105

[a] The concentration of Cu–L complexes was 5.0×10^{-4} M.

tinguishable step are included in Table 1. The results can be considered to be almost coincident for all the pH and metal : ligand ratios, showing that binuclear complexes convert rapidly to mononuclear species and that all the acid–base equilibria involving H_xML complexes are also rapid. So, the rate-determining step must be associated with the decomposition of the most acidic mononuclear species. According to equilibrium studies,[8] this species is H_2ML, which probably has a structure close to that shown in Scheme 1.

All the sets of values in Table 1 can be fitted to eq. (2) and the mean values for the parameters in the six series are $a = 14.6 \pm 2.2$, $b = 311 \pm 76$ and $c = 2.38 \pm 0.62$:

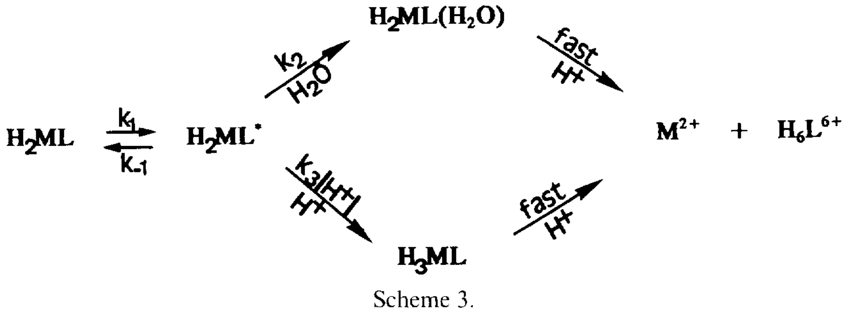
$$k_{obs} = \frac{a + b[H^+]}{1 + c[H^+]}. \qquad (2)$$

These results can be rationalized assuming the mechanism proposed by Margerum *et al.*[3] for the decomposition of metal chelates and widely discussed by Lan and Chung[10,11] for the case of Cu^{II} with linear and macrocyclic polyamine ligands. In this mechanism, one nitrogen dissociates from the metal ion without its replacement by a solvent molecule, resulting in the formation of an activated intermediate H_2ML^* susceptible to attack by the solvent or a proton, as shown in Scheme 3. Once the first nitrogen is completely released from the Cu^{II} coordination sphere all the following steps leading to complete decomposition occur rapidly. If the activated intermediate is formed under steady-state conditions, the rate law corresponding to this mechanism is eq. (3), which is equivalent to eq. (2) and so the values of a, b and c can be used to obtain the constants in Scheme 3:

$$k_{obs} = \frac{k_1 k_2 + k_1 k_3 [H^+]}{k_{-1} + k_2 + k_3 [H^+]}. \qquad (3)$$

Thus $k_1 = b/c = 131\ s^{-1}$, $k_3/k_2 = b/a = 21.3\ M^{-1}$ and $k_{-1}/k_2 = [b/(ac)] - 1 = 7.95$.

The value of k_1 has been proposed[11] to depend mainly on the number and size of chelate rings affected by nitrogen dissociation and so it must be close to the value found for the complex of the chelating polyamine 1,4,7,10-tetraazadecane,[12] i.e. 160.3 s^{-1}. Macrocyclic complexes usually have lower k_1 values (0.005–0.5 s^{-1}).[13] On the other hand, the ratio k_3/k_2 represents the relative rates of attack of H_2ML^* by proton and solvent, and its value (21.3 M^{-1}) is closer to those found for other polyazamacrocycles, such as 1,5,9,13-tetraazacyclohexadecane (6.96 M^{-1}),[13] than to the values obtained for complexes with linear polyamines (0–0.7 M^{-1}).[12] Thus, the decomposition of H_2ML can be considered to show a behaviour intermediate between complexes with linear polyamines and polyaza macrocycles. It resembles open-chain polyamines in the lability of the Cu—N bond, but the presence of coordinated and uncoordinated macrocyclic fragments makes the entry of a water molecule into the coordination sphere difficult and results in predominant decomposition through the protonation pathway in Scheme 3, as found for complexes with other macrocycles. The fast con-



Scheme 3.

Table 2. Observed rate constants for the formation of Cu–L complexes in basic solutions at 25°C and 1.0 M KNO_3[a]

$[OH^-]$	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45
$10^4[L]_0$					k_{obs} (s^{-1})				
1.0	152	137	—	—	—	—	—	—	—
1.4	—	202	—	120	—	—	—	—	—
1.6	267	213	—	—	—	—	—	—	—
1.8	300	258	—	—	—	—	—	—	—
2.0	322	292	185	—	135	—	115	126	102
2.5	—	—	256	242	186	132	154	154	125
3.2	—	—	338	277	222	167	206	191	176
4.0	—	—	401	334	265	201	245	216	204
5.0	—	—	—	—	380	293	292	—	240
10^{-6} k $(M^{-1} s^{-1})$[b]	1.74	1.52	1.08	0.81	0.77	0.63	0.58	0.45	0.47
10^{-6} k $(M^{-1} s^{-1})$[c]	1.58	1.48	1.07	0.88	0.79	0.62	0.63	0.57	0.54

[a] $[Cu]_0$ was 4.0×10^{-5} M except for experiments with $[OH^-] < 0.20$ M which were carried out using $[Cu^{2+}]_0 = 2.0 \times 10^{-5}$ M.

[b] These values for the second-order rate constant k were derived from k_{obs} *vs* $[L]_0$ plots.

[c] These values for k were obtained using eq. (1).

version of binuclear complexes in mononuclear species warrants additional comments. In solutions with metal : ligand ratios of 2 : 1, complexes exist mainly as M_2L and μ-hydroxo-bridged dimers[8] depending on the pH. Proton attack on the OH^- bridges will result in rapid conversion to M_2L which will decompose rapidly to avoid electrostatic repulsions between two close Cu^{2+} centres.

Kinetics of formation in highly basic media

The kinetics of formation of Cu^{II}–L complexes has been studied in highly basic solutions at 25°C and 1.0 M KNO_3 by following the absorbance changes observed at 260 nm. Under these conditions, Cu^{II} exists as an equilibrium mixture of $Cu(OH)_3^-$ and $Cu(OH)_4^{2-}$,[1,2,14] and the ligand L is completely deprotonated.[8] The OH^- concentration was changed from 0.05 to 0.45 M and experiments were carried out using different concentrations of Cu^{II} and L. Table 2 shows the rate constants obtained by fitting the curves corresponding to experiments using an excess of ligand to a single exponential. For all the nine $[OH^-]$ used, k_{obs} increases linearly with the concentration of the ligand and the data can be satisfactorily fitted to $k_{obs} = k[L]_0$ to obtain the second-order rate constants, k. However, pseudo-first-order conditions cannot be considered to be valid in some experiments and for this reason, the table also includes the values of k obtained with eq. (1). In general, there is a satisfactory agreement between both sets of k values, although those included in the last entry of Table 2 are more significant and will be used in the discussion below. Table 2 shows clearly that the values of k decrease with increasing $[OH^-]$ and, as shown in Fig. 1, there is an inverse relationship that can be represented by eq. (4) with $a = 4.48 \times 10^{-7}$ M s and $b = 3.30 \times 10^{-6}$ s:

$$\frac{1}{k} = a + b[OH^-]. \tag{4}$$

It is important to note that there are no sig-

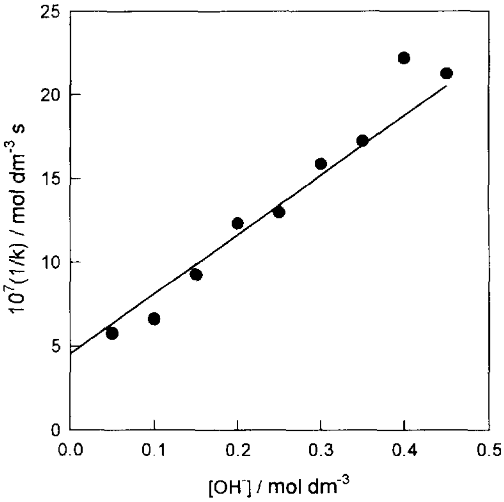


Fig. 1. Dependence of $1/k$ with the concentration of OH^- for the formation of Cu–L complexes in highly basic solutions.

nificant absorbance changes occurring at longer times and that results were similar for experiments with an excess of metal (formation of ML_2 species according to the stability data) and for experiments with ligand excess (formation of ML complexes), suggesting that the entry of the second metal ion in the macrocycle cavity is fast and the rate-determining step is formation of the mononuclear species.

Scheme 4 shows the mechanism usually proposed in the literature[1,2] for the formation of Cu^{II} complexes under basic conditions and the corresponding rate law is given in eq. (5)

$$k_{obs} = \frac{k_3 + k_4 K_{OH}[OH^-]}{1 + K_{OH}[OH^-]}. \qquad (5)$$

If we assume that $k_3 \gg k_4 K_{OH}[OH^-]$ and take the inverse of eq. (4), then

$$\frac{1}{k_{obs}} = \frac{1}{k_3} + \frac{K_{OH}}{k_3}[OH^-] \qquad (6)$$

and identification of coefficients in eqs (4) and (6) leads to $k_3 = (2.2 \pm 0.2) \times 10^6$ M^{-1} s^{-1} and $K_{OH} = 8 \pm 1$ M^{-1}. The value obtained for K_{OH} is in excellent agreement with those previously determined from equilibrium studies[1,15] and k_3 is close to the values reported[1,2] for complex formation with other polyamine ligands. If the data in Table 2 are fitted to eq. (5) using a non-linear least-squares procedure, no significant improvement is observed in the quality of the fit, i.e. the formation of complexes occurs essentially from $Cu(OH)_3^-$. This result is in agreement with studies with other ligands[1] that show that the rate of complex formation from $Cu(OH)_4^{2-}$ can be about 400 times slower than from $Cu(OH)_3^-$. The value of k_3 is very close to those obtained for linear tetraamines (3.0×10^6 M^{-1} s^{-1}) and cyclam (2.7×10^6 M^{-1} s^{-1})[1] and according to previous interpretation,[1] the rate-determining step in the formation of CuL complexes would be Jahn–Teller inversion following the formation of the first Cu—N bond. Thus, the structure of the macrocycle does not create important steric interactions that would lead to a change of the rate-determining step to Jahn–Teller inversion following the formation of the second Cu—N bond, as observed for the case of highly substituted linear tetraamines[1,2,16] and polymethylated derivatives of cyclam.[17] Moreover, in this case, the macrocycle seems to be flexible enough to accommodate the second metal ion in a fast process.

CONCLUSION

The data presented in this paper can be used as a first approximation for understanding the kinetic effects associated with the coordination and release of a second metal ion to a macrocyclic ligand that already contains a metal centre. Possible effects caused by coordination of the added anion electrolyte (KNO_3) are reduced to a minimum because the stability of the Cu^{II}–NO_3^- complex is very low ($\log K = -0.01$ at 1.0 M ionic strength).[18] Although it is clearly necessary to obtain experimental data for related systems, some conclusions can be advanced at this point. Thus, addition of a large excess of H^+ causes decomposition of all mono- and binuclear complexes, but the process is kinetically controlled by decomposition of mononuclear species. The fast conversion of binuclear complexes into mononuclear ones is probably a consequence of the rapid attack of H^+ on a bridging OH^- and the subsequent release of one Cu^{II} to avoid the strong electrostatic repulsions operating between two close dipositive ions. Actually, it is well known that macrocyclic binuclear complexes have a strong tendency to form OH^- bridges to avoid these repulsions.[8,9,19]

At very high pH, the kinetics of formation of mononuclear complexes with the binucleating macrocycle is similar to that observed with linear polyamines and mononucleating macrocycles. Binuclear complexes are formed rapidly by attack of $Cu(OH)_3^-$ on CuL^{2+}. The acceleration observed

$$Cu(OH)_3^- \quad + \quad OH^- \quad \overset{K_{OH}}{\rightleftharpoons} \quad Cu(OH)_4^{2-}$$

$$Cu(OH)_3^- \quad + \quad L \quad \xrightarrow{k_3} \quad CuL(OH)_x^{(2-x)+}$$

$$Cu(OH)_4^{2-} \quad + \quad L \quad \xrightarrow{k_4} \quad CuL(OH)_x^{(2-x)+}$$

Scheme 4.

for the coordination of the second Cu^{II} is probably favoured for electrostatic reasons and by enhanced stabilization of the OH-bridged reaction product.

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