Formation and dissociation kinetics of dinuclear metal complexes with pyrazole and triazole bridged bis-macrocycles

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The kinetics of dissociation and formation of the dinuclear Cu^{2+} and Ni^{2+} complexes with L^1 and L^2 have been measured by stopped-flow technique. Whereas the rates of dissociation of the two metal ions from the dinuclear species are very similar, the two steps of the formation of the dinuclear complexes differ by about a factor of 100, indicating that the coordination of the first metal ion strongly influences the binding of the second one.

Introduction

The interest in dinuclear metal complexes has been continuously growing because of their relevance as models for metalloenzymes containing two active metal centres[1] and because of their chemical and physical properties due to the proximity of the two metal ions, which thus can interact.[2] Structural, thermodynamical, spectral and magnetic properties of such systems have been studied in great detail,[3] whereas much less is known about their kinetics of formation and dissociation. Are dinuclear complexes formed in a similar way as mononuclear ones? Do cooperative effects play a role in their formation and dissociation or is the process governed by statistics?

In the literature a few examples of the kinetics of formation and dissociation are found. A study of the complexation kinetics of Cu^{2+} with two homoditopic bis-macrocycles[4] showed that these ligands incorporate Cu^{2+} in a sequential two step process of rates which do not drastically differ from each other. The rates were dependent on the protonation degree of the macrocycles, but not on the presence or absence of a metal ion in one of the rings. The two macrocyclic parts of the ligand behave independently of each other. In contrast a heteroditopic bis-macrocycle gave selectively a stable 1 : 1 intermediate,[4] which had a low reactivity towards the incorporation of a second Cu^{2+} ion. Because of the different nature of the binding sites this could be expected.

In another study the dissociation and formation of Cu^{2+} complexes of a large macrocycle, which can accommodate two Cu^{2+} ions inside its cavity, was measured.[5] The dissociation is governed by the decomposition of the mononuclear species, which is rapidly formed by protonation of the dinuclear complex. The formation in strongly alkaline solution is a two-step reaction, whereby the second Cu^{2+} is very rapidly complexed. The group of Basallote[6] published a paper on the complex formation of the dinuclear Cu^{2+} complex with a hexaaza macrocycle having a large cavity. In this case they found that there is no significant effect of the first metal ion on the rate of coordination of the second one, the complexation being statistically controlled. Similarly the dissociation kinetics of the dinuclear Cu^{2+} complex shows that the value for the dissociation of the first Cu^{2+} is twice as large as that of the second one. The kinetics of complexation and dissociation of the same hexaaza macrocycle with Ni^{2+} was also studied.[7] At neutral pH the complexation occurs in a single step, which indicates that here the binding of the metal ions is statistically controlled.

Our equilibrium studies on L^1 [8] and L^2 [8,9] showed that these ligands are able to form mono- and dinuclear species. In the dinuclear complexes the deprotonated heterocyclic base bridges the two metal ions so that the two metal centres, in contrast to the complexes described above, interact strongly.[9] It was therefore interesting to study the formation and dissociation of such

a system in order to find out whether a statistical complexation takes place or not.
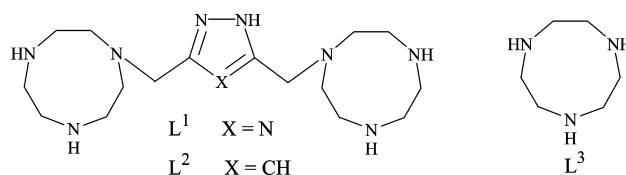
Experimental

Complex dissociation kinetics

The experiments were carried out at 25.0 ± 0.1 °C using a *KinTec Minimixer* stopped-flow instrument with a 2 cm cuvette, connected to a *J&M Tidas MMS16 VIS500/1* photodiode array with a range 300–1000 nm. The spectra were recorded with the program *Kinspec235*.[10] Typical concentrations of the complexes were: 7.50×10^{-4}–1.5×10^{-3} M, the acid solutions consisted of different concentrations of nitric acid and KNO_3 with a ionic strength of $I = 0.5$ M. The rate constants of the single experiments were calculated with the program *SPECFIT*.[11] The pH dependencies were fitted using the non-linear least-squares program *Microcal Origin 6.0*.[12]

Complex formation kinetics

All experiments were carried out at 25.0 ± 0.1 °C using a *Durrum D110* stopped-flow instrument with a 2 cm cuvette. The ionic strength of the solution was adjusted for all measurements to the desired value of $I = 0.5$ M by adding the required amount of KNO_3 in the case of Cu^{2+} and $NaClO_4$ in the case of Ni^{2+}. The data were stored on a personal computer and treated with the program *Labview 5.0*.[13] All experiments were carried out under pseudo-first order conditions. Reported values of the rate constants correspond to the mean value of at least four determinations. To obtain the rate law of the complex formations pH dependencies at a given metal concentration and dependencies on the metal concentration at a given pH-value were measured. Typical conditions for the Cu^{2+} measurements were: $[LH_4^{4+}] = 8.25 \times 10^{-4}$–$1.65 \times 10^{-3}$ M (with L = L^1, L^2), or $[CuL^2H_2]^{4+} = 8.25 \times 10^{-4}$–$1.65 \times 10^{-3}$ M mixed with $[Cu^{2+}] = 8.25 \times 10^{-3}$–$1.65 \times 10^{-2}$ M, pH = 2.7–4.5, using 2,6-lutidine-3-sulfonic acid[14] and piperazine-N,N'-bis(4-butane sulfonic acid)[15] as buffers (c[buffer] = 0.1 M), $\lambda = 648$ nm for L^1 and 650 nm for L^2. Typical conditions for the Ni^{2+} measurements were: $[L^2H_4^{4+}] = 5 \times 10^{-4}$ M mixed with $[Ni^{2+}] = 5 \times 10^{-3}$–$1 \times 10^{-2}$ M, pH = 5.2–6.2, using 2-morpholino ethane sulfonic acid[15] as a non-coordinating buffer (c[buffer] = 0.1 M), $\lambda = 260$ nm. The wavelength was selected in each case from preliminary spectral scanning experiments using an *ATI Unicam UV4* spectro-

photometer. The single-wavelength curves, the metal dependencies and the pH dependencies were fitted using the non-linear least-squares program *Microcal Origin 6. 0.*[12]

Results and discussion

Dissociation kinetics of the Cu²⁺ complexes

The acid promoted dissociation of the two dinuclear complexes $[Cu_2LH_{-1}]^{3+}$ (L = L^1 or L^2), which exist at pH > 5 in a 2 : 1 Cu^{2+}/ligand ratio is a monophasic process, which can be fitted with one exponential. This can mean that either the dissociation of the first metal ion is rate determining, or that the first metal ion rapidly dissociates in a preequilibrium and the dissociation of the second is responsible for the slow process, or that both metal ions dissociate at similar rates. To find out which of the three possibilities is the correct one we also measured the acid dissociation of the 1 : 1 species $[CuLH]^{3+}$ under similar conditions and found that the rates of this reaction are practically equal to those of the 2 : 1 species. Thus the first possibility cannot be correct since we expect that the 1 : 1 species is formed as an intermediate.

From a comparison of the amplitudes of the exponentials used to fit the dissociation of the 2 : 1 and 1 : 1 species we can also exclude the second possibility, since just after mixing the 2 : 1 complex with acid we have an absorptivity, which is twice that of the 1 : 1 species. This means that in the case of the 2 : 1 species there cannot be a rapid preequibrium to give the 1 : 1 complex. The last possibility mentioned above is thus the only one, which remains: the two metal ions dissociate at very similar or equal rates. The observed rate constants k_{obs} for the dissociation of the 1 : 1 and 2 : 1 complexes are dependent on [H⁺] (Fig. 1) and can be fitted with eqn. (1).

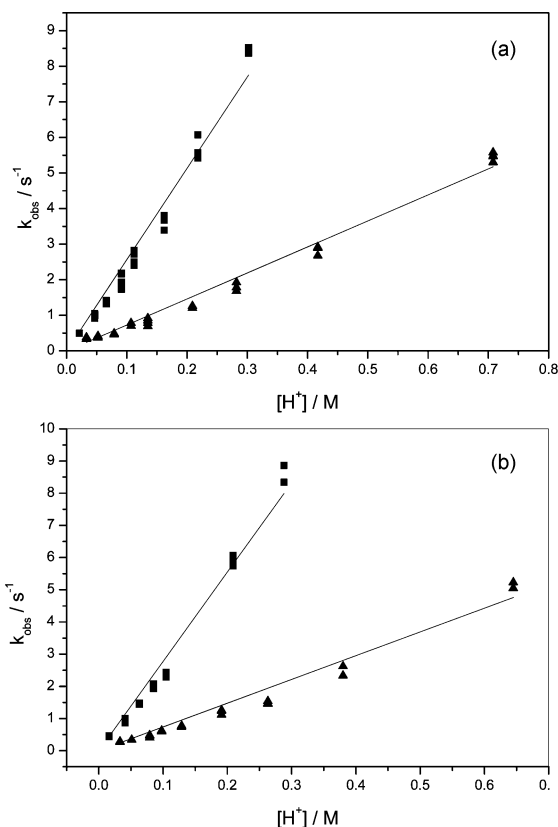$$k_{obs} = k_H[H^+] \qquad (1)$$

Fig. 1 Plots of the observed rate constant k_{obs} *vs.* the [H⁺] concentration for the acid promoted dissociation (a) of the 1 : 1 Cu²⁺ complexes $[CuLH]^{3+} = 0.5–1.0 \times 10^{-3}$ M with L^1 (■) and L^2 (▲) and (b) of the 2 : 1 Cu²⁺ complexes $[Cu_2LH_{-1}]^{3+} = 0.5–1.0 \times 10^{-3}$ M, (—) calculated curves with eqn. (1).

Table 1 Dissociation rate constants of the 2 : 1 and 1 : 1 Cu²⁺ complexes with L^1 and L^2 as well as of the 1 : 1 Cu²⁺ complex with L^3 at $I = 0.5$ M and 25 °C

Cu²⁺ complex	k_H/mol⁻¹ dm³ s⁻¹
$[Cu_2L^1]^{4+}$	27.7 ± 0.6
$[CuL^1H_2]^{4+}$	25.7 ± 0.5
$[Cu_2L^2]^{4+}$	7.4 ± 0.2
$[CuL^2H_2]^{4+}$	7.3 ± 0.1
$[CuL^3]^{2+}$	34.5[a]

[a] Ref. 16.

The so obtained values for k_H are given in Table 1 together with the value of the dissociation of the 1 : 1 complex of Cu²⁺ with 1,4,7-triazacylononane (L^3).

The results can be interpreted by using the species distribution diagrams given in the literature.[8,9] In the case of the 1 : 1 complex we start at pH ~ 5 with $[CuLH]^{3+}$ (Fig. 2a) which reacts to $[CuLH_2]^{4+}$ at pH < 2 after mixing with acid. This is the species, which dissociates reacting with a proton (eqn. (2)).
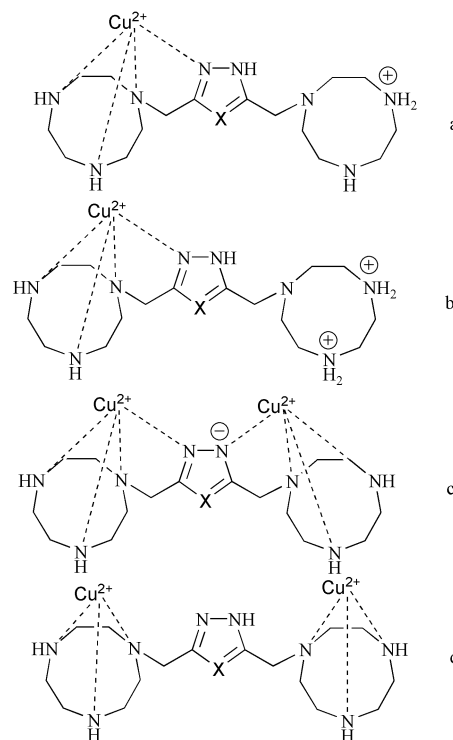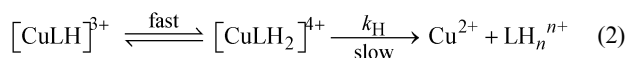
$$\left[CuLH\right]^{3+} \xrightleftharpoons{\text{fast}} \left[CuLH_2\right]^{4+} \xrightarrow[\text{slow}]{k_H} Cu^{2+} + LH_n^{n+} \qquad (2)$$

Fig. 2 Structures of (a) $[CuLH]^{3+}$, (b) $[CuLH_2]^{4+}$, (c) $[Cu_2LH_{-1}]^{3+}$ and (d) $[Cu_2L]^{4+}$.

The equilibrium between $[CuLH]^{3+}$ and $[CuLH_2]^{4+}$ is fast since it involves the protonation of one additional nitrogen of the noncoordinated 1,4,7-triazacyclononane ring. The structure of $[CuLH_2]^{4+}$ consists of a Cu²⁺ coordinated to one of the 1,4,7-triazacyclononane rings (perhaps with a weak interaction with the heterocyclic base) and a doubly protonated 1,4,7-triazacyclononane moiety, which does not bind to Cu²⁺ (Fig. 2b). Thus the dissociation should be similar to that of the Cu²⁺ complex with L^3.[16] A comparison of the k_H values (Table 1) shows that this indeed is the case for the triazole derivative L^1, whereas the pyrazole bridged ligand L^2 reacts about five times slower than L^3.

For the 2 : 1 species we start with $[Cu_2LH_{-1}]^{3+}$ (Fig. 2c), which reacts to $[Cu_2L]^{4+}$ after mixing with acid at pH < 2. Its structure (Fig. 2d) shows two Cu²⁺ ions coordinated to the two

macrocyclic moieties. This species reacts with protons to give the products (eqn. (3)).

$$\left[Cu_2LH_{-1}\right]^{3+} \xrightarrow{\text{fast}} \left[Cu_2L\right]^{4+} \xrightarrow[\text{slow}]{k_H} 2Cu^{2+} + LH_n^{n+} \quad (3)$$
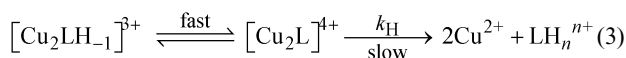
Therefore again the dissociation of a Cu^{2+}-1,4,7-triaza-cyclononane unit is the slow step and should be similar to the reaction of $[CuLH_2]^{4+}$ (Table 1).

Formation of the Cu^{2+} complex with L^1

The kinetics of complex formation of ligand L^1 with Cu^{2+} was measured under *pseudo*-first order conditions using a tenfold excess of Cu^{2+} over ligand. At fixed pH one observes a biphasic absorbance/time curve, which was fitted with eqn. (4).

$$A = A_1 e^{-k_{1,\text{obs}}t} + A_2 e^{-k_{2,\text{obs}}t} + A_3 \quad (4)$$

This implies that the formation of the 2 : 1 species consists of two steps in which first a 1 : 1 complex is formed followed by the incorporation of the second Cu^{2+}. In fact both $k_{1,\text{obs}}$ and $k_{2,\text{obs}}$ are proportional to the $[Cu^{2+}]$ concentration (Fig. 3).
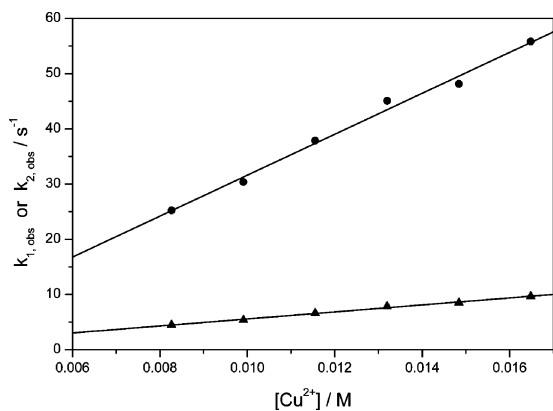

Fig. 3 Dependence of $k_{1,\text{obs}}$ and $k_{2,\text{obs}}$ from the Cu^{2+} concentration for the first (●) and second step (▲) of the formation of the dinuclear complex with L^1. $[L]_{\text{tot}} = 8.25 \times 10^{-4}$ M, pH = 2.93, (—) calculated curves as best straight lines.

In addition the rates of the two steps are also a function of the $[H^+]$ concentration. The $[H^+]$ dependence of the first step (Fig. 4) can be explained and fitted, if one takes into account the different reactivities of the protonated species of the ligand.
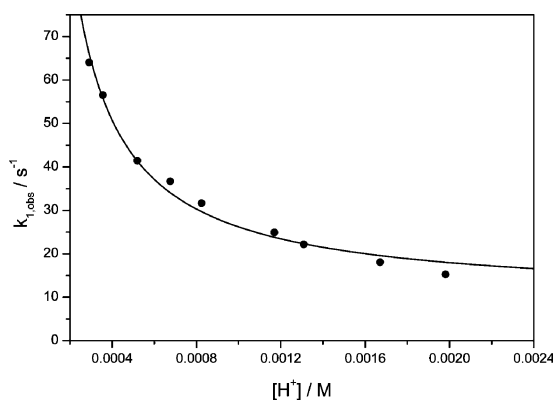

Fig. 4 $k_{1,\text{obs}}$ as a function of the $[H^+]$ concentration for the first step of the formation of the dinuclear complex with L^1. $[L]_{\text{tot}} = 8.25 \times 10^{-4}$ M, $[Cu^{2+}] = 8.25 \times 10^{-3}$ M. (●) exp., (—) calculated curve with eqn. (7).

In the pH-range studied only the species LH_4^{4+} and LH_3^{3+} are present.[8] The best fit was obtained with a model (eqn. (5)), which takes into consideration that both LH_4^{4+} and LH_3^{3+} are

reactive and that a fast equilibrium (K_1) between with LH_4^{4+} and LH_3^{3+} exists.

$$(5)$$
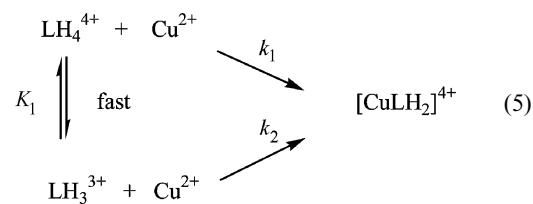
From eqn. (5) the rate of the first step can be written under *pseudo*-first order conditions as eqn. (6)

$$v = k_1[LH_4^{4+}] + k_2[LH_3^{3+}] = k_{1,\text{obs}}[L]_{\text{tot}} \quad (6)$$

from which eqn. (7) can be derived

$$k_{1,\text{obs}} = \frac{K_1 k_2 + k_1[H^+]}{K_1 + [H^+]} \quad (7)$$

The experimental points of Fig. 4 were fitted with eqn. (7) taking $K_1 = 1.26 \times 10^{-6}$ from the literature[8] as a fixed value and varying k_1 and k_2 to obtain the best non-linear fit. We get $k_1 = (9.7 \pm 1.2)$ s^{-1} and $k_2 = (1.31 \pm 0.05) \times 10^4$ s^{-1} at $[Cu^{2+}] = 8.25 \times 10^{-3}$ M, which allows one to calculate the second order constants $k_{LH_4} = (1.2 \pm 0.1) \times 10^3$ mol^{-1} dm^3 s^{-1} and $k_{LH_3} = (1.58 \pm 0.08) \times 10^6$ mol^{-1} dm^3 s^{-1} (Table 2).

The second step of the reaction is also dependent on the $[H^+]$ concentration (Fig. 5) and can be described by eqn. (8), where $[CuLH_2]^{4+}$ is the major species,[8]
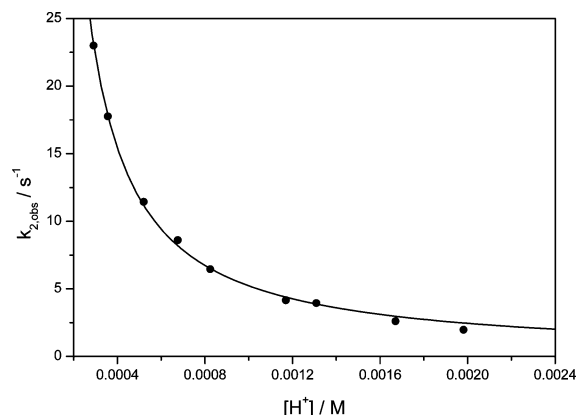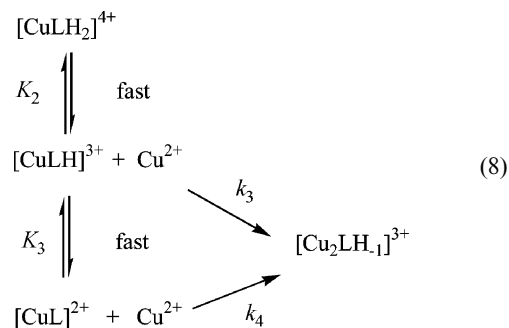

Fig. 5 $k_{2,\text{obs}}$ as a function of the $[H^+]$ concentration for the second step of the formation of the dinuclear Cu^{2+} complex with L^1. $[L]_{\text{tot}} = 8.25 \times 10^{-4}$ M, $[Cu^{2+}] = 8.25 \times 10^{-3}$ M. (●) exp., (—) calculated curve with eqn. (8).

$$(8)$$

but is in a rapid equilibrium with $[CuLH]^{3+}$ (K_2) and $[CuL]^{2+}$ (K_3), which both can react with the second Cu^{2+}. From the scheme the rate of the reaction can be written as eqn. (9), from

$$v = k_3[CuLH]^{3+} + k_4[CuL^{2+}] = k_{2,\text{obs}}[CuL]_{\text{tot}} \quad (9)$$

Table 2 Rate constants (mol^{-1} dm^3 s^{-1}) of the formation of the Cu^{2+} and Ni^{2+} complexes with ligands L^1, L^2, and L^3 at $I = 0.5$ M and 25 °C

Ligand	M^{2+}	k_{LH_4}	k_{LH_3}/k_{LH}[a]	k_{MLH}	k_{ML}
L^2	Cu^{2+}	—	$\geq 1 \times 10^6$	$(2.1 \pm 0.06) \times 10^4$	—
L^1	Cu^{2+}	$(1.2 \pm 0.1) \times 10^3$	$(1.58 \pm 0.08) \times 10^6$	$(2.9 \pm 0.1) \times 10^4$	$(1.7 \pm 0.2) \times 10^7$
L^2	Ni^{2+}	—	$(1.84 \pm 0.02) \times 10^2$	—	—
L^3	Cu^{2+}	—	$2.35 \times 10^{6\,a}$	—	—

[a] Ref. 16.

$$k_{2,obs} = \frac{K_2 K_3 k_4 + K_2 k_3 [H^+]}{K_2 K_3 + K_2 [H^+] + [H^+]^2} \qquad (10)$$

which eqn. (10) results, which was used to fit the data of Fig. 5. $K_2 = 1.90 \times 10^{-5}$ and $K_3 = 2.88 \times 10^{-7}$ were taken from previous equilibrium measurements[8] and the fitting gave $k_3 = 240 \pm 10$ s^{-1} and $k_4 = (1.4 \pm 0.1) \times 10^5$ s^{-1} at [Cu^{2+}] = 8.25×10^{-3} M. These values can be transformed into the second order rate constants $k_{CuLH} = (2.9 \pm 0.1) \times 10^4$ mol^{-1} dm^3 s^{-1} and $k_{CuL} = (1.7 \pm 0.2) \times 10^7$ mol^{-1} dm^3 s^{-1} (Table 2).

Formation of the Cu^{2+} complex with L^2

Under *pseudo* first-order conditions, the concentration/time curves of the complexation reaction between Cu^{2+} and L^2 exhibit a biphasic process (eqn. (4)). The first exponential was necessary to fit the data, but difficult to reproduce, since the amplitude A_1 was relatively small and the rate constant $k_{1,\,obs}$ relatively high. At higher pH-values (pH > 4.4) the reaction could be fitted with only one exponential since the first step became too fast to be measured. The observation of a biphasic reaction induced us to believe that the two steps correspond to the first and second incorporation of Cu^{2+} into L^2.

To prove it we studied the kinetics of the reaction between the already formed 1 : 1 complex [CuLH$_2$]$^{4+}$ and Cu^{2+}. The experimental data of this reaction can be fitted with one exponential. The amplitude change for this reaction ($A = -0.22$) is nearly identical with the amplitude change of the second reaction step ($A_2 = -0.23$) starting from the free ligand. Because of this we assume that the second reaction step observed starting from the free ligand corresponds to the incorporation of the second Cu^{2+} into the mononuclear complex [CuLH$_2$]$^{4+}$, which is an intermediate in the formation of the dinuclear species [Cu$_2$LH$_{-1}$]$^{3+}$. The faster first step of the reaction of the free ligand with Cu^{2+} corresponds to the incorporation of a first Cu^{2+} into the free ligand ($k_{1,obs}$).

For the second step of the reactions between the ligand and Cu^{2+} as well as for that between [CuLH$_2$]$^{2+}$ and Cu^{2+} the rate constants $k_{2,obs}$ and k_{obs}, respectively, are linearly dependent on the Cu^{2+} concentration (Fig. 6), which shows that the incorporation of Cu^{2+} into the mononuclear complex is first order with respect to the metal concentration and the concentration of the 1 : 1 complex.

The pH-dependence was investigated in a pH-range between 3.14 to 4.41. The rate constants for both reactions give the same dependence on the [H$^+$] concentration, one additional proof that they belong to the same chemical process (Fig. 7).

The scheme previously proposed (eqn. (8)) can be fitted to the experimental points. In this case eqn. (10), using the literature values[9] $K_2 = 1.60 \times 10^{-7}$, and $K_3 = 7.94 \times 10^{-7}$, gives $k_3 = (350 \pm 10)$ s^{-1} for [Cu^{2+}] = 1.65×10^{-2} M so that $k_{CuLH} = (2.1 \pm 0.06) \times 10^4$ mol^{-1} dm^3 s^{-1} results (Table 2), whereas k_4 could not be determined.

Formation of the Ni^{2+} complex with L^2

The kinetics of the complexation of L^2 with Ni^{2+} was measured at 260 nm and the concentration time curves could be explained with one exponential. Since the UV band at 260 nm is strongly affected by the complexation of the first Ni^{2+}, but practically
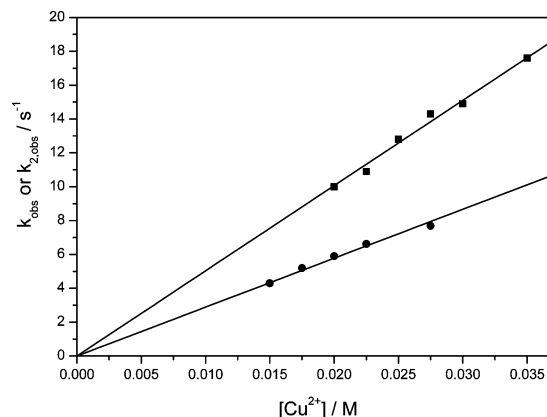

Fig. 6 Plots of the observed rate constants of the second step $k_{2,obs}$ (■) of the formation of the dinuclear Cu^{2+} complex with L^2 ([L]$_{tot}$ = 2×10^{-3} M, pH = 4.41) and of the complexation of the 1 : 1 complex with a second Cu^{2+}. (k_{obs} (●)), [CuL]$_{tot}$ = 1.5×10^{-3} M, pH = 4.19, (—) calculated curves as best straight lines.

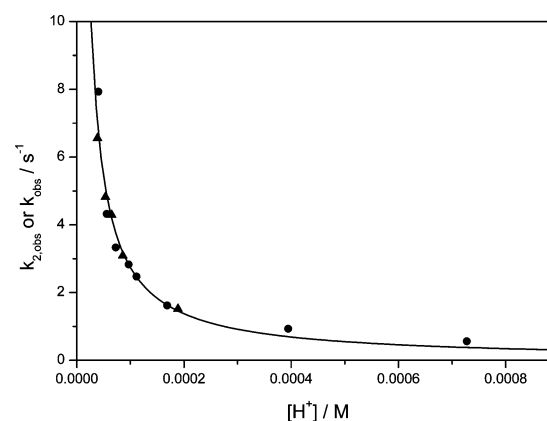**Fig. 7** Plots of $k_{2,\,obs}$ (●) and $k_{1,\,obs}$ (▲) as a function of the [H$^+$] concentration for the complexation of Cu^{2+} with L^2, [L]$_{tot}$ = 1.65×10^{-3} M, [Cu^{2+}] = 1.65×10^{-2} M, as well as [CuL]$_{tot}$ = 1.65×10^{-3} M, [Cu^{2+}] = 1.65×10^{-2} M, (—) calculated curves with eqn. (8).

does not change when the second Ni^{2+} coordinates, it is not surprising that we have only one exponential describing the incorporation of Ni^{2+}. The *pseudo* first order rate constant k_{obs} is proportional to the Ni^{2+} concentration (Fig. 8) and depends on the [H$^+$] concentration (Fig. 9).

As in the case of the Cu^{2+} complex the possible reactive species in the pH region studied are LH$_4^{4+}$ and LH$_3^{3+}$. The fitting using eqn. (7) gave $k_1 = 0$ indicating that LH$_4^{4+}$ is not reactive. Only k_2 could be determined as 0.92 ± 0.01 s^{-1} at [Ni^{2+}] = 5×10^{-3} from which the second order rate constant k_{LH_3} was calculated (Table 2). Again $K_1 = 8.32 \times 10^{-7}$ was taken from the literature.[8]

General discussion

The dissociation of the dinuclear complexes [Cu$_2$LH$_{-1}$]$^{3+}$ (L^1 and L^2) proceeds in two steps having very similar rate constants. In contrast to many of the dinuclear systems studied before the two Cu^{2+} in L^1 and L^2 are bridged by the anion of the heterocyclic base (Fig. 2c), so that they can interact with each other,
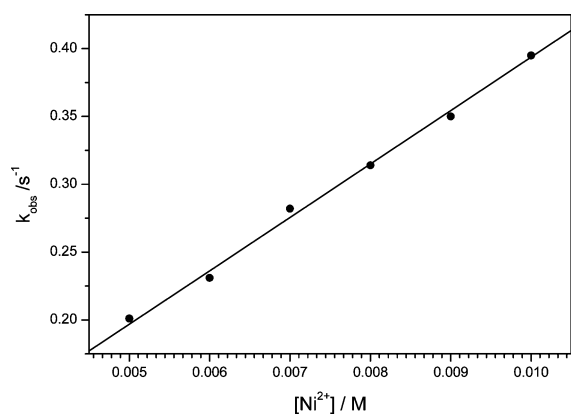
Fig. 8 Plot of k_{obs} as a function of the $[Ni^{2+}]$ concentration for the formation of the dinuclear Ni^{2+} complex with L^2. $[L]_{tot} = 5 \times 10^{-4}$ M, pH = 5.49. (●) exp., (—) calculated curve as best straight line.
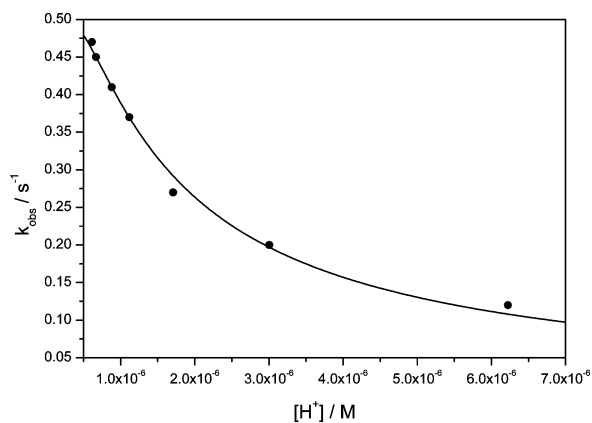

Fig. 9 Plot of k_{obs} as a function of the $[H^+]$ concentration for the formation of the dinuclear Ni^{2+} complex with L^2. $[L]_{tot} = 5 \times 10^{-4}$ M, $[Ni^{2+}] = 5 \times 10^{-3}$ M. (●) exp., (—) calculated curve with eqn. (7).

and this could be of importance for a stepwise dissociation with different rates. However, there is a fast protonation equilibrium before the rate-determining step. This turns off the influence of the heterocyclic bridge so that the two metal ions become practically independent of each other. It is therefore logical that they also react at very similar rates. The values for k_H (Table 1) obtained for L^1 and L^2 compare well to the value obtained for the dissociation of the Cu^{2+} complex with 1,4,7-triazacyclononane (L^3)[16] indicating that the rate determining step is the dissociation of this complex also with our ligands.

A comparative discussion of the results for the complex formation (Table 2) allows one to determine the factors which govern the kinetics in the two steps. In all instances the degree of protonation of the ligand or that of the 1 : 1 intermediate are of paramount importance for the reactivity. Therefore LH_4^{4+}, which carries two protons in each triazacyclononane ring is about 10^3 times less reactive than LH_3^{3+}, which has one mono- and one diprotonated ring. The high density of positive charges in LH_4^{4+} makes it difficult for Cu^{2+} to react, whereas in LH_3^{3+} the monoprotonated ring seems from an electrostatic point of view more ideal for complexation. The k_{LH_3} values compare well with the rate constant $k_{LH} = 2.35 \times 10^6$ mol^{-1} dm^3 s^{-1} (Table 2) obtained for the monoprotonated form of 1,4,7-triazacyclonoane.[16]

In the second step of the formation there is a strong difference in reactivity between $[CuLH]^{3+}$ and $[CuL]^{2+}$. In these species one triazacyclononane ring binds the Cu^{2+}, whereas the other one carries one ($[CuLH]^{3+}$, Fig. 2a) or no ($[CuL]^{2+}$) proton.

Thus $[CuLH]^{3+}$ should react with a rate constant similar to that of the monoprotonated form of 1,4,7-triazacyclononane (k_{LH}) or to that of LH_3^{3+} in our ligands (k_{LH_3}). However, the values are about 10^2 times lower. The presence of Cu^{2+} at one end of the ligand apparently slows down the reaction. This cannot be due only to the two positive charges associated with Cu^{2+}, since in LH_3^{3+} two positive charges are also present in the other unit, but must be due to the fact that Cu^{2+} not only binds to the 1,4,7-triazacyclononane ring, but also weakly to the pyrazole or triazole nitrogen. Therefore the two positive charges of Cu^{2+} come much closer to the reactive site of the ligand than in the case of the two positive charges of the two protons in LH_3^{3+}. Therefore for these ligands the incorporation of the two Cu^{2+} proceeds stepwise, but the binding of the first Cu^{2+} slows down the complexation of the second by a factor of about 100.

The difference in reactivity between Cu^{2+} and Ni^{2+} is well documented in the literature and is due to the different rates of water exchange according to the *Eigen-Wilkins* mechanism.[17] In our case we also observed at least a 5400 times slower complexation, which is comparable to the factor expected from their water exchange rates ($k_{H_2O, Cu}$[18]$/k_{H_2O, Ni}$[19] $= 2 \times 10^8/2.7 \times 10^4 = 7400$).

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