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KINETICS AND MECHANISM OF THE DISSOCIATION OF THE Cu^{2+} AND Ni^{2+} COMPLEXES WITH MONOOXO- AND DIOXOMACROCYCLIC TETRAAMINES

LISELOTTE C. SIEGFRIED AND THOMAS A. KADEN*

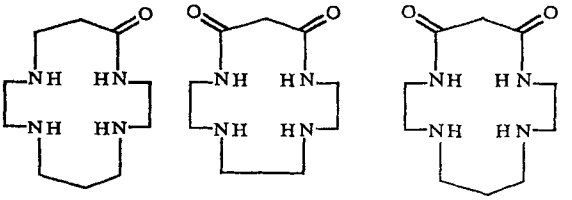
Institut für Anorganische Chemie, Spitalstr. 51, CH-4056 Basle, Switzerland

The kinetics of the acid-induced dissociation of the Ni^{2+} and Cu^{2+} complexes of a monooxo and two dioxo tetraaza macrocycles were studied by stopped-flow spectrophotometry at single wavelengths and using a photodiode array. For the monooxo derivative the dissociation rate follows the law $v_d = k_1 c_{com}[H^+]/(K_2 + [H^+])$, whereas for the dioxo derivatives the law is $v_d = k_2 c_{com}[H^+]^2/(K_1K_2 + K_2[H^+] + [H^+]^2)$. The dissociation kinetics are interpreted by a mechanism in which protonated intermediates are formed in a rapid pre-equibrium, the rate-determining step being the dissociation of this species. Comparison of the spectral results from multi-wavelength stopped-flow measurements with those acquired in the equilibium study using spectrophotometric titrations allows the nature and structure of these intermediates to be discussed. The order of the dissociation rates in strongly acidic solution, where a plateau in the pH dependence is reached, was determined and it demonstrates the importance of the ring size on one hand and of the number of amide groups on the other.

INTRODUCTION

Macrocyclic ligands are able to form metal complexes, which often are thermodynamically more stable and kinetically more inert than those with analogous open-chain ligands (macrocyclic effect).[1] Whereas the dissociation kinetics of open-chain ligands have been extensively studied,[2] only a few examples of acid-induced dissociation of macrocyclic complexes have been reported.[1,3,4] In general, the rates of dissociation of metal complexes with tetraazacycloalkanes are relatively slow. In some instances they are so slow that one can study them even under extreme conditions, such as in 10 M $HClO_4$.[5] However, the ring size and the degree of substitution at the nitrogens have important consequences on the dissociation kinetics. For example, the rate of the dissociation of the Cu^{2+} complexes with 12-aneN_4 and 13-aneN_4 determined in aqueous acetic acid solution indicate that the complex with the 12-membered macrocycle dissociates about 2000 times faster than that with the 13-membered macrocycle.[6] On the other hand, the tetra-*N*-methyl derivative of 14-aneN_4 forms metal complexes, which in the *trans*-I configuration rapidly dissociate in acidic solution.[4]

Most interesting is the observation that the replacement of the amino group by an amide function greatly affects the dissociation rate of metal complexes with tetraaza macrocycles. One paper[7] described the kinetics of the dissociation of the Cu^{2+} and Ni^{2+} complexes with **3** in the pH region 4–5, in which the analogous complexes with 14-aneN_4 gave no sign of dissociation. We have now systematically studied this reaction using the Ni^{2+} and Cu^{2+} complexes of the three macrocycles **1**–**3** with different ring sizes and numbers of amide groups, in order to determine the importance of these parameters and to clarify the mechanism of the dissociation process.



1 **2** **3**

EXPERIMENTAL

The ligands were prepared according to the literature: **1**,[8,9] **2**[10] and **3**,[11] but modified according to Fabbrizzi.[12] Ligand **1** was purified as a trihydrochloride:

* Author for correspondence.

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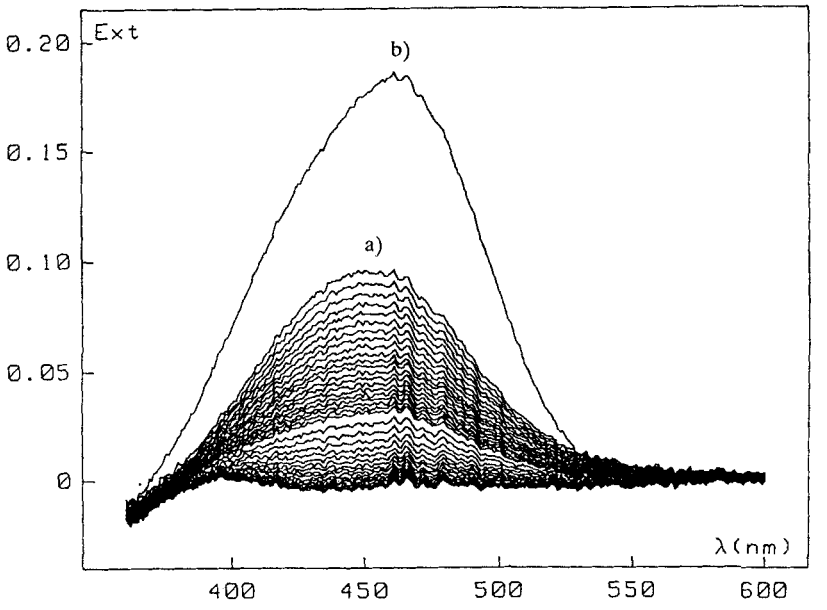


Figure 1. (a) Dissociation kinetics of $NiLH_{-2}$ (L = **3**): $[NiLH_{-2}] = 3 \times 10^{-3}$ M, pH = 0·84. Spectra taken every 17 ms until $t = 0{\cdot}34$ s, then every 51 ms. (b) Spectrum of $[NiLH_{-2}] = 3 \times 10^{-3}$ M at pH 7

m.p. 227–228 °C. Analysis: calculated for $C_{10}H_{25}Cl_3N_4O \cdot H_2O$ (311·71), C 35·15, H 7·96, Cl 31·12, N 16·39; found, C 35·13, H 7·81, Cl 30·96, N 16·36%. The other two ligands were isolated and purified as free bases. **2**: M.p. 179–181 °C. Analysis calculated for $C_9H_{18}N_4O_2$ (214·27), C 50·45, H 8·47, N 26·15; found, C 50·14, H 8·94, N 25·75. **3**: M.p. 177–178 °C (lit.[11] 176–177 °C).

Potentiometric studies were made using the fully automated pH titration unit described previously.[13] The experimental conditions were $I = 0{\cdot}5$ M (KNO_3), 25 °C, 0·4 M NaOH as titrating agent, [ligand] = 2×10^{-3} or $2{\cdot}5 \times 10^{-3}$ M with 0 or 90% Cu^{2+} added. The titration curves were fitted using the program TITFIT[14] adapted for an AT-286 computer. Equilibrium constants were calculated as concentration constants using the activity coefficient $\alpha = 0{\cdot}943$ for H^+ and log $K_w = -13{\cdot}85$, as determined separately from titration of HNO_3.

Spectrophotometric titrations were carried out using a fully automated set-up consisting of a Cary Model 118C spectrophotometer, a Metrohm Model E655 burette, a Metrohm Model E605 pH meter and an Apple II computer.[15] Typical conditions were $I = 0{\cdot}5$ M (KNO_3), 25 °C, [ligand] = 2×10^{-3} M, $[Cu^{2+}] = 1{\cdot}6 \times 10^{-3}$–$2{\cdot}0 \times 10^{-3}$ M, pH range 2–11, titrating agent 0·1 M NaOH. The evaluation of the equilibrium constants and the calculation of the species present at equilibrium were performed with the program SPECFIT[16] written for a Hewlett-Packard HP300 computer.

The dissociation kinetics were followed on a Durrum D110 stopped-flow instrument on-line with an Apple II computer, to which digitalized data of the Datalab DL901 transient recorder were transferred. The experimental conditions were [complex] = $2{\cdot}5 \times 10^{-3}$–$3{\cdot}8 \times 10^{-3}$ M, [buffer] = 0·02–0·1 M (2,6-lutidine-3-sulphonic acid, pH 3·5–5·2; chloroacetic acid, pH 1·9–3·6; sulphanilic acid, pH 2·7–3·7; and HNO_3), $I = 0{\cdot}5$ M (KNO_3), 25 °C. The complexes were prepared by mixing the desired metal ion with a 10%. excess of ligand at pH 5–7, at which the complex is fully formed. The dissociation was followed at 535 nm for Cu(**1**), 442 nm for Ni(**1**), 520 nm for Cu(**2**), 420 nm for Ni(**2**), 506 nm for Cu(**3**) and 460 nm for Ni(**3**). The calculations of the pseudo-first-order rate constants ($[H^+]$ = constant) were performed with the program SANYO.[17] To follow the spectra during the reaction, a few experiments were made using a Hitech stopped-flow instrument equipped with a Zeiss MCS 512 photodiode array on-line with a Hewlett-Packard HP300 computer.[18] An example of such a measurement is given in Figure 1. A comparison between the spectrum at time $t = 0$ in the dissociation experiment with that of the starting complex shows that a fast protonation pre-equilibrium must be present.

RESULTS AND DISCUSSION

The potentiometric titrations of the ligands **1**–**3** and the potentiometric and spectophotometric studies of their

Table 1. Logarithms of the ligand protonation and Cu^{2+} stability constants of **1–3** at 25 °C and $I = 0{\cdot}5$ M (KNO_3), with errors in parentheses

Ligand	Conditions[a]	β_{011}	β_{012}	β_{013}	β_{110}	β_{11-1}	β_{11-2}
1	(a)	10·87(2)	7·32(2)	3·37(3)	16·76(2)	13·00(5)	
	(b)				16·77(2)	13·21(5)	
	(c)	10·2	6·9	2·9			
	(d)	9·40	6·65	2·87	13·95	8·41	
2	(a)	9·20(2)	3·90(2)			1·85(2)	−2·63(2)
	(b)					1·87(2)	−2·55(3)
	(e)	9·05	3·82				−2·2
3	(a)	9·86(2)	6·01(2)			4·22(2)	−0·03(2)
	(b)					4·21(2)	−0·06(2)
	(e)	9·57	5·97				1·0
	(f)	9·51	5·80		8·75		0·44

[a](a) This work, potentiometric measurements. (b) This work, spectrophotometric titrations. (c) At 35 °C and $I = 0{\cdot}2$ M.[8] (d) At 25 °C and $I = 0{\cdot}1$ M ($NaClO_4$).[9] (e) At 25 °C and $I = 0{\cdot}2$ M ($NaClO_4$).[22] (f) At 25 °C and $I = 0{\cdot}1$ M ($NaClO_4$).[12] In this paper the neutral ligand is defined as LH_2.

Cu^{2+} complexes allow the protonation and Cu^{2+} stability constants to be determined (Table 1). The overall constants are defined according to equation (1):

$$\beta_{mln} = \frac{[M_m L_l H_n]}{[M]^m [L]^l [H^+]^n} \quad (1)$$

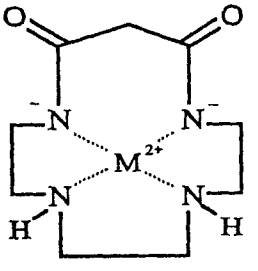
where m, l and n are the stoichiometric coefficients for the metal ion, the ligand and the proton, respectively.

The values of the protonation constants are as expected. The first protonation is typical for a secondary amine with no stabilization of the ammonium ion by an internal hydrogen bond. The second is lower than the first, because of the electrostatic interaction between the positive charges. The lowest value, $\log \beta_{012}$, is found for the 13-membered ring **2**, in which the two charges are closest, followed by those of the 14-membered rings **3** and **1**, the last having the possibility of fixing the two protons *trans* to each other. The third protonation constant of **1** is again lower owing to the even more pronounced electrostatic repulsion between the two charges already on the macrocycle and that of the third proton.

Our protonation constants for **1** differ considerably from those of Hay *et al.*[7] and are lower than those measured at 35 °C by Machida *et al.*[8] Whether this is due to the use of the ligand purified as hydrochloride (the free base was never analytically pure in our hands) or to other factors is not clear. The smaller differences in the protonation constants of the ligands **2** and **3** are acceptable and probably reflect differences in ionic strength.

The stability constants of the Cu^{2+} complexes, determined by potentiometric and spectrophotometric titrations, agree well. However, large differences between our values of $\log \beta_{110}$ and $\log \beta_{11-1}$ and the published values are found for the Cu^{2+} complexes of **1**. The value of the deprotonation of CuL to $CuLH_{-1}$ (L = **1**) also differs considerably (3·76 versus 5·54), although one would expect that this value, being independent of the protonation constants of the ligand, should give a better agreement. For ligand **2** the accordance between the $\log \beta_{11-2}$ values is relatively good, but we additionally find the species MLH_{-1}, which was not reported earlier. The same species was also observed for **3**, in contrast to the model proposed by Hay *et al.*,[7] in which ML appears instead. Figure 2 clearly shows, that the fitting with the model ML and MLH_{-2} is worse than that with MLH_{-1} and MLH_{-2}.

The differences between the three values of $\log \beta_{11-2}$ for **3** are probably due to the use of different models to fit the data. It is easy to propose a structure for MLH_{-1} with ligand **1** and for MLH_{-2} with ligands **2** and **3**, in which after deprotonation of the amide groups the Cu^{2+} can coordinate to all four nitrogens in a square planar coordination geometry (**4** and **5**).



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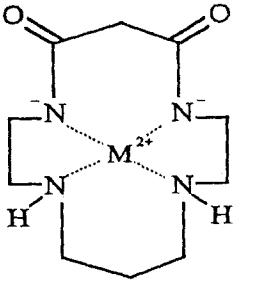

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More difficult is a proposal for the structures of ML for **1** and MLH_{-1} for **2** and **3**, since it is not clear *a priori* where the proton of the amide group sits. In this respect, the absorption spectra of these species obtained from the spectrophotometric titrations might be of some help (Table 2).

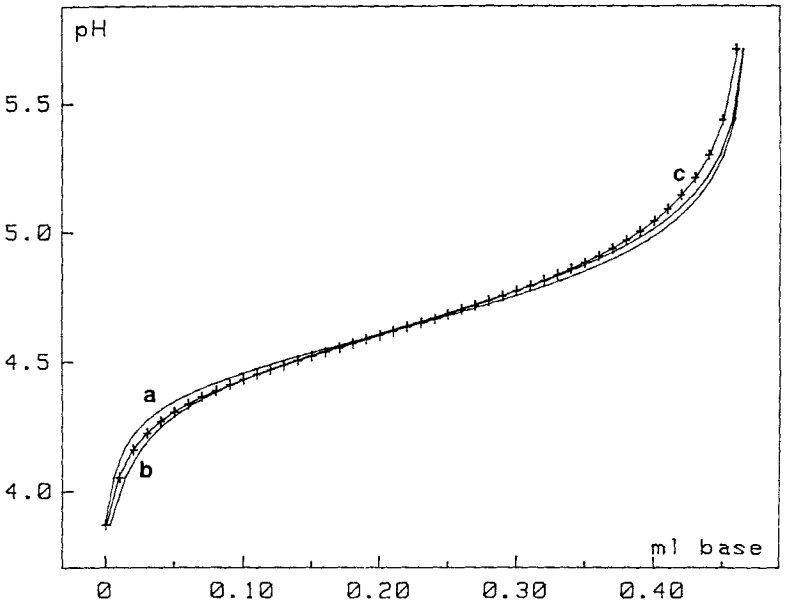

Figure 2. pH tritration of a mixture of $1{\cdot}70 \times 10^{-3}$ M Cu^{2+} and $1{\cdot}7 \times 10^{-3}$ M ligand **3** with 0·4 M NaOH. Fitting with different models: (a) with MLH_{-2} ($\sigma = 1 \times 10^{-2}$ ml), (b) with ML and MLH_{-2} ($\sigma = 4{\cdot}5 \times 10^{-3}$ ml) and (c) with MLH_{-1} and MLH_{-2} ($\sigma = 4{\cdot}2 \times 10^{-4}$ ml)

Table 2. Absorption maxima (nm) and (in parentheses) molar absorptivities (l mol^{-1} cm^{-1}) of the Cu^{2+} and Ni^{2+} complexes with ligands **1–3**

Ligand	Metal	ML	MLH_{-1}	MLH_{-2}	Method[a]
1	Cu^{2+}	521(86)	508(90)		Spec.
	Cu^{2+}	512(83)	510(83)		Kin.
	Ni^{2+}	447(34)	446(52)		Kin.
2	Cu^{2+}		559(110)	514(99)	Spec.
	Cu^{2+}		563[b]	514(100)	Kin.
	Ni^{2+}	410(43)	412(60)	415(78)	Kin.
3	Cu^{2+}		512(72)	501(85)	Spec.
	Cu^{2+}	514(61)	517(81)	502(96)	Kin.
	Ni^{2+}	451(33)	457(53)	461(65)	Kin.

[a] Spec. = from spectrophotometric titrations; Kin. = from kinetic measurements with the photodiode array.
[b] The value of the molar absoptivity cannot be determined since the reaction is too fast.

In the case of the Cu^{2+} complexes, the shift of λ_{max} between MLH_{-1} and ML for L = **1** and between MLH_{-2} and MLH_{-1} for L = **3** is relatively small and suggests that the same chromophore CuN_4 might be present in all of these species. Since the protonation does not displace a nitrogen from the coordination sphere of the metal ion, it follows that it must take place at the carbonyl oxygen. Protonation of the amide oxygen rather than of the amide nitrogen has been observed in the kinetically stable complexes $[Co(NH_3)_4(GlyNH)]^{2+}$ (Ref. 19) and $[Co(glygly)_2]^-$ (Ref. 20) in strong acid. For ligand **2**, however, a significant shift of λ_{max} from 514 nm for MLH_{-2} to 559 nm for MLH_{-1} is observed, and this could mean that in this case one nitrogen is displaced from the coordination sphere, so that a CuN_3O chromophore results and the protonation occurs at the nitrogen.

The kinetics of the acid dissociation of the Cu^{2+} and Ni^{2+} complexes follows the rate law

$$v_d = k_{obs} c_{com} \qquad (2)$$

where c_{com} is the total concentration of the complex and k_{obs} the pseudo-first-order rate constant; k_{obs}, however, is a function of the pH of the solution (Figures 3–5).

Before discussing the reaction scheme in more detail, we must consider two points. First, at low pH a plateau is observed for all complexes except Cu(**2**), which reacts so fast that the stopped-flow technique does not allow such low pH values to be reached. This means that in these cases the proton transfer to the coordinated amide nitrogen cannot be the rate-determining step, as has been found for other amide complexes.[21] Second, in most cases the photodiode-array measurements, which allow the spectral changes during the dissociation kinetics to be observed, clearly show that a pre-equilibrium is present, in which the intensity of the band decreases but its maximum is affected only slightly

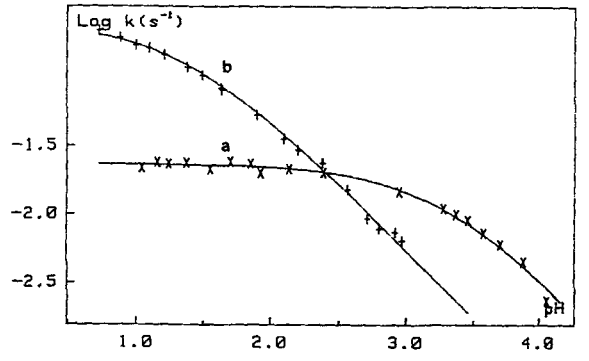

Figure 3. pH profile for the dissociation of the (a) Ni^{2+} and (b) Cu^{2+} complexes with **1**

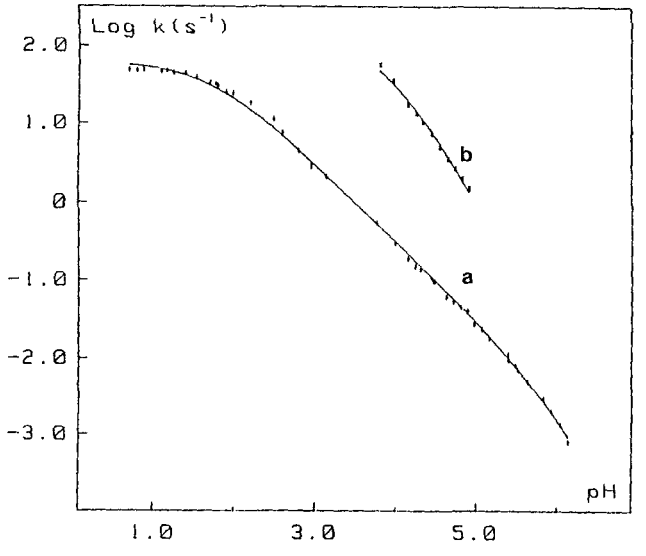

Figure 4. pH profile for the dissociation of the (a) Ni^{2+} and (b) Cu^{2+} complexes with **2**

except for Cu(**2**). We therefore propose a mechanism in which in a rapid pre-equilibrium MLH_{-1} for **1** and MLH_{-2} for **2** and **3** are rapidly protonated and the resulting complex ML is the reactive species, which dissociates in the rate-determining step to the products [equations 3–5)]:

$$MLH_{-1} \rightleftharpoons MLH_{-2} + H^+; \; K_1 \tag{3}$$

$$ML \rightleftharpoons MLH_{-1} + H^+; \; K_2 \tag{4}$$

$$ML \xrightarrow{k_1} \text{products} \tag{5}$$

Using the stoichiometric relation (6), one obtains the rate law (7) for the complexes with **2** and **3** and (8) for those with ligand **1**.

$$c_{com} = [ML] + [MLH_{-1}] + [MLH_{-2}] \tag{6}$$

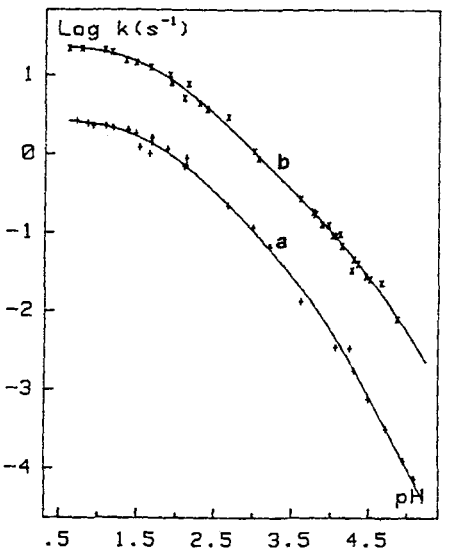

Figure 5. pH profile for the dissociation of the (a) Ni^{2+} and (b) Cu^{2+} complexes with **3**

$$v_d = \left(\frac{k_1[H^+]^2}{K_1K_2 + K_2[H^+] + [H^+]^2}\right)c_{com} \tag{7}$$

$$v_d = \left(\frac{k_1[H^+]}{k_2 + [H^+]}\right)c_{com} \tag{8}$$

The pH profiles in Figures 3 and 5 were fitted with these functions using the value of the limiting rate constant k_1 and the protonation constants K_1 and K_2 given in Table 3.The results show that the dissociations of the Ni^{2+} complexes are slower than those of the corresponding Cu^{2+} complexes by a factor of about 10. The number of amide functions also seems important, since the complexes with **1** react with acid at a rate which is about 100 times less than that of the complexes with **3**. Most interesting is the observation that the complexes with the 13-membered ring **2** are the most reactive against acid dissociation, probably because the metal ion does not fit so well into this macrocyclic cavity as compared with that of the the 14-membered ring.

Hay *et al.*[9] followed the dissociation rate of the Ni^{2+} and Cu^{2+} complexes of **3** in the pH range 3·7–4·4 and 4·7–5·2, respectively, and were able to determine the quadratic term in $[H^+]$. Their values of $k_{obs}/[H^+]^2 = 1{\cdot}15 \times 10^7$ l^2 mol^{-2} s^{-1} for Cu^{2+} and $k_{obs}/[H^+]^2 = 1{\cdot}23 \times 10^5$ l mol^{-1} s^{-1} for Ni^{2+} have to be compared with our values of $k_1/K_1K_2 = 6{\cdot}3 \times 10^7$ l^2 mol^{-2} s^{-1} for Cu^{2+} and $k_1/K_1K_2 = 1{\cdot}3 \times 10^6$ l^2 mol^{-2} s^{-1} for Ni^{2+}. The agreement is not especially good, the differences arising from the different ionic strength used in the two studies, but also from the fact that especially in the case of Ni^{2+} in the pH range 3·7–4·4 in addition

Table 3. Rate constants and protonation constants obtained from the dissociation kinetics of the Ni^{2+} and Cu^{2+} complexes of **1–3**

Complex	$k_1(s^{-1})$	K_2(M)	K_1(M)	K_1(M)[a]
Ni(**1**)	0·023(1)	$5·7(3) \times 10^{-4}$		
Ni(**2**)	62(2)	$1·9(2) \times 10^{-2}$	$9·3(8) \times 10^{-7}$	
Ni(**3**)	2·9(2)	$2·2(2) \times 10^{-2}$	$1·0(2) \times 10^{-4}$	
Cu(**1**)	0·25(1)	$4·3(3) \times 10^{-2}$		
Cu(**2**)	–[b]	–[b]	$2·7(2) \times 10^{-5}$	$3·6 \times 10^{-5}$
Cu(**3**)	24(2)	$1·9(1) \times 10^{-2}$	$1·8(2) \times 10^{-5}$	$5·5 \times 10^{-5}$

[a] Calculated from Table 1 using the equation $K_1 = \beta_{11-2}/\beta_{11-1}$, the mean values of the constants determined potentiometrically and spectrophotometrically being employed.
[b] Only K_2/k_1 can be determined to be $2·4(1) \times 10^{-6}$ mol l^{-1} s^{-1}.

to the quadratic also the linear term in $[H^+]$ plays a role, but this could not be taken into account by the authors.

The protonation constants K_1 for **2** and **3** determined from the fitting of the pH profiles compare well with those obtained from equilibria measurements (Table 3). In addition, the spectra obtained from the photodiode-array measurements also agree well with those obtained from the spectrophotometric titrations (Table 2). Both results indicate that for the Cu^{2+} complexes with **2** and **3** the species MLH_{-1} observed in the equilibrium and kinetic studies must be be same. We therefore propose a dissociation mechanism in which a rapid stepwise protonation of the two carbonyl oxygens to give MLH_{-1} and ML takes place, followed by the slow dissociation of ML to the products. In ML both metal—amide bonds are weakened, since through protonation of the oxygens the double bond character of the carbon—nitrogen bonds has been increased. It is difficult to prove the mechanism of the effective dissociation of ML, but one can argue that the weakening of the Cu—amide bond allows a partial dissociation, which, combined with an intramolecular proton transfer from the oxygen to the nitrogen, finally results in the complete breaking of the coordinative bond.

Finally, it is worth coming back to the extreme difference in reactivity between the complexes with the cyclic tetramines and those of the monooxo and dioxo derivatives against acid. In the case of the cyclic amines the free electron pairs on the nitrogens are not accessible to the proton since it is involved in a coordinative bond and because of the cyclic nature of the ligand it cannot easily rotate to the outside as in the case with the open-chain ligands. In the case of the monooxo and dioxo macrocyclic complexes, however, there is an easily accessible basic site at the carbonyl oxygen so that the proton can successfully attack the complex and induce the dissociation.

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REFERENCES

1. D. K. Cabiness and D. W. Margerum, *J. Am. Chem. Soc.* **92**, 2151 (1970).
2. D. W. Margerum, G. R. Cayley, D. C. Weatherburn and G. K. Pagenkopf, *ACS Monogr.* No, 174, 1 (1978).
3. C. C. Chang and C. S. Chung, *J. Chem. Soc., Dalton Trans.* 1965 (1991), and references cited therein.
4. L. Hertli and Th. A. Kaden, *Helv. Chim. Acta* **57**, 1328 (1974).
5. L. Fabbrizzi, *Comments Inorg. Chem.* **4**, 33 (1985).
6. M. Kodama and E. Kimura, *J. Chem. Soc., Chem. Commun.* 326, 891 (1975).
7. R. W. Hay, M. P. Pujari and F. McLaren, *Inorg. Chem.* **23**, 3033 (1984).
8. R. Machida, E. Kimura and M. Kodama, *Inorg. Chem.* **22**, 2055 (1983).
9. R. W. Hay, M. P. Pujari and A. Perotti, *Trans. Met. Chem.* **10**, 396 (1985).
10. W. Bachmann, PhD Thesis, Basle (1983).
11. I. Tabushi, T. Taniguchi and H. Kato, *Tetrahedron Lett.* 1049 (1977).
12. L. Fabbrizzi, *Inorg. Chem.* **23**, 807 (1984).
13. H. Gampp, M. Maeder, A. D. Zuberbühler and Th. A. Kaden, *Talanta* **27**, 573 (1980).
14. A. D. Zuberbühler and Th. A. Kaden, *Talanta* **29**, 201 (1982).
15. G. Hänish, Th. A. Kaden and A. D. Zuberbühler, *Talanta* **27**, 513 (1980).
16. Th. A. Kaden and A. D. Zuberbühler, *Talanta* **26**, 1111 (1979).
17. H. Gampp, M. Maeder and A. D. Zuberbühler, *Talanta* **27**, 1037 (1980).
18. C. J. Meyer, Th. A. Kaden, L. Siegfried and A. D. Zuberbühler, to be published; K. D. Karlin, N. Wei, B.

Jung, S. Kaderli and A. D. Zuberbühler, *J. Am. Chem. Soc.* **113**, 5868 (1991).
19. D. A. Buckingham, D. M. Foster and A. N. M. Sargeson, *J. Am. Chem. Soc.* **91**, 3451 (1969).
20. M. T. Barnet, H. C. Freeman, D. A. Buckingham and I. N. Hsu, *J. Chem. Soc. D* 367 (1970).
21. D. W. Margerum and G. R. Dukes, in *Metal Ions in Biological Systems*, edited by H. Sigel, Marcel Dekker, New York, Vol. 1, p. 157, and references cited therein. (1974).
22. M. Kodama and E. Kimura, *J. Chem. Soc., Dalton Trans.* 325 (1979).