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206. Formation and Dissociation Mechanism of Amide Complexes, IV[1]).

Protonation and Deprotonation of the Cu^{2+} and Ni^{2+} Complexes of 3,7-Diazanonanediamide and 3,7-Diazanonane-N,N'-diethylamide

by **Andreas D. Zuberbühler** and **Thomas A. Kaden**
Institut für Anorganische Chemie, Spitalstrasse 51, 4056 Basle (Switzerland)

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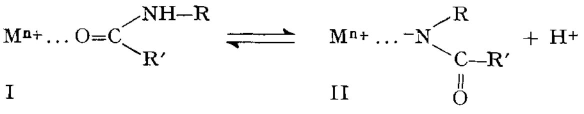
Summary. The protonation and deprotonation rates of the coordinated amide groups in the Ni^{2+} and Cu^{2+} complexes of 3,7-diazanonanediamide (DANA) and in the Cu^{2+} complex of 3,7-diazanonane-N,N'-diethylamide (DANEA) have been studied by stopped-flow techniques. For the interconversion $M(H_{-2}L) \rightleftharpoons ML$, two consecutive reactions are observed in the case of Cu^{2+} with DANA or DANEA, whereas there is only one reaction for Ni^{2+} with DANA. $Cu(H_{-2}DANEA)$ is unusually labile, indicating a strong interaction between the N-ethyl groups. The conversion of the O- into the N-coordinated amide groups in $NiDANA^{2+}$ is 25 times slower than in $CuDANA^{2+}$. In the case of Ni^{2+} this excludes a step with water substitution, which is involved in one of the reaction paths observed for the Cu^{2+} complexes, since the rates of water exchange differ by a factor of 10^5 for the two metal ions.

The neutral and anionic amide groups coordinate through the carbonyl oxygen (I) and through the deprotonated nitrogen (II), respectively. The kinetics of the interconversion I $\rightleftharpoons$ II (1) have been investigated for several oligopeptides [2] and other chelating amides [1] [3]. The formal acid-base reaction (1) is much slower than if simply diffusion controlled, since the protonation of II and deprotonation of I are accompanied by a conformation change of the ligand and a substitution in the first coordination sphere of the metal ion.

For a kinetic study of the interconversion I $\rightleftharpoons$ II (1), ligands with terminal amide groups have a great advantage over oligopeptides, since pre-equilibria have not to be taken into account, which render the interpretation of the kinetics difficult [1].



$$\underset{\text{I}}{M^{n+}\ldots O{=}C\genfrac{}{}{0pt}{}{\diagup NH{-}R}{\diagdown R'}} \rightleftharpoons \underset{\text{II}}{M^{n+}\ldots {}^{-}N\genfrac{}{}{0pt}{}{\diagup R}{\diagdown C(=O){-}R'}} + H^{+} \qquad (1)$$

Reaction (1) has been subdivided into three steps: a) opening of the chelate ring involving the carbonyl oxygen and water addition ($K = 10^3$–10^4), b) deprotonation of the free amide group ($pK_H \sim 14$) and c) complexation of the deprotonated amide group with the metal ion [1]. According to this mechanism the reaction is a 'normal' substitution of the first coordination sphere of the metal ion, the slow overall rate being due to the extremely low concentration of the reactive intermediate with a free deprotonated amide group. For the reverse reaction breaking of the metal nitro-

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[1]) Part III see [1].

gen bond is rate determining. Besides this stepwise mechanism a second must exist, since general acid-base catalysis has been observed in many of the systems studied [1–3].

In order to extend our knowledge about such interconversions and to investigate whether the proposed mechanism is also valid for metal ions with lower water substitution rates, we have studied the reactivity of the Cu^{2+} and Ni^{2+} complexes with 3,7-diazanonanediamide (DANA) and 3,7-diazanonane-N,N'-diethylamide (DANEA).

$$R{-}NH{-}CO{-}CH_2{-}NH{-}CH_2{-}CH_2{-}CH_2{-}NH{-}CH_2{-}CO{-}NH{-}R$$

$$-R = -H \text{ (DANA)} \qquad -R = -C_2H_5 \text{ (DANEA)}$$

Experimental Part. – 3,7-diazanonanediamide (DANA) and 3,7-diazanonane-N,N'-diethylamide (DANEA) were synthesized as described in [4]. Other reagents: analytical grade, used without further purification, except for the buffer bases which were freshly distilled. Buffers used: α-picoline pH 4.9–7.2; 2,6-lutidine pH 6.0–7.6; 2,4,6-collidine pH 6.6–8.6; N-methylmorpholine pH 6.9–8.5; N,N-bis-(2-hydroxypropyl)-ethanolamine pH 8.1–9.2; 2-*t*-butylaminoethanol pH 9.2–10.1; 2,2,6,6-tetramethylpiperidine pH 10.2–11,2; and NaOH pH 11.0–12.7.

The kinetic runs were followed spectrophotometrically on a *Durrum* D 110 stopped-flow instrument equipped with a *Durrum* 111 log-amplifier and a 2 cm KelF-cell on either the transmittance or absorbance mode at 25° and $I = 0.5$ (KCl). The reactions of the system Ni^{2+}/DANA were monitored at 450 nm using $2.4\text{–}6.0 \cdot 10^{-4}$ M $NiSO_4$ and $2.6\text{–}6.6 \cdot 10^{-4}$ M DANA · 2 HCl solutions adjusted to either pH 6.5 or 10.5 and 0.05–0.5 M buffer solutions. The system Cu^{2+}/DANA, for which two consecutive reactions were observed, was studied at 450, 570, 595 and 625 nm. Starting from pH 5.5 or 10.0, $2 \cdot 10^{-3}\text{–}8 \cdot 10^{-3}$ M $CuSO_4$ and $2.2 \cdot 10^{-3}\text{–}8.8 \cdot 10^{-3}$ M DANA · 2 HCl were mixed with different buffers. In the case of DANEA and Cu^{2+} the two reaction steps are distinctly separated. They were studied with similar concentrations and buffers as for the system Cu^{2+}/DANA. Starting pH values were 5.5 for the deprotonation and 11.6 or 10.2 for the protonation. Since the stability of $Cu(H_{-2}DANEA)$ is low and its dissociation is strongly catalyzed by HCO_3^-, care was taken to use solutions which were freshly prepared (10–20 min.) and kept under nitrogen. All reactions were shown to be independent of the buffer concentration.

Results. – At constant pH the complex-interconversion kinetics are all strictly pseudo-first order for the Cu^{2+} complexes with DANEA and for the Ni^{2+} complexes with DANA. In the case of Cu^{2+} and DANA two consecutive steps with similar rate constants are observed and thus biphasic curves result. Such curves, showing either an induction period (590 nm) or a U-shaped profile (570 nm), are fitted with an analog computer [5] program which takes into account the sequence of reactions (2):

$$\mathbf{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{B} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{C} \qquad (2)$$

The time dependence of $[\mathbf{A}]$, $[\mathbf{B}]$ or $[\mathbf{C}]$ is described by (3–5), where $[\mathbf{A}]_0$ is the initial concentration of **A**.

$$[\mathbf{A}] = [\mathbf{A}]_0 - [\mathbf{B}] - [\mathbf{C}] \qquad (3)$$

$$d[\mathbf{B}]/dt = k_1[\mathbf{A}] - k_{-1}[\mathbf{B}] - k_2[\mathbf{B}] + k_{-2}[\mathbf{C}] \qquad (4)$$

$$d[\mathbf{C}]/dt = k_2[\mathbf{B}] - k_{-2}[\mathbf{C}] \qquad (5)$$

The chart-flow diagram of the program, given in Fig. 1, shows how the equations (3–5) are integrated. $[\mathbf{A}]$, $[\mathbf{B}]$ and $[\mathbf{C}]$ as a function of time are obtained by connecting the exits of the corresponding amplifiers with the y-input of an x,y-recorder. Four variable potentiometers, corresponding to k_1, k_{-1}, k_2 and k_{-2}/k_2, are adjusted to fit the experimental curves. In order to reduce the number of independent variables

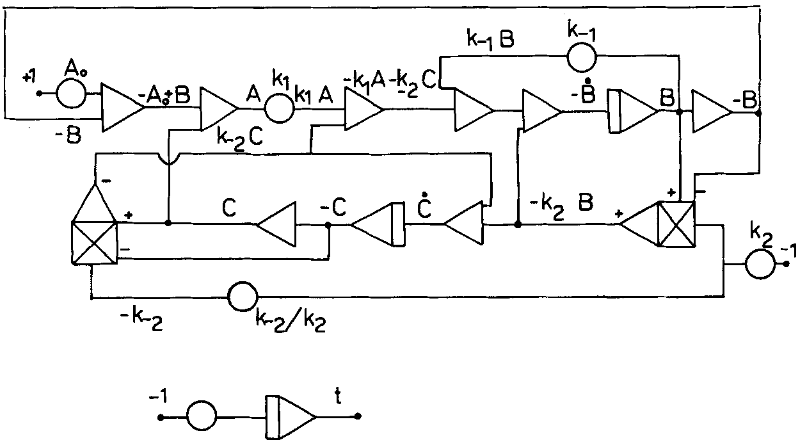


Fig. 1. *Chart-flow diagram of the analog computer program which allows the determination of the rate constants in* (2)

we have generally made use of the relations (at constant pH) between the stability constants K_1 and K_2 and the rate constants given in (6). The program must be slightly modified when $k_{-2}/k_2 > 1$. The rate constants k_1 obtained with the analog

$$K_1 = k_{-1}/k_1 \qquad K_2 = k_{-2}/k_2 \tag{6}$$

computer are in close agreement with those obtained at wave lengths (450 nm and 625 nm) at which only the first reaction can be followed.

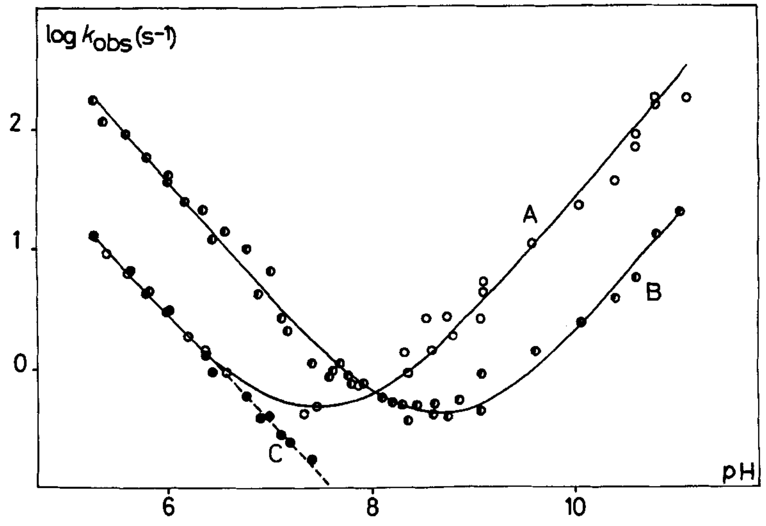


Fig. 2. *pH dependence of the rate constants for the interconversion* $CuDANA^{2+} \rightleftharpoons Cu(H_{-1}DANA)^+$ (**A**,**C**) *and* $Cu(H_{-1}DANA)^+ \rightleftharpoons Cu(H_{-2}DANA)$ (**B**)

A $k_{osb} = k_o + k_H[H^+] + k_{OH}[OH^-]$
C $k_{obs} = k_H[H^+]$

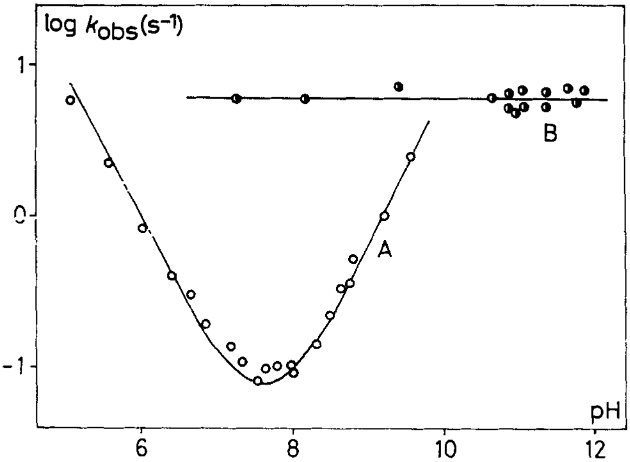


Fig. 3. *pH dependence of the rate constant for the interconversion CuDANEA*$^{2+} \rightleftharpoons$ *Cu* $(H_{-1}DANEA)^+$ (**A**) *and for the dissociation of Cu* $(H_{-2}DANEA)$ (**B**)

The pH-dependence of the pseudo-first order rate constants k_{obs} are shown in Fig. 2 for Cu^{2+}/DANA and in Fig. 3 for Cu^{2+}/DANEA.

$$k_{obs} = k_0 + k_H[H^+] + k_{OH}[OH^-] = k_0 + k_H[H^+] + k_{OH}\,K_w/[H^+] \tag{7}$$

For each step of (2) typical U-shaped pH profiles are obtained with M = Cu^{2+}. These are fitted by equation (7), with a pH-independent term (k_0), a term proportional to [H$^+$] (k_H) and one proportional to $1/[H^+]$ (k_{OH}). The pH dependence of k_{obs} for the reaction of the Ni^{2+} complexes is more complicated (Fig. 4) and has to be fitted by (8).

$$k_{obs} = k_0 + k_H[H^+] + k_a[OH^-]^2/(k_b + [OH^-]) \tag{8}$$

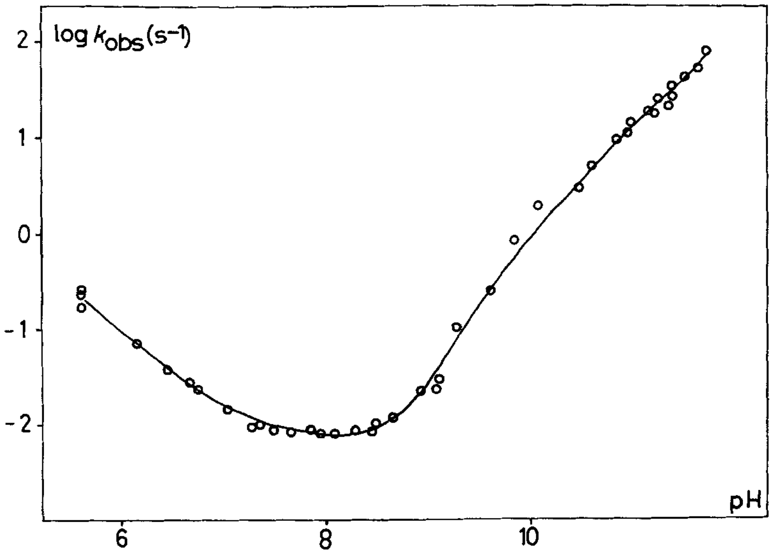


Fig. 4. *pH dependence of the rate constant for the interconversion NiDANA*$^{2+} \rightleftharpoons$ *Ni* $(H_{-2}DANA)$

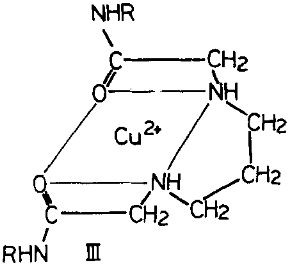
The best values of the constants for the three systems were obtained with the curve fitting program VARIAT [6] (Table 1) and the pH-dependence calculated therefrom is also shown in Figs. 2–4.

Table 1. *Rate constants for the protonation and deprotonation of the* Ni^{2+} *and* Cu^{2+} *complexes with DANA and the* Cu^{2+} *complexes with DANEA at 25° and* I = *0.5*

	DANA			DANEA	
	NiL/NiH₋₂L	CuL/CuH₋₁L	CuH₋₁L/CuH₋₂L	CuL/CuH₋₁L	CuH₋₁L/CuH₋₂L
k_{H_2O} (s^{-1})	$6.6 \cdot 10^{-3}$	0.30	0.26	$1.8 \cdot 10^{-2}$ a)	5.9
k'_{H_2O} (s^{-1})		$3.7 \cdot 10^{-2}$ a)	$4.5 \cdot 10^{-2}$ a)	$3.5 \cdot 10^{-2}$	
k_H ($M^{-1}s^{-1}$)	$1.0 \cdot 10^5$	$2.8 \cdot 10^6$	$4.1 \cdot 10^7$	$9.1 \cdot 10^5$	
k_{OH} ($M^{-1}s^{-1}$)	$6.3 \cdot 10^3$ b)	$1.3 \cdot 10^5$	$9.5 \cdot 10^3$	$3.2 \cdot 10^4$	
$k_{-1}/k_{2,OH}$ (M)	$9.5 \cdot 10^{-5}$				

a) calculated from the equilibrium constant and one of the reaction rates
b) $k_{1,OH}$ for Ni^{2+}

Discussion. – DANA and DANEA give three types of Cu^{2+} complexes CuL(III), $Cu(H_{-1}L)$ (IV) and $Cu(H_{-2}L)$ (V) in which the two amide groups are successively deprotonated [4]. For Cu^{2+} and DANA the two steps overlap considerably, whereas in the case of Cu^{2+} and DANEA the two buffer regions are well separated. DANA forms two complexes with Ni^{2+}, NiL with octahedral geometry and $Ni(H_{-2}L)$ with a configuration similar to V. With Ni^{2+}, DANEA only gives NiL and no deprotonation of the amide groups occurs up to pH 12 [4], so that no kinetic measurements were possible.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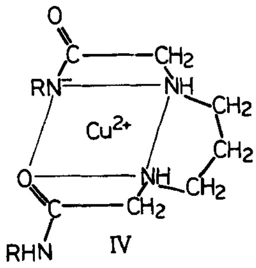
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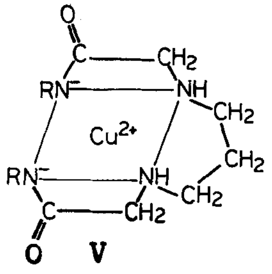
V

Cu^{2+}/DANA. The pH-dependence of the reversible interconversions between CuL, $Cu(H_{-1}L)$ and $Cu(H_{-2}L)$ (Fig. 2) exhibit three terms for each step (7). k_H, the term proportional to [H^+] can be accounted for by the protonation of $Cu(H_{-1}L)$ to CuL and of $Cu(H_{-2}L)$ to $Cu(H_{-1}L)$, respectively. k_{OH} describes the deprotonation

$$Cu(H_{-n}L) + H_2O \underset{k_{OH}}{\overset{k_{H_2O}}{\rightleftharpoons}} Cu(H_{-m}L) + OH^- \qquad (9)$$

$$n = 1,2$$
$$m = n-1$$

$$Cu(H_{-m}L) + H_2O \underset{k_H}{\overset{k'_{H_2O}}{\rightleftharpoons}} Cu(H_{-n}L) + H_3O^+ \qquad (10)$$

of CuL to $Cu(H_{-1}L)$ and of $Cu(H_{-1}L)$ to $Cu(H_{-2}L)$. The pH-independent term k_0 can be interpreted by the forward reaction of either (9) or (10) in which H_2O reacts either as an acid (k_{H_2O}) or as a base (k'_{H_2O}), respectively. The equilibrium constants for (9) and (10) can be calculated from kinetic data – $K_{kin} = k_{H_2O}/k_{OH} \cdot K_w$ and $K' = k_H/k'_{H_2O}$ – and can be compared with the potentiometric values [4]. As shown in Table 2 an agreement is obtained only when k_0 is taken as equal to k'_{H_2O}. Thus in this system water reacts as a base. k_{H_2O} can be calculated to be $3.7 \cdot 10^{-2}$ s^{-1} and $4.5 \cdot 10^{-2}$ s^{-1} for the protonation of $Cu(H_{-1}L)$ and $Cu(H_{-2}L)$ respectively. Whereas both k_{H_2O} and k'_{H_2O} are very similar for the two interconversion steps, k_H and k_{OH} differ by a factor of about 15, corresponding to the different charges of the complexes: OH^- reacts with $CuDANA^{2+}$ more readily than with $Cu(H_{-1}DANA)^+$, whereas H^+ attacks $Cu(H_{-2}DANA)$ more readily than $Cu(H_{-1}DANA)^+$. While the k_H and k'_{H_2O} values for $Cu(H_{-1}L)$ with L = DANA and L = N^α-(2-pyridyl-methyl)-glycine amide (PGA) [1] are very similar, k_{OH} and k_{H_2O} of the same two ligands differ by factors of 40 and 50 respectively, the DANA complexes reacting more slowly than their PGA analogs. In addition k_0 is equal to k'_{H_2O} for DANA, but equal to k_{H_2O} for PGA. According to the mechanism suggested in [1], this means that the opening of the chelate rings involving the terminal amide group is more difficult for DANA than for PGA. This is in accordance with the observation that fused five-membered rings, as in the Cu^{2+} complexes with PGA, are more strained than five-membered rings adjacent to six-membered chelate rings as in the Cu^{2+} complexes with DANA [7].

Table 2. *Comparison between the potentiometrically and kinetically determined equilibrium constants for the three systems Cu^{2+}/DANA, Cu^{2+}/DANEA and Ni^{2+}/DANA*

	$-\log K_{2,pot}$ a)	$\log K_{2,kin}$	$\log K'_{2,kin}$	$-\log K_{3,pot}$ a)	$\log K_{3,kin}$	$\log K'_{3,kin}$
Cu^{2+}/DANA	7.14	8.04	6.97	8.38	9.13	8.20
Cu^{2+}/DANEA	7.75	7.74	7.42	11.72		
	$\log K_4$ a)	$\log \frac{k_{1,OH}\, k_{2,OH}}{k_{-1}\, k_{-2}}$				
Ni^{2+}/DANA	17.82	17.50				

a) from Ref. [4].

Cu^{2+}/DANEA. The rate constant k_{H_2O} for the reaction CuL $\rightleftharpoons$ $Cu(H_{-1}L)$ is similar to that of the system Cu^{2+}/DANA. The reduction of k_H, k_{OH}, and k'_{H_2O} by factors of 3, 5, and 16 respectively parallels the results for L = PGA and N^α-(2-pyridyl-methyl)-glycine-ethylamide (PGEA) [1] and is due to N-ethyl substitution. However, the results of the second step $Cu(H_{-1}L) \rightleftharpoons Cu(H_{-2}L)$ differ considerably from those obtained with DANA. k_0, which in this case describes the reaction of $Cu(H_{-2}L)$ with H_2O (k_{H_2O}), dominates the pH dependence from pH 6 to 11.6. The high value of k_{H_2O} is due to the instability of the second metal-amide bond. The strong sterical interaction of the two adjacent N-ethyl groups, also shown by space filling models [4], results in a strong tendency for one or other of the amide groups to dissociate.

Ni^{2+}/DANA. The kinetics of the interconversion of the Ni^{2+} complexes with DANA can be explained by (11), in which $Ni(H_{-1}L)$ is an intermediate. Using the

$$NiL \underset{k_{-1}}{\overset{k_{1,OH}}{\rightleftharpoons}} Ni(H_{-1}L) \underset{k_{-2}}{\overset{k_{2,OH}}{\rightleftharpoons}} Ni(H_{-2}L) \tag{11}$$

steady state approximation for $Ni(H_{-1}L)$, equation (12) is obtained for the formation of $Ni(H_{-1}L)$ at high pH, which is equal to the last term in the experimental rate

$$v_f = k_{1,OH}\, k_{2,OH}\, [NiL]\,[OH^-]^2/(k_{-1} + k_{2,OH}\,[OH^-]) \tag{12}$$

law (8) with $k_a = k_{1,OH} = 6.3 \cdot 10^3\ s^{-1}$ and $k_b = k_{-1}/k_{2,OH} = 9.5 \cdot 10^{-5}$ M. As shown in Table 2, k_0 is the reverse reaction of the second step in (11) and thus $k_0 = k_{-2} = 6.6 \cdot 10^{-3}\ s^{-1}$.

Both k_0 and k_H, describing the unassisted and the proton-catalyzed dissociation of the negative amide nitrogen from the metal ion in $M(H_{-2}L)$, are slower by a factor of 40 and 28 in the case of Ni^{2+} as compared to Cu^{2+}, which may be due to a stronger binding in the Ni^{2+} complex or a lower basicity of the coordinated amide groups. The result that $k_{1,OH}$ for $NiDANA^{2+}$ is only 25 times smaller than k_{OH} for $CuDANA^{2+}$ is unexpected and cannot be explained by a mechanism in which water exchange plays a determining role, since the water substitution rates for Cu^{2+} and Ni^{2+} differ by a factor of nearly 10^5 [8]. When water exchange becomes slow, a second mechanism with deprotonation of the coordinated amide groups and direct conversion into the N-bound form must be operating.

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