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32. Transition Metal Ions and Amides, VI[1]). Complexation of the Neutral and the Anionic Forms of 3,7-Diazanonanedioic Acid Diamide and 3,7-Diazanonanedioic Acid Diethylamide with Cu^{2+} and Ni^{2+}

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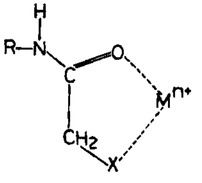
Summary. Two tetradentate ligands, 3,7-diazanonanedioic acid diamide (DANA) and 3,7-diazanonanedioic acid diethylamide (DANEA) have been synthesized and their complexes with Cu^{2+} and Ni^{2+} studied potentiometrically and spectrophotometrically. Three monomeric species, ML, $MH_{-1}L$, and $MH_{-2}L$, are formed. In ML, the two carbonyl oxygens are bound to the metal ions. Whilst Cu^{2+} gives complexes $CuH_{-1}DANA^+$ and $CuH_{-1}DANEA^+$ with one deprotonated amide group, the corresponding Ni^{2+} chelates do not exist in detectable concentrations. $CuH_{-2}DANA$ and $NiH_{-2}DANA$ are formed below pH 9. In the case of the diethyl derivative DANEA, however, steric interaction strongly hinders coordination of two deprotonated amide groups.

A straightforward study of the interconversion of complexes with the neutral (I) and the deprotonated (II) amide group is difficult with oligopeptides and similar ligands like N,N'-diglycyl-ethylenediamine, since pre-equilibria of unknown influence must be taken into account [2]. In two previous papers [2] [3] we have shown that ligands with terminal amide groups are especially suitable for that purpose.



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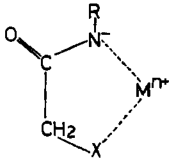

II

In the case of the terdentate ligands N$^{\alpha}$-(2-pyridylmethyl)-glycineamide and N$^{\alpha}$-(2-pyridylmethyl)-glycineethylamide, a stabilization by 3–4 orders of magnitude was observed when the carbonyl oxygen was coordinated to the metal ion forming a fivemembered chelate ring. The kinetics of the interconversion could be explained by

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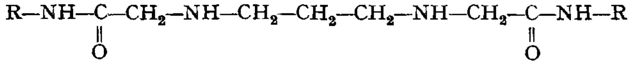
a mechanism with the exchange of water coordinated to Cu^{2+} as the rate limiting step [2].

To test the generality of the results obtained for Cu^{2+} in [2] and [3] and to extend the studies to other metal ions, we have synthesized a series of amides with more than three potentially coordinating groups. Here, we report on the stabilities and absorption spectra of the Cu^{2+} and Ni^{2+} complexes with 3,7-diazanonanedioic acid diamide (DANA = III a) and its diethyl derivative 3,7-diazanonanedioic acid diethylamide (DANEA = III b).



$$R{-}NH{-}\underset{\|}{\overset{}{C}}(=O){-}CH_2{-}NH{-}CH_2{-}CH_2{-}CH_2{-}NH{-}CH_2{-}C(=O){-}NH{-}R \qquad (III)$$

a: $-R = -H$ (DANA); b: $-R = -C_2H_5$ (DANEA)

The kinetics of these systems will be dealt with in a separate study.

Experimental. – A. Syntheses. – *3,7-diazanonanedioic acid diamide dihydrochloride* (*DANA · 2HCl*). 153 g (0.4 mol) N,N'-ditosyl-trimethylenediamine are converted into the disodium salt [4] and slowly added to a stirred solution of 114 g (1.2 mol) chloroacetamide in 1.2 l dimethylformamide. The mixture is stirred for 3 h at 70°, the solvent removed under vacuum, and the resulting oil dissolved in water. After addition of $CHCl_3$ a voluminous precipitate of 3,7-ditosyl-3,7-diazanonanedioic acid diamide (TsDANA) is formed. It is filtered off and recrystallized from ethanol. Yield 145 g (73%), m.p. 176–177°.

72 g (0.145 mol) of the finely ground TsDANA and 54.7 g (0.582 mol) phenol are dissolved in 360 ml 40% HBr in glacial acetic acid and stirred at 60° for 20 h. After cooling to room temperature the hygroscopic precipitate of DANA · 2HBr is filtered off and washed with ether. A second crop of crystals is obtained by addition of ether to the filtrate. The dihydrobromide is dissolved in the minimum of aqueous ethanol and converted into the free base with a strongly basic anion exchange resin. Evaporation of the effluent under vacuum gives an oil which is dissolved in CH_3OH. DANA · 2HCl precipitates upon addition of 2.5 equiv. of methanolic HCl. Recrystallization from aqueous CH_3OH yields 25.8 g (68%) DANA · 2HCl, m.p. 254–255°.

$C_7H_{18}Cl_2N_4O_2$	Calc.	C 32.19	H 6.95	Cl 27.15	N 21.45%
	Found	,, 32.21	,, 7.09	,, 26.93	,, 21.30%

3,7-diazanonanedioic acid diethylamide dihydrochloride (*DANEA · 2HCl*). 57.5 g (0.15 mol) N,N'-ditosyl-trimethylenediamine [4] and 44 g (0.375 mol) chloroacetic acid ethylamide [5] are reacted as described above. The reaction mixture is filtered from NaCl, the filtrate evaporated, and the residual oil shaken with 100 ml H_2O. After separation from the aqueous layer 3,7-ditosyl-3,7-diazanonanedioic acid diethylamide (TsDANEA) is crystallized from methanol. Yield 53 g (64%), m.p. 138°.

To remove the protecting groups, 17.7 g (0.032 mol) TsDANEA and 12.3 g (0.131 mol) phenol are reacted in 90 ml 40% HBr in acetic acid as described above. DANEA · 2HBr is precipitated from the reaction mixture by the addition of ether. The crystals are dissolved in water and the aqueous phase is extracted twice with ether. DANEA · 2HCl monohydrate is obtained from the dihydrobromide by the procedure given above and recrystallized from methanol/ether. Yield 7.0 g (65%), m.p. 228–229°.

$C_{11}H_{28}Cl_2N_4O_3$	Calc.	C 39.44	H 8.43	Cl 21.17	N 16.73%
	Found	,, 39.77	,, 8.36	,, 21.01	,, 16.82%

N,N'-dimethyl-trimethylenediamine dihydrochloride (DTDA · 2HCl) was prepared from N,N'-ditosyl-trimethylenediamine [4] and CH_3J according to *Boon* [6].

B. Measurements and equipment. – Reagents: Analytical grade, used without further purification. Temperature: 25° ± 0.5°. Ionic strenght: 0.5 (KCl). Potentiometric titration curves were obtained with a Compensator E 388 or a pH-meter E 510 (both *Metrohm*), fitted with glass and calomel electrodes. 50 ml samples of the ligands and $CuSO_4$ or $NiSO_4$ were titrated with NaOH Titrisol (*Merck*) under 99.99% N_2: $[DANA]_{tot} = 4 \cdot 10^{-3}$, no metal ion, 0.2, 0.5, or 0.9 equiv.

Cu^{2+}, 0.5 or 0.9 equiv. Ni^{2+}; $[DANA]_{tot} = 2 \cdot 10^{-3}$, 0.5 or 0.9 equiv. Ni^{2+}; $[DANA]_{tot} = 8 \cdot 10^{-4}$, 0.2, 0.5, or 0.9 equiv. Cu^{2+}; $[DANEA]_{tot} = 8 \cdot 10^{-4}$, 0.9 equiv. Cu^{2+} or Ni^{2+}; $[DANEA]_{tot} = 4 \cdot 10^{-4}$, no metal ion, 0.45 or 0.9 equiv. Cu^{2+}, 0.45 or 0.9 equiv. Ni^{2+}; $[DTDA]_{tot} = 3.2 \cdot 10^{-3}$, no metal ion.

Each experiment was run at least twice. Curves, which agreed within 0.02 pH units in the buffer regions and showed less than 0.5% difference at the equivalence point, were used for calculation of the equilibrium constants with a FORTRAN IV version [3] of VARIAT [7].

The constants yielding the minimum relative standard deviation σ_{rel} (1) were considered as the 'best values' for a particular

$$\sigma_{rel} = \sum_{n=1}^{N} \sqrt{(\alpha_{exp,n} - \alpha_{calc,n})^2/(N-NC)} \qquad (1)$$

N: number of experimental points; NC: number of constants; α: degree of neutralization

titration curve. For reasons discussed elsewhere [7] [8] the standard deviation of the equilibrium constants were not calculated from σ_{rel}.

Some of the equilibrium constants were obtained from spectrophotometric measurements. Conditions: $[DANA]_{tot} = 2.52 \cdot 10^{-3}$, $[Cu^{2+}]_{tot} = 2.5 \cdot 10^{-3}$, pH = 1.62–4.54; $[DANEA]_{tot} = 2 \cdot 10^{-3}$, $[Cu^{2+}]_{tot} = 2 \cdot 10^{-3}$, pH = 1.82–5.24; $[DANEA]_{tot} = 2 \cdot 10^{-3}$, $[Cu^{2+}]_{tot} = 1.8 \cdot 10^{-3}$, pH = 9.24–13.24; $[DTDA]_{tot} = 0.25$, $[Cu^{2+}]_{tot} = 5 \cdot 10^{-4}$, pH = 5.32–6.53; $[DTDA]_{tot} = 0.25$, $[Ni^{2+}]_{tot} = 10^{-3}$, pH = 7.08–9.10. The visible absorption spectra were run on a *Cary* 14 or a *Varian Techtron* 635. A modification (*cf.* [3]) of the computer programme SPANA [7] was used to calculate the absorption spectrum of each complex from the experimental data and to display the final results on a XY-plotter. Experimental mixtures: Cu^{2+}/DANA: $[Cu^{2+}]_{tot} = 1.8 \cdot 10^{-3}$, $[L]_{tot} = 2 \cdot 10^{-3}$, pH = 5.21, 6.41, 6.79, 7.20, 7.62, 8.04, 8.40, 8.79, 9.87; $[Cu^{2+}]_{tot} = 2.5 \cdot 10^{-3}$, $[L]_{tot} = 2.52 \cdot 10^{-3}$, pH = 2.24, 2.54, 3.04, 3.49, 4.53. Cu^{2+}/DANEA: $[Cu^{2+}]_{tot} = 3.6 \cdot 10^{-3}$, $[L]_{tot} = 4 \cdot 10^{-3}$, pH = 2.54, 2.81, 3.50, 5.12, 7.07, 7.47, 7.94, 9.42, 10.93, 11.55, 12.00, 12.84. The spectra of the individual nickel complexes were obtained directly from mixtures in which only one species was present: $NiDANA^{2+}$: $[Ni^{2+}] = 10^{-2}$, $[DANA] = 1.1 \cdot 10^{-2}$, pH = 6.7; $NiH_{-2}DANA$: $[Ni^{2+}] = 1.5 \cdot 10^{-3}$, $[DANA] = 3.0 \cdot 10^{-3}$, pH = 10.52; $NiDANEA^{2+}$: $[Ni^{2+}] = 10^{-2}$, $[DANEA] = 1.1 \cdot 10^{-2}$, pH = 7.1.

Results and discussion. – The titration curves of DANA · 2HCl with 0.9 equivalents Cu^{2+} or Ni^{2+} (Fig. 1) show that a total of four protons per metal ion are released. In order to explain the experimental data, we had to consider the following six species, defined by equations (2)–(6): H_2L, HL, L, ML, $MH_{-1}L$, and $MH_{-2}L$

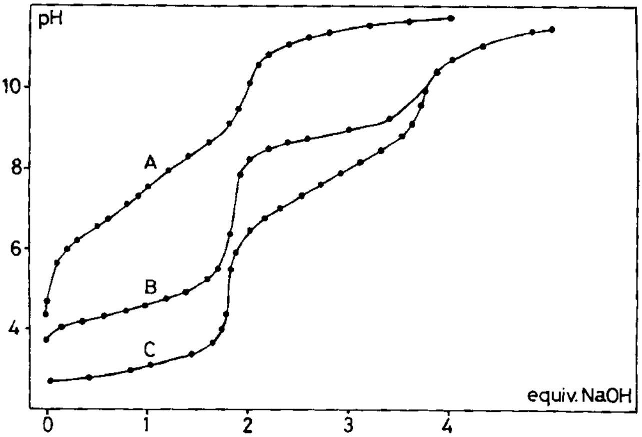


Fig. 1. *Potentiometric titration curves of 3,7-diazanonanedioic acid diamide*: [NaOH] = 0.2 $[L]_{tot} = 4 \cdot 10^{-3}$. A: no metal ion; B: $[Ni^{2+}]_{tot} = 3.6 \cdot 10^{-3}$; C: $[Cu^{2+}]_{tot} = 3.6 \cdot 10^{-3}$. ○ experimental points; —— calculated

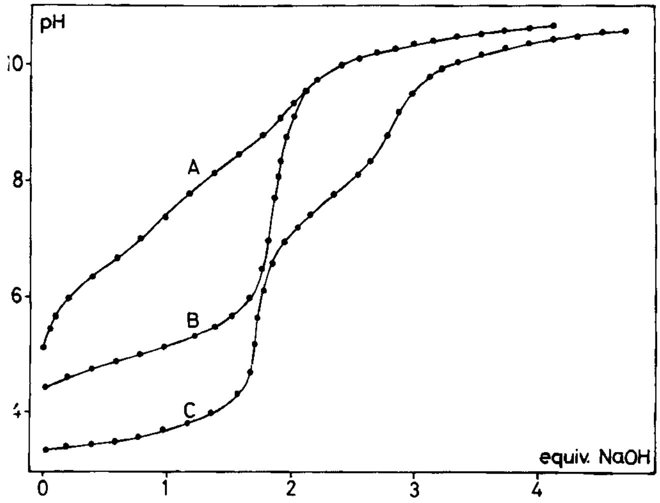


Fig. 2. *Potentiometric titration curves of 3,7-diazanonanedioic acid diethylamide.* $[NaOH] = 0.1$, $[L]_{tot} = 4 \cdot 10^{-4}$. A: no metal ion; B: $[Ni^{2+}]_{tot} = 3.6 \cdot 10^{-4}$; C: $[Cu^{2+}]_{tot} = 3.6 \cdot 10^{-4}$.
○ experimental points; —— calculated

(charges omitted).

$$H_2L \rightleftharpoons HL + H^+: \quad K_1^H = [H^+] \cdot [HL]/[H_2L] \qquad (2)$$

$$HL \rightleftharpoons L + H^+: \quad K_2^H = [H^+] \cdot [L]/[HL] \qquad (3)$$

$$ML \rightleftharpoons M + L: \quad K_1 = [M] \cdot [L]/[ML] \qquad (4)$$

$$ML \rightleftharpoons MH_{-1}L + H^+: \quad K_2 = [MH_{-1}L] \cdot [H^+]/[ML] \qquad (5)$$

$$MH_{-1}L \rightleftharpoons MH_{-2}L + H^+: \quad K_3 = [MH_{-2}L] \cdot [H^+]/[MH_{-1}L] \qquad (6)$$

Since $NiH_{-1}DANA^+$ is not formed in detectable amounts, K_4 was used to describe the direct conversion of ML into $MH_{-2}L$ (7).

$$ML \rightleftharpoons MH_{-2}L + 2H^+ \qquad K_4 = K_2 \cdot K_3 = [MH_{-2}L] \cdot [H^+]^2/[ML] \qquad (7)$$

In 1:1 mixtures with DANEA, three protons per Cu^{2+} and two protons per Ni^{2+} can be titrated (*cf.* Fig. 2). No polymeric species or complexes with ligand to metal ratios other than 1:1 were observed when the analytical concentrations of the ligand and/or metal ion were varied. σ_{rel}, which describes the accuracy of the curve fitting procedure, was always smaller than 0.5% and normally near 0.2%.

As $CuDANA^{2+}$ and $CuDANEA^{2+}$ are already completely formed at pH values corresponding to the beginning of the potentiometric titrations, their dissociation constants K_1 were obtained from spectrophotometric data. Similarly, potentiometric measurements were not useful to study the deprotonation of $CuH_{-1}DANEA^+$, which takes place above pH 11, and the formation of $CuDTDA^{2+}$ and $NiDTDA^{2+}$, which needs more than a 100-fold excess of DTDA · 2HCl to prevent hydrolysis. Even with this high excess of ligand, some turbidity occurred near pH 7 in the case of Ni^{2+}, and the corresponding K_1 may be in error by 0.2–0.3 logarithmic units.

Table 1. *Ligand deprotonation constants and dissociation constants of the Cu^{2+} and Ni^{2+} complexes*

	Ligand deprotonation		Cu^{2+} complexes			Ni^{2+} complexes	
	pK_1^H	pK_2^H	pK_1	pK_2	pK_3	pK_1	pK_4
DANA	6.55	8.40	10.23[a]	7.14 ± 0.02[b]	8.38 ± 0.01[b]	8.55 ± 0.02[b]	17.82 ± 0.04[b]
DANEA	6.54	8.38	10.73[a]	7.75 ± 0.02[b]	11.72[a]	8.45 ± 0.01[b]	–
DTDA	9.10 9.11[c]	10.80 10.81[c]	8.38[a]	–	–	5.1[a]	–

[a] Values determined spectrophotometrically.

[b] Calculated from 3 to 6 different titration curves.

[c] From [13].

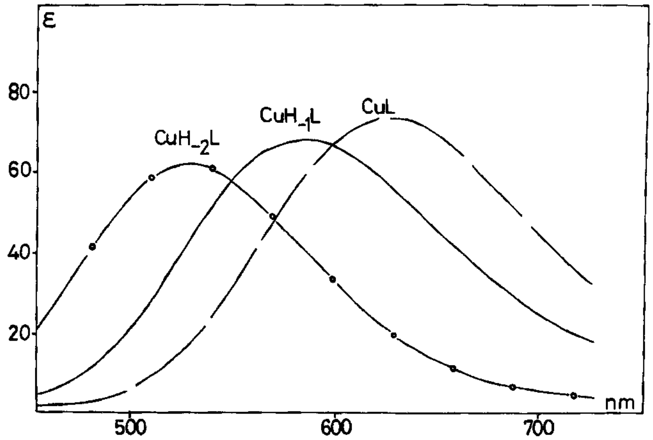


Fig. 3. *Visible absorption spectra of Cu^{2+} complexes with DANA*. $\lambda_{max}(\varepsilon)$: CuL: 628 (73), $CuH_{-1}L$: 584 (68), $CuH_{-2}L$: 526 (62)

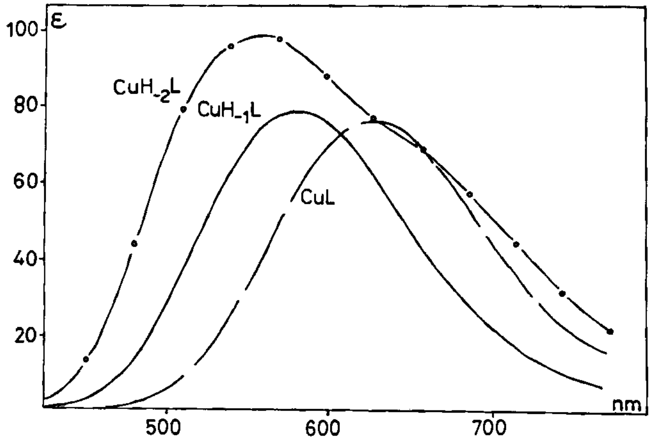


Fig. 4. *Visible absorption spectra of Cu^{2+} complexes with DANEA*. $\lambda_{max}(\varepsilon)$: CuL: 626 (80), $CuH_{-1}L$: 578 (82), $CuH_{-2}L$: 556 (102)

The equilibrium constants obtained by both methods are summarized in Tab. 1. Spectra taken at suitable pH values were used to calculate the spectra of the individual complexes (*cf.* Fig. 3–5) and to check the equilibrium constants.

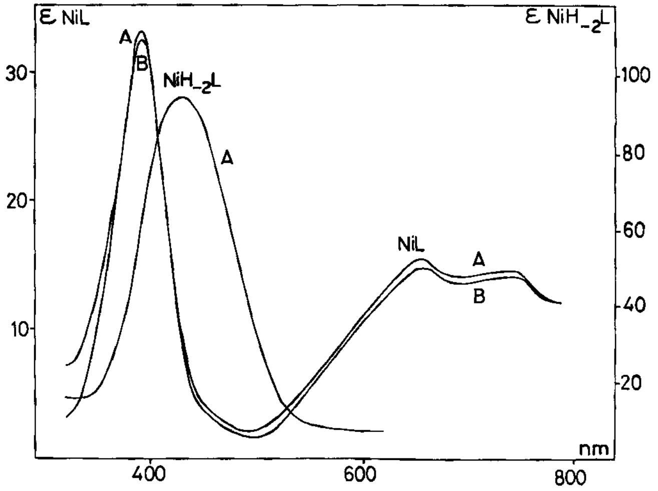


Fig. 5. *Visible absorption spectra of Ni^{2+} complexes with DANA (A) and DANEA (B).* $\lambda_{max}(\varepsilon)$: $NiDANA^{2+}$: 390 (16.0), 652 (6.9), 730 (6.4); $NiH_{-2}DANA$: 428 (92); $NiDANEA^{2+}$: 392 (16.4), 654 (7.2), 738 (6.6)

ML is formed with both ligands and both metal ions. Substitution of the two amide protons in DANA by ethyl groups to give DANEA has little influence on the basicity and complex forming ability of the neutral ligands (*cf.* Tab. 1). Similarities between $CuDANA^{2+}$ and $CuDANEA^{2+}$ as well as between $NiDANA^{2+}$ and $NiDANEA^{2+}$ are further documented by their spectral characteristics (*cf.* Fig. 3–5).

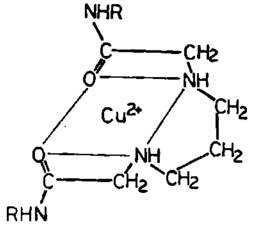
As has been discussed for N^{α}-(2-pyridylmethyl)-glycineamide and N^{α}-(2-pyridylmethyl)-glycineethylamide [3], the formation of chelate rings involving the carbonyl oxygens of the neutral amide group can be inferred from the stabilities of the complexes ML. Using the linear relation between pK^{H}-values and complex formation constants of structurally similar ligands [9], the stabilizing effect may be estimated by inspection of $\Delta pK = pK_1^H + pK_2^H - pK_1$ for the different systems (Tab. 2). Taking

Table 2. *Stabilization of $CuDANA^{2+}$, $CuDANEA^{2+}$, $NiDANA^{2+}$, and $NiDANEA^{2+}$ by chelation of the neutral amide groups*

Metal ion	Cu^{2+}		Ni^{2+}	
L	$pK_1^H + pK_2^H - pK_1 = \Delta pK_L$	Stab. E.[a]	$pK_1^H + pK_2^H - pK_1 = \Delta pK_L$	Stab. E.[a]
DANA	$6.55 + 8.40 - 10.23 = 4.72$	6.8	$6.55 + 8.40 - 8.55 = 6.4$	8.4
DANEA	$6.54 + 8.38 - 10.73 = 4.19$	7.3	$6.54 + 8.38 - 8.45 = 6.5$	8.3
DTDA	$9.10 + 10.80 - 8.38 = 11.52$	–	$9.10 + 10.80 - 5.1 = 14.8$	–

[a]) Stab. E. $= \Delta pK_{DTDA} - \Delta pK_L$

N,N′-dimethyl-trimethylenediamine as reference, stabilizing effects of 6.8, 7.3, 8.4, and 8.3 logarithmic units are obtained for $CuDANA^{2+}$, $CuDANEA^{2+}$, $NiDANA^{2+}$, and $NiDANEA^{2+}$, respectively. The stabilization observed with Cu^{2+} is roughly 3.5 logarithmic units per carbonyl group bound and comparable to that observed for terdentate ligands [3]. The structure of CuL is thus given by IV. With Ni^{2+}, the stabilization is 4.2 logarithmic units per carbonyl group. This somewhat larger value is in line with the fact that three configurations (V, VI, VII) of the ligand are possible in octahedral NiL, but only one in the square planar Cu^{2+} complexes (IV).



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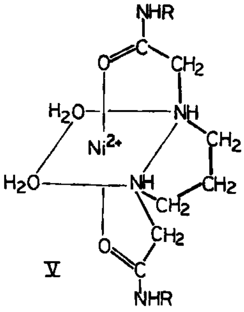

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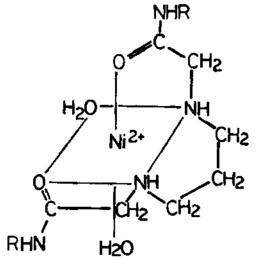

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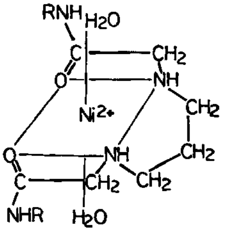

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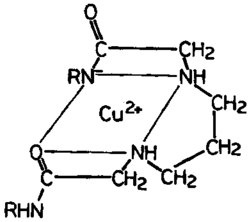

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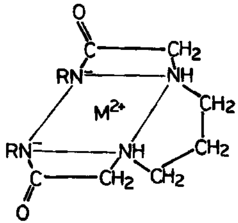
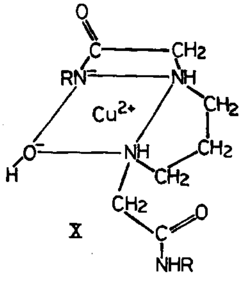


IX



X

$MH_{-1}L$. $CuH_{-1}DANA^+$ and $CuH_{-1}DANEA^+$ form with pK_2-values of 7.14 and 7.75, respectively. Deprotonation and binding of the peptide nitrogen (*cf.* VIII) is clearly indicated by the blueshift from 628 to 584 nm for DANA and from 626 to 578 nm for DANEA [3] [10]. The acidities of $CuDANA^{2+}$ and $CuDANEA^{2+}$ are surprisingly similar to those obtained with N^{α}-(2-pyridylmethyl)-glycineamide (7.11) and N^{α}-(2-pyridylmethyl)-glycine ethylamide (7.93), respectively [3].

In line with results reported by *Kim & Martell* [11] for triglycine and by *Kaden* [12] for N,N'-diglycyl-ethylenediamine and N,N'-diglycyl-trimethylenediamine, two protons are displaced in one step from $NiDANA^{2+}$, leading directly to $NiH_{-2}DANA$.

With DANEA the formation of a square planar species $NiH_{-2}DANEA$ is sterically impossible (see below) and $NiH_{-1}DANEA^+$ is not observed up to pH 12. These results suggest that in dilute aqueous solutions Ni^{2+} exclusively forms square planar complexes with deprotonated amide groups and that the ligand field exerted by two nitrogen donors is not sufficient ot stabilize this structure.

$MH_{-2}L$. Both $CuH_{-2}DANA$ and $NiH_{-2}DANA$ are fully formed below pH 9 and show spectra (*cf.* Fig. 3 and 5) typical for square planar Cu^{2+} and Ni^{2+} complexes with four nitrogen donor atoms (IX). In contrast, $CuH_{-2}DANEA$ only exists above pH 11.70 and absorbs at a considerably longer wavelength ($\lambda_{max} = 556$ nm) than $CuH_{-2}DANA$ ($\lambda_{max} = 526$ nm). The spectrum additionally exhibits a pronounced shoulder near 655 nm (*cf.* Fig. 4). Both features are not compatible with a Cu^{2+} ion coordinated to two amino nitrogens and two deprotonated amide groups in a square planar arrangement. Inspection of space filling models shows a strongly distorted complex. The spectrum could also be explained by a mixture of the two species $CuH_{-2}DANEA$ (IX) and $CuH_{-1}DANEA$ (OH) (X). Up to pH 12 we did not detect deprotonation of $NiDANEA^{2+}$. However, in 1–5 M NaOH containing a considerable excess of ligand, an unstable pale pink compound of unknown composition is formed. The nonexistence of a stable $NiH_{-2}DANEA$ indicates the importance of steric interaction between the two deprotonated ethyl amide groups. By analogy we assume that the two ethyl groups also prevent a regular planar arrangement for $CuH_{-2}DANEA$.

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