207. Stability, Formation and Dissociation Kinetics of the Pentacoordinate Ni^{2+} and Co^{2+} Complexes with 1,5-Diazacyclooctane-N,N'-diacetic Acid

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(5. V. 75)

Summary. The stability constants of the Ni^{2+} and Co^{2+} complexes with 1,5-diazacyclooctane-N,N'-diacetic acid ($H_2DACODA$) have been determined potentiometrically in 0.5M KNO_3 at 25°. Only M(DACODA) and M(DACODA)OH^- were observed.

In addition the formation and dissociation kinetics of the pentacoordinate complexes M(DACODA) has been studied in aqueous solution using a stopped-flow technique. Formation follows the rate law $v_f = k_f [M^{2+}] [HDACODA^-]/[H^+]$, which can be interpreted as a bimolecular process either between M^{2+} and $DACODA^{2-}$ ($k^{ML}_{M,L}$) or between MOH^+ and $HDACODA^-$ ($k^{ML}_{MOH,HL}$). The second order rate constants $k^{ML}_{M,L}$ are much higher than those expected from water exchange and can only be explained by a strong internal conjugate base effect. In the limiting case, however, this is equivalent to the second possible explanation, which assumes MOH^+ and $HDACODA^-$ as reactive species. The dissociation rate is given by $v_d = (k^{ML} + k^{ML}_H [H^+]) \cdot [M(DACODA)]$.

Most of our knowledge on the kinetics of complexation reactions has been obtained from studies on four- or six-coordinate transition metal ions. In general octahedral complexes react by a dissociative process, whereas ligand substitution of square planar compounds involves an associative mechanism [1].

Although in recent years the preparation and characterization of pentacoordinate complexes has shown that this coordination number is widespread [2], little detailed knowledge on mechanisms by which such complexes can react is available as yet. A few studies of five-coordinate systems in non-aqueous solutions have shown that the dissociative type is prevalent [3]. However, pentacoordinate dithiolene complexes react by both dissociative and associative pathways, the S_{N^2} component predominating [4]. Even less is known about reactions in aqueous solution. This is surprising since in view of the considerable volume of data available for complexes with other geometries, a comparative study seems obviously desirable in this solvent. *Lincoln & Hubbard* [5] have reported that the mechanism of the dissociation of the pentacoordinate Co^{2+}, Ni^{2+} and Cu^{2+} complexes with tris-(2-dimethylaminoethyl)-amine contrasts with that observed for six-coordinate systems, the rate limiting step being the dissiciation of the first amino group.

To increase our understanding of the reactivity of pentacoordinate metal ions and to see whether similar mechanisms can be found for other ligands, we have studied the formation and dissociation of Ni^{2+} and Co^{2+} complexes of 1,5-diazacyclooctane-

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N,N'-diacetic acid (H_2DACODA), which have been shown to be square pyramidal both in the crystalline state and in aqueous solution [6].

Experimental Part. – *1,5-Diazacyclooctane-N,N'-diacetic acid dihydrochloride (H_2DACODA. 2 HCl)* A slurry of the barium salt of DACODA [6] was treated at 50° with 0.2M H_2SO_4 until pH 3 was reached. The solution was filtered and evaporated. The residual oil was then dissolved in abs. EtOH and an excess of ethanolic HCl was added. On cooling white crystals of H_2DACODA. 2 HCl were obtained and dried *in vacuo*. Mp. 246–247°.

$C_{10}H_{20}Cl_2N_2O_4$	Calc.	C 39.62	H 6.65	Cl 23.39	N 9.24%
(303.20)	Found	„ 39.66	„ 6.74	„ 23.31	„ 9.11%

All reagents were of analytical grade and were used without further purification except the buffer bases, which were freshly distilled.

Equilibrium measurements were obtained on a Compensator E398 (*Metrohm*) with a combined glass electrode UX under 99.99% nitrogen at 25° and I = 0.5 (KNO_3). Ligand concentrations were varied from $7 \cdot 10^{-4}$ to $1.5 \cdot 10^{-2}$M and the metal to ligand ratio from 0.25 to 0.9. Only curves, which on duplication agreed within 0.02 pH units in the buffer regions and showed less than 0.5% deviation at the equivalence point, were used for the calculation of the equilibrium constants with the computer program VARIAT [7].

Kinetics measurements were made on a *Durrum* stopped-flow spectrophotometer with Kel-F blocks and a 2 cm cuvette at 25° and I = 0.5. Slower reactions were obtained on a *Techtron* 635 spectrophotometer with a *Honeywell* recorder 196 and a self made manual stopped-flow block. The reactions with Ni^{2+} were measured at 378 nm, those with Co^{2+} at 548 nm. All kinetics curves were of excellent first order character (excess of metal ion) and the standard deviation of the derived rate constants never exceeded 5%.

The formation of the Ni^{2+} and Co^{2+} complexes was studied in 0.05M α-picoline (pH 6.0–6.9) and 2,6-lutidine buffer (pH 6.9–7.2) with [H_2DACODA] = $2 \cdot 10^{-4}$ – $5 \cdot 10^{-4}$M and generally a 20 fold excess of metal ion. The dissociation reactions were measured in 0.1M acetate (pH 3.6–4.5), chloroacetate (pH 2.1–3.3), dichloroacetate (pH 1.4–2.2) buffers, or in HNO_3 of different concentrations (pH < 1) using complex concentrations of $5 \cdot 10^{-4}$ – $1 \cdot 10^{-3}$M. Solution of the metal complexes were prepared by mixing the ligand with a 20% excess of metal ion, increasing the pH to about 10 with NaOH, filtering the precipitated metal hydroxide and readjusting the pH to 6.8. The concentration of the stock solutions was then checked by optical analysis, using the molar absorptivities given in the literature [6].

The activation parameters were obtained by measuring the reaction rates at different temperatures under otherwise identical conditions.

Results and Discussion. – *Equilibrium constants.* The titration curve of 1,5-diazacyclooctane-N,N'-diacetic acid dihydrochloride (H_2DACODA. 2 HCl) shows that the two protons from the carboxylic groups are released below pH 3, whereas the two ammonium protons can be titrated in two steps with $pK_{H,1}$ –12.5 and $pK_{H,2}$ –4.82 (Fig. 1). The high value of $pK_{H,1}$ was calculated from the differences between the ligand curve and that of a strong acid, thus eliminating the necessity of an accurate pK_w determination. However, since even with [H_2DACODA] = $1.5 \cdot 10^{-2}$M the differences are relatively small and difficult to determine exactly, $pK_{H,1}$ may be subject to an error of ± 0.2 log units.

The large difference between the two pK_H as well as the extremely high value of $pK_{H,1}$ are unusual when compared to the results obtained from 1,5-diazacyclooctane ($pK_{H,1} = -10.74$ and $pK_{H,2} = -7.25$ [8]) or from ethylenediamine-N,N'-diacetic acid (EDDA) ($pK_{H,1} = -9.46$ and $pK_{H,2} = -6.42$ [9]), both of which contain structural elements of H_2DACODA. This is probably due to a strong intramolecular hydrogen bond as previously suggested for other N-substituted 1,5-diazacyclooctanes [10].

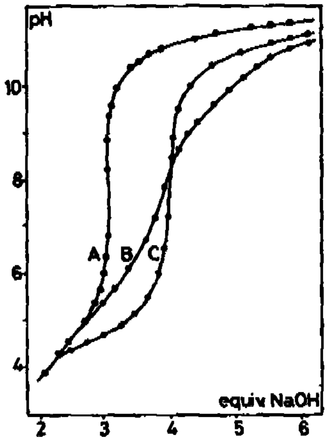

Fig. 1. *pH Titration of 1.25 · 10^{-4}M H_2DACODA. 2 HCl (A), 1.25 · 10^{-4}M H_2DACODA. 2 HCl and 1.1 · 10^{-4}M Co^{2+} (B) and of 1.25 · 10^{-4}M H_2DACODA. 2 HCl and 1.1 · 10^{-4}M Ni^{2+} (C).*
.... Experimental measurements, —— titration curve calculated with the constants given in Table 1.

In the presence of Ni^{2+} or Co^{2+} five protons per metal ion can be titrated (Fig. 1), indicating that besides the complexation reaction (1), hydrolysis of a coordinated water molecule also takes place (2).

$$M^{2+} + DACODA^{2-} \xrightleftharpoons{K_{M,1}} M(DACODA)OH_2 \qquad (1)$$

$$M(DACODA)OH_2 \xrightleftharpoons{K_{M,2}} M(DACODA)OH^- + H^+ \qquad (2)$$

The results, given in Table 1, show that the complexes with $DACODA^{2-}$ are less stable than those with $EDDA^{2-}$ by 2–3 log-units. In addition no hydrolysis has been observed for the EDDA complexes, whereas reaction (2) clearly takes place in the case of DACODA. This is not surprising, since it has been shown that the geometry and structure of the complexes with the two ligands differ [6]; whereas EDDA forms octahedral complexes, the coordination geometry of the Ni^{2+} and Co^{2+} complexes with DACODA is square pyramidal.

Table 1. *Dissociation constants of H_2DACODA and H_2EDDA and stability constants of their Ni^{2+} and Co^{2+} complexes*

X	$\log K_{X,1}^{DACODA}$[a]	$\log K_{X,2}^{DACODA}$[a]	$\log K_{X,1}^{EDDA}$[b]	$\log K_{X,2}^{EDDA}$[b]
H^+	12.5	4.82	9.46	6.42
Ni^{2+}	10.90	10.55	13.5	
Co^{2+}	9.14	9.48	11.2	

[a] At 25° and I = 0.5. [b] At 30° and I = 0.1 [9].

Kinetics and Mechanism. The kinetics of the formation of the Ni^{2+} and Co^{2+} complexes were followed between pH 6 and 7.5, where the ligand is present as $HDACODA^-$

The rate of this reaction is proportional to the metal concentration, the total ligand concentration and $1/[H^+]$ (3) (Fig. 2). The expression (3) can be transformed into a

$$v_f = k_f\,[M^{2+}]\,[HDACODA^-]/[H^+] = \qquad (3)$$

$$= k^{ML}_{M,L}\,[M^{2+}]\,[DACODA^{2-}] = \qquad (3a)$$

$$= k^{ML}_{MOH,HL}\,[MOH^+]\,[HDACODA^-] \qquad (3b)$$

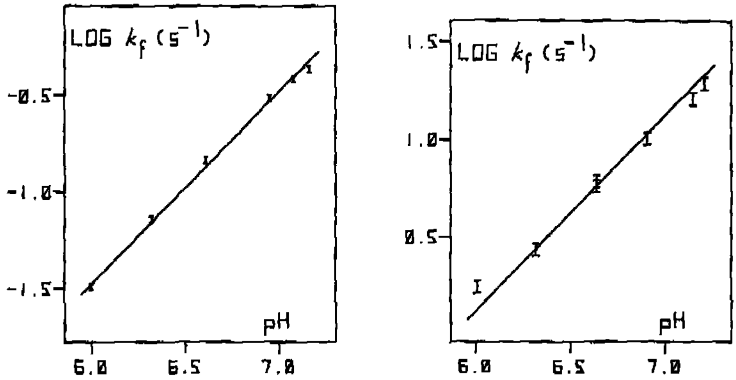

Fig. 2. *Relation between pH and rate of complex formation of DACODA^{2-} (2 · 10^{-4}M) with Ni^{2+} (8 · 10^{-3}M) (left) and of DACODA^{2-} (5 · 10^{-4}M) with Co^{2+} (10^{-2}M) (right) at 25° and I = 0.5.*
The calculated straight lines were obtained by using the k_f values of Table 2.

second-order rate law by replacing $[HDACODA^-]/[H^+]$ by $[DACODA^{2-}] \cdot K_{H,1}$ and putting $k^{ML}_{M,L} = k_f \cdot K_{H,1}$ (3a) or by taking $[M^{2+}]/[H^+] = [MOH^+] \cdot K_{MOH}$ and $k^{ML}_{MOH,HL} = k_f \cdot K_{MOH}$ (3b).

The dissociation rate measured between pH 1 and 4 follows equation (4) with one term independent of pH and one proportional to $[H^+]$ (Fig. 3).

$$v_d = (k^{ML} + k^{ML}_H[H^+])\,[M(DACODA)] \qquad (4)$$

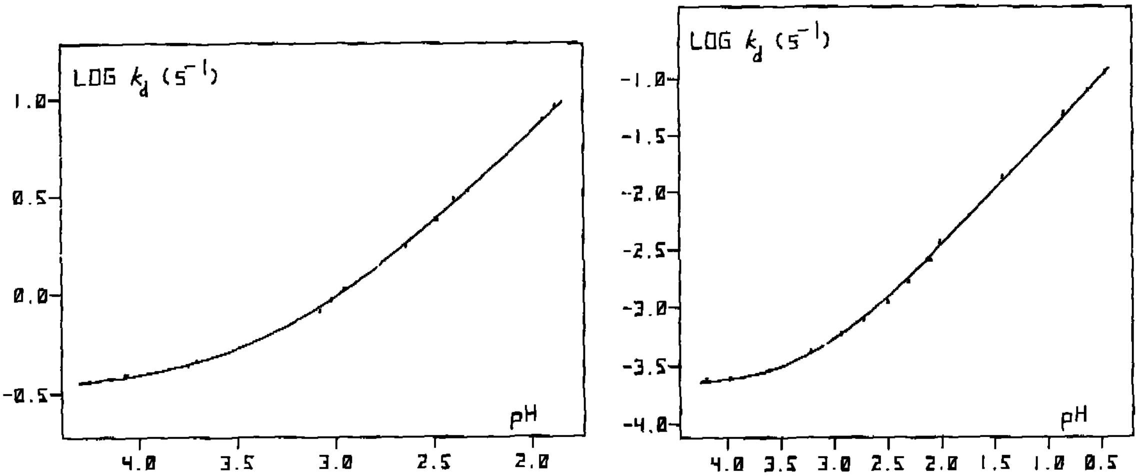

Fig. 3. *Relation between pH and rate of dissociation for Ni(DACODA) (10^{-3}M) (left) and for Co(DACODA) (5 · 10^{-4}M) (right) at 25° and I = 0.5.*
The curves were calculated using the k^{ML} and k^{ML}_H values of Table 2.

The rate constants as well as the activation enthalpies and entropies for the formation and dissociation of the Ni^{2+} and Co^{2+} complexes are given in Table 2.

Table 2. *Experimental rate constants, activation enthalpies and entropies for the formation and dissociation of the Ni^{2+} and Co^{2+} complex with DACODA^{2} at 25° and $I = 0.5$*

	k_f[a])	ΔH_f	ΔS_f	k^{ML}	ΔH^{ML}	ΔS^{ML}	k_H^{ML}	ΔH_H^{ML}	ΔS_H^{ML}
Ni^{2+}	$4.1 \cdot 10^{-6}$	16.6	−6.8	$2.1 \cdot 10^{-4}$	13.5	−29	0.33	11.7	−27
Co^{2+}	$1.3 \cdot 10^{-4}$	9.7	−22	0.33	7.6	−35	640	6.9	−34

a) Units: k_f and k^{ML} in s^{-1}; k_H^{ML} in $M^{-1}s^{-1}$; ΔH in kcal/mol and ΔS in cal/mol · degree.

For complexation reactions between transition metal ions and other amino carboxylate ligands a stepwise mechanism with an intermediate, in which a carboxylate is already bound to the metal ion, and coordination of the nitrogen as rate determining step has been proposed [11]. However, the second order rate constants $k_{M,L}^{ML}$ (Table 3) for Ni^{2+} and Co^{2+} with DACODA^{2-} are unusually high when compared to those of other aminocarboxylate ligands, which react by such a mechanism [14]. The most probable reason for the high value of $k_{M,L}^{ML}$ is the internal conjugate base effect [15]. Following *Turan* [16] a strongly basic amino group with $pK_{H,1} = -12.5$ as for DACODA^{2-} should enhance the reaction with Ni^{2+} by 4–5 orders of magnitude, although it is clear that internal conjugate base factors cannot be linearly extrapolated, when rates approach the diffusion controlled limit.

Table 3. *Resolved rate constants for the formation of the Ni^{2+} and Co^{2+} complexes with DACODA and equilibrium constants obtained from kinetics*

	$k_{M,L}^{ML}$ ($M^{-1}s^{-1}$)	$k_{MOH,HL}^{ML}$ a) ($M^{-1}s^{-1}$)	k^{ML} (s^{-1})	$\log K_{M,1} = \log(k_{M,L}^{ML}/k^{ML})$
Ni^{2+}	$1.3 \cdot 10^{7}$	$6.5 \cdot 10^{4}$	$2.1 \cdot 10^{-4}$	10.79 (10.90 b))
Co^{2+}	$4.1 \cdot 10^{8}$	$8.6 \cdot 10^{5}$	0.33	9.09 (9.14 b))

a) Calculated using the hydrolysis constant of 10.2 for Ni^{2+} [12] and 9.82 for Co^{2+} [13].
b) Values determined potentiometrically.

The extremely high conjugate base effect observed in the case of DACODA^{2-} indicates that the proton transfer from the solvated metal ion to DACODA^{2-} has taken place to a considerable extent in the outer-sphere complex. It is therefore legitimate to ask whether the pH-dependence of formation does not arise from a reaction between the hydrolysed species MOH^{+} and HDACODA^{-}, which represent the limiting case of the internal conjugate base mechanism. The second-order rate constants for this reaction are $6.5 \cdot 10^{4}\ M^{-1}s^{-1}$ for Ni^{2+} and $8.6 \cdot 10^{5}\ M^{-1}s^{-1}$ for Co^{2+} (Table 3), which seem more reasonable in view of the rate of water exchange for the two metal ions.

The dissociation kinetics is described by the two rate constants k^{ML} and k_H^{ML}, the second one reflecting the protonation of the free amino group.

Finally it is worth pointing out that the ratios $k^{ML}_{M,L}/k^{ML}$ agree nicely with the equilibrium constants measured potentiometrically (Table 3).

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208. Biosynthesis of Cytochalasans. Part 4. The Mode of Incorporation of Common Naturally-Occurring Carboxylic Acids into Cytochalasin D[1])

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(13. VI. 75)

Summary. Utilization of sodium [1-^{14}C]-, [2-^{14}C]-, and [1,2-^{13}C]-acetates, [1-^{14}C]-, [1-^{13}C]-, or [2-^{14}C]-propionates, [1-^{14}C]- or [2-^{14}C]-malonates, of [1-^{14}C]- or of [1-^{13}C]-myristic acid, or of [1-^{14}C]- and [1-^{13}C]-palmitic acid in the biosynthesis of cytochalasin D (**1**) by *Zygosporium masonii* was determined by degradation studies or by carbon magnetic resonance spectroscopy. The precursors were incorporated primarily *via* the acetate-malonate pathway to generate **1** from nine intact acetate units, eight of which are coupled in a head to tail fashion to form the C_{16}-polyketide moiety.

1. Introduction. – The nineteen cytochalasans isolated since 1966 comprise a class of microbial metabolites with great potential as tools in cell biology and medicine.

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[1]) Part 3 see [1].