Monatshefte für Chemie 124, 267–276 (1993)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Ternary Complexes of Nickel(II) with *AMP*, *ADP* and *ATP* as Primary Ligands and Some Biologically Important Polybasic Oxygen Acids as Secondary Ligands

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Summary. Potentiometric equilibrium measurements have been made at 25 ± 0.1 °C ($\mu = 0.1$ mol dm^{-3} KNO_3) for the interaction of adenosine-5′-mono-, -di-, and -triphosphate (*AMP*, *ADP*, and *ATP*) and Ni(II) with biologically important secondary ligand acids (malic, maleic, succinic, tartaric, citric and oxalic acids) in a 1:1:1 ratio and the formation of various 1:1:1 mixed ligand complex species inferred from the potentiometric *pH* titration curves. Initial estimates of the formation constants of the resulting species and the acid dissociation constants of *AMP*, *ADP*, *ATP* and secondary ligand acid, have been refined with SUPERQUAD computer program. In some systems $\Delta \log K$ values are positive, i.e. the ternary complexes are found to be more stable than the corresponding binary complexes. H-bond formation seems to be most effective in deciding the stability of the ternary complexes formed in solution. Stabilities of mixed ligand complexes increases in the order *AMP* < *ADP* < *ATP*. With respect to the secondary ligands, the formation constants of the mixed lignads complexes decrease in the order succinic > maleic > tartaric > malic > citric > oxalic acid.

Keywords. Ternary complexes; Nickel(II); *AMP*; *ADP*; *ATP*; Polybasic oxygen acids; Potentiometry.

Ternäre Komplexe von Nickel(II) mit *AMP*, *ADP* und *ATP* als Primärliganden und einigen biologisch wichtigen polyfunktionellen Carbonsäuren als Sekundärliganden

Zusammenfassung. Es wurde die Wechselwirkung von Adenosin-5′-mono-, -di- und -triphosphat (*AMP*, *ADP* und *ATP*) und Ni(II) mit biologisch relevanten Säuren als Sekundärliganden (Äpfel-, Malein-, Bernstein-, Wein-, Zitronen- und Oxalsäure) im Verhältnis 1:1:1 mittels potentiometrischer Gleichgewichtsmessungen bei 25 ± 0.1 °C und $\mu = 0.1$ mol dm^{-3} KNO_3 untersucht. Aus den potentiometrische *pH*-Titrationen ergaben sich verschiedene 1:1:1-Komplexe mit gemischten Liganden. Zunächst abgeschätzte Komplexbildungskonstanten und Säuredissoziations-konstanten von *AMP*, *ADP*, *ATP* mit den als Sekundärliganden eingesetzten Säuren wurden über das SUPERQUAD-Rechenprogramm verfeinert. In einigen Systemen sind die Werte von $\Delta \log K$ positiv, was bedeutet, daß die ternären Komplexe stabiler sind als die entsprechenden binären Komplexe. In einige ternären Komplexen scheinen die Wasserstoffbrücken zwischen den Liganden entscheidend zu sein. Die Stabilitäten der gemischten Liganden steigen in der Reihe *AMP* < *ADP* < *ATP* an. Bezüglich der Sekundärliganden ergibt sich die absteigende Stabilitätsreihung Bernsteinsäure > Maleinsäure > Weinsäure > Äpfelsäure > Zitronensäure > Oxalsäure.

Introduction

Metal ion complex formations are among the prominent interactions in nature [1–3] and the polybasic oxygen acid residues are important metabolic intermediates in biological systems, while ribonucleotides adenosine-5′-mono, -di-, and -triphosphates (*AMP*, *ADP*, and *ATP*) are equally important as substrates for many enzymic reactions [4–7]. Ternary complexes of divalent transition metal ions with *AMP*, *ADP*, and *ATP* and other secondary ligands, viz. catechols, ethanolamines, 2,2′-bipyridyl, ethylene diamine, pyrocatecholate, biogenic amines, 1,10-phenanthroline, tyrosine, phenylalanine, glycine, histidine, imidazole, amonia, and aliphatic dipeptides have been investigated using several techniques [8–22] (*pH*-potentiometric, spectrophotometric, and calorimetric). For an improved understanding of the driving forces leading to mixed ligand complexes of the type Ni(II)-nucleotide-polybasic carboxylic acids (Ni(II)-NU-CA), where nucleotide = *AMP*, *ADP* or *ATP* and carboxylic acid = malic, maleic, succinic, tartaric, citric or oxalic acid, have been investigated by potentiometric *pH* titrations to determine the stability constants of the complexes formed, as these systems mimic many biological reactions which may involve ribonucleotides-metal ion-metabolic intermediates interaction.

Experimental Part

Adenosine-5′-monophosphoric acid disodium salt $C_{10}H_{12}N_5Na_2O_7P \cdot H_2O$ ($Na_2AMP \cdot H_2O$), adenosine-5′-diphosphoric acid disodium salt $C_{10}H_{12}N_5Na_2O_{10}P_2 \cdot 2H_2O$ ($Na_2ADP \cdot 2H_2O$) and adenosine-5′-triphosphoric acid disodium salt $C_{10}H_{14}N_5Na_2O_{13}P_3 \cdot 3H_2O$ ($Na_2ATP \cdot 3H_2O$) were purchased from Sigma Chemical Co. and were used without purification. The amount of free phosphates initially present in the nucleotides were determined [23]. To account for this and to prepare metal ion nucleotide solutions of exactly 1:1 ratio, we also determined by potentiometric *pH* titrations the molecular weight of the purchased nucleotides. $Ni(NO_3)_2 \cdot 6H_2O$, nitric acid, NaOH and organic carboxylic acids (malic, maleic, succinic, tartaric, citric, and oxalic acids) were of p.a. grade. The concentration of NaOH used for the titrations was determined with potassium hydrogen phthalate (Merck AG). The concentrations of the metal ion stock solutions were determined with *EDTA*.

Potentiometric *pH* measurements were made with solutions in a double-walled glass vessel using a Beckman model 4500 digital *pH* meter with a precision of ± 0.1 mV. The potentiometric system was connected to a glass electrode (Metrohm 1028) connected against a double junction reference electrode (Orion 9020). The titrant was delivered by an Amel 882 dispenser, readable to 1 μl. The measurement-cell was kept at a temperature constant within ± 0.1 °C and a magnetic stirrer was used. Purified nitrogen was bubbled through the solutions during titrations.

The test solution (50 ml) was titrated with standard CO_2-free potassium hydroxide. The electrodes were calibrated, in both the acidic and alkaline regions, by titrating 0.01 mol dm^{-3} nitric acid with standard potassium hydroxide under the same experimental conditions. Carbonate free KOH was standardised against standard potassium hydrogen phthalate by using a Gran plot.

The concentration of free hydrogen ion h, at each point of the titration is related to the measured *emf*, E° of the cell by the Nernst equation:

$$E = E^\circ + Q \log h \tag{1}$$

where E° is a constant which includes the standard potential of the glass electrode, and Q is the slope of the glass electrode response. The value of E° for the electrode was determined from a Gran plot derived from a separate titration, using measurements in volts, of nitric acid with standard KOH solution under the same temperature and medium conditions as for the test solution titration. The

data so obtained were analysed by the non-linear least-squares computer program ESAB2M [24] to refine E° and the autoprotolysis constant of water, K_W.

In order to avoid hydrolysis prior to potentiometric measurements, samples of the nucleotides were weighed as the solid and added to the reaction vessel just prior to performing the titration. The solutions titrated can be represented according to the following scheme:

HNO_3 (a); HNO_3 + nucleotide (b); HNO_3 + nucleotide + Ni(II) (c); HNO_3 + polybasic carboxylic acid (d); HNO_3 + polybasic carboxylic acid + Ni(II) (e); HNO_3 + nucleotide + polybasic carboxylic acid + Ni(II) (f). A constant ionic strength was obtained with 0.1 mol dm^{-3} KNO_3 and the total volume was kept constant at 50 ml.

Results and Discussion

To calculate the initial estimates of the stability constants of the ternary complexes of Ni(II) with *AMP*, *ADP*, *ATP* and malic, maleic, succinic, tartaric or oxalic acid the following equations were used:

$$\mathrm{Ni(II)}(NU) + CA \rightleftharpoons \mathrm{Ni(II)}(NU)(CA) \tag{2}$$

$$K^{\mathrm{Ni(II)}(NU)}_{\mathrm{Ni(II)}(NU)(CA)} = \frac{[\mathrm{Ni(II)}(NU)(CA)]}{[\mathrm{Ni(II)}(NU)][CA]} \tag{3}$$

[$\mu = 0.1\ M\ (KNO_3)$, 25 °C]

$$\mathrm{Ni(II)} + NU \rightleftharpoons \mathrm{Ni(II)}(NU) \tag{4}$$

$$K^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(NU)} = \frac{[\mathrm{Ni(II)}(NU)]}{[\mathrm{Ni(II)}][NU]} \tag{5}$$

$$\mathrm{Ni(II)} + CA \rightleftharpoons \mathrm{Ni(II)}(CA) \tag{6}$$

$$K^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(CA)} = \frac{[\mathrm{Ni(II)}(CA)]}{[\mathrm{Ni(II)}][CA]} \tag{7}$$

where CA is a polybasic carboxylic acid and NU a nucleotide.

It is assumed, for convenience, that complexation of the secondary ligand (CA) starts after the complete formation of the Ni(II)(NU) 1:1 complex. Thus, the overall stability constant $\beta^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(NU)(CA)}$ may be represented by Eq. (8).

$$\mathrm{Ni(II)} + NU + CA \rightleftharpoons \mathrm{Ni(II)}(NU)(CA) \tag{8}$$

$$\beta^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(NU)(CA)} = \frac{[\mathrm{Ni(II)}(NU)(CA)]}{[\mathrm{Ni(II)}][NU][CA]} = K^{\mathrm{Ni(II)}(NU)}_{\mathrm{Ni(II)}(NU)(CA)} \cdot K^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(NU)} \tag{9}$$

Formation constants and protonation constants were refined with the SUPERQUAD computer program [25]. All calculations were performed on a IBM XT 286 personal computer. The constants were refined by minimizing the error-square sum, U, of the potentials:

$$U = \Sigma W_i (E_{obs} - E_{calc})^2 \tag{10}$$

where E_{obs} and E_{calc} refer to the measured potential and that calculated from Eq. (1). The weighing factor W_i is defined as the reciprocal of the estimated variance of the

measurement

$$W_i = 1/\sigma^2 = 1/[\sigma^2 + (\delta E/\delta V)\sigma^2] \tag{11}$$

where σ_E and σ_V are the estimated variances of the potential and volume readings, respectively. The quality of fit was judged by the values of the sample standard deviation, S, and the goodness of fit, X^2, (Pearson's test). At $\sigma_E = 0.1$ mV (0.001 pH error) and $\sigma_V = 0.005$ ml, the values of S in different sets of titrations were between 1.0 and 1.8, and X^2 was between 12.0 and 13.0. The scatter of residuals ($E_{obs} - E_{calc}$) vs. pH was reasonably random, without any significant systematic trends, thus indicating a good fit of the experimental data.

At the experimental pH values used in the calculation in this work the interfering effects of hydroxo complexes are negligible. Thus the secondary ligand, CA, combine with the binary 1:1 Ni(II)(NU)$\{$[Ni(II)(AMP)], [Ni(II)$(ADP)^{-1}$] and [Ni(II)$(ATP)]^{2-}\}$ complex in a similar manner as its interaction with aquated metal ions $[Ni(H_2O)_6]^{2+}$ in solutions. Thus the initial estimates of the stability constants of the ternary complexes formed in solution have been determined using the Rossotti and Irving formula [26]. These values were then refined using the SUPERQUAD computer program [25]. The determined acidity constants of malic, maleic, succinic, tartaric, citric, and oxalic acids and the stability constants of their binary Ni(II) complexes are in a good agreement with those reported in literature [27, 28]. The two acid formation constants values for AMP, ADP, and ATP and the stability

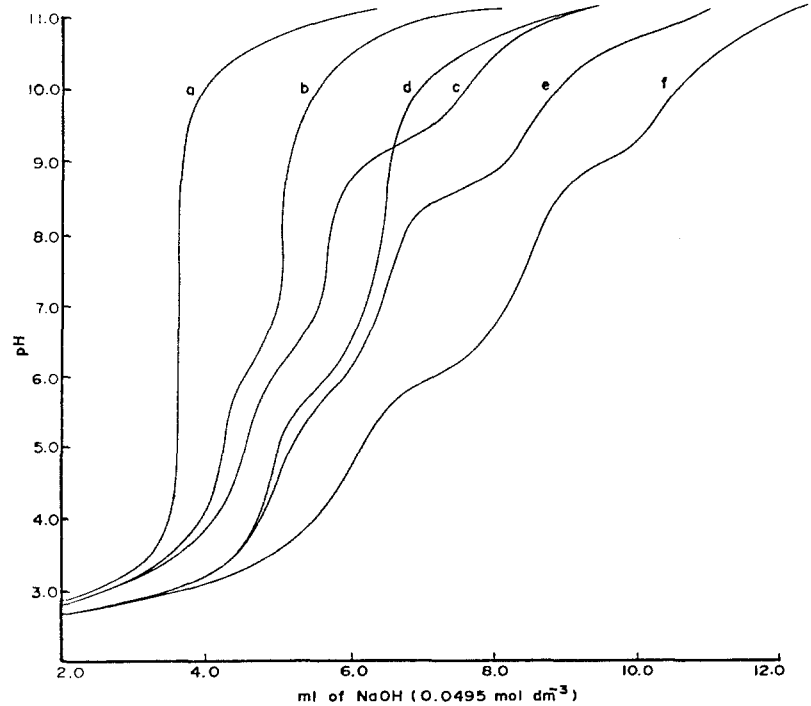

Fig. 1. Potentiometric titration curves for the Ni(II)-AMP-maleic acid system at 25 °C and $\mu = 0.1$ mol dm^{-3} KNO_3: (a) 0.0037 mol dm^{-3} HNO_3; (b) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} AMP; (c) solution (b) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (d) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} maleic acid; (e) solution (d) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (f) solution (e) + $1 \cdot 10^{-3}$ mol dm^{-3} AMP

constants of their Ni(II) complexes were determined from the titration curves and the results were found to cope much with those reported in literature [27, 29, 30, 31].

Early workers [32–35] found pKa_1 values of 3.5–4.2 to be associated with proton ionization from the protonated forms of *AMP*, *ADP* and *ATP*. By analogy with aniline (protonated aniline, $pK = 4.6$) [36], it was stated by them and later workers [37, 38] that ionization is from the $C_6NH_3^+$ group. The second proton ionization was attributed to the phosphate groups.

Coordination of Ni(II) with the phosphate groups of ribonucleotides has been demonstrated in aqueous [39, 40] solutions for *AMP*, *ADP*, and/or *ATP* by ^{31}P NMR and potentiometric [41] studies. Interaction with all available phosphates is indicated by ^{31}P NMR spectra in the cases of *AMP* [40], *ADP* [39], and *ATP* [39, 42]. A Raman spectral study [43] of Ni(II)-*ATP* interactions shows the Ni(II) to bind the base moiety and to promote intra-molecular base-phosphate interaction. Proton NMR data indicate that Ni(II) binds the adenine ring of *ADP* [39] and *ATP* [39, 44]. Since the C_8H peak is broadened [39], coordination apparently occurs at the N_7 site of *ADP* and *ATP* with possible participation from the C_6NH_2 group [45]. However, in an examination [46] of the conformational possibilities for metal-nucleotide interaction the author discounts the C_6NH_2 group as a complexing site. He points out that the amino group in adenine is highly conjugated with the ring and has considerable double bond character with a

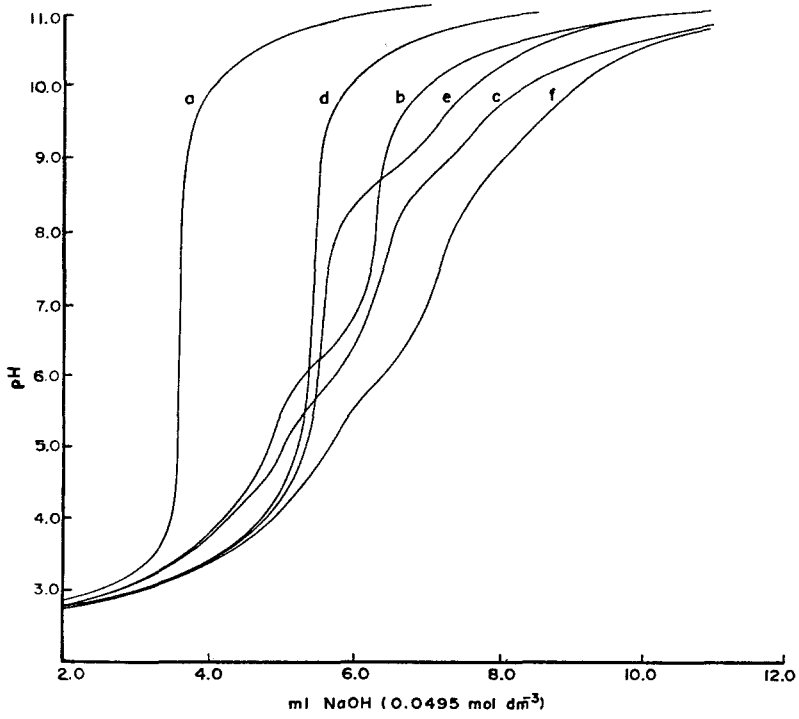

Fig. 2. Potentiometric titration curves for the Ni(II)-*ADP*-tartaric acid system at 25 °C and $\mu = 0.1$ mol dm^{-3} KNO_3: (a) 0.0037 mol dm^{-3} HNO_3; (b) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} *ADP*; (c) solution (b) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (d) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} tartaric acid; (e) solution (d) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (f) solution (e) + $1 \cdot 10^{-3}$ mol dm^{-3} *ADP*

resulting lowered basicity compared to the amino groups of aniline or amino acids. Support for the binding of metal ion to the base moiety of *ATP* is found in a proton NMR and kinetic study [47]. The experimental data were accounted for by assuming that a water molecule forms a bridge between the Ni(II) and the N_7 site. The remaining metal coordination sites were phosphate oxygen atoms. Thus, there is lack of agreement as to the assignment of the site of coordination. Our opinion in this point will be discussed later.

In Figs. 1–3 representative set of experimental titration curves obtained according to the sequence described in the experimental section for the different Ni(II)-*NU*-*CA* systems are displayed. It is observed that the Ni(II)-*NU* titration curves (c) diverge from the nucleotide curve (b) in the lower *pH* range ($pH \sim 3.50$), indicating the formation of a Ni(II)-NU complex. Generally, the complex titration curves show an inflection after addition of two moles of base per one mole of the nucleotide (*AMP*, *ADP* or *ATP*). This indicates the simultaneous dissociation of two protons from the nucleotide. Ni(II)-*NU* are quite stable up to high *pH* values, i.e. they have no tendency to form hydroxo complexes. With respect to the titration curves of the Ni(II) carboxylic acid binary complex solutions studied, one may deduce that these complexes begin to form at $pH > 4.0$. Generally, for all Ni(II) carboxylic acid complexes studied precipitation occurred at *pH*'s > 10.5. In all cases no calculations

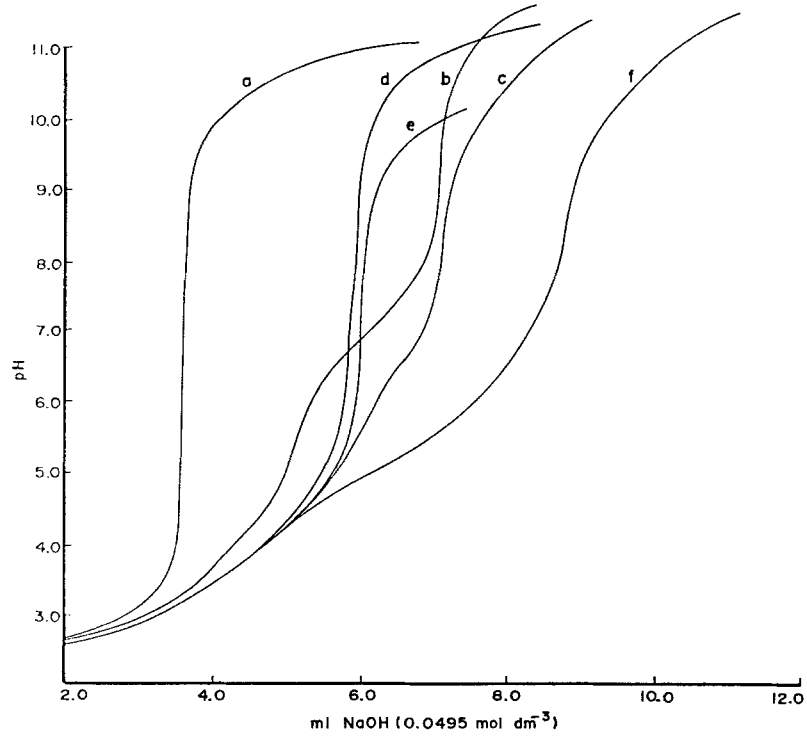

Fig. 3. Potentiometric titration curves for the Ni(II)-*ATP*-malic acid system at 25 °C and $\mu = 0.1$ mol dm^{-3} KNO_3: (a) 0.0037 mol dm^{-3} HNO_3; (b) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} *ATP*; (c) solution (b) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (d) solution (a) + $1 \cdot 10^{-3}$ mol dm^{-3} malic acid; (e) solution (d) + $1 \cdot 10^{-3}$ mol dm^{-3} Ni(II); (f) solution (e) + $1 \cdot 10^{-3}$ mol dm^{-3} *ATP*

Table 1. Formation constants for the binary Ni(II)-nucleotide or -carboxylic acid complexes and those for the mixed ligand complexes Ni(II)-nucleotide-carboxylic acid at 25 °C and $\mu = 0.1\ M\ KNO_3$

Ligand	$\log K^{Ni(II)}_{Ni(II)(Nucleotide)}$ or $\log K^{Ni(II)}_{Ni(II)(CA)}$	$\log K^{Ni(II)(AMP)}_{Ni(II)(AMP)(CA)}$	$\log K^{Ni(II)(ADP)}_{Ni(II)(ADP)(CA)}$	$\log K^{Ni(II)(ATP)}_{Ni(II)(ATP)(CA)}$	$\log \beta^{Ni(II)}_{Ni(II)(AMP)(CA)}$	$\log \beta^{Ni(II)}_{Ni(II)(ADP)(CA)}$	$\log \beta^{Ni(II)}_{Ni(II)(ATP)(CA)}$	$\Delta \log K'$	$\Delta \log K''$	$\Delta \log K'''$
AMP	4.001 ± 0.04	–	–	–	–	–	–	–	–	–
ADP	4.471 ± 0.03	–	–	–	–	–	–	–	–	–
ATP	4.949 ± 0.060	–	–	–	–	–	–	–	–	–
Oxalic acid	4.432 ± 0.03	4.090 ± 0.02	4.320 ± 0.03	5.002 ± 0.04	8.091	8.791	9.951	−0.342	−0.112	+0.57
Succinic acid	5.921 ± 0.04	4.969 ± 0.03	5.520 ± 0.05	5.986 ± 0.04	8.970	9.991	10.935	−0.952	−0.401	+0.065
Tartaric acid	4.682 ± 0.02	4.635 ± 0.02	5.138 ± 0.04	5.412 ± 0.02	8.636	9.609	10.361	−0.047	+0.456	+0.73
Malic acid	4.583 ± 0.04	4.352 ± 0.04	4.742 ± 0.03	5.163 ± 0.03	8.353	9.213	10.112	−0.231	+0.159	+0.58
Maleic acid	5.270 ± 0.03	4.740 ± 0.02	5.373 ± 0.02	5.523 ± 0.02	8.741	9.844	10.472	−1.030	+0.103	+0.053
Citric acid	4.536 ± 0.04	4.126 ± 0.03	4.548 ± 0.03	5.082 ± 0.03	8.127	9.019	10.031	−0.410	+0.012	+0.546

$\Delta \log K' = \log K^{Ni(II)(AMP)}_{Ni(II)(AMP)(CA)} - \log K^{Ni(II)}_{Ni(II)(CA)}$

$\Delta \log K'' = \log K^{Ni(II)(ADP)}_{Ni(II)(ADP)(CA)} - \log K^{Ni(II)}_{Ni(II)(CA)}$

$\Delta \log K''' = \log K^{Ni(II)(ATP)}_{Ni(II)(ATP)(CA)} - \log K^{Ni(II)}_{Ni(II)(CA)}$

have been performed beyond the precipitation point, since the hydroxospecies likely to be formed after this point could not be studied.

For the titration curves of the ternary systems, Ni(II)-*NU*-*CA*, one observes that the (C, F) are well separated at $pH \sim 4.50$. This behaviour reveals that in these *pH* ranges coordination of the secondary ligand, carboxylic acid, with Ni(II)-*NU* starts.

Examination of the different formation constants values listed in Table 1 clearly reveals that the formation constants of the mixed ligand complexes increase in the order $AMP < ADP < ATP$. Though many studies in solution favoured the phosphate group rather than the base as the primary metal binding site, the simultaneous binding of Ni(II) ion to base moiety and phosphate may be reported in the mixed ligand complexes formed in the present work. Thus the Ni(II) bound to the base moiety may promote intra-molecular base–phosphate interaction. Thus, the mixed ligands studied may be considered as relatively simple models from which information may be gained about the properties of nucleotides and their base moieties regarding the strength of their interactions with important metabolic intermediates (polybasic oxygen acids) and even insight into the factors which influence this strength is thus becoming available.

With respect to the secondary ligands, the formation constants of the mixed ligand complexes decrease in the following order: succinic > maleic > tartaric > malic > citric > oxalic. This behavior can be interpreted in terms of the basicities ($\Sigma pKa_1 + pKa_2$) of the secondary ligand carboxylic acids used. It is well known that the increase in basicity of a ligand increases the stability of its metal complexes.

$\Delta \log K$, defined by Eq. (12), is a measure for the stability of the ternary complexes

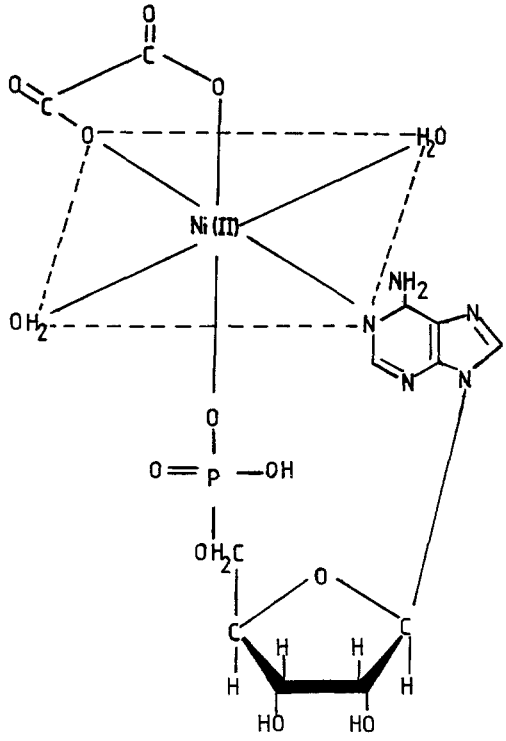

Fig. 4. Tentative structure of Ni(II)-AMP-oxalic acid (1:1:1) ternary complex

with respect to the binary complexes,

$$\Delta \log K = \log K^{\mathrm{Ni(II)}(NU)}_{\mathrm{Ni(II)}(NU)(CA)} - \log \mathrm{K}^{\mathrm{Ni(II)}}_{\mathrm{Ni(II)}(NU)} \quad (12)$$

In the case of Ni(II)-*NU*-*CA* systems, $\Delta \log K$ is found to be slightly positive or negative (Table 1) in accordance with statistical expectations [48]. The $\Delta \log K$ values for the Ni(II)-*AMP*-*CA* systems are negative in accordance with the statistical considerations [44] where the statistical, steric, and electrostatic factors result in a lower stability constant for the 1:1:1 metal/ligand complexes as compared with those for the binary systems. The higher stability constant of Ni(II)-*ATP*-*CA* ternary complexes compared with the binary systems may be attributed to some interligand interactions, possibly H-bond formation.

Based on these results we propose Fig. 4 as a representative structure of the ternary metal complexes, (in this case Ni(II)-*AMP*-oxalic acid) formed in solution. The structure allows: (i) minimum stric hindrance between two ligands, and (ii) simultaneous binding of Nickel(II) ion to base and phosphate residue during the formation of the ternary complex.

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Received February 26, 1992. Revised April 3, 1992. Accepted April 10, 1992