Potentiometric Studies on the Formation Equilibria of Binary and Ternary Complexes of Some Metal Ions with Dipicolinic Acid and Amino Acids

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The binary and ternary complexes of Mg^{2+}, Ca^{2+} , Sr^{2+} , Ba^{2+} , Co^{2+} , Ni^{2+}, Mn^{2+}, and Cd^{2+} metal ions with dipicolinic acid as a primary ligand and some selected mono- and dicarboxylic amino acids as biologically relevant secondary ligands were studied in solution using a potentiometric technique. The acidity constants of the ligands selected were determined potentiometrically and used for determining the stability constants of the complexes formed in aqueous solution at 25 °C and ionic strength $I = 0.10$ mol dm^{-3} ($NaNO_3$). The lower stability of 1:2 binary complexes of amino acids compared to that of the corresponding 1:1 systems is in accord with statistical considerations. The formation of ternary complexes was found to take place in a stepwise manner. The order of stability of the binary and ternary complexes in terms of the nature of the amino acid is investigated and discussed. The values of $\Delta \log K$ for ternary systems involving amino acids have been evaluated and discussed.

Introduction

Over the years there has been a steadily increasing interest in studying the binary and ternary complexes of pyridine derivatives[1−13] arising in part due to their physiological properties. The importance of pyridinecarboxylic acids stems from their presence in many natural products such as alkaloids, vitamins, and coenzymes. These compounds are of particular interest to medicinal chemists because of the wide variety of physiological properties displayed by natural and synthetic acids. Moreover, many of the pyridinecarboxylates are versatile ligands and their complexes with some metal ions have found use in medicine and in quantitative analysis. Pyridinecarboxylic acid metal complexes are, therefore, especially interesting model systems. Amino acids and their metal complexes are equally important compounds, since they have frequent utilization in both biological and chemical applications.[14−17]

In continuation of our research program to study the complexation equilibria and stabilities of binary and ternary complexes with biologically important ligands,[18−20] this paper reports on the formation equilibria of binary and ternary complexes of some alkaline earth and transition metal(II) ions involving dipicolinic acid as a primary ligand and some selected amino acids as secondary ligands. The stability constants of the investigated complexes are studied at 25 °C and ionic strength $I = 0.10$ mol dm^{-3} $NaNO_3$ using potentiometric pH titrations.

Experimental Section

Apparatus. Potentiometric pH measurements were performed on solutions in a double-walled glass vessel at 25 °C using a Griffin pH J-300-010 G digital pH meter. The temperature was controlled by circulating water through the jacket, from a constant-temperature bath. The cell was equipped with a magnetic stirrer and a tightly fitting rubber stopper, through which an Amel 882 delivery dispenser, readable to 1 μL, and an electrode system were inserted. The electrode system was calibrated in terms of hydrogen ion concentrations instead of activities. It is to be assumed that the activity coefficient is constant, an assumption usually justified by performing the experiments with a medium of high ionic strength (0.1 mol dm^{-3} $NaNO_3$). The electrode system was calibrated by periodic titrations of HNO_3 (or NaOH) solution (0.1 mol dm^{-3} in $NaNO_3$) with standard NaOH (or HNO_3) solution. Thus, all constants determined in the present work are concentration constants.

Materials and Solutions. Dipicolinic acid was an A.R. product (Fluka). The reagent was repeatedly recrystallized from water, dried at 115 °C, and checked by its melting point (250−255)°C. Stock solutions were prepared by dissolving precisely weighed amounts of the anhydrous acid in suitably bidistilled water. Amino acids were also provided by Fluka and used without further purification. The metal salts were provided by BDH as nitrates or chlorides. All solutions of metal(II) ions were prepared and standardized complexometrically by EDTA using suitable indicators.[21] Carbonate-free sodium hydroxide (titrant, prepared in 0.1 mol dm^{-3} $NaNO_3$ solution) was prepared by dissolving the Analar pellets in CO_2-free bidistilled water, and the solution was standardized potentiometrically with KH-phthalate (Merck AG). Nitric acid, sodium hydroxide, and sodium nitrate were from Merck p.a.

Procedure. The following solutions were prepared (total volume 50 mL) and titrated potentiometrically against standard carbonate-free NaOH (0.2003 mol dm^{-3}) solution: (a) HNO_3 (0.0041 mol dm^{-3}) + $NaNO_3$ (0.10 mol dm^{-3}); (b) solution a + (0.001 mol dm^{-3}) dipicolinic acid; (c) solution b + (0.0004 mol dm^{-3}) metal ion; (d) solution a + (0.001 mol dm^{-3}) amino acid; (e) solution d + (0.0004 mol dm^{-3}) metal ion; (f) solution a + (0.001 mol dm^{-3}) metal ion + (0.001 mol dm^{-3}) dipicolinic acid + (0.001 mol dm^{-3}) amino acid.

Each of the above solutions was thermostated at 25 °C with an accuracy of ±0.1 °C, where the solutions were left

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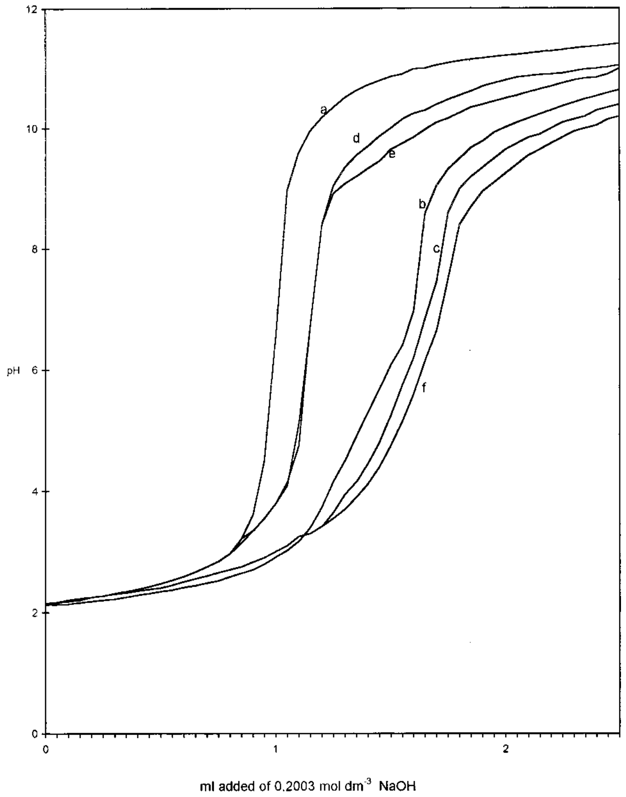

Figure 1. Potentiometric titration curves for the Mg(II)−DPA−glutamic acid system at 25 °C and $I = 0.1$ mol dm^{-3} NaNO$_3$.

Table 1. Acidity Constants of Dipicolinic Acid[a] and Stability Constants of Its 1:1 Binary Complexes at 25 °C and $I = 0.1$ mol dm^{-3} NaNO$_3$

cation	Mg(II)	Ca(II)	Sr(II)	Ba(II)
log K^{M}_{MA}	2.50 ± 0.05	4.50 ± 0.08	3.98 ± 0.06	3.60 ± 0.06

[a] log $K^{H}_{1} = 4.53 \pm 0.06$ and log $K^{H}_{2} = 2.32 \pm 0.05$.

to stand for about 15 min before titration. The equations of Irving and Rossotti[22,23] were used to determine the equilibrium constants of the investigated ligands and their metal complexes. Multiple titrations have been performed for each system.

Results and Discussion

Figure 1 displays a representative set of potentiometric titration curves obtained according to the sequence described in the experimental part, for the Mg(II)−DPA−glutamic acid system.

The first and second proton association constants of neutral DPA were determined potentiometrically in aqueous solutions, under the experimental conditions ($t = 25$ °C, ionic strength $I = 0.1$ mol dm^{-3} NaNO$_3$), from the titration curves a and b. The values obtained (Table 1) are in a good agreement with the literature data.[2] The second and third proton association constants of mono-and dicarboxylic amino acids, respectively, have been determined under identical conditions from the potentiometric titration curves a and d, and the obtained values agree quite well with those previously reported,[24] after allowing for changes in experimental conditions and calculation methods.

The constructed titration curves clearly reveal that the different binary complexes of dipicolinic acid are formed at lower pH's (2.0−3.2). This is attained from the observed divergence of the binary titration curve c from that of the corresponding free dipicolinic acid solution, curve b. The complex solutions of such binary systems do not show any precipitation due to hydrolysis up to higher pH's, where nearly complete complex formation occurs. This behavior strongly suggests that the complexing agent dipicolinic acid is characterized by a high affinity to form stable metal complexes in solution. Concerning the titration curves of the different amino acid complexes, it is evident that these complexes begin to form at relatively higher pH's, as compared to those for the systems involving dipicolinic acid. The titration curves of the different 1:1:1 ternary complexes strongly overlap with the corresponding titration curves of metal−dipicolinic acid at lower pH's. Generally, above a certain pH value which is mainly dependent on the nature of both amino acid and metal ion, one observes a divergence of the ternary complex titration curve from that of the binary complex titration curve. Therefore, it is assumed that, in the presence of both ligands, dipicolinic acid is ligated to the metal ion, followed by interaction of amino acid; that is, the ternary complex formation could be considered in stepwise equilibria (eqs 1 and 3).

$$\mathrm{M} + \mathrm{A} \rightleftharpoons \mathrm{MA} \tag{1}$$

$$K^{\mathrm{M}}_{\mathrm{MA}} = \frac{[\mathrm{MA}]}{[\mathrm{M}][\mathrm{A}]} \tag{2}$$

$$\mathrm{MA} + \mathrm{L} \rightleftharpoons \mathrm{MAL} \tag{3}$$

$$K^{\mathrm{MA}}_{\mathrm{MAL}} = \frac{[\mathrm{MAL}]}{[\mathrm{MA}][\mathrm{L}]} \tag{4}$$

The overall stability constant $\beta^{\mathrm{M}}_{\mathrm{MAL}}$ may be represented by eq 5.

$$\mathrm{M} + \mathrm{A} + \mathrm{L} \rightleftharpoons \mathrm{MAL} \tag{5}$$

$$\beta^{\mathrm{M}}_{\mathrm{MAL}} = \frac{[\mathrm{MAL}]}{[\mathrm{M}][\mathrm{A}][\mathrm{L}]} = K^{\mathrm{MA}}_{\mathrm{MAL}} K^{\mathrm{M}}_{\mathrm{MA}} \tag{6}$$

where A = dipicolinic acid and L = amino acid.

The mean log K^{H}, log $K^{\mathrm{M}}_{\mathrm{MA}}$, log $K^{\mathrm{M}}_{\mathrm{ML}}$, log $K^{\mathrm{ML}}_{\mathrm{ML}_2}$, and log $K^{\mathrm{MA}}_{\mathrm{MAL}}$ values are determined from the corresponding experimental formation curves applying both the average value and straight line methods. The values obtained along with the estimated error using the method of least-squares are given in Tables 1−5.

In the cases of alkaline earth metal complexes of dipicolinic acid, only 1:1 binary complexes could be detected under the experimental conditions, and the values of stability constants are shown in Table 1. However, the stability constants of binary complexes of transition metal ions with dipicolinic acid could not be determined using the pH-metric technique. This behavior can be ascribed to the combination of the acid strength of the complexing agent with the great stabilities of the complexes, which made the determination very inaccurate.

It was found that the values of stability constants for the 1:2 binary complexes of amino acids investigated are lower than those of the corresponding 1:1 systems, as expected from statistical considerations. The Δ log K' (log $K^{\mathrm{ML}}_{\mathrm{ML}_2}$ − log $K^{\mathrm{M}}_{\mathrm{ML}}$) values for the amino acid complexes are negative (Tables 2−5). This is the normal trend where the enthalpy is more favorable for a 1:1 species (exothermic) as compared to a 1:2 species.

The relative stabilities of the binary or ternary complexes of glycine and norvaline follow their relative basicities,

Table 2. Acidity Constant of Glycine and Stability Constants of Its 1:1 and 1:2 Binary Complexes and 1:1:1 Ternary Complexes Involving Dipicolinic Acid at 25 °C and $I = 0.1$ mol dm^{-3} $NaNO_3$

cation	$\log K_1^{H}$	$\log K_{ML}^{M}$	$\log K_{ML_2}^{ML}$	$\Delta \log K'$	$\log K_{MAL}^{MA}$	$\log \beta_{MAL}^{M}$	$\Delta \log K''$
H	9.76 ± 0.08						
Mg		3.45 ± 0.08			3.92 ± 0.05	6.42	0.47
Ca		5.12 ± 0.06			3.80 ± 0.04	8.30	−1.32
Sr		3.90 ± 0.08			3.99 ± 0.06	7.97	0.09
Ba		3.45 ± 0.04			3.73 ± 0.06	7.33	0.28
Co		4.90 ± 0.05	3.79 ± 0.02	−1.11	3.10 ± 0.06		−1.80
Ni		5.90 ± 0.06	4.88 ± 0.07	−1.02	4.77 ± 0.08		−1.13
Zn		5.46 ± 0.06	4.50 ± 0.06	−0.96	3.58 ± 0.05		−1.88
Mn		5.12 ± 0.04			3.74 ± 0.07		−1.38
Cd		4.30 ± 0.05			1.65 ± 0.08		−2.65

Table 3. Acidity Constant of Norvaline and Stability Constants of Its 1:1 and 1:2 Binary Complexes and 1:1:1 Ternary Complexes Involving Dipicolinic Acid at 25 °C and $I = 0.1$ mol dm^{-3} $NaNO_3$

cation	$\log K_1^{H}$	$\log K_{ML}^{M}$	$\log K_{ML_2}^{ML}$	$\Delta \log K'$	$\log K_{MAL}^{MA}$	$\log \beta_{MAL}^{M}$	$\Delta \log K''$
H	9.70 ± 0.03						
Mg		3.35 ± 0.09			3.85 ± 0.08	6.35	0.50
Ca		4.92 ± 0.03			3.70 ± 0.02	8.20	−1.22
Sr		3.80 ± 0.05			3.86 ± 0.05	7.78	0.06
Ba		3.35 ± 0.05			3.65 ± 0.02	7.25	0.30
Co		4.80 ± 0.02	3.65 ± 0.06	- 1.15	3.05 ± 0.08		−1.75
Ni		5.70 ± 0.06	4.70 ± 0.08	- 1.00	4.60 ± 0.03		−1.10
Zn		5.30 ± 0.05	4.34 ± 0.05	- 0.96	3.52 ± 0.05		−1.78
Mn		4.92 ± 0.02			3.60 ± 0.03		−1.32
Cd		4.15 ± 0.07			1.60 ± 0.04		−2.50

Table 4. Acidity Constants of Aspartic Acid and Stability Constants of Its 1:1 and 1:2 Binary Complexes and 1:1:1 Ternary Complexes Involving Dipicolinic Acid at 25 °C and $I = 0.1$ mol dm^{-3} $NaNO_3$

cation	$\log K_1^{H}$	$\log K_2^{H}$	$\log K_{ML}^{M}$	$\log K_{ML_2}^{ML}$	$\Delta \log K'$	$\log K_{MAL}^{MA}$	$\log \beta_{MAL}^{M}$	$\Delta \log K''$
H	9.80 ± 0.02	3.86 ± 0.04						
Mg			4.35 ± 0.03			4.59 ± 0.09	7.09	0.24
Ca			4.13 ± 0.08			4.35 ± 0.09	8.85	0.22
Sr			3.93 ± 0.07			4.13 ± 0.03	8.11	0.20
Ba			3.75 ± 0.03			3.93 ± 0.06	7.53	0.18
Co			5.81 ± 0.07	4.31 ± 0.05	−1.50	6.06 ± 0.05		0.25
Ni			7.07 ± 0.09	5.37 ± 0.04	−1.70	7.48 ± 0.05		0.41
Zn			6.82 ± 0.08	4.82 ± 0.03	−2.00	7.08 ± 0.09		0.26
Mn			4.82 ± 0.09			5.07 ± 0.02		0.25
Cd			4.58 ± 0.04			4.83 ± 0.07		0.25

Table 5. Acidity Constants of Glutamic Acid and Stability Constants of Its 1:1 and 1:2 Binary Complexes and 1:1:1 Ternary Complexes Involving Dipicolinic Acid at 25 °C and $I = 0.1$ mol dm^{-3} $NaNO_3$

cation	$\log K_1^{H}$	$\log K_2^{H}$	$\log K_{ML}^{M}$	$\log K_{ML_2}^{ML}$	$\Delta \log K'$	$\log K_{MAL}^{MA}$	$\log \beta_{MAL}^{M}$	$\Delta \log K''$
H	9.42 ± 0.04	4.20 ± 0.07						
Mg			3.20 ± 0.09			3.32 ± 0.09	5.82	0.12
Ca			2.95 ± 0.02			3.05 ± 0.09	7.55	0.10
Sr			2.45 ± 0.06			2.53 ± 0.03	6.51	0.08
Ba			1.96 ± 0.09			2.01 ± 0.09	5.61	0.05
Co			4.96 ± 0.03	3.62 ± 0.04	- 1.34	5.19 ± 0.09		0.23
Ni			5.96 ± 0.08	4.21 ± 0.03	- 1.75	6.26 ± 0.04		0.30
Zn			5.70 ± 0.08	4.04 ± 0.06	- 1.66	5.95 ± 0.09		0.25
Mn			4.04 ± 0.05			4.25 ± 0.07		0.21
Cd			3.78 ± 0.03			3.98 ± 0.05		0.20

since it is well-known that the increase in basicity of a complexing agent increases the stability of its metal complexes. With respect to dicarboxylic amino acids, the observed little difference in stability of the binary or ternary systems involving α,β-dicarboxylic aspartate compared to the corresponding ones containing α,γ-dicarboxylic glutamate can be mainly ascribed to steric effects, since both amino acid anions behave as tridentate ligands where two chelated rings are formed; five- and six-membered rings in the case of aspartate and five- and seven-membered rings in the case of glutamate.

The relative stability of the ternary complexes, as compared to that of the corresponding binary systems, can be quantitatively expressed in different ways. A review of those methods[25] has shown that, for a variety of reasons, the most suitable comparison is in terms of Δ log *K*″. Tables 2−5 demonstrate the difference in stabilities of the 1:1 binary complexes of the secondary ligand amino acid and 1:1:1 ternary complexes, in terms of Δ log *K*″ as defined by the following equation:

$$\Delta \log K'' = \log K_{MAL}^{MA} - \log K_{ML}^{M} \tag{7}$$

It can be observed that, in general, the values of Δ log *K*″ for the systems involving glycine and norvaline are negative, as expected from the statistical considerations (Tables 2 and 3). There is π acidic character in the primary ligand (dipicolinic acid), due to the possibility of M → N π bond formation. This behavior is similar to that observed previously by Chidambaram and Bhattacharya[26] in [M−dipyridyl−L] systems. In contrast, positive values of Δ log *K*″ for both aspartic acid and glutamic acid systems are obtained, which means that ternary complexes of these dicarboxylic amino acids are more stable than the corresponding binary ones.

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