

Intramolecular interligand interaction in zinc(II) and cadmium(II) mixed ligand complexes of ATP and aminoacids or dipeptides or phenolic compounds

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Abstract. The stability constants of (MATPL) complexes in aqueous medium have been determined potentiometrically, at 25°C and at an ionic strength of 0.2 M (NaClO₄), by using the SCOGS computer program, where M = Zn(II) or Cd(II), ATP = adenosine 5'-triphosphate, L = α -alanine (Ala), phenylalanine (Phe), L-tyrosine (Tyr), L-tryptophan (Trp), glycyl glycine (gg), glycyl L-alanine (ga), catechol (cat), orthoaminophenol (oap) and 2,3-dihydroxy naphthalene (dhn). The stability of these ternary complexes is discussed in terms of $\Delta \log k$ values. Probable reasons for the stabilization or destabilization of the ternary complexes are suggested, with reference to the tetrahedral geometry of the complexes, a point of relevance in the environment around Zn(II) in the metalloenzyme.

Keywords. Stability constants ternary complexes; adenosine 5'-phosphate; amino acids; dipeptides; catechol or analogue.

1. Introduction

Nucleotides play a very prominent role in biology as constituents of nucleic acids. They consist of three structural units, a purine or pyrimidine base, a ribose unit and a mono, di or triphosphate group. Out of these units, the ribose unit is the least coordinating. In the binary complexes, nucleotide coordinates from the phosphate end (Taqui Khan and Martell 1962, 1967; Schneider *et al* 1964; Sigel and McCormick 1970; Eichhorn 1973; Sigel 1975), while the base may or may not be coordinating, depending on the base itself and on the metal ion.

Metal complexes of adenosine triphosphate have been extensively studied because of their biological importance (Taqui Khan and Martell 1962, 1966, 1976; Taqui Khan and Reddy 1975, 1976; Kiss *et al* 1991). Extensive work has been reported on the noncovalent interligand interaction in ternary complexes involving nucleotide and other ligands like amino acids (Suzuki *et al* 1975; Schwarz and Gilligan 1977; Lohman *et al* 1980; Maurizot *et al* 1978). Since Zn(II) ions are involved in nucleic acid or nucleotide related reactions (Shin and Eichhorn 1968), we thought that investigating a series of ternary complexes of Zn(II) with ATP, in order to understand the various interactions operating in metal nucleotide systems and the factors that stabilize their structures, would be interesting.

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2. Experimental

All the reagents used were of AR grade. The potentiometric titrations were carried out in aqueous media at 25°C and at an ionic strength of 0.2 M (NaClO₄). The perchlorate solutions of Zn(II) and Cd(II) were prepared and standardised by titration with EDTA solution. The formation constants of the ternary complexes were determined from the titration data with metal–ligand ratios of 1:1:1 and 1:1:2.

The titrations were carried out against standard alkali (0.2 M NaOH). The summary of other experimental parameters for the Zn(II) and Cd(II) binary and mixed ligand systems has been given below as per the pattern suggested by IUPAC (Tuck 1989).

Ligand system (a) 0.02 M HClO₄; 0.002 M ATP; 0.178 M NaClO₄;
(b) 0.02 M HClO₄; 0.004 M ATP; 0.176 M NaClO₄.

Binary system (a) 0.02 M HClO₄; 0.001 M metal perchlorate [Zn(ClO₄)₂ or Cd(ClO₄)₂]; 0.001 M ATP; 0.180 M NaClO₄.
(b) 0.02 M HClO₄; 0.001 M metal perchlorate; 0.002 M ATP; 0.177 M NaClO₄.

Mixed ligand system (a) 0.02 M HClO₄; 0.002 M metal perchlorate; 0.001 M ATP; 0.002 M ligand L; 0.175 M NaClO₄.
(b) 0.02 M HClO₄; 0.001 M metal perchlorate; 0.001 M ATP; 0.002 M ligand and L; 0.176 M NaClO₄.

Ionic strength electrolyte: 0.2 m dm⁻³, NaClO₄.

Experimental method: pH titration using Orion ion analyzer/901

Accuracy: 0.001 pH unit, calibrated with buffers at pH 4.0, 7.0 and 9.0.

pH range: M(II) complexation – 5.50–8.00.

Temperature: 25°C

Method of calculation: SCOGS (Sayce 1968, 1971; Sayce and Sharma 1972).

Species considered: Protonation – AH₂AH; M(II) Binary system – AH₂, AH and MA, where M = Zn(II) or Cd(II). M(II) mixed ligand system – AH₂, AH, LH, LH₂, MA, ML, ML₂ and MAL, where M = Zn(II) or Cd(II).

The total volume of the solution was adjusted to 50 cm³ by adding double-distilled water. The protonation constants of the ligands L, and the formation constants of their binary complexes were determined under the same experimental conditions. These values were found to be in close agreement with the literature values.

The refined values of the protonation constants of the ligand L and A and the formation constants of their binary complexes have been used as fixed parameters for the refinement of the formation constants of the mixed ligand species. The values of the protonation constants of the ligand (A), formation constants of the binary (MA) and ternary complexes and $\Delta \log k$ values are presented in tables 1 and 2.

3. Results and discussion

It is seen that a ternary species MAL, where M = Zn(II) or Cd(II), A = ATP, L = amino acid, dipeptide or phenolic compound, forms at about pH 6 and the concentration of the species increases with increase in the pH (figure 1). At lower pH values, the major

Table 1. Protonation constants of the ligands and the formation constants of their binary complexes with Zn(II) and Cd(II) in aqueous medium at $I = 0.2 \text{ m dm}^{-3}$ (NaClO_4) and temperature 25°C . Standard deviation (σ) in parentheses.

Ligand	$\log K_1^{\text{H}}$	$\log K_2^{\text{H}}$	$\log K_{\text{ZnL}}^{\text{Zn}}$	$\log K_{\text{CdL}}^{\text{Cd}}$
ATP	6.420(0.02)	4.060(0.03)	4.904(0.02)	4.382(0.04)
α -Alanine (Ala)	9.661(0.02)	2.099(0.03)	5.330(0.01)	5.038(0.03)
Phenylalanine (Phe)	9.214(0.01)	2.037(0.02)	4.785(0.008)	4.505(0.02)
Tyrosine (Tyr)	9.074(0.03)	1.887(0.01)	4.634(0.02)	4.415(0.02)
Tryptophan (Trp)	9.448(0.03)	2.003(0.01)	4.835(0.02)	4.551(0.010)
Glycyl glycine (gg)	7.992(0.02)	3.042(0.03)	2.745(0.01)	2.920(0.03)
Glycyl L-alanine (ga)	8.073(0.03)	3.029(0.02)	3.789(0.02)	2.990(0.01)
Catechol (cat)	13.061(0.03)	8.945(0.04)	9.702(0.03)	8.324(0.01)
Ortho-aminophenol (oap)	9.782(0.04)	4.913(0.03)	4.945(0.03)	3.764(0.04)
2,3-Dihydroxynaphthalene (dnn)	10.261(0.03)	8.251(0.04)	7.660(0.01)	6.283(0.04)

Table 2. Stability constants of mixed ligand complexes of Zn(II) and Cd(II) in aqueous medium at $I = 0.2 \text{ m dm}^{-3}$ (NaClO_4) and temperature 25°C . Standard deviation (σ) in parentheses.

System	$\log K_{\text{MAL}}^{\text{M}}$	$\Delta \log k$
Zn·ATP·Ala	9.532(0.02)	-0.702
Zn·ATP·Phe	9.759(0.01)	+0.070
Zn·ATP·Tyr	9.789(0.03)	+0.251
Zn·ATP·Trp	9.913(0.02)	+0.154
Zn·ATP·gg	7.847(0.01)	-0.802
Zn·ATP·ga	7.899(0.02)	-0.794
Zn·ATP·oap	8.692(0.01)	-1.252
Zn·ATP·cat	13.060(0.03)	-1.546
Zn·ATP·dnn	11.011(0.03)	-1.553
Cd·ATP·Ala	8.899(0.02)	-0.804
Cd·ATP·Phe	8.725(0.01)	-0.162
Cd·ATP·Tyr	8.920(0.01)	+0.123
Cd·ATP·Trp	9.008(0.02)	+0.075
Cd·ATP·gg	6.408(0.01)	-0.844
Cd·ATP·ga	6.507(0.03)	-0.865
Cd·ATP·oap	6.649(0.03)	-1.497
Cd·ATP·cat	10.872(0.02)	-1.834
Cd·ATP·dnn	8.752(0.01)	-1.913

species is the binary MATP. In Zn(II) binary complexes, it was established by ^1H NMR studies that ATP binds to the metal ion strongly from the phosphate end and there is a weak coordination from the base part of the ATP (Eichhorn *et al* 1971). In ternary complexes the second ligand binds from O-N (amino acid), O-N (dipeptide) and O-O or O-N (phenol or aminophenol) sites.

The stability of ternary complex could be quantified in terms of $\Delta \log k$, which is defined as $\Delta \log k = \log K_{\text{MAL}}^{\text{M}} - (\log K_{\text{MA}}^{\text{M}} + \log K_{\text{ML}}^{\text{M}})$. $\Delta \log k$ can also be represented as

$$\Delta \log k = \log K_{\text{MAL}}^{\text{MA}} - \log K_{\text{ML}}^{\text{M}} = \log K_{\text{MLA}}^{\text{ML}} - \log K_{\text{MA}}^{\text{M}}$$

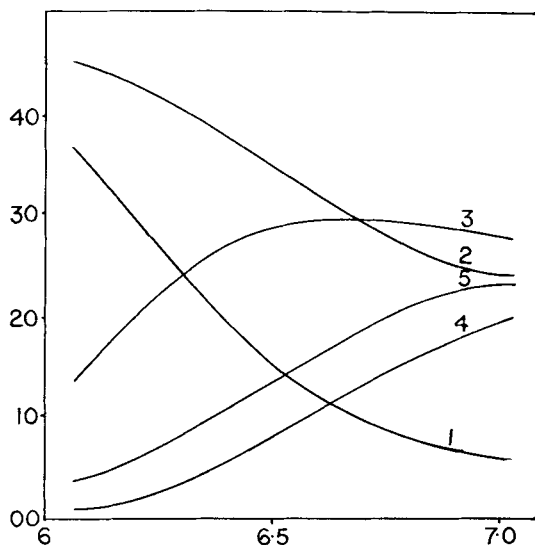


Figure 1. Distribution of species of Zn·ATP(A)·CAT(L) system at 2:1:2 ratio of M, A and L. (1) Free Zn(II), (2) ZnA, (3) ZnL, (4) ZnL₂, (5) ZnAl.

From statistical and electrostatical considerations, the value of K_{MAL}^{MA} should be less than the K_{ML}^M value and $\Delta \log k$ values should be negative. However, it is observed that for the complexes of amino acids with non-coordinating side groups like phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp), $\Delta \log k$ values are more positive or less negative than those of the complexes of ligands without side groups like alanine (Ala). This can be explained as due to the stacking interaction between the base part of ATP and the phenyl, hydroxy phenyl or indole moiety of the phenylalanine, tyrosine or tryptophan (Sigel 1975; Orioli *et al* 1981; Chakraborty and Bhattacharya 1990). Moreover, the $\Delta \log k$ value for MATP–Tyr is more positive or less negative than that for the MATP–Trp complex. This may be explained by considering the possibility of H-bonding between the hydroxy group of the tyrosine ligand and the NH₂ of the ATP. It is observed that ternary complexes of Zn(II) and Cd(II) are more stabilized as compared to the analogous Cu(II) or Ni(II) complexes. This can be due to the fact that Zn(II) and Cd(II) can assume tetrahedral geometry which enables the non-covalent interaction between the non-coordinating groups to be stronger leading to more positive or less negative $\Delta \log k$ values (Arena *et al* 1983, 1984; Varghese and Bhattacharya 1992).

In the case of the M–dipeptide (M = Zn(II), Cd(II)) systems, the nitrogen of the amino group and the oxygen of the peptide get bound to the metal ion while the carboxylate group remains free (Martell and Smith 1974; Nair *et al* 1980). Hence, in the ternary species MATP dipeptide also, the coordination of the dipeptide has been considered from the peptide oxygen and the NH₂ end. The $\Delta \log k$ values for the ternary complexes containing dipeptide are nearly of the same order as for the corresponding MATP–Ala complex. This shows that there is no intramolecular interligand interaction between the ATP and dipeptide ligands. For the (MATPL) system, where L = catechol (cat), orthoaminophenol (oap) or 2,3-dihydroxynaphthalene (dnn), the $\Delta \log k$ values were found to be negative. The tendency of a negatively charged ligand

ATP to bind with ML decreases with the increase in the negative charge on L and hence the ternary complex formed will be less stable.

It is also noticed that the Zn(II) and Cd(II) complexes are not more stabilized than the corresponding Cu(II) complexes, as observed in other systems, indicating that the tetrahedral geometry of Zn(II) and Cd(II) complexes has no favourable effect, due to absence of intramolecular interligand interaction in these complexes.

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