Thermodynamic Quantities Associated with the Interaction of Adenosinediphosphoric and Adenosinemonophosphoric Acids with Metal Ions[1,2]

M. M. Taqui Khan and A. E. Martell[3]

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois. *Received February 17, 1967*

Abstract: Potentiometric equilibrium measurements have been made at 0.4, 12, 25, and 40° for the combination of protonated and fully dissociated (trinegative) anions of adenosine diphosphate (ADP), and of the dinegative anions of adenosine-2-monophosphoric acid (AMP-2), adenosine-3-monophosphoric acid (AMP-3), and adenosine-5-monophosphoric acid (AMP-5), with nine bivalent metal ions, at a 1:1 molar ratio of ligand to metal ion. Equilibrium constants are reported at these temperatures for the formation of the monohydroxo mononuclear complexes, and of the μ-dihydroxo binuclear complexes of Cu(II)- and Zn(II)-ADP. The enthalpy and entropy changes for the formation of protonated and normal chelate species, and for the hydrolysis and olation reactions of Cu(II)-ADP and Zn(II)-ADP chelates, are calculated from temperature-coefficient data. The enthalpy terms for the formation of the protonated and normal chelate species of ADP and the normal chelate species of AMP are relatively small. As in the case of the ATP chelates, the entropy appears to be the principal driving force for the formation of ADP, AMP-2, AMP-3, and AMP-5 metal chelate species in solution. A correlation is observed for the entropy of complex formation, $\Delta S°$, which increases with the number of donor groups on the ligands, and with the reciprocal square of an effective ionic radius of the cation. For a given ligand, the constant that corrects the Pauling ionic radius to the effective radius is found to increase linearly with the electronegativities of the metal ions. The entropies of formation, $\Delta S°$, of the normal metal chelate species of the three adenosinemonophosphoric acids are practically the same.

In a previous publication,[4] thermodynamic quantities associated with the interaction of ATP with alkaline earths and transition metal chelates were reported. The present paper extends the investigation to the stability constants and thermodynamics of the metal chelate species formed by adenosinediphosphoric acid (ADP), adenosine 2-monophosphate (AMP-2), adenosine 3-monophosphate (AMP-3), and adensoine 5-monophosphate (AMP-5) with bivalent metal ions. Previous investigations by Nanninga[5] and George, *et al.*,[6,7] were restricted to normal (or unprotonated) calcium and magnesium complexes of ADP (except for the protonated Mg(II) chelate[7b]). Heats and entropies of formation have not been reported for the metal chelates of adenosine monophosphates.

In this study, stability constants of monoprotonated and normal chelate species of ADP and normal chelate species of AMP-2, AMP-3, and AMP-5, with Mg(II), Ba(II), Sr(II), Ca(II), Co(II), Mn(II), Zn(II), Ni(II), and Cu(II), are measured at 0.4, 12, 25, and 40°, and the corresponding thermodynamic quantities $\Delta H°$, $\Delta F°$, and $\Delta S°$ are calculated. The thermodynamic quantities are compared with the values obtained for ATP complexes.[4]

Experimental Section

The experimental method employed consisted of potentiometric titration of ADP, AMP-2, AMP-3, and AMP-5, in the absence and in the presence of the metal ion being investigated, as described previously.[8] The ionic strength was maintained constant by using 0.10 M KNO_3 as the supporting electrolyte and relatively low concentrations of ligand and metal ion. The titrations were carried out using a 1:1 ratio of concentrations of ligand to metal ion. All measurements were carried out at 0.4, 12, 25, and 50 ± 0.02°. The pK values of acetic acid at 0.4, 12, 25, and 40° used in the calibration of the electrode system were obtained from Harned and Owen.[9] The pH regions below 3.5 and above 10.5 were calibrated by measurements in HCl and NaOH solutions, respectively.

As described in the previous paper,[4] the thermodynamic constants reported in this investigation correspond to the reference state of infinitely dilute reacting species in a medium of 0.100 M KNO_3 solution as solvent. On this basis all of the equilibrium constants determined are very close to true thermodynamic constants, as are the values of $\Delta H°$ and $\Delta S°$ calculated from the temperature coefficients of these equilibrium constants.

Reagents. The ADP used in this investigation was obtained from Sigma Chemical Co. in the form of the sodium salt. AMP-2, AMP-3, and AMP-5 were obtained from the same source as free acids. Appropriate samples were weighed individually before each titration to obtain the concentration desired, since a stock solution could not be prepared and kept for long periods of time. During the course of the experimental work, the ADP was frequently checked for purity (and for hydrolysis) by potentiometric titration. Adenosinemonophosphoric acids are quite stable if stored below 0°. The results were always consistent with the titration of the purified materials, so that no decomposition appeared to take place. The metal salt solutions were standardized by titration with the disodium salt of EDTA as described by Schwarzenbach.[10] Carbonate-free sodium hydroxide was prepared by the standard procedure.

Calculations. The acid dissociation constants, K_a and K_{2a}, for the monosodium salt of ADP (H_2L^-) and AMP-2, AMP-3, and AMP-5 (H_2L) were calculated by a direct algebraic method. The

---

[1] This work was supported by a grant, GM 10834, from the Institute of General Medical Sciences, Public Health Service.

[2] Presented in part before the Division of Physical Chemistry at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 4-9, 1965.

[3] Department of Chemistry, Texas A&M University, College Station, Texas.

[4] M. M. T. Khan and A. E. Martell, *J. Am. Chem. Soc.*, **88**, 668 (1966).

[5] L. B. Nanninga, *J. Phys. Chem.*, **61**, 1144 (1957).

[6] P. George, R. C. Phillips, and R. J. Rutman, *Biochemistry*, **2**, 508 (1963).

[7] (a) P. George, R. C. Phillips, and R. J. Rutman, *Federation Proc.*, **23**, Abstract 986 (1964); (b) R. C. Phillips, P. George, and R. J. Rutman, *J. Am. Chem. Soc.*, **88**, 2631 (1966).

[8] M. M. T. Khan and A. E. Martell, *ibid.*, **84**, 3037 (1962).

[9] H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 638, 752.

[10] G. Schwarzenbach, "Complexometric Titrations," Interscience Publishers, Inc., New York, N. Y., 1957, pp 77-82.

equilibria involved in the formation of a 1:1 complex of ADP and a divalent metal ion may be expressed as

$$\mathrm{M^{2+} + HL^{2-} \rightleftarrows MHL} \quad K^{\mathrm{M}}{}_{\mathrm{MHL}} = \frac{[\mathrm{MHL}]}{[\mathrm{M^{2+}}][\mathrm{HL^{2-}}]} \tag{1}$$

$$\mathrm{M^{2+} + L^{3-} \rightleftarrows ML^-} \quad K_1 = \frac{[\mathrm{ML^-}]}{[\mathrm{M^{2+}}][\mathrm{L^{3-}}]} \tag{2}$$

Related equilibria may be defined as

$$\mathrm{M^{2+} + H_2L^- \rightleftarrows MHL + H^+} \quad K_{\mathrm{MHL}} = \frac{[\mathrm{MHL}][\mathrm{H^+}]}{\mathrm{M^{2+}}][\mathrm{H_2L^-}]} \tag{3}$$

$$\mathrm{MHL \rightleftarrows ML^- + H^+} \quad K^{\mathrm{H}}{}_{\mathrm{MHL}} = \frac{[\mathrm{MHL}]}{[\mathrm{ML^-}][\mathrm{H^+}]} \tag{4}$$

The constants K_1 and $K^{\mathrm{M}}{}_{\mathrm{MHL}}$ were calculated from the potentiometric data with the help of the procedure previously described.[11]

The method of calculating the formation constants for adenosine-2-, adenosine-3-, and adenosine-5-phosphoric acids is relatively simple, no protonic complexes being formed in these cases. The equilibria involved in metal chelate formation in the titration of a 1:1 ratio of ligand to metal ion may be expressed as

$$\mathrm{M^{2+} + L^{2-} \rightleftarrows ML} \quad K_1 = \frac{[\mathrm{ML}]}{[\mathrm{M^{2+}}][\mathrm{L^{2-}}]} \tag{5}$$

Hydrolytic Equilibria for Cu(II)- and Zn(II)-ADP Complexes. As reported in a previous paper,[4] titration of the Cu(II)-ADP and Zn(II)-ADP systems beyond 2 equiv of base produces concentration-dependent buffer regions characteristic of polymerization through hydroxo bridges. The data were treated mathematically on the basis that four species are present: the normal 1:1 chelate, a monohydroxo complex $\mathrm{M(OH)L^{2-}}$, a dihydroxo form $\mathrm{M(OH)_2L^{3-}}$, and a binuclear complex $\mathrm{[M(OH)L]_2{}^{4-}}$. The corresponding solution equilibria may be represented by the equations

$$\mathrm{ML^- \rightleftarrows M(OH)L^{2-} + H^+} \quad K^{\mathrm{H}}{}_{\mathrm{M(OH)L}} = \frac{[\mathrm{M(OH)L^{2-}}][\mathrm{H^+}]}{[\mathrm{ML^-}]} \tag{6}$$

$$\mathrm{ML^- \rightleftarrows M(OH)_2L^{3-} + 2H^+}$$

$$K^{\mathrm{H}}{}_{\mathrm{M(OH)_2L}} = \frac{[\mathrm{M(OH)_2L^{3-}}][\mathrm{H^+}]^2}{[\mathrm{ML^-}]} \tag{7}$$

$$\mathrm{2ML^- \rightleftarrows (M(OH)L)_2{}^{4-} + 2H^+}$$

$$K^{\mathrm{H}}{}_{\mathrm{(M(OH)L)_2}} = \frac{[\mathrm{(M(OH)L)_2{}^{4-}}][\mathrm{H^+}]^2}{[\mathrm{ML^-}]^2} \tag{8}$$

$$\mathrm{2M(OH)L^{2-} \rightleftarrows (M(OH)L)_2{}^{4-}} \quad K_{\mathrm{d}} = \frac{[\mathrm{(M(OH)L)_2{}^{4-}}]}{[\mathrm{M(OH)L^{2-}}]^2} \tag{9}$$

The amounts of various chelate species present under varying conditions of pH and total concentration may be calculated from the above equilibria with the relationship outlined in a previous paper.[11]

Values of $\Delta H°$ were obtained at each temperature interval by the relationship

$$\Delta H° = \frac{2.303RT_2T_1(\log K_2 - \log K_1)}{T_2 - T_1} \tag{10}$$

Values of $\Delta F°$ and $\Delta S°$ for the various reactions involved were calculated with the usual thermodynamic relationships.

Results

ADP, AMP-2, AMP-3, AMP-5. The proton association constants of ADP, AMP-3, and AMP-5 were determined from the corresponding titration curves at 0.4, 12, and 40° and AMP-2 at 0.4, 12, 25, and 40°. The titration curves of AMP-2 are similar to those of AMP-3, AMP-5, and ADP with two sharp inflections separated by a buffer region.[4] The association constants obtained at several temperatures are shown in Table I. The thermodynamic constants obtained for the ionization of ADP, AMP-2, AMP-3, and AMP-5 are given in Table II.

Table I. Proton Association Constants of ADP, AMP-2, AMP-3, and AMP-5 ($\mu = 0.1\ M$ ($\mathrm{KNO_3}$))

	$\mathrm{p}K_{\mathrm{a}}$[a]				$\mathrm{p}K_{2\mathrm{a}}$[b]			
Ligand	0.4°	12°	25°	40°	0.4°	12°	25°	40°
ADP	4.20	4.09	3.93	3.73	6.51	6.48	6.44	6.41
AMP-2	4.03	3.88	3.71	3.54	6.12	6.07	6.01	5.95
AMP-3	3.95	3.80	3.65	3.49	5.93	5.88	5.83	5.78
AMP-5	4.15	3.98	3.80	3.62	6.38	6.31	6.23	6.16

[a] Standard deviation ±0.01 pK unit. [b] Standard deviation ±0.02 pK unit.

Mg(II), Ba(II), Sr(II), Ca(II), Co(II), Mn(II), Zn(II), Ni(II), and Cu(II) Complexes. Titration of equimolar amounts of ADP and the metal ions mentioned above gave an inflection at $a = 2$, corresponding to the formation of 1:1 chelates. The titration curves for these metal ions at 0.4, 12, and 40° are similar to those reported[8] at 25°. The stability constants at the temperatures investigated are given in Table III. The stabilities of the normal complexes, ML, increase in the order Ba < Sr < Ca < Mg < Co < Mn < Zn < Ni < Cu. The same order is also followed by the acido complexes of ADP at 25°. Thermodynamic constants pertaining to the interaction of the above-mentioned ions with ADP are given in Table IV.

Titration of AMP-2, AMP-3, and AMP-5 with Mg(II), Ca(II), Sr(II), and Ba(II) in a 1:1 ratio produced an inflection at $a = 2$, indicating the formation of 1:1 chelates. Precipitates were invariably obtained in the 1:1 titrations of Cu(II), Zn(II), Ni(II), Co(II), and Mn(II) ions with $a = 1$ for AMP-2, AMP-3, and AMP-5. For these ions, stabilities were calculated in a pH range far below the precipitation point. The stability constants of complexes of AMP-2, AMP-3, and AMP-5 are presented in Table V. Thermodynamic constants pertaining to the interaction of the above-mentioned ions with AMP-5, AMP-3, and AMP-2 are given in Table VI.

ADP Chelates of Cu(II) and Zn(II). The 1:1 titration curves of Cu(II)-ADP and Zn(II)-ADP at 0.4, 12, and 40° are similar to those reported earlier[8] at 25°. The curves show a steep inflection at $a = 2$, corresponding to the formation of a 1:1 chelate compound, followed by an additional concentration-dependent buffer region of the type characteristic of polynuclear metal complex formation. A precipitate was obtained after $a = 3.5$ for both Cu(II) and Zn(II) complexes. The monohydroxo and dimerization constants were calculated throughout the range $a = 2$ to $a = 3.5$. A reasonably constant value for the dihydroxo constant could not be calculated because of the appearence of the solid phase beyond $a = 3.5$. A summary of the equilibrium constants obtained at the four temperatures is given in Table VII. Thermodynamic constants for the hydrolysis and olation reactions of Cu(II)-ADP and Zn(II)-ADP are presented in Table VIII.

Discussion

It is of interest to compare (Table II) the enthalpy changes for the first and second ionizations of AMP with those of the second and third ionizations of ADP, and third and fourth ionizations of ATP, respectively. For the dissociation of both the first and second protons in AMP and the last two protons in ADP and ATP, the enthalpy changes become less positive (less endothermic) along the series AMP, ADP, and ATP. The trend is reasonably regular for the enthalpy changes of the last

---

[11] M. M. T. Khan and A. E. Martell, *J. Phys. Chem.*, 66, 10 (1962).

Table II. Thermodynamic Constants for Ionization Reactions of ATP, ADP, AMP-2, AMP-3, and AMP-5 (μ = 0.1 M (KNO_3))

Ligand	Reaction	$\Delta H°$, kcal/mole	$\Delta F°$, kcal/mole (25°)	$\Delta S°$, cal/deg mole (25°)
ATP[a]	$H_2L^{2-} \rightleftarrows HL^{3-} + H^+$	+4.1 ± 0.1	+5.53 ± 0.01	−4.5 ± 0.5
	$HL^{3-} \rightleftarrows L^{4-} + H^+$	+0.5 ± 0.1	+8.90 ± 0.01	−27.8 ± 0.5
ADP	$H_2L \rightleftarrows HL^{2-} + H^+$	+4.8 ± 0.1	+5.36 ± 0.02	−1.9 ± 0.5
	$HL^{2-} \rightleftarrows L^{3-} + H^+$	+1.2 ± 0.1	+8.78 ± 0.02	−25.4 ± 0.5
AMP-2	$H_2L \rightleftarrows HL^- + H^+$	+4.7 ± 0.1	+5.06 ± 0.02	−1.2 ± 0.3
	$HL^- \rightleftarrows L^{2-} + H^+$	+1.6 ± 0.1	+8.19 ± 0.02	−22.2 ± 0.5
AMP-3	$H_2L \rightleftarrows HL^{1-} + H^+$	+4.6 ± 0.1	+4.97 ± 0.02	−1.3 ± 0.3
	$HL^- \rightleftarrows L^{2-} + H^+$	+1.5 ± 0.1	+7.94 ± 0.02	−22.3 ± 0.5
AMP-5	$H_2L \rightleftarrows HL^{1-} + H^+$	+4.9 ± 0.1	+5.18 ± 0.02	−1.0 ± 0.3
	$HL^{1-} \rightleftarrows L^{2-} + H^+$	+1.9 ± 0.1	+8.49 ± 0.02	−22.0 ± 0.5

[a] See ref 4.

Table III. Stability Constants[a] of 1:1 Metal–ADP Complexes (μ = 0.1 M (KNO_3))

Metal ion	0.4° Log $K^M{}_{MHL}$	0.4° Log K_1	12° Log $K^M{}_{MHL}$	12° Log K_1	25° Log $K^M{}_{MHL}$	25° Log K_1	40° Log $K^M{}_{MHL}$	40° Log K_1
Ba(II)	1.55	2.53	1.50	2.45	1.44	2.36	1.37	2.25
Sr(II)	1.60	2.70	1.57	2.63	1.53	2.54	1.48	2.43
Ca(II)	1.61	2.91	1.60	2.88	1.58	2.86	1.54	2.80
Mg(II)	1.39	2.94	1.51	3.05	1.64	3.17	1.78	3.30
Co(II)	2.12	2.63	2.07	4.27	2.01	4.20	1.93	4.12
Mn(II)	2.00	2.47	1.95	4.24	1.89	4.16	1.81	4.06
Zn(II)	2.15	4.40	2.11	4.35	2.04	4.28	1.96	4.20
Ni(II)	2.43	4.62	2.37	4.57	2.30	4.50	2.22	4.42
Cu(II)	2.80	6.16	2.72	6.04	2.63	5.90	2.52	5.75

[a] The constants are accurate to ±0.02 log K unit.

Table IV. Values of $\Delta H°$, $\Delta F°$, and $\Delta S°$ for the Interaction of ADP with Various Metal Ions (μ = 0.10 M (KNO_3))

Metal ion	$\Delta H°$, kcal/mole $K^M{}_{MHL}$	$\Delta H°$, kcal/mole K_1	$\Delta F°$, kcal/mole (25°) $K^M{}_{MHL}$	$\Delta F°$, kcal/mole (25°) K_1	$\Delta S°$, cal/deg mole (25°) $K^M{}_{MHL}$	$\Delta S°$, cal/deg mole (25°) K_1
Ba(II)	−1.8 ± 0.3	−2.9 ± 0.4	−1.96 ± 0.02	−3.22 ± 0.02	+0.6 ± 1	+1.1 ± 1
Sr(II)	−1.2 ± 0.3	−2.68 ± 0.5	−2.07 ± 0.02	−3.46 ± 0.02	+3.0 ± 1	+5.5 ± 1
Ca(II)	−0.6 ± 0.4	−1.2 ± 0.4	−2.15 ± 0.02	−3.90 ± 0.02	+5.2 ± 1	+9.1 ± 1
Mg(II)	+3.9 ± 0.2	+3.6 ± 0.2	−2.24 ± 0.02	−4.32 ± 0.02	+20.5 ± 1	+26.6 ± 1
Co(II)	−1.9 ± 0.3	−2.0 ± 0.4	−2.74 ± 0.02	−5.72 ± 0.02	+2.8 ± 1	+12.5 ± 1
Mn(II)	−1.9 ± 0.3	−2.4 ± 0.4	−2.57 ± 0.02	−5.67 ± 0.02	+2.2 ± 1	±11.0 ± 1
Zn(II)	−1.9 ± 0.3	−2.0 ± 0.4	−2.78 ± 0.02	−5.83 ± 0.02	+3.0 ± 1	+12.5 ± 1
Ni(II)	−2.1 ± 0.2	−1.9 ± 0.3	−3.13 ± 0.02	−6.13 ± 0.02	+3.3 ± 1	+14.1 ± 1
Cu(II)	−2.7 ± 0.3	−4.1 ± 0.3	−3.58 ± 0.02	−8.04 ± 0.02	+3.0 ± 1	+13.0 ± 1

ionizations, which become less endothermic by about 0.7 kcal/mole with the addition of each phosphate group to the adenosine residue. Though the increasing number of the phosphate residues tends to make the ionization of the last proton weaker by an entropy effect, the charge seems to spread out over the phosphate groups and adenosine moiety making the enthalpies less endothermic, and hence favoring greater dissociation, in the series AMP, ADP, and ATP.

The inductive effect of the ester group becomes apparent if one compares the enthalpy changes corresponding to the last ionization of AMP and of orthophosphate.[5] The presence of the adenosine residue in AMP makes the enthalpy of the last ionization less endothermic by about 1 kcal when compared to orthophosphate.

The enthalpies of the first ionization reactions, and of the second ionizations of the monophosphates, remain about the same for the series AMP-2, AMP-3, and AMP-5. The position of the phosphate residue on the riboside residue appears to have very little effect, if any, on the dissociation of protons from the phosphate group.

The entropies of the first and second ionizations of AMP and the second and third ionizations of ADP are less negative than the last two ionizations of ATP. The entropy of the last ionization of the phosphate residue increases by about three entropy units in passing from ATP to AMP. Differences of about the same order of magnitude (3.3 eu) have been observed by George, *et al.*,[6] for the entropy of the last ionization of ATP, ADP, and AMP calculated from their pK's corrected to zero ionic strength. The entropies of first and second ionization within the series of three monophosphates, AMP-2, AMP-3, and AMP-5, are practically the same.

The enthalpies of the formation in solution of metal chelates of ADP, AMP-2, AMP-3, and AMP-5 are in general small and exothermic, with the exception of Mg(II) chelates, for which $\Delta H°$ is positive. The enthalpies of combination of the normal and protonated

Table V. Stability Constants[a] of 1:1 Metal–AMP Complexes (μ = 0.1 M (KNO$_3$))

Metal ion	0.4° AMP-2	0.4° AMP-3	0.4° AMP-5	12° AMP-2	12° AMP-3	12° AMP-5	25° AMP-2	25° AMP-3	25° AMP-5	40° AMP-2	40° AMP-3	40° AMP-5
Ba(II)	1.82	1.81	1.85	1.77	1.75	1.80	1.71	1.69	1.73	1.64	1.62	1.66
Sr(II)	1.85	1.81	1.88	1.79	1.75	1.83	1.74	1.71	1.79	1.71	1.68	1.74
Ca(II)	1.87	1.86	1.88	1.85	1.84	1.87	1.83	1.80	1.85	1.81	1.78	1.83
Mg(II)	1.71	1.68	1.75	1.82	1.78	1.85	1.93	1.89	1.97	2.05	2.01	2.09
Co(II)	2.15	2.11	2.44	2.19	2.15	2.49	2.24	2.20	2.53	2.28	2.24	2.57
Mn(II)	2.43	2.34	2.46	2.41	2.31	2.43	2.38	2.28	2.40	2.35	2.25	2.37
Zn(II)	2.72	2.65	2.80	2.68	2.62	2.76	2.64	2.60	2.72	2.60	2.56	2.68
Ni(II)	2.86	2.85	2.90	2.84	2.82	2.87	2.81	2.79	2.84	2.78	2.75	2.84
Cu(II)	3.28	3.06	3.30	3.23	3.00	3.24	3.16	2.96	3.18	3.10	2.90	3.12

[a] The constants are accurate to ±0.02 log K unit.

Table VI. Values of $\Delta H°$, $\Delta F°$,[a] and $\Delta S°$[a] for the Interaction of AMP-2, AMP-3, and AMP-5 with Various Metal Ions (μ = 0.1 M (KNO$_3$))

Metal ion	AMP-2 $\Delta H°$, kcal/mole	AMP-2 $\Delta F°$, kcal/mole	AMP-2 $\Delta S°$, cal/deg mole	AMP-3 $\Delta H°$, kcal/mole	AMP-3 $\Delta F°$, kcal/mole	AMP-3 $\Delta S°$, cal/deg mole	AMP-5 $\Delta H°$, kcal/mole	AMP-5 $\Delta F°$, kcal/mole	AMP-5 $\Delta S°$, cal/deg mole
Ba(II)	−2.0 ± 0.2	−2.33 ± 0.02	1.2 ± 0.5	−1.9 ± 0.2	−2.30 ± 0.02	1.2 ± 0.5	−2.0 ± 0.2	−2.36 ± 0.02	1.2 ± 0.5
Sr(II)	−1.0 ± 0.2	−2.37 ± 0.02	4.5 ± 0.5	−0.9 ± 0.2	−2.33 ± 0.02	4.5 ± 0.5	−1.4 ± 0.2	−2.44 ± 0.02	4.4 ± 0.5
Ca(II)	−0.6 ± 0.2	−2.49 ± 0.02	6.5 ± 0.5	−0.6 ± 0.2	−2.45 ± 0.02	6.5 ± 0.5	−0.6 ± 0.2	−2.52 ± 0.02	6.4 ± 0.5
Mg(II)	3.5 ± 0.1	−2.63 ± 0.02	20.5 ± 0.3	3.5 ± 0.1	−2.58 ± 0.02	20.5 ± 0.3	3.4 ± 0.2	−2.68 ± 0.02	20.4 ± 0.5
Co(II)	−0.7 ± 0.2	−3.19 ± 0.02	8.5 ± 0.5	−0.6 ± 0.2	−3.05 ± 0.02	8.5 ± 0.5	−1.1 ± 0.2	−3.60 ± 0.02	8.4 ± 0.5
Mn(II)	−1.0 ± 0.2	−3.24 ± 0.02	7.5 ± 0.5	−0.9 ± 0.2	−3.11 ± 0.02	7.6 ± 0.5	−1.0 ± 0.2	−3.27 ± 0.02	7.6 ± 0.5
Zn(II)	−1.2 ± 0.2	−3.60 ± 0.02	8.0 ± 0.5	−1.1 ± 0.2	−3.54 ± 0.02	8.2 ± 0.5	−1.2 ± 0.2	−3.70 ± 0.02	8.2 ± 0.5
Ni(II)	−1.0 ± 0.2	−3.83 ± 0.02	9.5 ± 0.5	−1.0 ± 0.2	−3.80 ± 0.02	9.6 ± 0.5	−1.0 ± 0.2	−3.87 ± 0.02	9.6 ± 0.5
Cu(II)	−1.9 ± 0.1	−4.31 ± 0.02	8.0 ± 0.3	−1.7 ± 0.1	−4.03 ± 0.02	8.0 ± 0.3	−2.0 ± 0.1	−4.33 ± 0.02	8.0 ± 0.3

[a] At 25°.

Table VII. Hydrolysis and Olation of Cu(II)–ADP and Zn(II)–ADP (μ = 0 1 M (KNO$_3$))

Temp, °C	Log K_1[a] Cu(II)	Log K_1[a] Zn(II)	Log $K^{H}_{M(OH)L}$[b] Cu(II)	Log $K^{H}_{M(OH)L}$[b] Zn(II)	Log $K^{H}_{(M(OH)L)_2}$[c] Cu(II)	Log $K^{H}_{(M(OH)L)_2}$[c] Zn(II)	Log K_d[d] Cu(II)	Log K_d[d] Zn(II)
0.4	4.40	6.16	7.65	9.14	11.45	14.62	3.85	3.66
12	4.35	6.04	7.38	8.83	11.11	14.16	3.65	3.50
25	4.28	5.90	7.08	8.51	10.73	13.68	3.42	3.34
40	4.20	5.75	6.76	8.18	10.33	13.20	3.19	3.16

[a] Log K_1 values are accurate to ±0.02 log K unit. [b] Log $K^{H}_{M(OH)L}$ are accurate to ±0.05 p$K_{M(OH)L}$ unit. [c] p$K^{H}_{(M(OH)L)_2}$ are accurate to ±0.07 p$K_{(M(OH)L)_2}$ unit. [d] Log K_d are accurate to ±0.06 log K_d unit

Table VIII. Thermodynamic Constants for Hydrolysis and Olation Reactions of Cu(II)–ADP, Zn(II)–ADP, and Cu(II)–ATP[a] (μ = 0.1 M (KNO$_3$))

Metal chelate, ML	Reaction	$\Delta H°$, kcal/mole	$\Delta F°$, kcal/mole	$\Delta S°$, cal/deg mole
Cu(II)–ADP	$2ML^- \rightleftharpoons (M(OH)L)_2^{4-} + 2H^+$	−11.4 ± 1	−14.60 ± 0.1	+10.7 ± 3
	$ML^- \rightleftharpoons M(OH)L^{2-} + H^+$	−9.0 ± 0.5	−9.65 ± 0.04	+2.3 ± 1
	$2M(OH)L^{2-} \rightleftharpoons (M(OH)L)_2^{4-}$	−6.2 ± 0.6	−4.70 ± 0.04	+5.0 ± 2
Zn(II)–ADP	$2ML^- \rightleftharpoons (M(OH)L))_2^{4-} + 2H^+$	−13.4 ± 1	−18.6 ± 0.1	+17.4 ± 3
	$ML^- \rightleftharpoons M(OH)L^{2-} + H^+$	−9.9 ± 0.3	−11.60 ± 0.05	+5.7 ± 1
	$2M(OH)L^{2-} \rightleftharpoons (M(OH)L)_2^{4-}$	−5.1 ± 0.2	−4.60 ± 0.05	−2.0 ± 1
Cu(II)–ATP	$2ML^{2-} \rightleftharpoons (M(OH)L)_2^{6-} + H^+$	−9.9 ± 0.3	−14.1 ± 0.1	+14 ± 1
	$ML^{2-} \rightleftharpoons M(OH)L^{3-} + H^+$	−8.0 ± 0.3	−8.80 ± 0.04	+3 ± 1
	$2M(OH)L^{3-} \rightleftharpoons (M(OH)L)_2^{6-}$	−6.4 ± 0.5	−3.50 ± 0.04	−10 ± 2

[a] See ref 4.

complexes of ADP, and of the normal complexes of the three monophosphates, with metal ions are more positive (endothermic) than are those of ATP.[4] The more positive values of the enthalpies of ADP and AMP complexes in comparison to those of ATP are expected because of weaker interaction of ADP and AMP with both protons and metal ions. The enthalpy changes for the combination of ADP with transition metal ions and magnesium(II) are about the same as the enthalpy of combination with the corresponding monoprotonated ligand. The enthalpy values vary in a regular manner for alkaline earth complexes; the value of $\Delta H°$ becomes more exothermic the larger the metal ion. The trend is again in accord with the heats of hydration of alkaline earths which steadily decrease through the series Mg(II), Ca(II), Sr(II), and Ba(II). The trend in the entalpy values for the formation of normal chelates of AMP-2, AMP-3, and AMP-5 is similar to those of the corresponding ATP and ADP complexes. The enthalpy values for the normal complexes of AMP-2,

Table IX. Correlation of Entropy of Chelate Formation with Effective Radius of the Metal Ion and Number of Coordinated Negative Donor Groups of Ligand[a]

Divalent metal ion	r_p, A	ATP $\Delta S°$, eu	ATP Z_e	ATP r_e, A	ATP Z_e/r_e^2	ADP $\Delta S°$, eu	ADP Z_e	ADP r_e, A	ADP Z_e/r_e^2	AMP $\Delta S°$, eu	AMP Z_e	AMP r_e, A	AMP Z_e/r_e^2
Mg	0.65	28	3	1.63	1.17	27	3	1.63	1.17	21	2	1.45	0.95
Ca	0.99	12	3	1.92	0.80	10	3	1.92	0.80	7	2	1.74	0.68
Sr	1.13	6	3	2.04	0.71	6	3	2.04	0.71	5	2	1.84	0.60
Ba	1.35	2	3	2.26	0.58	1	3	2.26	0.58	1	2	2.06	0.48
Mn	0.80	12	3	1.94	0.79	11	3	1.94	0.79	8	2	1.74	0.66
Co	0.72	14	3	1.90	0.83	13	3	1.90	0.83	9	2	1.68	0.71
Ni	0.69	15	3	1.89	0.84	14	3	1.89	0.84	10	2	1.67	0.72
Cu	0.65	14	3	1.85	0.88	13	3	1.85	0.88	8	2	1.63	0.75
Zn	0.74	13	3	1.92	0.81	13	3	1.92	0.81	8	2	1.70	0.69

[a] r_p = Pauling ionic radii (angstrom units); r_e = effective ionic radius; Z_e = number of coordinated negative donor groups of ligand.

Table X. Correlation of the Effective Radius of the Metal Ion with Electronegativities and Number of Coordinated Negative Donor Groups of Ligand[a]

Divalent metal ion	r_p, A	X_M	ATP, ADP r_e, A	ATP, ADP $r_e - r_p$, A	ATP, ADP Z_e	ATP, ADP Z_eX_M	AMP r_e, A	AMP $r_e - r_p$, A	AMP Z_e	AMP Z_eX_M
Mg	0.65	1.23	1.63	0.98	3	3.69	1.45	0.80	2	2.46
Ca	0.99	1.04	1.92	0.93	3	3.12	1.74	0.75	2	2.08
Sr	1.13	0.99	2.04	0.91	3	2.97	1.84	0.71	2	1.98
Ba	1.35	0.97	2.26	0.91	3	2.91	2.06	0.71	2	1.94
Mn	0.80	1.60	1.94	1.14	3	4.80	1.74	0.94	2	3.20
Co	0.72	1.70	1.90	1.18	3	5.10	1.68	0.96	2	3.40
Ni	0.69	1.75	1.89	1.20	3	5.25	1.67	0.98	2	3.50
Cu	0.65	1.75	1.85	1.20	2	5.25	1.63	0.98	2	3.50
Zn	0.74	1.66	1.92	1.18	3	4.98	1.70	0.96	2	3.32

[a] r_p = Pauling ionic radii and r_e = effective ionic radii (angstrom units); Z_e = number of coordinated negative donor groups of ligand; X_M = electronegativity of metal ion on Allred–Rochow scale.

AMP-3, and AMP-5 are almost the same. The stabilities of these complexes decrease in the order AMP-5 > AMP-2 > AMP-3 and follow the acid dissociation constants of the three monophosphoric acids (*i.e.*, chelate formation constants increase as last dissociation constants decrease). The difference in the relative basicities of the three ligands toward both metal ions and hydrogen ion must be due to a steric effect involving differences in proximity to the weakly coordinating hydroxyl groups of the adenosine residue and purine ring nitrogens.

The entropies of formation in solution of both the protonated and normal chelate species of ADP and the normal chelate species of AMP-2, AMP-3, and AMP-5, with the divalent metal ions, are roughly proportional to the reciprocal of the ionic radii of the metal ions, a trend that has also been observed[4] for ATP chelates. The entropies for the formation of protonated and normal complexes of ADP are about the same as for ATP within experimental error, whereas the entropies of the normal complexes of AMP-2, AMP-3, and AMP-5 are about the same or less than those of ADP and ATP complexes. The entropies of chelate formation of of ATP, ADP, and AMP show a linear correlation with the square of the reciprocal of the effective ionic radius of the metal ion, r_e, and with the number of negative phosphate groups of the ligand, Z_e, that combine with the metal ion. The agreement between the coordination entropies, effective metal ion radii, and the number of coordinated donor groups is indicated in Table IX and illustrated graphically in Figure 1. The radius of the ligand donor groups is not taken into consideration, since only one type of donor, the phosphate group, is involved in charge neutralization with the metal ion, (*i.e.*, the values of r_e for the phosphate group remain constant).

Powell and Latimer[12] have proposed an empirical relationship for the partial molal entropies, $\bar{S}°$, of aqueous ions

$$\bar{S}° = {}^3/_2R \ln M + 37 - 270Z/r_e^2 \qquad (11)$$

where M is the molecular weight, Z is the charge of the ion, and r_e is the effective radius in angstrom units, equivalent to the crystal radius (+2 A) for cations and crystal radius (+1 A) for anions. The empirical corrections of +2 and +1 A, respectively, for cations and anions in order to obtain a value of r_e in expression 11 are purely arbitrary. In the present study, the effective radii of the metal ion in the case of ATP, ADP, and AMP complexes are correlated with the electronegativity of the metal ion, X_M, and the number of coordinated negative donor groups Z_e

$$r_e = r_p + 0.14Z_eX_M \qquad (12)$$

where r_e is the effective radius of the metal ion, r_p is the Pauling crystal radius of the metal ion, and X_M is the electronegativity on the Allred–Rochow[13] scale. The correlation between the effective radius of the metal ion, the electronegativity, and the number of metal–phosphate bonds as given by eq 12 is indicated in Table X

---

(12) R. E. Powell and W. H. Latimer, *J. Chem. Phys.*, 19, 1139 (1951).

(13) A. L. Allred and E. C. Rochow, *J. Inorg. Nucl. Chem.*, 5, 264 (1958).

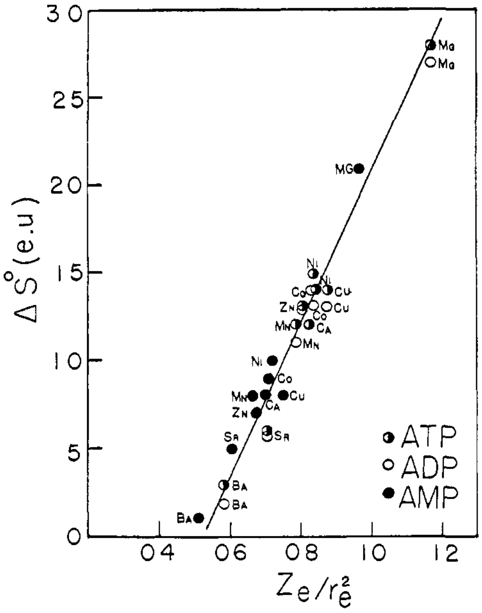

Figure 1. Correlation of entropies of formation of adenosinephosphoric acid chelates in aqueous solution with effective radius of the metal ion, r_e, and number of negative donor groups of the ligand, Z_e, that become coordinated with the metal ion: r_e = effective ionic radii (Pauling crystal radius + constant, in angstroms); ATP = adenosine triphosphate; ADP = adenosinediphosphoric acid; AMP = adenosinemonophosphoric acids.

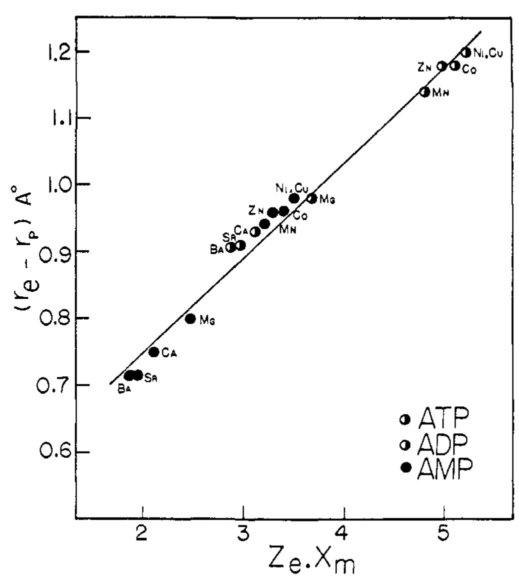

Figure 2. Correlation of the effective radius of the metal ion with electronegativities and number of negative donor groups of the ligand, Z_e, that become coordinated with the metal ion: r_p = Pauling crystal radius in angstroms; r_e = effective ionic radius; X_M = electronegativities of metal ions on Allred-Rochow scale; ATP = adenosine triphosphate; ADP = adenosine diphosphate; AMP = adenosinemonophosphoric acids.

and illustrated graphically in Figure 2. The relationship shown in Figure 2 is the first correlation of this type in which the effective metal ion radius is represented as depending on metal ion electronegativity and the number of ligand donor groups. The success of correlations in Figures 1 and 2 provides added support to the assumptions in Tables IX and X regarding the number of donor groups of ATP, ADP, and AMP involved in metal chelate formation.

The thermodynamic constants for the hydrolysis and dimerization of the Cu(II)–ADP complex merit comparison with the corresponding reactions of ATP (Table VIII). The enthalpy value for the hydrolysis of Cu(II)–ADP is less negative than that for corresponding Cu(II)–ATP reaction.[4] The entropy values of the two reactions are about the same within experimental error. The hydrolysis of Cu(II)–ADP thus takes place as the result of a favorable enthalpy change. The enthalpy value for the dimerization of Cu(II)–ADP is about the same as for Cu(II)–ATP within experimental error, but the entropy is about 5 eu more positive than that of the ATP complex. The dimerization of the hydroxo Cu(II)–ADP complex thus appears to take place as the consequence of a favorable entropy change.

It is also of further interest to compare the hydrolysis and dimerization of the Zn(II)–ADP complex with the Cu(II)–ADP complex. The enthalpy value for the hydrolysis of Zn(II)–ADP is less negative than that for Cu(II)–ADP. The entropy value is, however, less positive than that of the Cu(II)–ADP complex, and the hydrolysis of Zn(II)–ADP takes place as the result of a favorable enthalpy change. The enthalpy value for the dimerization of Zn(II)–ADP is considerably less exothermic than that for Cu(II)–ADP; here also the entropy of dimerization is unfavorable and dimerization of Zn(II)–ADP complex is due entirely to a favorable heat of reaction.