Comparison of the Effectiveness of Various Metal Ions on the Formation of the Ternary Complexes Containing Adenosine 5′-Mono-, 5′-Di-, and 5′-Triphosphate and Some Zwitterionic Buffers for Biochemical and Physiological Research

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Potentiometric equilibrium measurements have been performed at (25.0 ± 0.1) °C and ionic strength I = 0.1 mol dm^{-3} KNO_3 for the interaction of adenosine 5′-mono-, 5′-di-, and 5′-triphosphate and Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), and Mg(II) with the biologically important secondary ligand zwitterionic buffers 3-[*N*-bis(hydroxyethyl)amino]-2-hydroxypropanesulfonic acid, 3-[*N*-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid, (3-[*N*-morpholinol)-2-hydroxy propanesulfonic acid, *N*-(2-acetamido)-2-aminoethanesulfonic acid, and 2-(cyclohexylamino)ethanesulfonic acid in a 1:1:1 ratio, and the formation of various 1:1:1 normal and protonated mixed ligand complex species was inferred from the potentiometric pH titration curves. The experimental conditions were selected such that self-association of the nucleotides and their complexes was negligibly small; i.e., the monomeric normal and protonated ternary complexes were studied. Initial estimates of the formation constants of the resulting species and the acid dissociation constants of adenosine 5′-monophosphate, adenosine 5′-diphosphate, and adenosine 5′-triphosphate and the zwitterionic buffers secondary ligands have been refined with the SUPERQUAD computer program. In some M(II) ternary systems the interligand interactions or some cooperativity between the coordinate ligands, possibly H bond formation, have been found to be most effective in deciding the stability of the ternary complexes formed in solutions.

Introduction

The participation of metal ions in biochemical reactions of nucleotides and nucleic acids provided a great deal of interest in determination of structures of metal−nucleotide complexes (Rifkind and Eichhorn, 1972). For the standardization of pH and control of acidity in the physiological region of pH 7−9, Good and co-workers (1966) and Ferguson and co-workers (1980) have listed hydrogen buffers which are zwitterionic amino acids either N-substituted taurines or N-substituted glycines and zwitterionic N-substituted amino sulfonic acids. These compounds are all ampholytes (with zwitterionic structures) and are useful buffers compatible with most media of physiological interest. Potentially useful zwitterionic buffers for use in biochemistry now include 3-[*N*-bis(2-hydroxyethyl)amino]-2-hydroxypropanesulfonic acid (DIPSO), 3-[*N*-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid (TAPSO), (3-[*N*-morpholinol)-2-hydroxypropanesulfonic acid (MOPSO), *N*-(2-acetamido)-2-aminoethanesulfonic acid (ACES), and 2-(cyclohexylamino)ethanesulfonic acid (CHES) because of their low toxicity. Ternary complexes containing metal ions and two different types of biologically important ligands, namely, nucleotides (AMP, ADP, or ATP) and zwitterionic buffer ligands may be considered as models for ternary interactions in which a metal entity cross-links a protein and a nucleic acid. Alternative ternary interactions include metal binding to a protein, which subsequently associates with a nucleic acid, or initial binding of metal ion to a nucleic acid which then causes a protein to bind to the metalated nucleic acid. Biologically relevant examples for all three cases are known (O'Halloran, 1989).

Artificial chemical DNA nucleases frequently are based on metal−protein conjugates (Wienken et al., 1997) thereby representing an application of ternary complex formation in molecular biology. Ternary complexes of transition divalent metal ions and Ca(II) and Mg(II) with AMP, ADP, and ATP and other secondary ligands have been investigated (Azab et al., 1993, 1993, 1994, 1994, 1995; Fisher et al., 1979; Scheller et al., 1980). For an improved understanding of the mechanism leading to mixed ligand complexes, the systems [M(II) + NU + Z], where NU = AMP, ADP, ATP, Z = MOPSO, DIPSO, TAPSO, ACES, or CHES, and M(II) = Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), or Mg(II), have been investigated by potentiometric pH titrations. The stability constants of the normal and protonated mixed ligand complexes formed in solution have been determined. These systems mimic many biological reactions (M(II) + buffer + substrate interactions) and also may be considered as models for protein + M(II) ion + nucleic acid complexes. Expression of genitic information is controlled predominantly through the interaction of regulatory proteins with DNA. Numerous protein−metal ion complexes are involved in DNA packing, repair, recombination, and replication. Such complexes also perform important functions in RNA splicing, storage, and transport.

Experimental Section

Material and Solutions. $Na_2AMP·H_2O$, $Na_2ADP·2H_2O$, and $Na_2ATP·3H_2O$, were purchased from Sigma Chemical Co. and were used without purification. The amount of free phosphates initially present in the nucleotides was determined (Buisson et al., 1974). It was found to be 2% for ATP and 3% for ADP and AMP. To account for this and to prepare metal ion nucleotide solutions in a

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1:1 molar ratio, we determined, by potentiometric pH titrations, the molar mass of these purine nucleotides. DIPSO, TAPSO, MOPSO, ACES, and CHES were from Sigma. We determined the molecular weight of ACES, CHES, TAPSO, DIPSO, and MOPSO by potentiometric pH titration to determine the purity, especially for acidic/basic contaminants. The purity averages 99.5% for the five biological buffers, with a standard deviation of 0.04%. The nitrate salts of the metal ions, nitric acid, and KOH were from Merck. Stock solutions were prepared using distilled, CO_2-free water. The concentration of KOH used for the titrations was determined by titration with a standard solution of potassium hydrogen phthalate (Merck AG). HNO_3 solutions were prepared and standardized potentiometrically with tris(hydroxymethyl)aminomethane. The concentrations of the metal ion stock solutions were determined by titration with ethylenediaminetetraacetic acid (EDTA).

Apparatus. Potentiometric pH measurements were performed on the solutions in a double-walled glass vessel at (25 ± 0.1) °C with a commercial Fisher combined electrode. A Fisher Accumet pH/ion meter, model 825 MP, was used. Purified nitrogen was bubbeled through the solutions during titrations, and a magnetic stirrer was used.

Procedure. The test solution was titrated with standard CO_2-free KOH. The pH range (3.0−10.0) was covered for the calculation for each system. The electrode was calibrated, in both the acidic and alkaline regions, by titrating 0.01 mol dm^{-3} nitric acid with standard KOH under the same experimental conditions. The concentration of the free hydrogen ion, C_{H^+}, at each point of the titration is related to the measured emf, $E°$, of the cell by the Nernest equation

$$E = E° + Q \log C_{H^+} \tag{1}$$

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 of nitric acid with standard KOH solution under the same temperature and medium conditions as for the test solution titration. The results so obtained were analyzed by the nonlinear least-squares computer program ESAB2M (De Stefano et al., 1987) to refine $E°$ and the autoprotolysis constant of water, K_w. During these calculation the K_w was refined until the best value for Q was obtained. The results obtained indicated the reversible Nernstian response of the glass electrode used. The solutions titrated can be presented according to the following scheme: HNO_3 (4×10^{-3} mol dm^{-3}) + nucleotide (1×10^{-3} mol dm^{-3}) (a); HNO_3 (4×10^{-3} mol dm^{-3}) + nucleotide (1×10^{-3} mol dm^{-3}) + M(II) (1×10^{-3} mol dm^{-3}) (b); HNO_3 (4×10^{-3} mol dm^{-3}) + zwitterionic buffer ligands (1×10^{-3} mol dm^{-3}) (c); HNO_3 (4×10^{-3} mol dm^{-3}) + zwitterionic buffer ligands (1×10^{-3} mol dm^{-3}) + M(II) (1×10^{-3} mol dm^{-3}) (d); HNO_3 (4×10^{-3} mol dm^{-3}) + nucleotide (1×10^{-3} mol dm^{-3}) + zwitterionic buffer ligands (1×10^{-3} mol dm^{-3}) + M(II) (1×10^{-3} mol dm^{-3}) (e). A constant ionic strength was obtained with 0.1 mol dm^{-3} KNO_3, and the total volume was kept constant at 50 cm^3. At least four titrations were performed for each system. For both ligand protonation and metal complex formation equilibria, data were recorded over the largest possible pH interval, although a number of experimental points were frequently discarded for the final stability constant calculations, especially within the range where the complexation observed was insignificant. Typically about 50 data points were collected for each system. To avoid hydrolysis prior to the potentiometric measurements, a known mass of the nucleotides as solid was added to the reaction vessel just prior to performing the titration.

Initial estimates of the formation constants of the normal and protonated ternary complexes and the stability constants of the binary 1:1 complexes have been refined using the SUPERQUAD computer program (Gans et al., 1985). During this refinement the stability constant for the species $M_p(NU)_q(Z)_r(H)_s$, β_{pqrs} is defined by the following equation (eq 2 charges are omitted for clarity)

$$pM + qNU + rZ + sH \rightleftharpoons M_p(NU)_q(Z)_r(H)_s \tag{2}$$

$$\beta_{pqrs} = \frac{[M_p(NU)_q(Z)_r(H)_s]}{[M]^p[NU]^q[Z]^r[H]^s} \tag{3}$$

where p, q, r, and s are the moles of M, NU, Z, and H in $M_p(NU)_q(Z)_r(H)_s$, respectively. NU = nucleotide (AMP, ADP, or ATP), Z = zwitterionic buffer ligands (TAPSO, DIPSO, MOPSO, ACES, or CHES). and M = Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), or Mg(II). In addition the protonation and complexation reactions of the free phosphate initially present in solutions have been included in the calculations to get better conditional stability constants. The constants were refined by minimizing U, defined by

$$U = \sum W_i(E_{obs} - E_{calc})^2 \tag{4}$$

where E_{obs} and E_{calc} refer to the measured and calculated potential. The weighting factor W_i is defined as the reciprocal of the estimated variance of measurement

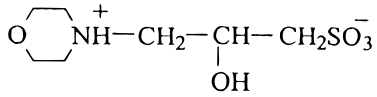
$$W_i = 1/\sigma^2 = 1/[\sigma_E{}^2 + (\delta E/\delta V)^2\sigma_v{}^2] \tag{5}$$

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.

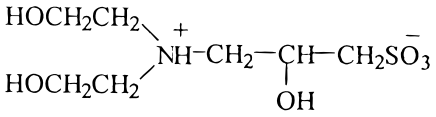
Results and Discussion

The acidity constants determined at 25 °C of ACES (pK_{a2} = 6.83 ± 0.02), CHES (pK_{a2} = 9.38 ± 0.03), MOPSO (pK_{a2} = 6.86 ± 0.02), TAPSO (pK_{a2} = 7.62 ± 0.02), and DIPSO (pK_{a2} = 7.48 ± 0.03) are in good agreement with those found in the literature (Good et al., 1966; Ferguson et al., 1980; Roy et al., 1997; Perrin, 1979). The two acid formation constant values for AMP (pK_{a1} = 3.81 ± 0.03, pK_{a2} = 6.24 ± 0.03), ADP (pK_{a1} = 3.94 ± 0.03, pK_{a2} = 6.38 ± 0.04), and ATP (pK_{a1} = 4.05 ± 0.03, pK_{a2} = 6.51 ± 0.03) and the stability constants of their M(II) complexes were determined from the titration curves, and the results were found to agree will with those reported in the literature (Smith et al., 1991). The pK values for primary ionizations of the adenine nucleotides AMP, ADP, and ATP have been estimated as follows: AMP (one primary phosphate hydrogen), 1.0; ADP (two primary phosphate hydrogens), 1.0 and 2.0; ATP (three primary phosphate hydrogens), 1.0, 1.0, and 2.0 (Phillips, 1966). Given these pK values at the lower pH initial conditions of the experiments described in this work (pH 2.3−2.5) roughly 10% of the final primary

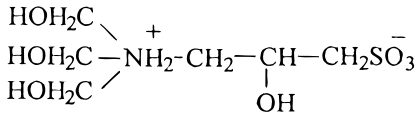
Chart 1



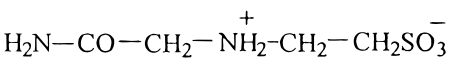
MOPSO



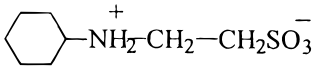
DIPSO



TAPSO



ACES



CHES

phosphate hydrogen would be un-ionized for ATP and ADP. At lower pH values even more primary phosphate hydrogen would be un-ionized, including the pK = 1.0 phosphate ionizations. Therefore, the net charge on the phosphate chain of ATP and ADP at pH < 3 would be an average value for several differently protonated species.

MOPSO, DIPSO, TAPSO, ACES, and CHES possess the zwitterionic structures Shown in Chart 1.

The second dissociation step involves the deprotonation of the substituted methylammonium of TAPSO and the deprotonation of the cationic group $-N^+H$ of MOPSO and DIPSO. For ACES and CHES this step involves the deprotonation of the cationic group $-N^+H_2$.

At the experimental pH values used in the calculation in this work the secondary ligand, Z, combines with the binary 1:1 M^{II}(NU) {$[M^{II}(AMP)]$, $[M^{II}(ADP)]^-$, and $[M^{II}(ATP)]^{2-}$ complex in a manner similar to its interaction with aquated metal ions $[M^{II}(H_2O)_6]^{2+}$ in solutions. Thus, the initial estimates of the stability constants of the normal ternary complexes formed in solution have been determined using the Irving and Rossotti formula (Irving and Rossotti, 1953, 1954). The side effects due to hydrolysis of metal ions which may occur at higher pH values have been included during the refinement of the calculated formation constants of the different binary and ternary complexes formed in solution.

In Figures 1−3 representative sets of experimental titration curves obtained according to the sequence described in the Experimental Section for the different M(II) + NU + Z systems studied are displayed. Generally, the complex titration curves show an inflection after addition of 2 mol of base per 1 mol of the nucleotide (AMP, ADP, and ATP). This indicates the simultaneous dissociation of two protons from AMP while in the case of ADP and ATP the complex species M(HADP), M(ADP), M(HATP)$^-$, and M(ATP) have been formed in solution. log K values for these binary protonated complexes are available in the literature (Smith et al., 1991). With respect to the titration curves of the M(II) + Z binary complex solutions studied,

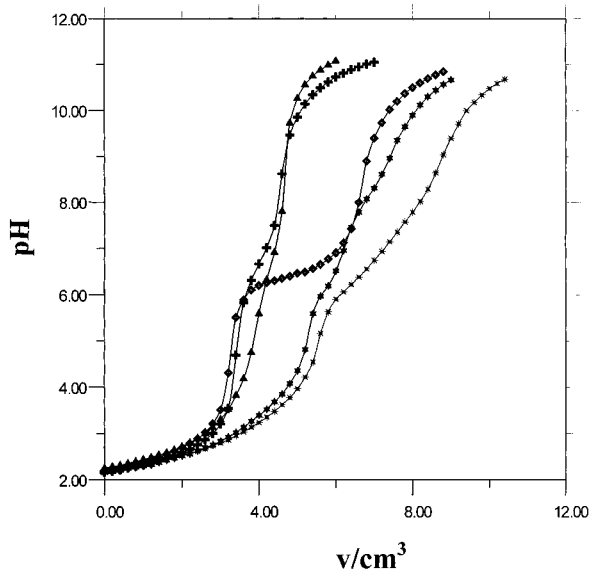


Figure 1. pH against volume of 0.0315 mol dm^{-3} KOH for the Cu(II) + ATP + MOPSO system at 25 °C and I = 0.1 mol dm^{-3} KNO_3: **(a)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP (▲); **(b)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP + 0.001 mol dm^{-3} Cu(II) (★); **(c)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} MOPSO (+); **(d)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} MOPSO + 0.001 mol dm^{-3} Cu(II) (◇); **(e)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP + 0.001 mol dm^{-3} MOPSO + 0.001 mol dm^{-3} Cu(II) (*)

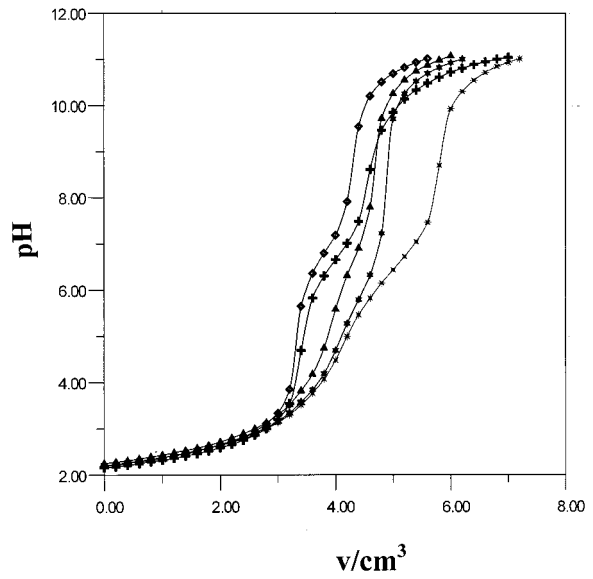


Figure 2. pH against volume of 0.0315 mol dm^{-3} KOH for the Ca(II) + ATP + MOPSO system at 25 °C and I = 0.1 mol dm^{-3} KNO_3: **(a)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP (▲); **(b)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP + 0.001 mol dm^{-3} Ca(II) (★); **(c)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} MOPSO (+); **(d)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} MOPSO + 0.001 mol dm^{-3} Ca(II) (☆); **(e)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} ATP + 0.001 mol dm^{-3} MOPSO + 0.001 mol dm^{-3} Ca(II) (*).

one may deduce that these complexes begin to form in the pH range 2.4−3.0. In all cases no calculations have been performed beyond the precipitation point; hence, the hydroxy species likely to be formed after this point could not be studied.

For the titration curves of the ternary systems studied (M(II) + NU + ACES), it was observed that complexation starts in the pH range 2.9−4.5 for all M(II) + AMP + ACES

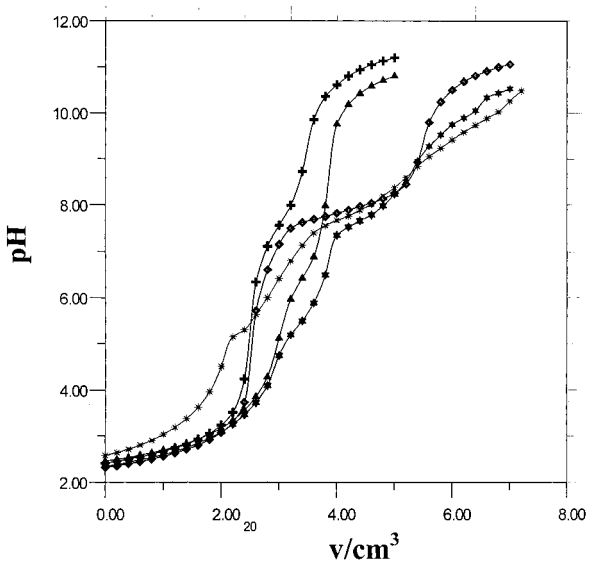


Figure 3. pH against volume of 0.0315 mol dm^{-3} KOH for the Zn(II) + AMP + TAPSO system at 25 °C and I = 0.1 mol dm^{-3} KNO_3: **(**a**)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} AMP (▲); **(**b**)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} AMP + 0.001 mol dm^{-3} Zn(II) (★); **(**c**)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} TAPSO (+); **(**d**)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} TAPSO + 0.001 mol dm^{-3} Zn(II) (☆); **(e)** 0.004 mol dm^{-3} HNO_3 + 0.001 mol dm^{-3} AMP + 0.001 mol dm^{-3} TAPSO + 0.001 mol dm^{-3} Zn(II) (*)

systems. For M(II) + ADP + ACES and M(II) + ATP + ACES systems, coordination of the secondary ligands and the binary complex M(II) + NU starts in the pH ranges 2.7−3.9 and 2.9−7.1, respectively.

Different values for log K and log β which have been calculated and refined using the experimental data are given in Tables 1−7. Examination of the different formation constant values listed in these tables clearly reveals that the order of the overall stability constants of the different normal ternary complexes in the systems M(II) + NU + ACES in terms of metal ion generally follows the trend Zn(II) < Cu(II) > Ni(II) > Co(II) > Mn(II) > Mg(II) > Ca(II) for M(II) + ATP + ACES systems, and for M(II) + AMP + ACES and M(II) + ADP + ACES the stability constant values decrease in the order Ni(II) > Co(II) > Mn(II) > Mg(II) > Ca(II) and Ni(II) > Mn(II) > Zn(II) > Cu(II) > Co(II), respectively. This may be explained by the presence of different types of interligand interactions depending on the nature of the metal ion. The instability of the Cu(II) + ADP + ACES complex may be due to its low coordination number as compared to the Ni(II) complex.

The ternary systems Cu(II) + AMP + ACES and Zn(II) + AMP + ACES could not be studied due to precipitation. To the authors' knowledge, no data for the ternary complexes of the newer buffers ACES, MOPSO, DIPSO, TAPSO, or CHES with the purine nucleotides AMP, ADP, or ATP are available in the literature for comparison. Examination of the different formation constant values listed in Tables 1−7 clearly reveals that the formation constant of the mixed ligand complexes increases in the order AMP < ADP < ATP in the case of the complexes of the type M(II) + NU + MOPSO where M(II) = Cu(II) and

Table 1. Formation Constants for the Binary Cu(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Mixed Ligand Complexes Cu(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} (KNO_3)[a]

ligand	log $K^{Cu(II)}_{Cu(II)(NU)}$ or log $K^{Cu(II)}_{Cu(II)(Z)}$	log $K^{Cu(II)(AMP)}_{Cu(II)(AMP)(Z)}$ or log $\beta^{Cu(II)}_{Cu(II)(AMP)(Z)}$	log $K^{Cu(II)(ADP)}_{Cu(II)(ADP)(Z)}$ or log $\beta^{Cu(II)}_{Cu(II)(ADP)(Z)}$	log $K^{Cu(II)(ATP)}_{Cu(II)(ATP)(Z)}$ or log $\beta^{Cu(II)}_{Cu(II)(ATP)(Z)}$
AMP	3.18 ± 0.03			
ADP	5.90 ± 0.04			
ATP	6.01 ± 0.05			
ACES	4.76 ± 0.02		3.70 ± 0.02	3.50 ± 0.02
			9.60 ± 0.05	9.51 ± 0.04
MOPSO	4.07 ± 0.02		3.85 ± 0.02	4.30 ± 0.02
			9.75 ± 0.04	10.31 ± 0.04
CHES			10.04 ± 0.05[b]	3.40 ± 0.02
				9.41 ± 0.03
TAPSO	5.04 ± 0.03	8.50 ± 0.03[b]	12.46 ± 0.04[b]	3.41 ± 0.02
				9.42 ± 0.03
DIPSO	4.96 ± 0.03	9.05 ± 0.03[b]	3.41 ± 0.02	4.30 ± 0.02
			9.31 ± 0.05	10.31 ± 0.04

[a] ± uncertainties refer to three times the standard deviation (3s). log $\beta^{Cu(II)}_{Cu(II)(NU)(Z)}$ = log $K^{Cu(II)(NU)}_{Cu(II)(NU)(Z)}$ + log $K^{Cu(II)}_{Cu(II)(NU)}$. [b] log $K^{Cu(II)}_{Cu(II)(NU)(HZ)}$.

Table 2. Formation Constants for the Binary Co(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes and Those for the Mixed Ligand Complexes Co(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} (KNO_3)[a]

ligand	log $K^{Co(II)}_{Co(II)(NU)}$ or log $K^{Co(II)}_{Co(II)(Z)}$	log $K^{Co(II)(AMP)}_{Co(II)(AMP)(Z)}$ or log $\beta^{Co(II)}_{Co(II)(AMP)(Z)}$	log $K^{Co(II)(ADP)}_{Co(II)(ADP)(Z)}$ or log $\beta^{Co(II)}_{Co(II)(ADP)(Z)}$	log $K^{Co(II)(ATP)}_{Co(II)(ATP)(Z)}$ or log $\beta^{Co(II)}_{Co(II)(ATP)(Z)}$
AMP	2.53 ± 0.03			
ADP	4.20 ± 0.04			
ATP	4.66 ± 0.05			
ACES	3.52 ± 0.03	6.11 ± 0.02	4.32 ± 0.03	3.69 ± 0.02
		8.64 ± 0.04	8.52 ± 0.03	8.35 ± 0.03
MOPSO		3.93 ± 0.02	3.84 ± 0.03	4.09 ± 0.02
		6.46 ± 0.02	8.05 ± 0.03	8.75 ± 0.02
CHES		3.60 ± 0.02[b]	7.65 ± 0.03[b]	11.38 ± 0.05[b]
TAPSO	3.53 ± 0.02	7.55 ± 0.03[b]	10.70 ± 0.04[b]	9.50 ± 0.04[b]
		2.17 ± 0.02[c]	2.27 ± 0.02[c]	4.08 ± 0.03[c]
DIPSO	3.56 ± 0.02	7.41 ± 0.03[b,]	9.87 ± 0.03[b,]	7.30 ± 0.02[b,]
		2.16 ± 0.02[c]	2.46 ± 0.02[c]	1.69 ± 0.02[c]

[a] ± uncertainties refer to three times the standard deviation (3s). log $\beta^{Co(II)}_{Co(II)(NU)(Z)}$ = log $K^{Co(II)(NU)}_{Co(II)(NU)(Z)}$ + log $K^{Co(II)}_{Co(II)(NU)}$. [b] log $K^{Co(II)}_{Co(II)(NU)(HZ)}$. [c] log $K^{Co(II)(NU)(HZ)}_{Co(II)(NU)(Z)}$.

Table 3. Formation Constants for the Binary Ni(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes and Those for the Mixed Ligand Complexes Ni(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} (KNO_3)[a]

ligand	$\log K^{Ni(II)}_{Ni(II)(NU)}$ or $\log K^{Ni(II)}_{Ni(II)(Z)}$	$\log K^{Ni(II)(AMP)}_{Ni(II)(AMP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(AMP)(Z)}$	$\log K^{Ni(II)(ADP)}_{Ni(II)(ADP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(ADP)(Z)}$	$\log K^{Ni(II)(ATP)}_{Ni(II)(ATP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(ATP)(Z)}$
AMP	2.84 ±0.03			
ADP	3.71 ± 0.04			
ATP	4.83 ± 0.03			
ACES	3.67 ± 0.03	5.96 ± 0.02	8.60 ± 0.03	4.00 ± 0.03
		8.80 ± 0.02	12.31 ± 0.03	8.83 ± 0.03
MOPSO	3.68 ± 0.02	3.80 ± 0.02	3.93 ± 0.02	4.38 ± 0.03
		6.64 ± 0.02	7.64 ± 0.03	9.21 ± 0.03
CHES		3.42 ± 0.02	7.50 ± 0.03[b]	3.34 ± 0.02
		6.26 ± 0.02	4.73 ± 0.02[c]	8.17 ± 0.02
TAPSO	3.70 ± 0.03	7.42 ± 0.03[b]	10.04 ± 0.03[b]	10.80 ± 0.04[b]
		1.98 ± 0.02[c]	3.08 ± 0.02[c]	4.17 ± 0.02[c]
DIPSO	3.76 ± 0.03	7.40 ± 0.03[b]	10.29 ± 0.05[b]	14.33 ± 0.05[b]
		2.16 ± 0.02[c]	2.86 ± 0.02[c]	4.67 ± 0.03[c]

[a] ± uncertainties refer to three times the standard deviation (3s). $\log \beta^{Ni(II)}_{Ni(II)(NU)(Z)} = \log K^{Ni(II)(NU)}_{Ni(II)(NU)(Z)} + \log K^{Ni(II)}_{Ni(II)(NU)}$. [b] $\log K^{Ni(II)}_{Ni(II)(NU)(HZ)}$. [c] $\log K^{Ni(II)(NU)(HZ)}_{Ni(II)(NU)(Z)}$.

Table 4. Formation Constants for the Binary Mn(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes and Those for the Mixed Ligand Complexes Mn(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} (KNO_3)[a]

ligand	$\log K^{Mn(II)}_{Mn(II)(NU)}$ or $\log K^{Mn(II)}_{Mn(II)(Z)}$	$\log K^{Mn(II)(AMP)}_{Mn(II)(AMP)(NU)}$ or $\log \beta^{Mn(II)}_{Mn(II)(AMP)(Z)}$	$\log K^{Mn(II)(ADP)}_{Mn(II)(ADP)(Z)}$ or $\log \beta^{Mn(II)}_{Mn(II)(ADP)(Z)}$	$\log K^{Mn(II)(ATP)}_{Mn(II)(ATP)(Z)}$ or $\log \beta^{Mn(II)}_{Mn(II)(ATP)(Z)}$
AMP	2.35 ± 0.04			
ADP	4.16 ± 0.03			
ATP	4.70 ± 0.04			
ACES	3.85 ± 0.02	4.74 ± 0.02	7.40 ± 0.04	3.47 ± 0.02
		7.09 ± 0.03	11.56 ± 0.03	8.17 ± 0.04
MOPSO		3.92 ± 0.02	3.75 ± 0.02	3.75 ± 0.02
		6.27 ± 0.03	7.91 ± 0.03	8.45 ± 0.03
CHES		3.45 ± 0.02	7.40 ± 0.02[b]	3.39 ± 0.02
		5.80 ± 0.03	4.08 ± 0.02[c]	8.09 ± 0.02
TAPSO	3.83 ± 0.03	7.40 ± 0.03[b]	9.68 ± 0.03[b]	14.50 ± 0.05[b]
		1.98 ± 0.02[c]	2.98 ± 0.02[c]	4.78 ± 0.03[c]
DIPSO	3.52 ± 0.02	7.30 ± 0.03[b]	9.40 ± 0.05[b]	14.70 ± 0.05[b]
		2.69 ± 0.02[c]	2.86 ± 0.02[c]	5.18 ± 0.02[c]

[a] ± uncertainties refer to three times the standard deviation (3s). $\log \beta^{Mn(II)}_{Mn(II)(NU)(Z)} = \log K^{Mn(II)(NU)}_{Mn(II)(NU)(Z)} + \log K^{Mn(II)}_{Mn(II)(NU)}$. [b] $\log K^{Mn(II)}_{Mn(II)(NU)(HZ)}$. [c] $\log K^{Mn(II)(NU)(HZ)}_{Mn(II)(NU)(Z)}$.

Table 5. Formation Constants for the Binary Zn(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes and Those for the Mixed Ligand Complexes Zn(II) + NU+ Z at 25.0 ± 0.1 °C and I = 0.1 Mol·dm^{-3} (KNO_3)[a]

ligand	$\log K^{Zn(II)}_{Zn(II)(NU)}$ or $\log K^{Zn(II)}_{Zn(II)(Z)}$	$\log K^{Zn(II)(AMP)}_{Zn(II)(AMP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(AMP)(Z)}$	$\log K^{Zn(II)(ADP)}_{Zn(II)(ADP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(ADP)(Z)}$	$\log K^{Zn(II)(ATP)}_{Zn(II)(ATP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(ATP)(Z)}$
AMP	2.72 ± 0.05			
ADP	4.28 ± 0.03			
ATP	4.85 ± 0.04			
ACES	3.85 ± 0.03		6.90 ± 0.03	3.49 ± 0.02
			11.18 ± 0.05	8.34 ± 0.04
MOPSO			3.72 ± 0.02	3.73 ± 0.02
			8.33 ± 0.03	8.58 ± 0.04
CHES			8.80 ± 0.03[b]	3.20 ± 0.02
			5.73 ± 0.03[c]	8.05 ± 0.04
TAPSO	3.61 ± 0.02	7.06 ± 0.03[b]	9.44 ± 0.04[b]	3.40 ± 0.02
		2.68 ± 0.03[c]	2.87 ± 0.02[c]	8.25 ± 0.02
DIPSO	3.83 ± 0.02	8.29 ± 0.03[b]	3.40 ± 0.02	14.16 ± 0.05[b]
		1.76 ± 0.02[c]	7.68 ± 0.04	3.76 ± 0.02[c]

[a] ± uncertainties refer to three times the standard deviation (3s). $\log \beta^{Zn(II)}_{Zn(II)(NU)(Z)} = \log K^{Zn(II)(NU)}_{Zn(II)(NU)(Z)} + \log K^{Zn(II)}_{Zn(II)(NU)}$. [b] $\log K^{Zn(II)}_{Zn(II)(NU)(HZ)}$. [c] $\log K^{Zn(II)(NU)(HZ)}_{Zn(II)(NU)(Z)}$.

Ni(II) ions. This behavior may be attributed to the participation of the phosphate groups in the formation of the ternary complexes in solution.

During SUPERQUAD (Gans et al., 1985) refinement the titration data of the ternary complexes Ni(II) + ADP + CHES, Mn(II) + ADP + CHES, Zn(II) + ADP + CHES, Ca(II) + AMP + CHES, and Mg(II) + AMP + CHES fit satisfactorily on the basis of the monoprotonated ternary complexes which dissociate to give normal complexes. The formation constants of the ternary complexes of the type M(II) + NU + CHES are given in Tables 1−7. It is worthy to indicate that in the case of the ternary complexes of the type M(II) + AMP + CHES, where M(II) = Cu(II) or Zn(II), precipitation has been observed during titration.

Table 6. Formation Constants for the Binary Ca(II) + Nucleotide (NU) or Zwitterionic Buffer Ligand (Z) Complexes and Those for the Mixed Ligand Complexes Ca(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol.dm^{-3} (KNO_3)[a]

ligand	$\log K^{Ca(II)}_{Ca(II)(NU)}$ or $\log K^{Ca(II)}_{Ca(II)(Z)}$	$\log K^{Ca(II)(AMP)}_{Ca(II)(AMP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(AMP)(Z)}$	$\log K^{Ca(II)(ADP)}_{Ca(II)(ADP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(ADP)(Z)}$	$\log K^{Ca(II)(ATP)}_{Ca(II)(ATP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(ATP)(Z)}$
AMP	1.85 ± 0.02			
ADP	2.86 ± 0.02			
ATP	3.97 ± 0.03			
ACES	3.38 ± 0.02	4.26 ± 0.02	6.90 ± 0.04	3.45 ± 0.02
		6.11 ± 0.02	9.76 ± 0.04	7.42 ± 0.02
MOPSO		4.03 ± 0.02	3.78 ± 0.02	3.80 ± 0.02
		5.88 ± 0.03	6.64 ± 0.02	7.77 ± 0.03
CHES	3.86 ± 0.02	6.37 ± 0.03[b]	3.60 ± 0.02	3.46 ± 0.03
		3.38 ± 0.02[c]	6.46 ± 0.02	7.43 ± 0.03
TAPSO	3.50 ± 0.02	7.40 ± 0.04[b]	9.38 ± 0.04[b]	14.02 ± 0.04[b]
		2.68 ± 0.02[c]	2.87 ± 0.02[c]	4.17 ± 0.02[c]
DIPSO	3.47 ± 0.02	8.35 ± 0.03[b]	8.30 ± 0.04[b]	3.40 ± 0.02
		1.27 ± 0.02[c]	1.69 ± 0.02[c]	7.37 ± 0.04

[a] ± uncertainties refer to three times the standard deviation (3s). $\log \beta^{Ca(II)}_{Ca(II)(NU)(Z)} = \log K^{Ca(II)(NU)}_{Ca(II)(NU)(Z)} + \log K^{Ca(II)}_{Ca(II)(NU)}$. [b] $\log K^{Ca(II)}_{Ca(II)(NU)(HZ)}$. [c] $\log K^{Ca(II)(NU)(HZ)}_{Ca(II)(NU)(Z)}$.

Table 7. Formation Constants for the Binary Mg(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Mixed Ligand Complexes Mg(II) + NU + Z at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO_3[a]

ligand	$\log K^{Mg(II)}_{Mg(II)(NU)}$ or $\log K^{Mg(II)}_{Mg(II)(Z)}$	$\log K^{Mg(II)(AMP)}_{Mg(II)(AMP)(Z)}$ or $\log \beta^{Mg(II)}_{Mg(II)(AMP)(Z)}$	$\log K^{Mg(II)(ADP)}_{Mg(II)(ADP)(Z)}$ or $\log \beta^{Mg(II)}_{Mg(II)(ADP)(Z)}$	$\log K^{Mg(II)(ATP)}_{Mg(II)(ATP)(Z)}$or $\log \beta^{Mg(II)}_{Mg(II)(ATP)(Z)}$
AMP	1.97 ± 0.02			
ADP	3.17 ± 0.03			
ATP	3.99 ± 0.02			
ACES	3.55 ± 0.02	4.40 ± 0.02	6.60 ± 0.02	3.48 ± 0.02
		6.37 ± 0.02	9.77 ± 0.03	7.47 ± 0.03
MOPSO		3.81 ± 0.02	4.12 ± 0.02	3.82 ± 0.02
		5.78 ± 0.02	7.29 ± 0.03	7.81 ± 0.03
CHES	3.84 ± 0.02	6.30 ± 0.03[b]	3.80 ± 0.02	3.43 ± 0.02
		3.75 ± 0.02[c]	6.97 ± 0.03	7.42 ± 0.04
TAPSO	3.37 ± 0.02	7.27 ± 0.03[b]	3.39 ± 0.02	14.13 ± 0.05[b]
		2.17 ± 0.02[c]	6.56 ± 0.02	4.68 ± 0.02[c]
DIPSO	3.42 ± 0.02	7.29 ± 0.03[b]	3.40 ± 0.02	12.25 ± 0.04[b]
		1.10 ± 0.01[c]	6.57 ± 0.02	3.66 ± 0.02[c]

[a] ± uncertainties refer to three times the standard deviation (3s). $\log \beta^{Mg(II)}_{Mg(II)(NU)(Z)} = \log K^{Mg(II)(NU)}_{Mg(II)(NU)(Z)} + \log K^{Mg(II)}_{Mg(II)(NU)}$. [b] $\log K^{Mg(II)}_{Mg(II)(NU)(HZ)}$. [c] $\log K^{Mg(II)(NU)(HZ)}_{Mg(II)(NU)(Z)}$.

This can be likely ascribed to the behavior that these complexes undergo hydrolysis where hydroxo complex species are probably formed.

The higher values of stability constants of protonated 1:1 ternary complexes containing M(II), purine nucleotide, and CHES compared with the other normal ternary complexes of the type M(II) + NU + CHES may be attributed to extra hydrogen bonding of the proton with oxygen atom of the secondary ligand molecules.

The weaker binding of the CHESate anion by the binary M(II)−nucleotide complexes as compared with that of the ACESate anions has been observed. The fact that the CHESate anion is more basic tends to make it more strongly bound. The effect from the poorer structural matching between the secondary ligand and M(II)−nucleotide complex prevails over that from the basicity, and the binding of the CHESate anion secondary ligand by a M(II)−nucleotide complex is weaker than the bonding between the ACESate anion with the same binary M(II)−nucleotide complex. Also the participation of the carbonyl group of ACESate anion during the formation of the mixed ligand complexes may also enhance the stability of the resulting species.

In Figure 3 the titration curve of a 1:1 mixture of Zn(II) and 5′-AMP is compared with titration curve of 5′-AMP. It was observed that complex formation lowers the pK of the secondary phosphate and the hydrolysis of Zn(II) occurs at higher pH in the presence of the nucleotide. These results indicate that the complex formed involves the phosphate of the nucleotide and that the complexed zinc is protected from the action of hydroxide ion. The requirement of doubly negative phosphate prevents formation of the complex at low pH, and the hydrolysis above pH 8 destabilizes the complex at high pH.

To quantify the stability of ternary complexes relative to the stability of the binary parent complexes (Sigel et al., 1983); one may consider the equilibrium

$$M(NU) + M(Z) \rightleftharpoons M(NU)(Z) + M \qquad (6)$$

the corresponding equilibrium constant is defined by eq 7

$$10^{\Delta \log K_M} = \frac{[M(NU)(Z)][M(II)]}{[M(NU)][M(Z)]} \qquad (7)$$

values for $\Delta \log K_M$ may be calculated according to

$$\Delta \log K_M = \log K^{M(NU)}_{M(NU)(Z)} - \log K^{M}_{M(Z)} \qquad (8)$$

The results are given in Table 8. $\Delta \log K_M$ values are positive for some of the ternary complexes studied. The higher values for the formation constants of ternary complexes compared with the binary systems may be attributed to the interligand interactions or some cooperativity between the coordinate ligands, possibly H-bond formation. This also may be explained on the basis of the

Table 8. Δ log K_M[a] Values for the 1:1:1 M(II) + Nucleotide (NU) + Zwitterionic Buffer (Z) Ternary Complexes, As Determined by Potentiometric pH Titrations at 25.0 ± 0.1 °C and I = 0.1 mol dm^{-3} KNO_3

	Δ log K_M[a]						
	Cu(II)	Ni(II)	Co(II)	Mn(II)	Zn(II)	Ca(II)	Mg(II)
M(II)(AMP)(Z)							
ACES		+2.29	+2.59	+0.89		+0.88	+0.85
MOPSO		+0.12					
CHES							
DIPSO							
TAPSO							
M(II)(ADP)(Z)							
ACES	−1.06	+4.93	+0.80	+3.55		+3.52	+3.05
MOPSO	−0.22	+0.25					
CHES						−0.26	−0.04
DIPSO	−1.55						−0.02
TAPSO							+0.02
M(II)(ATP)(Z)							
ACES	−1.26	+0.33	+0.17	−0.38	−0.36	+0.07	−0.07
MOPSO	+ 0.23	+0.70					
CHES						−0.40	−0.41
DIPSO	−0.66					−0.07	
TAPSO	−1.63				−0.21		

[a] $\Delta \log K_M = \log K^{M(II)(NU)}_{M(II)(NU)(Z)} - \log K^{M(II)}_{M(II)(Z)}$.

π-acceptor qualities of the adenine base. Thus the π-electron-donating tendency of the M(II) ion to the antibonding π^* orbitals of heteroaromatic N base, such as adenine base, causes strengthing of the M(II)−N bond. Due to the π-acceptor qualities of the adenine base (i.e., back-donation from metal to ligand), the d-electron content on the metal decreases, which renders the metal more electrophilic. The interaction of the p-electrons of the phosphate O atoms with the metal will increase to a greater extent and consequently influence the stability of ternary complexes.

The ternary complexes of the type M(II) + NU + Z may be considered as relatively simple models from which information may be gained about the properties of purine nucleotides and their base moieties regarding the strength of their interactions with the biologically important zwitterionic buffer ligands (ACES, MOPSO, DIPSO, TAPSO, or CHES), and even insight into the factors which influence the strength is thus becoming available as these systems may mimic enzyme−metal ion−substrate complexes. Our investigation confirmed the formation of mixed ligand complexes of the type M(II) + NU + Z (where Z = ACES, MOPSO, DIPSO, TAPSO, or CHES and M(II) = Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), or Mg(II)) in solution; hence, great reservations should be exercised in employing these biologically important zwitterionic buffer ligands in aqueous solutions in systems containing the above-mentioned metal ions and the purine nucleotides AMP, ADP, or ATP. The likelihood for the formation of ternary complexes is also rather high, as was demonstrated in the present study with AMP, ADP, or ATP; this will affect the properties of these purine nucleotides in various ways when they are used as substrates. The ternary systems M + NU + Z, where M = Pd(II), Cr(III), or AL(III), NU = AMP, CMP, IMP, GMP, ADP, or ATP, and Z = ACES, MOPSO, and TAPSO, are now under consideration in our laboratory. The study of these systems as well as the transition metal ion systems in the present investigation may lead to guidelines for the synthesis of possible antitumor drugs.

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