Role of Biologically Important Zwitterionic Buffer Secondary Ligands in the Stability of the Ternary Complexes Containing Some Metal Ions and Guanosine 5′-Monophosphate, Inosine 5′-Monophosphate, and Cytidine 5′-Monophosphate

Zeinab M. Anwar and Hassan A. Azab*

Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

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 guanosine 5′-monophosphate, inosine 5′-monophosphate, and cytidine 5′-monophosphate and Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Pd(II), Ca(II), and Mg(II) with the biologically important secondary ligand zwitterionic buffers 3-[*N*-morpholinol]-2-hydroxypropanesulfonic acid, 3-[*N*-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid, and *N*-2-acetamido-2-aminoethanesulfonic acid in a 1:1:1 ratio. The experimental conditions were selected such that self-association of the nucleotides and their complexes was negligibly small; that is, the monomeric complexes were studied. The formation of various 1:1:1 mixed ligand complexes was inferred from the potentiometric titration curves. Initial estimates of the formation constants of the resulting species and the acid dissociation constants of guanosine 5′-monophosphate, inosine 5′-monophosphate, cytidine 5′-monophosphate, and the secondary ligands 3-[*N*-morpholinol]-2-hydroxypropanesulfonic acid, 3-[*N*-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid, and *N*-2-acetamido-2-aminoethane sulfonic acid have been refined with the SUPERQUAD computer program.

Introduction

Complexes between metal ions and two different types of bioligands, namely nucleotides and zwitterionic buffer ligands,[1,2] may be considered as models for ternary interactions in which a metal entity cross-links a protein and a nucleic acid. Artificial chemical DNA-nucleases frequently are based on metal−protein conjugates, thereby representing an application of ternary complex formation in molecular biology. Ternary complexes of some metal ions with 5′-GMP, 5′-IMP, and 5′-CMP and other secondary ligands have been investigated using several techniques.[3−9] For an improved understanding of the driving forces leading to mixed-ligand complexes of the type metal−nucleotide−zwitterionic buffer [M−NU−Z] (see Chart 1), where the nucleotide = 5′-GMP, 5′-IMP, or 5′-CMP and the zwitterionic buffer = MOPSO, TAPSO, or ACES and M = Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Pd(II), Ca(II), or Mg(II), the title systems have been investigated by potentiometric pH-titrations to determine the stability constants of the complexes formed, as these systems may serve as models for metalloenzyme reactions in biological systems. They also provide useful information in understanding the specific and selective interactions that take place in many biochemical processes.

The present investigation is in continuation of our studies of the ternary complexes of biological importance.[10−13]

Experimental Section

Materials and Solutions. Reagent grade MOPSO, TAPSO, and ACES were from Sigma Chemical Co. We determined by potentiometric pH titrations the molecular weight of MOPSO, TAPSO, and ACES to verify/determine the purity, especially for acidic/basic contaminants. The purity averaged 99.5% for the three compounds, with a standard deviation of 0.05%.

Guanosine 5′-monophosphoric acid disodium salt ($C_{10}H_{12}N_5O_8PNa_2·8H_2O$, $Na_2GMP·8H_2O$), inosine 5′-monophosphoric acid disodium salt ($C_{10}H_{11}N_4O_8PNa_2·8H_2O$, Na_2-IMP·$8H_2O$), and cytidine 5′-monophosphoric acid disodium salt ($C_9H_{12}N_3O_8PNa_2·6H_2O$, $Na_2CMP·6H_2O$) were purchased from Sigma Chemical Co. The amount of free phosphates initially present in the nucleotides was determined.[14] Fresh solid ligand was weighed out for each titration to avoid hydrolysis prior to the potentiometric measurements.

Copper nitrate $Cu(NO_3)·6H_2O$, nickel nitrate $Ni(NO_3)_2·6H_2O$, cobalt nitrate $Co(NO_3)_2·6H_2O$, manganese nitrate $Mn(NO_3)_2·6H_2O$, and zinc nitrate $Zn(NO_3)_2·6H_2O$ were from Merck p.a. Calcium nitrate $Ca(NO_3)_2·4H_2O$ and magnesium nitrate $Mg(NO_3)_2·6H_2O$ were from BDH. Stock solutions were prepared using bidistilled, CO_2-free water. Palladium chloride $PdCl_2$ was from BDH. A stock solution of palladium was prepared by dissolving the appropriate solid palladium chloride in concentrated HCl and then diluting to the required volume using bidistilled, CO_2-free water.

Nitric acid and KOH were from Merck p.a. Stock solutions were prepared using bidistilled, CO_2-free water. The concentration of KOH used for the titrations was determined by titrations 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 made on the solutions in a double-walled glass vessel at (25.0 ± 0.1)°C with a commercial Fisher combined electrode, and a magnetic stirrer was used. A Fischer Accumet

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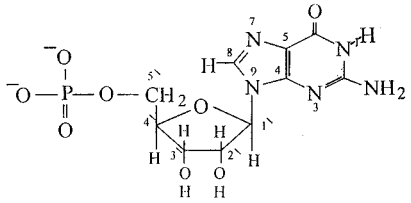
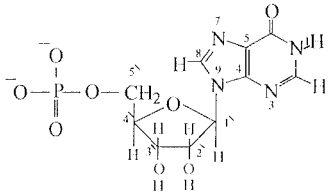
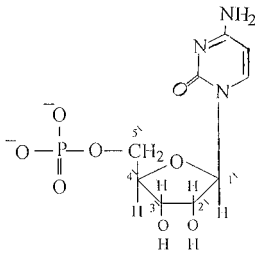
Chart 1



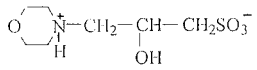
Guanosine 5`-monophosphate (5`-GMP)



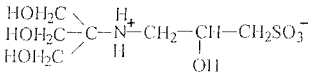
Inosine 5`-monophosphate (5`-IMP)



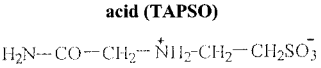
Cytidine 5`-monophosphate (5`-CMP)



3-[N-morpholinol]-2-hydroxypropanesulfonic acid (MOPSO)



3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropane-sulfonic acid (TAPSO)



N-2-acetamido-2-aminoethanesulfonic acid (ACES)

pH/ion meter Model 825 MP was used. Purified nitrogen was bubbled through the solutions during titrations.

Procedure. The test solution was titrated with standard CO_2-free KOH. The electrodes were calibrated, in both the acidic and alkaline regions, by titrating 0.01 mol dm^{-3} nitric acid with standard potassium hydroxide under the same experimental conditions. The concentration of free hydrogen ion, C_{H^+}, at each point of the titration is related to the measured emf, $E°$, of the cell by the Nernst equation.

$$E = E° + Q \log C_{H^+} \qquad (1)$$

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 a 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[15] to refine $E°$ and the autoprotrolysis constant of water, K_w.

During these calculations 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 ligand (1×10^{-3} mol dm^{-3}) (c); HNO_3 (4×10^{-3} mol dm^{-3}) + zwitterionic buffer ligand (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 ligand (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 25 cm^3. At least four titrations were performed 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.

The acidity constant pK_{a1} for 5′-IMP was determined at 25 °C and $I = 0.1$ mol dm^{-3} (KNO_3) from titrations of 25 mL solutions containing 48.00 mmol dm^{-3} HNO_3 and 22.7 mmol dm^{-3} IMP^{2-} with 0.2 mol dm^{-3} KOH.

Results and Discussion

Formation constants for the different ternary complexes and protonation constants for primary and secondary ligands were refined with the SUPERQUAD computer program.[16] 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 (charges are omitted for clarity):

$$pM + qNU + rZ + sH \rightleftharpoons M_p(Nu)_q(Z)_r(H)_s \qquad (2)$$

where p, q, r, and s are the moles of M, NU, Z, and H in $M_p(NU)_q(Z)_r(H)_s$. The data points collected in the pH range 3−10 were used for the calculations. The constants were refined by minimizing U, defined by

$$U = \sum_i W_i (E_{obs} - E_{calc})^2 \qquad (3)$$

where E_{obs} and E_{calc} refer to the measured potential and that calculated from eq 1. The weighting factor W_i is defined as the reciprocal of the estimated variance of the measurement.

$$W_i = 1/\sigma^2 = 1/[\sigma_E{}^2 + (\delta E/\delta V)^2 \sigma_V{}^2] \qquad (4)$$

where σ_E and σ_V are the estimated variances of the potential and volume readings, respectively. The quality of the 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 ($E_{obs} - E_{calc}$) versus pH was reasonably random, without any significant systematic trends, thus indicating a good fit of the experimental data.

At the experimental pH values used in the calculation in this work, the interfering effects of hydroxy complexes are negligible [for Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), or Mg(II)]. Thus, the secondary ligand Z combines with the binary 1:1 M(II)−NU complexes [M(II)−GMP, M(II)−IMP, and M(II)−CMP] in a manner similar to that for its interaction with aquated metal ions in solutions.

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) + Nucleotide + Zwitterionic Buffer Ligand at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO_3[a]

ligand	$\log K^{Cu(II)}_{Cu(II)(Z)}$	$\log K^{Cu(II)(GMP)}_{Cu(II)(GMP)(Z)}$ or $\log \beta^{Cu(II)}_{Cu(II)(GMP)(Z)}$	$\log K^{Cu(II)(IMP)}_{Cu(II)(IMP)(Z)}$ or $\log \beta^{Cu(II)}_{Cu(II)(IMP)(Z)}$	$\log K^{Cu(II)(CMP)}_{Cu(II)(CMP)(Z)}$ or $\log \beta^{Cu(II)}_{Cu(II)(CMP)(Z)}$
MOPSO	4.01 ± 0.02	8.05[c]± 0.03	6.70[c]± 0.03	8.54[c]± 0.04
TAPSO	4.90 ± 0.02	6.74[c]± 0.03, 3.76 ± 0.02	4.20 ± 0.02	3.67 ± 0.02
			7.60 ± 0.03	6.97 ± 0.03
ACES	5.55 ± 0.02	5.80[b]± 0.02	5.37 ± 0.02	7.03[c]± 0.03
			8.77 ± 0.03	

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Cu(II)}_{Cu(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	3.61 ± 0.04	45.93	21.45	33.09
5′-IMP	3.40 ± 0.02	38.22	23.96	30.64
5′-CMP	3.30 ± 0.02	48.72	20.94	40.11

[a] $\log \beta^{Cu(II)}_{Cu(II)(NU)(Z)} = \log K^{Cu(II)(NU)}_{Cu(II)(NU)(Z)} + \log K^{Cu(II).}_{Cu(II)(NU)}$ [b] Log formation constant of protonated binary metal complex, $\log K^{Cu(II)}_{Cu(II)(HNU)}$, or protonated ternary complex, $\log K^{Cu(II)(HNU)}_{Cu(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Cu(II)(HNU)}_{Cu(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Cu(II)(NU)}_{Cu(II)(NU)(Z)}$ or $-2.303RT \log K^{Cu(II)(HNU)}_{Cu(II)(HNU)(Z)}$ or $-2.303RT \log K^{Cu(II)(HNU)}_{Cu(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

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

ligand	$\log K^{Ni(II)}_{Ni(II)(Z)}$	$\log K^{Ni(II)(GMP)}_{Ni(II)(GMP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(GMP)(Z)}$	$\log K^{Ni(II)(IMP)}_{Ni(II)(IMP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(IMP)(Z)}$	$\log K^{Ni(II)(CMP)}_{Ni(II)(CMP)(Z)}$ or $\log \beta^{Ni(II)}_{Ni(II)(CMP)(Z)}$
MOPSO	3.50 ± 0.02	10.84[c] ± 0.04, 3.82 ± 0.02	3.71[c]± 0.02	3.89 ± 0.02
			6.66 ± 0.03	6.97 ± 0.03
TAPSO	3.55 ± 0.02	6.67[c]± 0.04, 3.65 ± 0.02	3.95 ± 0.02	4.01 ± 0.02
			6.90 ± 0.03	7.09 ± 0.03
ACES	3.85 ± 0.02	4.74[b]± 0.02, 7.28 ± 0.03	4.88 ± 0.02	4.31 ± 0.03
			7.83 ± 0.03	7.39 ± 0.03

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Ni(II)}_{Ni(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	3.16 ± 0.03	21.79	20.82	41.53
5′-IMP	2.95 ± 0.02	21.16	22.53	27.84
5′-CMP	3.08 ± 0.02	22.19	22.88	24.59

[a] $\log \beta^{Ni(II)}_{Ni(II)(NU)(Z)} = \log K^{Ni(II)(NU)}_{Ni(II)(NU)(Z)} + \log K^{Ni(II)}_{Ni(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Ni(II)}_{Ni(II)(HNU)}$, or protonated ternary complex, $\log K^{Ni(II)(HNU)}_{Ni(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Ni(II)(HNU)}_{Ni(II)(HNU)(HZ)}$. [d] ΔG, free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Ni(II)(NU)}_{Ni(II)(NU)(Z)}$ or $-2.303RT \log K^{Ni(II)(HNU)}_{Ni(II)(HNU)(Z)}$ or $-2.303RT \log K^{Ni(II)(HNU)}_{Ni(II)(HNU)(HZ)}$.± uncertainties refer to 3 times the standard deviation (3s).

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.[17,18]

The acidity constants determined at 25 °C and ionic strength I = 0.1 mol dm^{-3} (KNO_3) of MOPSO (pk_{a2} = 6.89 ± 0.02), TAPSO (pk_{a2} = 7.61 ± 0.02), and ACES (pk_{a2} = 7.16 ± 0.02) are in good agreement with those found in the literature.[19,20] The acid formation constant values for 5′-GMP (pk_{a1} = 2.45 ± 0.05, pk_{a2} = 6.38 ± 0.04, pk_{a3} = 9.48 ± 0.05), 5′-IMP (pk_{a1} = 1.32 ± 0.03, pk_{a2} = 6.41 ± 0.04, pk_{a3} = 9.06 ± 0.05), and 5′-CMP (pk_{a1} = 4.40 ± 0.04, pk_{a2} = 6.56 ± 0.04) and the stability constants of their Cu(II), Co(II), Ni(II) Mn(II), Zn(II), Ca(II), Mg(II), or Pd(II) complexes were determined from the titration curves, at 25 °C and ionic strength I = 0.1 mol dm^{-3} (KNO_3), and the results agree fairly well with those reported in the literature.[21,4,22,5] For the determination of the protonation constants of nueclotides, at least four titrations have been performed for each system and the individual results showed no dependence on the concentration of the nucleotide employed in the various experiments. The plus/minus values refer to statistically determined uncertainties at small 95% confidence intervals of the reported values.

Initial estimates of the stability constants of different protonated binary and ternary complexes formed in solution have been refined with the SUPERQUAD computer program.[16]

For the ternary systems studied [M + NU + Z], it was observed that coordination of the secondary ligand and M−NU starts in the pH range 5.3−6.5 for Pd(II) + GMP + MOPSO, Ca(II) + GMP + MOPSO, Mg(II) + GMP + MOPSO, Cu(II) + GMP + MOPSO, Ni(II) + GMP + MOPSO, and Co(II) + GMP + MOPSO. For the ternary systems [M(II) + IMP + MOPSO] formation of the mixed ligand complexes starts in the pH range 3.0−6.6. To the authors' knowledge, no data for the ternary complexes of the newer buffers MOPSO, TAPSO, or ACES with 5′-GMP, 5′-IMP, or 5′-CMP are available in the literature for comparison.

The observed weaker binding of the TAPSOate anion by the binary M(II)−nucleotide complexes as compared with that of the MOPSOate or ACESate in the normal ternary systems Co(II) + IMP + Z, Mn(II) + IMP + Z, Mn(II) + CMP + Z, Ca(II) + IMP + Z, Ca(II) + CMP + Z, Mg(II) + IMP + Z, Mg(II) + CMP + Z, and Pd(II) + CMP + Z may be attributed to the poorer structural matching between

Table 3. Formation Constants for the Binary Co(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Mixed-Ligand Complexes Co(II) + Nucleotide + Zwitterionic Buffer Ligand at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO$_3$[a]

ligand	$\log K^{Co(II)}_{Co(II)(Z)}$	$\log K^{Co(II)(GMP)}_{Co(II)(GMP)(Z)}$ or $\log \beta^{Co(II)}_{Co(II)(GMP)(Z)}$	$\log K^{Co(II)(IMP)}_{Co(II)(IMP)(Z)}$ or $\log \beta^{Co(II)}_{Co(II)(IMP)(Z)}$	$\log K^{Co(II)(CMP)}_{Co(II)(CMP)(Z)}$ or $\log \beta^{Co(II)}_{Co(II)(CMP)(Z)}$
MOPSO		7.48[c] ± 0.03, 3.68 ± 0.02	3.81 ± 0.03	3.82 ± 0.02
			6.46 ± 0.03	6.67 ± 0.02
TAPSO	3.45 ± 0.02	6.68[c] ± 0.03, 3.62 ± 0.02	3.52 ± 0.03	3.96 ± 0.02
			6.17 ± 0.02	6.81 ± 0.02
ACES	3.78 ± 0.02	5.49[b] ± 0.02, 7.79 ± 0.03	4.98 ± 0.02	4.14 ± 0.03
			7.63 ± 0.02	6.99 ± 0.03

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Co(II)}_{Co(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	2.75 ± 0.02	20.99	20.65	44.44
5′-IMP	2.65 ± 0.02	21.73	20.08	28.41
5′-CMP	2.85 ± 0.02	21.79	22.59	23.62

[a] $\log \beta^{Co(II)}_{Co(II)(NU)(Z)} = \log K^{Co(II)(NU)}_{Co(II)(NU)(Z)} + \log K^{Co(II)}_{Co(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Co(II)}_{Co(II)(HNU)}$, or protonated ternary complex, $\log K^{Co(II)(HNU)}_{Co(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Co(II)(HNU)}_{Co(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Co(II)(NU)}_{Co(II)(NU)(Z)}$ or $-2.303RT \log K^{Co(II)(HNU)}_{Co(II)(HNU)(Z)}$ or $-2.303RT \log K^{Co(II)(HNU)}_{Co(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

Table 4. Formation Constants for the Binary Mn(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Mixed-Ligand Complexes Mn(II) + Nucleotide + Zwitterionic Buffer Ligand at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO$_3$[a]

ligand	$\log K^{Mn(II)}_{Mn(II)(Z)}$	$\log K^{Mn(II)(GMP)}_{Mn(II)(GMP)(Z)}$ or $\log \beta^{Mn(II)}_{Mn(II)(GMP)(Z)}$	$\log K^{Mn(II)(IMP)}_{Mn(II)(IMP)(Z)}$ or $\log \beta^{Mn(II)}_{Mn(II)(IMP)(Z)}$	$\log K^{Mn(II)(CMP)}_{Mn(II)(CMP)(Z)}$ or $\log \beta^{Mn(II)}_{Mn(II)(CMP)(Z)}$
MOPSO		8.20[c] ± 0.05, 4.08 ± 0.05	3.93 ± 0.03	4.10 ± 0.02
			6.28 ± 0.03	6.89 ± 0.02
TAPSO	3.48 ± 0.02	6.71[c] ± 0.04, 3.78 ± 0.04	3.38 ± 0.02	3.76 ± 0.02
			5.73 ± 0.02	6.55 ± 0.02
ACES	3.68 ± 0.02	6.67[b] ± 0.04	4.49 ± 0.02	4.01 ± 0.03
			6.84 ± 0.02	6.80 ± 0.03

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Mn(II)}_{Mn(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	2.37 ± 0.02	23.27	21.56	38.05
5′-IMP	2.35 ± 0.02	22.42	19.28	25.61
5′-CMP	2.79 ± 0.02	23.39	21.45	22.88

[a] $\log \beta^{Mn(II)}_{Mn(II)(NU)(Z)} = \log K^{Mn(II)(NU)}_{Mn(II)(NU)(Z)} + \log K^{Mn(II)}_{Mn(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Mn(II)}_{Mn(II)(HNU)}$, or protonated ternary complex, $\log K^{Mn(II)(HNU)}_{Mn(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Mn(II)(HNU)}_{Mn(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Mn(II)(NU)}_{Mn(II)(NU)(Z)}$ or $-2.303RT \log K^{Mn(II)(HNU)}_{Mn(II)(HNU)(Z)}$ or $-2.303RT \log K^{Mn(II)(HNU)}_{Mn(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

the TAPSOate secondary ligand and the M(II)−nucleotide complex. The higher binding of the ACESate anion by the binary M−nucleotide complexes as compared with that of the MOPSOate or TAPSOate anions in the ternary systems Ni(II) + IMP + Z, Ni(II) + CMP + Z, Co(II) + IMP + Z, Co(II) + CMP + Z, Mn(II) + IMP + Z, Mg(II) + IMP + Z, or Pd(II) + CMP + Z may be attributed to the participation of the carbonyl group of the ACESate anion during the formation of the mixed ligand complexes. This behavior may enhance the stability of the resulting species.

During SUPERQUAD[16] refinement the titration data of some ternary complexes fit satisfactorily on the basis of the monoprotonated and diprotonated ternary complexes which dissociate to give normal complexes as indicated in Tables 1−8.

The most unexpected result for the ternary systems of the type M(II) + CMP + ACES is certainly the high stability of the mixed ligand complex Zn(II) + CMP + ACES compared to that of the other divalent metal ions. This means that equilibrium 5 is on its right-hand side.

$$\mathrm{Zn(CMP)} + \mathrm{Zn(ACES)} \rightleftharpoons \mathrm{Z(CMP)(ACES)} + \mathrm{Zn} \quad (5)$$

This effect of a stability enhancement for the Zn(II) complexes is clearly beyond the effect that may be attributed to the combination of an O donor ligand and a heteroaromatic π accepting amine. It seems that the explanation for the above observation is linked to the varying coordination sphere of Zn(II), which apparently easily switches from coordination number 6 to 4 or 5. On this basis this behavior may be explained: if the primary ligand CMP binds to an octahedral Zn(II), and there is a very high probability for this structure, and if upon the further binding of ACESate anion the coordination is reduced to 4 or 5, two water molecules are released upon the coordination of the secondary ligand. Such a process is entropically favored.

Clearly, for Co(II) and Ni(II) with their well defined octahedral coordination spheres, such a process is considerably less probable.

The observed higher stability constants of the protonated Mn(II) + GMP + TAPSO, Mn(II) + GMP + ACES ternary systems compared with those of Co(II) and Ni(II) ternary complexes may be attributed to the presence of hydrophobic ligand−ligand interactions in those complexes.

It is evident from Tables 1−8 that the formation constant values for the protonated mixed-ligand 1:1:1 systems M(II)

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

ligand	$\log K^{Zn(II)}_{Zn(II)(Z)}$	$\log K^{Zn(II)(GMP)}_{Zn(II)(GMP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(GMP)(Z)}$	$\log K^{Zn(II)(IMP)}_{Zn(II)(IMP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(IMP)(Z)}$	$\log K^{Zn(II)(CMP)}_{Zn(II)(CMP)(Z)}$ or $\log \beta^{Zn(II)}_{Zn(II)(CMP)(Z)}$
MOPSO		8.59[c] ± 0.05	8.60[c] ± 0.04, 5.88[b] ± 0.04	3.92 ± 0.02 6.88 ± 0.03
TAPSO	3.80 ± 0.02	6.70[c] ± 0.04	7.05[b] ± 0.04	7.66[c] ± 0.03, 3.64[b] ± 0.02
ACES	4.39 ± 0.02	6.71[c] ± 0.04	9.40[c] ± 0.04, 5.00[b] ± 0.03	4.92 ± 0.02 7.88 ± 0.03

		$-\Delta G$[d]/kJ·mol^{-1}		
ligand	$\log K^{Zn(II)}_{Zn(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	2.65 ± 0.02	49.01	38.22	38.28
5′-IMP	2.57 ± 0.02	33.55	40.22	28.52
5′-CMP	2.96 ± 0.02	22.36	20.76	28.07

[a] $\log \beta^{Zn(II)}_{Zn(II)(NU)(Z)} = \log K^{Zn(II)(NU)}_{Zn(II)(NU)(Z)} + \log K^{Zn(II)}_{Zn(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Zn(II)}_{Zn(II)(HNU)}$, or protonated ternary complex, $\log K^{Zn(II)(HNU)}_{Zn(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Zn(II)(HNU)}_{Zn(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Zn(II)(NU)}_{Zn(II)(NU)(Z)}$ or $-2.303RT \log K^{Zn(II)(HNU)}_{Zn(II)(HNU)(Z)}$ or $-2.303RT \log K^{Zn(II)(HNU)}_{Zn(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

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

ligand	$\log K^{Ca(II)}_{Ca(II)(Z)}$	$\log K^{Ca(II)(GMP)}_{Ca(II)(GMP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(GMP)(Z)}$	$\log K^{Ca(II)(IMP)}_{Ca(II)(IMP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(IMP)(Z)}$	$\log K^{Ca(II)(CMP)}_{Ca(II)(CMP)(Z)}$ or $\log \beta^{Ca(II)}_{Ca(II)(CMP)(Z)}$
MOPSO		6.93[c] ± 0.04, 4.38 ± 0.03	4.35 ± 0.03 5.87 ± 0.02	4.12 ± 0.03 6.52 ± 0.03
TAPSO	4.21 ± 0.02	6.71[c] ± 0.05, 3.39 ± 0.03	3.58 ± 0.02 5.10 ± 0.02	3.37 ± 0.02 5.77 ± 0.03
ACES	4.86 ± 0.02	4.20[b] ± 0.03 5.74 ± 0.03	3.75 ± 0.02 5.27 ± 0.02	3.89 ± 0.02 6.29 ± 0.02

		$-\Delta G$[d]/kJ·mol^{-1}		
ligand	$\log K^{Ca(II)}_{Ca(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	1.54 ± 0.01	24.99	19.34	23.96
5′-IMP	1.52 ± 0.01	24.82	20.42	21.39
5′-CMP	2.40 ± 0.02	23.50	19.22	22.19

[a] $\log \beta^{Ca(II)}_{Ca(II)(NU)(Z)} = \log K^{Ca(II)(NU)}_{Ca(II)(NU)(Z)} + \log K^{Ca(II)}_{Ca(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Ca(II)}_{Ca(II)(HNU)}$, or protonated ternary complex, $\log K^{Ca(II)(HNU)}_{Ca(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Ca(II)(HNU)}_{Ca(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Ca(II)(NU)}_{Ca(II)(NU)(Z)}$ or $-2.303RT \log K^{Ca(II)(HNU)}_{Ca(II)(HNU)(Z)}$ or $-2.303RT \log K^{Ca(II)(HNU)}_{Ca(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

+ GMP + MOPSO, M(II) + GMP + TAPSO, M(II) + GMP + ACES decrease in the order Ni(II) > Zn(II) > Mn(II) > Cu(II) > Co(II), Zn(II) > Cu(II) > Mn(II) > Co(II) > Ni(II), Zn(II) > Mn(II) > Cu(II) > Co(II) > Ni(II), respectively. This may be explained by the presence of different types of interligand interactions depending on the nature of the metal ion.

One of the most interesting results in this work is the formation of a highly stable protonated ternary complex Ni(II) + GMP + MOPSO. The properties of nickel(II) coordination compounds lend themselves well to the study of nucleic acid chemistry. The Ni(II) ion is known to bind to guanine's N7,[23] and it is in fact this property that is thought to be responsible for nickel's ability to induce B to Z transitions in duplex DNA.[24]

In addition, compounds derived from nickel ores have been found to be carcinogenic, and this activity has been linked to oxidative chemistry mediated by nickel leading to DNA strand breaks, DNA−DNA cross-links, and DNA−protein cross-links.[25,26] Therefore, the ternary complexes of the type Ni(II) + NU + Z investigated in this study may be considered as relatively simple models from which information may be gained about the properties of nucleotides (GMP, IMP, CMP) and their base moieties regarding the strength of their interactions with the biologically important zwitterionic buffers (ACES, TAPSO, or MOPSO), and even insight into the factors which influence the strength is thus becoming available, as these systems may mimic the DNA−protein cross-links mediated by Ni(II) ions.

The enormous complexity of the biological metal ion−nucleic acid−protein systems has prompted several efforts to design and study smaller model compounds. In these complexes, the assumed metal binding sites in biological systems are modeled by single amino acids or small peptides and nucleotides. Thus, the ternary systems of the type Pd(11) + NU + Z may be considered as model systems mimicking the nucleic acid−protein cross-links which are thought to be involved in the cytotoxic activity of the antitumor drug cisplatin. The data obtained for the solution chemistry of the model systems of the type Pd(11) + NU + Z, (NU) = 5′-GMP, 5′-IMP, or 5′-CMP and Z = MOPSO, TAPSO, or ACES) may be considered as a guideline for the preparation of possible antitumor drugs.

Taking into consideration the factors affecting metal−nucleotide interactions which include binding conditions

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) + Nucleotide + Zwitterionic Buffer Ligand at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO_3[a]

ligand	$\log K^{Mg(II)}_{Mg(II)(Z)}$	$\log K^{Mg(II)(GMP)}_{Mg(II)(GMP)(Z)}$ or $\log \beta^{Mg(II)}_{Mg(II)(GMP)(Z)}$	$\log K^{Mg(II)(IMP)}_{Mg(II)(IMP)(Z)}$ or $\log \beta^{Mg(II)}_{Mg(II)(IMP)(Z)}$	$\log K^{Mg(II)(CMP)}_{Mg(II)(CMP)(Z)}$ or $\log \beta^{Mg(II)}_{Mg(II)(CMP)(Z)}$
MOPSO		6.81[c] ± 0.04, 4.16 ± 0.03	3.80 ± 0.02	4.03 ± 0.03
			5.49 ± 0.02	6.98 ± 0.03
TAPSO	3.77 ± 0.02	6.69[c] ± 0.04, 3.48 ± 0.02	3.78 ± 0.02	3.10 ± 0.02
			5.47 ± 0.02	6.05 ± 0.02
ACES	3.72 ± 0.02	3.78[b] ± 0.03	3.97 ± 0.03	3.64 ± 0.02
		5.51 ± 0.03	5.66 ± 0.03	6.59 ± 0.02

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Mg(II)}_{Mg(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	1.73 ± 0.02	23.73	19.85	21.55
5′-IMP	1.69 ± 0.02	21.68	21.56	22.65
5′-CMP	2.95 ± 0.02	22.99	17.68	20.76

[a] $\log \beta^{Mg(II)}_{Mg(II)(NU)(Z)} = \log K^{Mg(II)(NU)}_{Mg(II)(NU)(Z)} + \log K^{Mg(II)}_{Mg(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Mg(II)}_{Mg(II)(HNU)}$, or protonated ternary complex, $\log K^{Mg(II)(HNU)}_{Mg(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Mg(II)(HNU)}_{Mg(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Mg(II)(NU)}_{Mg(II)(NU)(Z)}$ or $-2.303RT \log K^{Mg(II)(HNU)}_{Mg(II)(HNU)(Z)}$ or $-2.303RT \log K^{Mg(II)(HNU)}_{Mg(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

Table 8. Formation Constants for the Binary Pd(II) + Nucleotide (NU) or Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Mixed-Ligand Complexes Pd(II) + Nucleotide + Zwitterionic Buffer Ligand at 25.0 ± 0.1 °C and I = 0.1 mol·dm^{-3} KNO_3[a]

ligand	$\log K^{Pd(II)}_{Pd(II)(Z)}$	$\log K^{Pd(II)(GMP)}_{Pd(II)(GMP)(Z)}$ or $\log \beta^{Pd(II)}_{Pd(II)(GMP)(Z)}$	$\log K^{Pd(II)(IMP)}_{Pd(II)(IMP)(Z)}$ or $\log \beta^{Pd(II)}_{Pd(II)(IMP)(Z)}$	$\log K^{Pd(II)(CMP)}_{Pd(II)(CMP)(Z)}$ or $\log \beta^{Pd(II)}_{Pd(II)(CMP)(Z)}$
MOPSO	3.50 ± 0.03	6.74[c] ± 0.04, 4.25 ± 0.03	4.02 ± 0.02	3.97 ± 0.02
			7.29 ± 0.02	7.32 ± 0.02
TAPSO		6.54[c] ± 0.04, 3.38 ± 0.02	6.71[c] ± 0.02 → 3.03[b] ± 0.02	3.34 ± 0.02
				6.69 ± 0.02
ACES		3.63 ± 0.02	4.21 ± 0.02	3.97 ± 0.02
		6.98 ± 0.02	7.48 ± 0.02	7.32 ± 0.02

		$-\Delta G^d$/kJ·mol^{-1}		
ligand	$\log K^{Pd(II)}_{Pd(II)(NU)}$	Z = MOPSO	Z = TAPSO	Z = ACES
5′-GMP	3.60[b] ± 0.02	24.24	19.28	20.71
5′-IMP	3.27 ± 0.02	22.93	17.28	24.02
5′-CMP	3.35 ± 0.02	22.65	19.05	22.65

[a] $\log \beta^{Pd(II)}_{Pd(II)(NU)(Z)} = \log K^{Pd(II)(NU)}_{Pd(II)(NU)(Z)} + \log K^{Pd(II)}_{Pd(II)(NU)}$. [b] Log formation constant of protonated binary metal complex, $\log K^{Pd(II)}_{Pd(II)(HNU)}$, or protonated ternary complex, $\log K^{Pd(II)(HNU)}_{Pd(II)(HNU)(Z)}$. [c] Log formation constant of diprotonated ternary metal complex, $\log K^{Pd(II)(HNU)}_{Pd(II)(HNU)(HZ)}$. [d] ΔG free energy of formation of the normal or protonated ternary complex (final step). $\Delta G = -2.303RT \log K^{Pd(II)(NU)}_{Pd(II)(NU)(Z)}$ or $-2.303RT \log K^{Pd(II)(HNU)}_{Pd(II)(HNU)(Z)}$ or $-2.303RT \log K^{Pd(II)(HNU)}_{Pd(II)(HNU)(HZ)}$. ± uncertainties refer to 3 times the standard deviation (3s).

Table 9. 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							
system	Cu(II)	Ni(II)	Co(II)	Mn(II)	Zn(II)	Ca(II)	Mg(II)	Pd(II)
M(II) + GMP + Z								
MOPSO		+0.32						+0.75
Z = TAPSO	−1.14	+0.10	+0.17	+0.30		−0.82	−0.29	
ACES		+3.43	+4.01			−0.66	+0.06	
M(II) + IMP + Z								
MOPSO		+0.21						+0.52
Z = TAPSO	−0.70	+0.40	+0.07	−0.10		−0.63	+0.01	
ACES	−0.18	+1.03	+1.20	+0.81			+0.25	
M(II) + CMP + Z								
MOPSO		+0.39						+0.47
Z = TAPSO	−1.23	+0.46	+0.51	+0.28		−0.84	−0.67	
ACES		+0.46	+0.36	+0.33	+0.53	−0.97	−0.08	

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

such as pH, temperature, and metal ion concentration as well as factors associated with the metal ion chemistry, one can account for the trend observed for the stability constants of the different ternary complexes of type M + NU + Z. Via the formation of mixed-ligand complexes, certain ligand−ligand associations and interactions may be favored and thus distinct structures may be created in a way that involves only small changes from an energetic point of view.

To quantify the stability of ternary complexes relative to the stability of the binary parent complexes, one may consider the equilibrium

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

The corresponding equilibrium constant is defined by the equation

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

values for $10^{\Delta \log K_M}$ may be calculated according to the equation

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

The results are given in Table 9. $\Delta \log K_M$ values are positive for some of the ternary complexes studied. The higher values for the formation constants of ternary complexes compared with those of 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 π acceptor qualities of the purine bases guanine and hypoxanthine and the pyrimidine base cytosine. Thus, the π-electron-donating tendency of the M(II) ion to the antibonding π orbitals of the heteroaromatic N base causes strengthening of the M(II)−N bond. Due to the π acceptor qualities of the purine and pyrimidine bases (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.

Our investigation confirmed the formation of mixed ligand complexes of the type M + NU + Z (where Z = MOPSO, TAPSO, or ACES and M = Cu(II), Co(II), Ni(II), Mn(II), Zn(II), Ca(II), Mg(II), or Pd(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 nucleotides 5′-GMP, 5′-IMP, or 5′-CMP. The likelihood for the formation of ternary complexes is also rather high, as was demonstrated in the present study with 5′-GMP, 5′-IMP, or 5′-CMP; this will affect the properties of these nucleotides in various ways when they are used as substrates.

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