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Ternary Complexes Formed by Trivalent Lanthanide Ions, Nucleotides, and Biological Buffers

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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′-monophosphate, guanosine 5′-monophosphate, cytidine 5′-monophosphate, and La(III), Ce(III), Pr(III), and Eu(III) with the biologically important secondary ligand zwitterionic buffers (3-[*N*-morpholinol])-2-hydroxypropanesulfonic acid, 2-(*N*-morpholino)-ethanesulfonic acid, *N*-2-acetamido-2-aminoethanesulfonic acid, and *N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid. Measurements were made in a 1:1:1 ratio. Formation constants for the monohydroxy, dihydroxy, and dimeric ligand complexes for the binary systems Ln(III) + adenosine 5′-monophosphate, Ln(III) + guanosine 5′-monophosphate, Ln(III) + cytidine 5′-monophosphate, and Ln(III) + zwitterionic buffers have been evaluated. 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 due to stacking interaction was negligibly small; that is, the monomeric normal and protonated ternary complexes were studied.

Introduction

Complexes between metal ions and two different types of bioligands, namely nucleobases or nucleotides, and amino acids or zwitterionic buffers 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. Attention has been drawn to the use of zwitterionic amino acids and zwitterionic *N*-substituted aminosulfonic acids as buffers of biological interest.[1,2] 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*-morpholinol])-2-hydroxy propanesulfonic acid (MOPSO), 2-(*N*-morpholino)ethanesulfonic acid (MES), *N*-2-acetamido-2-aminoethanesulfonic acid (ACES), and *N*-2-hydroxyethylpiperazine-*N*′-ethanesulfonic acid (HEPES) because of their low toxicity.

Ternary complexes of trivalent lanthanides with ATP and EDTA have been investigated.[3,4] In continuation of our previous work on ternary complexes containing nucleotides[5−9] the mixed ligand complexes of the type Ln(III) + nucleotide + zwitterionic buffer ligands (Ln(III) + NU + Z) (see Chart 1) where nucleotide = AMP, GMP, or CMP, zwitterionic buffer ligands = MOPSO, MES, ACES, or HEPES, and Ln(III) = La(III), Ce(III), Pr(III), or Eu(III) have been investigated by potentiometric pH-titrations to determine the formation constants of the normal and protonated mixed ligand complexes formed in solution.

The most prominent reactions of nucleic acids in aqueous solution are the acid-catalyzed depurination of the 2′-deoxyribonucleoside units of deoxyribonucleic acids (DNA) and hydrolysis and isomerization of the internucleosidic phosphodiester bonds of ribonucleic acids (RNAs). The rate of these reactions is influenced by lanthanide ions and lanthanide(III) complexes. The hydrolysis of the triphosphate nucleotides was reviewed.[10] Lanthanide ions and lanthanide ion chelates have been reported to hydrolyze the phosphodiester bonds of 2′-deoxyribonucleosides, in contrast to divalent metal ions.[11]

The ternary complexes of the type Ln(III) + NU + Z may be considered as relatively simple models from which information may be gained about the properties of purine nucleotides (AMP, GMP) and pyrimidine nucleotide (CMP) and their base moieties regarding the strength of their interactions with the biologically important zwitterionic buffer ligands (ACES, MOPSO, MES, or HEPES). Insight into the factors which influence the strength is thus becoming available, as these systems may mimic the biological process in which lanthanide complexes may be involved in the catalytic cleavage of DNA and RNA.

Cleavage of nucleotides and of DNA or RNA by lanthanide catalysts is an area of much current activity.[12] In particular, lanthanide ions and their complexes are known to be excellent catalysts for the hydrolysis of biozide-type phenyl phosphate esters, of DNA, and of related oligonucleotides. Different trivalent lanthanide ions have been reported to show different efficiencies.[13]

Experimental Section

Materials and Solutions. MOPSO, MES, ACES, and HEPES were obtained from Sigma. We determined by potentiometric pH titrations the molar mass of MOPSO, MES, ACES, and HEPES to verify/determine the purity, especially for acidic/basic contaminants. The purity averaged 99.5% for the four studied compounds, with a standard deviation of 0.05%.

Adenosine 5′-monophosphoric acid disodium salt $C_{10}H_{12}N_5Na_2O_7P\cdot H_2O$ ($Na_2AMP\cdot H_2O$), guanosine 5′-monophosphoric acid disodium salt $C_{10}H_{12}N_5O_8PNa_2\cdot 8H_2O$ ($Na_2GMP\cdot 8H_2O$), and cytidine 5′-monophosphoric acid disodium salt $C_9H_{12}N_3O_8PNa\cdot 6H_2O$ ($Na_2CMP\cdot 6H_2O$) were purchased from Sigma Chemical Co. and were used without purification. The amount of free phosphates initially present in the

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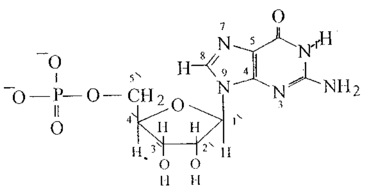
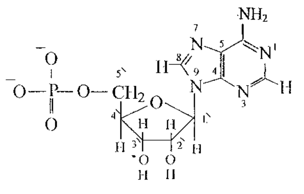
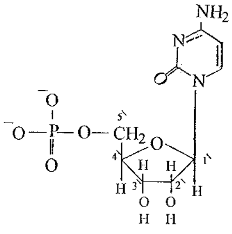
Chart 1



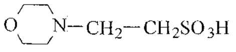
Guanosine 5′-monophosphate (5′-GMP)



Adenosine 5′-monophosphate (5′-AMP^{2-})



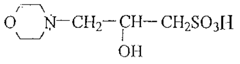
Cytidine 5′-monophosphate (5′-CMP)



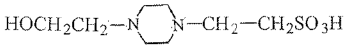
2-(N-morpholino) ethanesulfonic acid (MES)

$H_2N{-}CO{-}CH_2{-}NH_2{-}CH_2{-}CH_2SO_3H$

N-2-acetamido-2-aminoethane-sulfonic acid (ACES)



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



N-2-hydroxyethylpiperazine-N′-2-ethane-sulfonic acid (HEPES)

nucleotides was determined.[14] It was found to be 3% for the investigated nucleotides.

Lanthanum nitrate hexahydrate $La(NO_3){\cdot}6H_2O$ (Janssen Chimica), praseodymium nitrate pentahydrate $Pr(NO_3)_3{\cdot}5H_2O$ (Fluka), europium nitrate hexahydrate $Eu(NO_3)_3{\cdot}6H_2O$ (Fluka), and cerous nitrate hexahydrate $Ce(NO_3)_3{\cdot}6H_2O$ (BDH) solutions were prepared and standardized with the disodium salt of EDTA.[15]

Nitric acid and KOH were from Merck p.a. Stock solutions were prepared using bidistilled water free from CO_2. The KOH used for the titrations was standardized against potassium hydrogen phthalate (Merck AG). HNO_3 solutions were prepared and standardized potentiometrically against tris(hydroxymethyl)aminomethane.

Apparatus. Potentiometric pH-measurements were made on the solutions in a double-walled glass vessel at (25.0 ± 0.1) °C using a commercial Fisher combined electrode coupled to a Fisher Accumet pH/ion meter model 825 MP. Purified nitrogen was bubbled through the solutions during titrations.

Procedure. The test solutions were titrated with standard CO_2-free KOH. A constant ionic strength was obtained with 0.1 mol dm^{-3} KNO_3, and the initial total volume was kept constant at 25 cm^3. Data from the pH range (3.0 to 10.0) were used for the calculations for each system. 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.

$$E = E° + Q \log C_{H^+} \tag{1}$$

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 results so obtained were analyzed by the nonlinear least-squares computer program ESAB2M[16] to refine $E°$ and the autoprotolysis constant of water, K_W. The results obtained indicated the reversible Nernstian response of the glass electrode used. The apparent ionic product of water, pK_W, was determined to be 13.88 ± 0.02.

The solutions titrated can be presented according to the following scheme: HNO_3 (4 × 10^{-3}mol dm^{-3}); 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}) + Ln(III) (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}) + Ln(III) (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 + Ln(III) (1 × 10^{-3} mol dm^{-3}) (e).

At least four titrations were performed for each system. Typically about 100 data points were collected 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. To minimize hydrolysis of the nucleotides, a known mass of the solid was added to the reaction vessel prior to performing the titration.

Results and Discussion

The stability constant for the species $M_p(NU)_q(Z)_r(H)_s$, β_{pqrs}, is defined by 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 NU = nucleotide (5′-AMP, 5′-GMP, or 5′-CMP), Z = zwitterionic buffer ligands (MOPSO, MES, ACES, or HEPES), and Ln = La(III), Ce(III), Pr(III), or Eu(III). The protonation and complexation reaction of the free phosphate initially present in solutions as well as all side reactions due to lanthanide hydrolysis[17−19] have been included in the calculations.

All the constants for binary and ternary systems were refined using the SUPERQUAD computer program[20] by minimizing U:

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

where E_{obs} and E_{calc} refer to the measured and calculated potential. The quality of fit was judged by the values of the sample standard deviation, S, and the goodness of fit, χ^2 (Pearson's test).

The values of S in different sets of titrations were between 1.0 and 1.8, and χ^2 was between 12.0 and 13.0.

Table 1. Formation Constants for the Binary Ln(III) + Zwitterionic Buffer (Z) Ligand Complexes Together with the Corresponding Monohydroxy, Dihydroxy, and Dimeric Ligand Complexes at (25.0 ± 0.1) °C and $I = 0.1$ mol·dm $^{-3}$ KNO_3

lanthanide ion	$\log K^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(Z)}}$	$\log K^{\mathrm{Ln(III)(Z)}}_{\mathrm{Ln(III)(Z)(OH)}}$	$\log K^{\mathrm{2[Ln(III)(Z)(OH)]}}_{\mathrm{\{Ln(III)(Z)(OH)\}_2}}$	$\log K^{\mathrm{Ln(III)(Z)(OH)}}_{\mathrm{Ln(III)(Z)(OH)_2}}$
		MOPSO (Z)		
La(III)	3.34 ± 0.02	−5.82 ± 0.03	9.62 ± 0.05	11.64 ± 0.05
Ce(III)	3.31 ± 0.02	−5.80 ± 0.02	9.54 ± 0.05	12.22 ± 0.05
Pr(III)	3.36 ± 0.02	−5.44 ± 0.03	8.82 ± 0.05	8.09 ± 0.04
Eu(III)	3.39 ± 0.02	−5.33 ± 0.02	8.61 ± 0.04	7.91 ± 0.03
		MES (Z)		
La(III)	3.40 ± 0.02	−6.12 ± 0.03	10.13 ± 0.05	12.24 ± 0.05
Ce(III)	3.36 ± 0.02	−5.74 ± 0.02	9.42 ± 0.05	12.05 ± 0.05
Pr(III)	3.39 ± 0.02	−7.00 ± 0.03	9.28 ± 0.05	11.86 ± 0.05
Eu(III)	3.38 ± 0.02	−5.52 ± 0.02	8.41 ± 0.04	12.71 ± 0.04
		ACES (Z)		
La(III)	3.35 ± 0.02	−5.65 ± 0.03	8.69 ± 0.04	11.30 ± 0.05
Ce(III)	3.42 ± 0.02	−6.08 ± 0.02	10.13 ± 0.05	12.76 ± 0.05
Pr(III)	3.33 ± 0.02	−5.58 ± 0.03	9.09 ± 0.04	11.32 ± 0.05
Eu(III)	3.35 ± 0.02	−5.56 ± 0.02	9.02 ± 0.04	11.30 ± 0.06
		HEPES (Z)		
La(III)	3.33 ± 0.02	−6.15 ± 0.03	10.21 ± 0.05	11.72 ± 0.05
Ce(III)	3.40 ± 0.02	−5.25 ± 0.02	8.63 ± 0.05	10.50 ± 0.04
Pr(III)	3.44 ± 0.02	−6.02 ± 0.03	9.89 ± 0.04	13.31 ± 0.05
Eu(III)	3.43 ± 0.02	−6.06 ± 0.03	10.01 ± 0.05	13.62 ± 0.06

Table 2. Formation Constants for the Binary Ln(III) + Nucleotide (NU) Complexes Together with the Corresponding Monohydroxy, Dihydroxy, and Dimeric Ligand Complexes at (25.0 ± 0.1 °C) and $I = 0.1$ mol·dm^{-3} KNO_3

lanthanide ion	$\log K^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(NU)}}$	$\log K^{\mathrm{Ln(III)(NU)}}_{\mathrm{Ln(III)(NU)(OH)}}$	$\log K^{\mathrm{2[Ln(III)(NU)(OH)]}}_{\mathrm{\{Ln(III)(NU)(OH)\}_2}}$	$\log K^{\mathrm{Ln(III)(NU)(OH)}}_{\mathrm{Ln(III)(NU)(OH)_2}}$
		GMP (NU)		
La(III)	4.50 ± 0.04	−7.82 ± 0.03	12.90 ± 0.05	14.09 ± 0.04
Ce(III)	5.16 ± 0.04	−5.61 ± 0.02	9.22 ± 0.04	11.30 ± 0.05
Pr(III)	5.35 ± 0.04	−6.20 ± 0.02	10.30 ± 0.05	12.59 ± 0.04
Eu(III)	5.26 ± 0.04	−5.63 ± 0.02	9.09 ± 0.04	12.32 ± 0.03
		CMP (NU)		
La(III)	4.72 ± 0.04	−5.82 ± 0.02	10.60 ± 0.05	12.95 ± 0.05
Ce(III)	4.80 ± 0.04	−6.37 ± 0.02	9.50 ± 0.04	12.89 ± 0.05
Pr(III)	4.60 ± 0.04	−7.12 ± 0.02	12.13 ± 0.05	14.29 ± 0.04
Eu(III)	4.91 ± 0.04	−5.60 ± 0.02	9.13 ± 0.04	9.72 ± 0.03
		AMP (NU)		
La(III)	4.20 ± 0.04	−5.52 ± 0.02	11.00 ± 0.05	13.31 ± 0.05
Ce(III)	4.25 ± 0.04	−5.50 ± 0.02	8.89 ± 0.04	12.23 ± 0.05
Pr(III)	4.30 ± 0.03	−5.66 ± 0.03	8.01 ± 0.05	14.17 ± 0.04
Eu(III)	4.65 ± 0.02	−6.93 ± 0.02	11.80 ± 0.04	14.74 ± 0.05

Table 3. Formation Constants for the Mixed Ligand Complexes Ln(III) + GMP + Z at (25.0 ± 0.1) °C and $I = 0.1$ mol·dm^{-3} KNO_3[a]

lanthanide ion	$\log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(MOPSO)}}$ or $\log \beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(GMP)(MOPSO)}}$	$\log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(MES)}}$ or $\log \beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(GMP)(MES)}}$	$\log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(ACES)}}$ or $\log \beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(GMP)(ACES)}}$	$\log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(HEPES)}}$ or $\log \beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(GMP)(HEPES)}}$
La(III)	7.14 ± 0.03,[a] 3.52 ± 0.02,[b] 8.02 ± 0.02[c]	8.00 ± 0.03,[a] 3.76 ± 0.02,[b] 8.26 ± 0.02[c]	7.01 ± 0.03,[a] 2.83 ± 0.02,[b] 7.33 ± 0.02[c]	3.10 ± 0.02,[a] 2.34 ± 0.02,[b] 6.84 ± 0.02[c]
Ce(III)	9.58 ± 0.04,[a] 4.52 ± 0.02,[b] 9.68 ± 0.02[c]	8.89 ± 0.03,[a] 3.83 ± 0.02,[b] 8.99 ± 0.02[c]	10.14 ± 0.05,[a] 4.58 ± 0.02,[b] 9.74 ± 0.02[c]	7.89 ± 0.04,[a] 4.24 ± 0.02,[b] 9.40 ± 0.02[c]
Pr(III)	8.06 ± 0.04,[a] 3.92 ± 0.02,[b] 9.27 ± 0.02[c]	7.94 ± 0.03,[a] 2.83 ± 0.02,[b] 8.18 ± 0.02[c]	8.93 ± 0.04,[a] 3.88 ± 0.02,[b] 9.23 ± 0.02[c]	6.38 ± 0.05,[a] 2.64 ± 0.02,[b] 7.99 ± 0.02[c]
Eu(III)	10.18 ± 0.03,[a] 4.52 ± 0.02,[b] 9.78 ± 0.02[c]	9.16 ± 0.03,[a] 3.83 ± 0.02,[b] 9.09± 0.02[c]	10.44 ± 0.05,[a] 4.88 ± 0.02,[b] 10.14 ± 0.02[c]	6.99 ± 0.04,[a] 3.74 ± 0.02,[b] 9.00 ± 0.02[c]

[a] Log formation constant of protonated ternary complex: $\log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(HZ)}}$. [b] Log $K^{\mathrm{Ln(III)(GMP)(HZ)}}_{\mathrm{Ln(III)(GMP)(Z)}}$ [calculated using the following equilibria:[28] $\mathrm{Ln(III)(HZ)(GMP)} \rightleftharpoons \mathrm{Ln(III)(GMP)(Z)} + \mathrm{H}^+$ and

$$\mathrm{Ln(III)} + \mathrm{GMP} + \mathrm{Z} \xrightleftharpoons{K^{\mathrm{Ln(III)(GMP)(HZ)}}_{\mathrm{Ln(III)(GMP)(Z)}}} \mathrm{Ln(III)(GMP)(Z)}]$$

[c] Log overall formation constant of ternary complex: $\log \beta^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(GMP)(Z)}} = \log K^{\mathrm{Ln(III)(GMP)}}_{\mathrm{Ln(III)(GMP)(Z)}} + \log K^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(GMP)}}$.

The scatter of residuals ($E_{\mathrm{obs}} - E_{\mathrm{calc}}$) versus pH was reasonably random, without any significant systematic trends, thus indicating a correct model selection.

Formation constants of the different monohydroxy, dihydroxy, and dimeric ligand complexes formed in solution which were calculated[21] and refined using the SUPERQUAD computer program[20] are shown in Tables 1−5. The acidity constants determined at 25 °C of ACES (pK_{a2}= 6.83 ± 0.02), MOPSO ($pK_{a2} = 6.86 \pm 0.02$), MES ($pK_{a2} = 6.24 \pm 0.02$), and HEPES ($pK_{a2} = 7.54 \pm 0.02$) are in good agreement with those found in the literature.[2,22] The acid dissociation constant values are for AMP ($pK_{a1} = 3.81 \pm 0.03$), ($pK_{a2} = 6.24 \pm 0.03$); for GMP ($pK_{a1} = 2.45 \pm 0.05$), ($pK_{a2} = 6.38 \pm 0.04$), ($pK_{a3} = 9.48 \pm 0.05$); and for CMP ($pK_{a1} = 4.40 \pm 0.04$), ($pK_{a2} = 6.56 \pm 0.04$). The second dissociation step involves the deprotonation of the cationic

Table 4. Formation Constants for the Mixed Ligand Complexes Ln(III) + CMP + Z at (25.0 ± 0.1) °C and $I = 0.1$ mol·dm^{-3} KNO$_3$[a]

lanthanide ion	log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(MOPSO)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(CMP)(MOPSO)}}$	log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(MES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(CMP)(MES)}}$	log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(ACES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(CMP)(ACES)}}$	log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(HEPES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(CMP)(HEPES)}}$
La(III)	5.86 ± 0.03,[a] 3.73 ± 0.02[b] 8.45 ± 0.02[c]	6.35 ± 0.03,[a] 3.43 ± 0.02[b] 8.15 ± 0.02[c]	6.42 ± 0.03,[a] 3.98 ± 0.02[b] 8.70 ± 0.02[c]	2.65 ± 0.01,[a] 1.94 ± 0.01[b] 6.66 ± 0.02[c]
Ce(III)	7.36 ± 0.03,[a] 4.14 ± 0.02[b] 8.93 ± 0.02[c]	6.34 ± 0.03,[a] 3.33 ± 0.02[b] 8.13 ± 0.02[c]	7.16 ± 0.03,[a] 4.48 ± 0.02[b] 9.28 ± 0.02[c]	6.88 ± 0.02,[a] 4.04 ± 0.02[b] 8.84 ± 0.02[c]
Pr(III)	6.75 ± 0.03,[a] 3.82 ± 0.02[b] 8.42 ± 0.02[c]	6.34 ± 0.03,[a] 2.93 ± 0.02[b] 7.53 ± 0.02[c]	7.01 ± 0.03,[a] 4.08 ± 0.02[b] 8.68 ± 0.02[c]	3.97 ± 0.01,[a] 2.34 ± 0.01[b] 6.94 ± 0.01[c]
Eu(III)	7.36 ± 0.04,[a] 4.13 ± 0.02[b] 8.73 ± 0.02[c]	6.96 ± 0.03,[a] 3.83 ± 0.02[b] 8.34± 0.02[c]	7.32 ± 0.03,[a] 4.48 ± 0.02[b] 9.08 ± 0.02[c]	6.00 ± 0.02,[a] 3.94 ± 0.02[b] 8.54 ± 0.02[c]

[a] Log formation constant of protonated ternary complex: log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(HZ)}}$. [b] Log $K^{\mathrm{Ln(III)(CMP)(HZ)}}_{\mathrm{Ln(III)(CMP)(Z)}}$ [calculated using the following equilibria:[28] Ln(III)(HZ)(CMP) $\rightleftharpoons$ Ln(III)(CMP)(Z) + H$^+$ and

$$\mathrm{Ln(III)} + \mathrm{CMP} + \mathrm{Z} \xrightleftharpoons{K^{\mathrm{Ln(II)(CMP)(HZ)}}_{\mathrm{Ln(III)(CMP)(Z)}}} \mathrm{Ln(III)(CMP)(Z)]}$$

[c] Log overall formation constant of ternary complex: log $\beta^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(CMP)(Z)}}$ = log $K^{\mathrm{Ln(III)(CMP)}}_{\mathrm{Ln(III)(CMP)(Z)}}$ + log $K^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(CMP)}}$.

Table 5. Formation Constants for the Mixed Ligand Complexes Ln(III) + AMP + Z at (25.0 ± 0.1) °C and $I = 0.1$ mol·dm^{-3} KNO$_3$[a]

lanthanide ion	log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(MOPSO)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(AMP)(MOPSO)}}$	log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(MES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(AMP)(MES)}}$	log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(ACES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(AMP)(ACES)}}$	log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(HEPES)}}$ or log $\beta^{\mathbf{Ln}\mathrm{(III)}}_{\mathrm{Ln(III)(AMP)(HEPES)}}$
La(III)	8.04 ± 0.03,[a] 4.22 ± 0.02,[b] 8.42 ± 0.02[c]	6.72 ± 0.03,[a] 3.23 ± 0.02,[b] 7.43 ± 0.02[c]	8.01 ± 0.04,[a] 4.38 ± 0.02,[b] 8.58 ± 0.02[c]	4.24 ± 0.02,[a] 2.74 ± 0.01,[b] 6.94 ± 0.02[c]
Ce(III)	7.76 ± 0.03,[a] 4.22 ± 0.02,[b] 8.74 ± 0.02[c]	4.60 ± 0.02,[a] 3.53 ± 0.02,[b] 7.78 ± 0.02[c]	7.70 ± 0.04,[a] 4.13 ± 0.02,[b] 8.38 ± 0.02[c]	4.62 ± 0.02,[a] 3.54 ± 0.02,[b] 7.79 ± 0.02[c]
Pr(III)	8.65 ± 0.03,[a] 4.82 ± 0.02,[b] 9.12 ± 0.02[c]	8.41 ± 0.03,[a] 3.83± 0.02,[b] 8.13 ± 0.02[c]	10.30 ± 0.04,[a] 4.48 ± 0.02,[b] 8.78± 0.02[c]	7.26 ± 0.01,[a] 3.64 ± 0.01,[b] 7.94 ± 0.01[c]
Eu(III)	9.25 ± 0.04,[a] 4.62 ± 0.02,[b] 9.27 ± 0.02[c]	8.24 ± 0.03,[a] 3.93 ± 0.02,[b] 8.58± 0.02[c]	10.44 ± 0.05,[a] 4.88 ± 0.02,[b] 8.63 ± 0.02[c]	6.09 ± 0.02,[a] 2.94 ± 0.02,[b] 7.59 ± 0.02[c]

[a] Log formation constant of protonated ternary complex: log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(HZ)}}$. [b] Log $K^{\mathrm{Ln(III)(AMP)(HZ)}}_{\mathrm{Ln(III)(AMP)(Z)}}$ [calculated using the following equilibria:[28] Ln(III)(HZ)(AMP) $\rightleftharpoons$ Ln(III)(AMP)(Z) + H$^+$ and

$$\mathrm{Ln(III)} + \mathrm{AMP} + \mathrm{Z} \xrightleftharpoons{K^{\mathrm{Ln(III)(AMP)(HZ)}}_{\mathrm{Ln(III)(AMP)(Z)}}} \mathrm{Ln(III)(AMP)(Z)]}$$

[c] Log overall formation constant of ternary complex: log $\beta^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(AMP)(Z)}}$ = log $K^{\mathrm{Ln(III)(AMP)}}_{\mathrm{Ln(III)(AMP)(Z)}}$ + log $K^{\mathrm{Ln(III)}}_{\mathrm{Ln(III)(AMP)}}$.

group $-\mathrm{N^+H}$ of MES, MOPSO, and HEPES. For ACES this step involves the deprotonation of the cationic group $-\mathrm{N^+H_2}$.

The stability constants of their Ln(III) complexes are given in Tables 1−5. The results agree with those reported in the literature.[23] The plus/minus values obtained from SUPERQUAD calculations refer to statistically determined uncertainties at small 95% confidence intervals of the reported values.

In Figure 1 representative sets of experimental titration curves obtained according to the sequence described in the Experimental Section are displayed for the system La(III) + GMP + MES. Generally, the complex titration curves show an inflection after addition of 2 mol of base per mole of the nucleotide (AMP, GMP, and CMP). This indicates the stoichiometry of the final product formed in this buffer region. With respect to the solutions studied, one may deduce that these binary complexes begin to form at pH > 4.5 for La(III) + ACES, at pH > 5.0 for Ce(III) + ACES, at pH > 4.5 for Pr(III) + ACES, and at pH > 5.1 for Eu(III) + ACES systems.

For the ternary systems studied [Ln(III) + NU + ACES] it was observed that the ternary complex formation started at a pH > 5.3 for La(III) + AMP + ACES, at pH > 5.4 for Ce(III) + AMP + ACES, at pH > 5.4 for Pr(III) + AMP + ACES, and at pH > 5.0 for Eu(III) + AMP + ACES systems. For La(III) + GMP + ACES, Ce(III) + GMP + ACES, Pr(III) + GMP + ACES, and Eu(III) + GMP + ACES systems, mixed ligand complexes started to form at pH > 5.5, pH > 4.0, pH > 6.9, and pH > 4.0, respectively.

Ternary complex formation for La(III) + CMP + ACES, Ce(III) + CMP + ACES, Pr(III) + CMP + ACES, and Eu(III) + CMP + ACES systems occurs at pH > 6.0, pH > 6.4, pH > 4.0, and pH > 6.4, respectively.

Regarding the ternary systems of the type (Ln(III) + NU + MOPSO), it was observed that mixed ligand complex formation started at a pH > 5.0 for La(III) + AMP + MOPSO, at pH > 5.2 for Ce(III) + AMP + MOPSO, at pH > 6.8 for Pr(III) + AMP + MOPSO, and at pH > 4.0 for Eu(III) + AMP + MOPSO systems. For La(III) + GMP + MOPSO, Ce(III) + GMP + MOPSO, Pr(III) + GMP + MOPSO, and Eu(III) + GMP + MOPSO systems complexation has been observed at pH > 6.2, pH > 6.6, pH > 5.6, and pH > 5.1, respectively. For La(III) + CMP + MOPSO, Ce(III) + CMP + MOPSO, Pr(III) + CMP + MOPSO, and Eu(III) + CMP + MOPSO systems complexation occurs at pH > 5.0, pH > 6.0, pH > 5.0, and pH > 6.5, respectively. Separations between the ternary complex titration curves and the binary ones (not shown in the text) for La(III) + AMP + MES, Ce(III) + AMP + MES, Pr(III) + AMP + MES, and Eu(III) + AMP + MES ternary systems occur at pH > 6.2, pH > 6.0, pH > 5.6, and pH > 4.0, respectively. While for La(III) + GMP + MES, Ce(III) + GMP + MES, Pr(III) + GMP + MES, and Eu(III) + GMP + MES systems these separations have been observed at pH > 5.8, pH > 5.3, pH > 4.0, and pH > 5.1, respectively. For La(III) + CMP + MES, Ce(III) + CMP + MES, Pr(III) + CMP + MES, and Eu(III) + CMP + MES systems mixed ligand

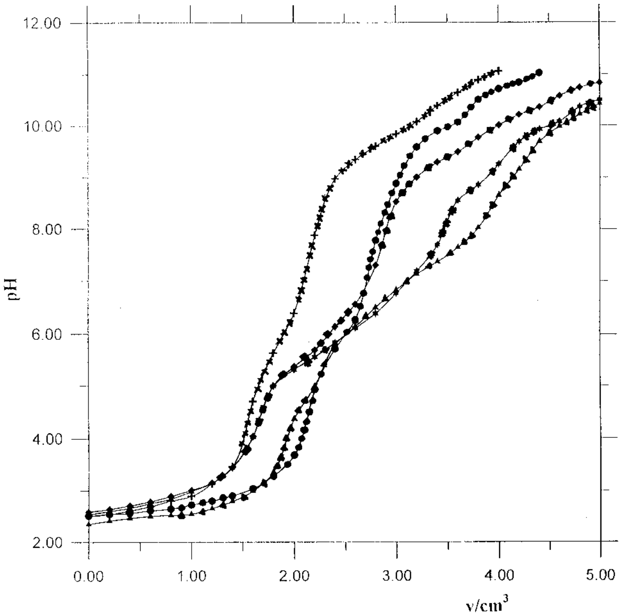


Figure 1. pH against volume of 0.0465 mol dm^{-3} KOH for the La(III) + 5′-GMP + MES system at 25 °C and I = 0.1 mol dm^{-3} KNO_3: (+) 4 × 10^{-3} mol dm^{-3} HNO_3 + 1 × 10^{-3} mol dm^{-3} (5′-GMP); (♦) solution a + 1 × 10^{-3} mol dm^{-3} La(III); (●) 4 × 10^{-3} mol dm^{-3} HNO_3 + 1 × 10^{-3} mol dm^{-3} MES; (▲) solution c + 1 × 10^{-3} mol dm^{-3} La(III); (∗) solution b + 1 × 10^{-3} mol dm^{-3} MES.

complex formation occurs at pH > 5.5, pH > 6.2, pH > 4.0, and pH > 4.1, respectively.

Examination of the different formation constant values listed in Tables 3−5 clearly reveals that the order of the overall stability constants of the different ternary complexes in the systems Ln(III) + NU + ACES in terms of metals ion follows generally the trend Pr(III) > La(III) > Ce(III) > Eu(III) for Ln(III) + AMP + ACES systems and Eu(III) > Ce(III) > Pr(III) > La(III) for Ln(III) + GMP + ACES and Ln(III) + CMP + ACES systems, respectively. To the author's knowledge no data for the ternary complexes of the newer buffers ACES, MOPSO, MES, or HEPES with the nucleotides AMP, GMP, or CMP are available in the literature for comparison. The order of formation constants of the different normal ternary complexes of the type Ln(III) + NU + MOPSO in terms of lanthanide ion follows generally the trend Pr(III) > Eu(III) > Ce(III) > La(III) for Ln(III) + AMP + MOPSO systems, Eu(III) > Ce(III) > Pr(III) > La(III), and La(III) > Ce(III) > Pr (III) > Eu(III) for Ln(III) + GMP + MOPSO and Ln(III) + CMP + MOPSO systems, respectively. As is shown in Tables 3−5, the formation constants of the ternary complexes of the type Ln(III) + NU + MES in terms of lanthanide ion follow generally the trend Eu(III) > Pr(III) > Ce(III) > La(III) for Ln(III) + AMP + MES systems, Eu(III) > Ce(III) > La(III) > Pr(III) for Ln(III) + GMP + MES systems, and Eu(III) > La(III) > Ce (III) > Pr(III) for Ln(III) + CMP + MES systems, respectively. During SUPERQUAD[20] refinement of the titration data of the ternary complexes Ln(III) + NU + Z, it was observed that they 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 Ln(III) + NU + HEPES are given in Tables 3−5. The stability constants for the protonated mixed ligand complexes of the type Ln(III) + NU + HEPES follow the order Pr(III) > Eu(III) > Ce(III) > La(III) for Ln(III) + AMP + HEPES systems and Ce(III) > Eu(III) > Pr(III) > La(III) for Ln(III) + GMP + HEPES and Ln(III) + CMP + HEPES systems, respectively.

The factors affecting the binding of metal ion to nucleic acid bases include the affinity of the bases for the metal ion, the nature of the metal ion, the pH of the solution, and the length and structure (single-stranded or duplex) of the polynucleotide. At neutral pH, the affinity for the metal ion binding of the sites available in the nucleobases in single-stranded nucleic acids decreases along the series[24] N7G > N3C > N7A > N1A > N3A, N3G.

The nature of the metal ion plays an important role in nucleic acid−metal ion interactions. Generally, three groups of metal ions have been distinguished with respect to their binding preferences in interactions with nucleic acids:[25,26] (1) ions preferring oxygen donors, that is, alkali and alkaline earth metal ions, lanthanides, Cr(III), and Fe(III); (2) ions favoring mixed oxygen and nitrogen donors, that is, Mn(II), Fe(II), Zn(II), Co(II), Cd(II), Ni(II), and Cu(II); and (3) ions favoring nitrogen donors, that is, Ag(I), Pd(II), Pt(II), and Hg(II).

Taking into consideration the factors which affect metal−nucleotide interactions, which include binding conditions such as pH, temperature, and metal ion concentrations 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 the type Ln(III) + 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.

The weaker binding of the HEPESate anion to the binary Ln(III) + AMP, Ln(III) + GMP, or Ln(III) + CMP complexes as compared with that of the ACEate, MOPSOate, or MESate anions was observed. The effect from the poorer structural matching between the secondary ligands and the Ln(III) + nucleotide complex prevails over that from the basicity, and the binding of the HEPESate anion secondary ligand by Ln(III) + nucleotide complexes is weaker than the bonding between the above-mentioned secondary ligand anions and the same binary Ln(III) + nucleotide complex.

To quantify the stability of ternary complexes relative to the stability of the binary lanthanide complexes, one may consider the equilibrium:[27]

$$\mathrm{M(NU) + M(Z) \rightleftharpoons M(NU)(Z) + M} \qquad (5)$$

The corresponding equilibrium constant is defined by the equation

$$10^{\Delta \log K_{\mathrm{M}}} = \frac{[\mathrm{M(NU)(Z)}][\mathrm{M}]}{[\mathrm{M(NU)}][\mathrm{M(Z)}]} \qquad (6)$$

Values for $10^{\Delta \log K_{\mathrm{M}}}$ may be calculated according to

$$\Delta \log K_{\mathrm{M}} = \log K^{\mathrm{M(NU)}}_{\mathrm{M(NU)(Z)}} - \log K^{\mathrm{M}}_{\mathrm{M(Z)}} \qquad (7)$$

The results are given in Table 6. Δ 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.

Our investigation confirmed the formation of mixed ligand complexes of the type Ln(III) + NU + Z (where Z = ACES, MOPSO, MES, or HEPES and Ln(III) = La(III), Ce(III), Pr(III), or Eu(III)) in solution. This forms a basis

Table 6. Δ log $K_M{}^a$ Values for the 1:1:1 Ln(III) + Nucleotide (NU) + Zwitterionic Buffer (Z) Ternary Complexes As Determined by Potentiometric pH-Titrations at (25.0 ± 0.01) °C and I = 0.1 mol dm^{-3} KNO$_3$

	Δ log K_M			
system	La(III)	Ce(III)	Pr(III)	Eu(III)
Ln(III) + GMP + Z	+0.18	+1.21	+0.56	+1.13
MOPSO	+0.36	+0.47	−0.56	+0.45
MES	−0.52	+1.16	+0.55	+1.53
ACES	−0.99	+0.84	−0.80	+0.31
HEPES				
Ln(III) + CMP + Z		+0.82	+0.46	+0.74
MOPSO	+0.39	−0.03	−0.46	+0.45
MES	+0.03	+1.06	+0.75	+1.13
ACES	+0.63	+0.64	−1.10	+0.51
HEPES	−1.39			
Ln(III) + AMP + Z		+0.91	+1.46	+1.23
MOPSO	+0.88	+0.17	+0.44	+0.55
MES	−0.17	+0.71	+1.15	+0.63
ACES	+1.03	+0.14	+0.20	−0.49
HEPES	−0.59			

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

for the exploitation of lanthanide ion chelates as research tools in nucleic acid chemistry and molecular biology. The lanthanide(III)−zwitterionic buffer complexes under investigation may also be used as catalysts for cleaving the phosphodiester bonds of nucleic acids either sequence-specifically or in a completely unselective manner. Both approaches will undoubtedly find applications in chemical tailoring of DNA and RNA or in selective inhibition of gene expression, and hence in chemotherapy. Also, great reservation should be exercised in employing the biologically important zwitterionic buffer ligands (ACES, MOPSO, MES, or HEPES) in aqueous solutions in systems containing La(III), Ce(III), Pr(III), or Eu(III) ions and the nucleotides AMP, GMP, or CMP. The likelihood for the formation of ternary complexes is also rather high, as was demonstrated in the present study with AMP, GMP, or CMP; this will affect the properties of these nucleotides in various ways when they are used as substrates.

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