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Complexing of 3d Transition Metal Ions with 9-Substituted Purines. II. Stoichiometry and Thermodynamics of the Complex Formation

JORMA ARPALAHTI and HARRI LÖNNBERG

Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku, Finland

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Complexing of cobalt(II), nickel(II), and copper(II) ions with 9-methylpurine and its 2- and 8-methyl derivatives have been studied in aqueous solution spectrophotometrically over a wide range of ligand concentrations. The copper(II) ion has been shown to form 1:2 complexes more readily than the other metal ions. The thermodynamics of the complex formation have been evaluated by combining the spectrophotometric equilibrium data and the enthalpies of interaction obtained calorimetrically. The relationships between the site of coordination and the thermodynamic quantities have been discussed.

Introduction

The interactions between metal ions and monomeric constituents of nucleic acids have attracted much attention in recent years [1–6], particularly after the discovery of the antineoplastic nature of some platinum(II) compounds [7]. Spectroscopic measurements [4, 8–16] have given valuable information about the structures of the complexes that metal ions form with the nucleosides occuring as main components in nucleic acids. In contrast, the data on the thermodynamics of the complex formation are scanty [1, 17].

We have previously elucidated the binding properties of 9-(β-D-ribofuranosyl)purine, the parent compound of purine nucleosides, employing 9-methylpurine as model compound. The ribofuranosyl moiety has been replaced by the methyl group to avoid interference of the glycosyl hydroxyl groups in complexing. The effects that 2-, 6-, and 8-methyl substituents have on the complexing-ability of 9-methylpurine have been accounted for by competitive attachment of metal ions to N1 and N7 of the unsubstituted 9-methylpurine. We now report on our studies concerning the stoichiometry of the complex formation at high ligand concentrations. The equilibrium data combined with the results of the calorimetric measurements are used to evaluate the thermodynamics of the complex formation.

Experimental

Materials

9-Methylpurine and its 2- and 8-methyl derivatives were prepared as described previously [18]. The metal perchlorates employed were products of G. Frederick Smith Company and Fluka AG, and they were used as received. Solutions were made in distilled and degassed water.

Spectrophotometric Measurements

The VIS-absorption spectra of the metal ions at various ligand concentrations were recorded on a Cary 17 D spectrophotometer, the cell housing compartment of which was kept at 298.2 ± 0.1 K with water circulating from a thermostatted bath. The measurements were performed against aqueous ligand solutions to avoid the tailing of the strong UV-absorption bands of the purine ring. The ionic strength was adjusted with sodium perchlorate.

Calorimetric Measurements

The calorimetric measurements were carried out on a LKB 10700-2 Batch Microcalorimeter. The technique employed has been described earlier [19]. The enthalpies of interaction, ΔH(int.), of metal ions with 9-methylpurines were obtained by subtracting the dilution enthalpies of the salt and ligand solutions from the observed enthalpies of mixing of the same solutions. The effect of ionic strength on ΔH(int.) values was examined by performing the measurements in solutions of sodium perchlorate, the concentration of which was varied from 0 to 0.5 mol dm^{-3}.

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TABLE I. The Stability Constants, $K(\mathrm{ML}_n^{2+})$, for the Complexes of Cobalt(II), Nickel(II), and Copper(II) Ions with Some 9-Methylpurines in Aqueous Solution at 298.2 K.[a]

Metal ion	$\lg [K(\mathrm{ML}_n^{2+})/\mathrm{dm}^3\ \mathrm{mol}^{-1}]$					
	9-Methylpurine		2,9-Dimethylpurine		8,9-Dimethylpurine	
	n = 1	n = 2	n = 1	n = 2	n = 1	n = 2
Co^{2+}	0.9 ± 0.1					
	(1.04 ± 0.07)[b]					
Ni^{2+}	1.50 ± 0.18	0.26 ± 0.22	1.23 ± 0.06		1.25 ± 0.06	
	(1.56 ± 0.06)		(1.26 ± 0.03)		(1.28 ± 0.04)	
Cu^{2+}	1.70 ± 0.07	0.73 ± 0.10	1.56 ± 0.13	0.96 ± 0.19	1.48 ± 0.07	0.85 ± 0.15
	(1.88 ± 0.05)		(1.78 ± 0.04)		(1.62 ± 0.03)	

[a] The ionic strength was adjusted to 0.18 mol dm^{-3} with sodium perchlorate. The concentrations of cobalt(II), nickel(II), and copper(II) ions were 0.020, 0.040 and 0.020 mol dm^{-3}, respectively. The ligand concentrations were varied from 0 to 0.24 mol dm^{-3}. [b] The values in parentheses refer to the potentiometric measurements at the ionic strength of 1.0 mol dm^{-3} [18].

TABLE II. The Molar Absorption Coefficients, ϵ, at Different Wavelengths for the Complexes of Cobalt(II), Nickel(II), and Copper(II) Ions with Some 9-Methylpurines in Aqueous Solution at 298.2 K.[a]

λ/nm	$\epsilon(\mathrm{M}^{2+})$[b]	9-Methylpurine		2,9-Dimethylpurine		8,9-Dimethylpurine	
		$\epsilon(\mathrm{ML}^{2+})$	$\epsilon(\mathrm{ML}_2^{2+})$	$\epsilon(\mathrm{ML}^{2+})$	$\epsilon(\mathrm{ML}_2^{2+})$	$\epsilon(\mathrm{ML}^{2+})$	$\epsilon(\mathrm{ML}_2^{2+})$
Co^{2+}							
440	1.6	4.9					
460	3.0	10.2					
480	3.8	12.9					
500	4.6	14.5					
520	4.3	12.3					
Ni^{2+}							
620	1.0	2.2	5.2	2.9		2.6	
640	1.5	2.8	5.2	3.5		3.2	
660	1.7	2.9	4.4	3.5		3.3	
680	1.7	2.6	3.7	3.1		3.0	
700	1.9	2.5	3.0	3.0		2.8	
720	2.0	2.3	2.8	2.8		2.6	
Cu^{2+}							
670	4.5	12.6	40.0	14.5	28.1	17.8	28.4
690	5.9	15.1	40.3	17.3	29.5	20.2	30.6
710	7.4	17.4	38.7	19.9	29.6	22.3	31.5
730	9.0	18.8	35.9	21.0	28.9	23.5	31.3
750	10.4	19.1	33.8	21.1	28.0	24.3	29.7
770	11.4	18.9	31.3	20.7	26.7	23.9	28.3
790	11.7	18.5	28.5	19.9	25.1	23.5	26.3
810	11.8	17.7	26.2	19.1	23.6	22.6	24.8
830	11.5	16.7	24.3	18.2	21.8	21.8	22.6
850	11.0	15.9	22.0	17.3	19.9	20.8	20.9
870	10.6	15.1	20.0	16.5	18.3	19.7	19.3
890	10.0	14.2	18.4	15.5	16.8	18.5	18.2

[a] See footnote a in Table I. [b] The concentration expressed in mol dm^{-3} and the optical path in cm.

Calculation of the Stability Constants

The stability constants for the successive complexes of metal ions with 9-methylpurines and their molar absorption coefficients were computed from the spectrophotometric data by the method described by Kankare [20].

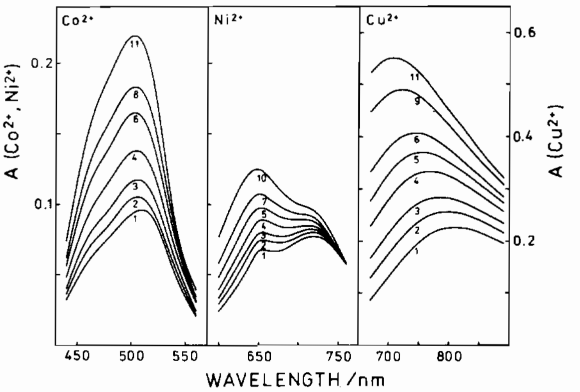

Fig. 1. The VIS-absorption spectra of cobalt(II), nickel(II), and copper(II) ions in aqueous solutions of 9-methylpurine at 298.2 K. The ligand concentrations referring to curves 1–11 are 0, 0.010, 0.020, 0.040, 0.060, 0.080, 0.10, 0.12, 0.16, 0.20 and 0.24 mol dm^{-3}, respectively. The ionic strength was adjusted to 0.18 mol dm^{-3} with sodium perchlorate. [Co^{2+}] = 0.020 mol dm^{-3}, [Ni^{2+}] = 0.040 mol dm^{-3} and [Cu^{2+}] = 0.020 mol dm^{-3}.

Results and Discussion

Figure 1 shows the effect that complexing of 9-methylpurine with cobalt(II), nickel(II), and copper(II) ions has on the VIS-absorption spectra of the metal ions. The absorbances are markedly increased with increasing ligand concentration and the maxima are shifted towards shorter wavelengths. The influences of 2,9- and 8,9-dimethylpurines are qualitatively similar. Application of the computational method described by Kankare [20] to the spectrophotometric data yields the stability constants and molar absorption coefficients listed in Tables I and II. The experimental observations concerning the complexing of cobalt(II) ion with 9-methylpurine and nickel(II) ion with 2,9- and 8,9-dimethylpurines can be accounted for completely by formation of 1:1 complexes only. The stability constants obtained are, within the limits of experimental errors, equal to those determined earlier potentiometrically [18] for the same complexes in excess of metal ions. In contrast, copper(II) ion exhibits formation of both 1:1 and 1:2 complexes with all the ligands studied, as does nickel(II) ion with 9-methylpurine. Again the stability constants for the 1:1 complexes agree with the values obtained potentiometrically [18].

Application of the method of continuous variation [21] to the spectrophotometric measurements lends further support to the suggested stoichiometry of the complex formation. The changes that complexing with 9-methylpurines induces in the absorptivity of copper(II) ion at 700 nm are plotted against the mole fraction of the ligand in Fig. 2. All the curves are clearly asymmetric and go through maxima as the mole fraction of the ligand passes 0.6. The corresponding plots obtained with nickel(II) and cobalt(II) ions are symmetrical (Fig. 2), as expected for formation of 1:1 complexes. At higher sum concentrations of ligand and metal ion complexing of nickel(II) ion with 9-methylpurine exhibited some deviation from symmetrical behavior.

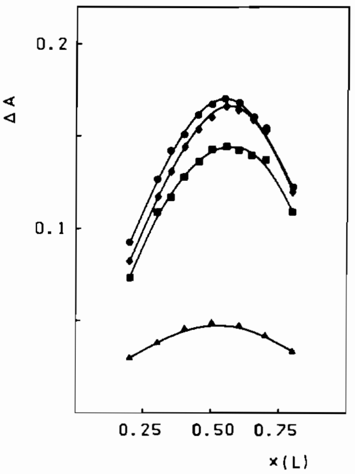

Fig. 2. Application of the method of continuous variation to the spectrophotometric data concerning the complexing of copper(II) ion with 9-methylpurine (■), 2,9-dimethylpurine (◆), and 8,9-dimethylpurine (●), and cobalt(II) ion with 9-methylpurine (▲). The sum concentration of the ligand and metal ion was 0.060 mol dm^{-3}. The ionic strength was adjusted to 0.18 mol dm^{-3} with sodium perchlorate. The absorbances were measured against the corresponding metal ion solutions at 498 nm for cobalt(II) ion, at 700 nm for copper(II)–dimethylpurine systems and at 720 nm for the copper(II)–9-methylpurine system.

As seen from Table II, the molar absorption coefficients of the metal complexes increase with the number of ligand molecules. The absorption maxima are simultaneously shifted towards shorter wavelengths. This is expected considering that water molecules are replaced by more strongly bonded nitrogen ligands. The alterations are, however, too small to allow any firm conclusions to be made concerning the changes in the geometry of the ligand field due to complexation.

Table III records the enthalpies of interaction, ΔH(int.), of copper(II) ion with the 9-methylpurines studied. With each ligand the ΔH(int.) values are moderately increased with increasing ionic strength. Comparison of the calorimetric and equilibrium data in Table III reveals that the increments in the observed enthalpies can be satisfactorily explained by the changes that varying the ionic strength causes in the concentrations of the metal ion complexes. Accordingly, the molar enthalpies of the complex formation appear to be practically independent of ionic strength. The relationship between these

TABLE III. The Effect of Ionic Strength on the Observed Enthalpies of Interaction, ΔH(int.), between Copper(II) Ion and Some 9-Methylpurines in Aqueous Solution at 298.2 K.[a]

I/mol dm^{-3}	ΔH(int.)/mJ	$[ML^{2+}]^b/10^{-3}$ mol dm^{-3}	$[ML_2^{2+}]/10^{-3}$ mol dm^{-3}
9-Methylpurine			
0.045	301	4.59	0.22
0.105	329	4.70	0.23
0.195	360	4.80	0.24
0.545	417	5.18	0.29
2,9-Dimethylpurine			
0.045	267	3.77	0.33
0.105	291	3.87	0.35
0.165	319	3.92	0.36
0.245	337	4.03	0.39
8,9-Dimethylpurine			
0.045	178	3.46	0.24
0.105	197	3.56	0.26
0.165	203	3.62	0.27
0.245	213	3.72	0.29

[a] Obtained by mixing aliquots of 1.75 cm^3 of copper(II) perchlorate and ligand solutions, the concentrations of which were 0.030 mol dm^{-3}. The ionic strength was adjusted with sodium perchlorate. [b] Calculated by the equilibrium constants determined at various ionic strengths [18].

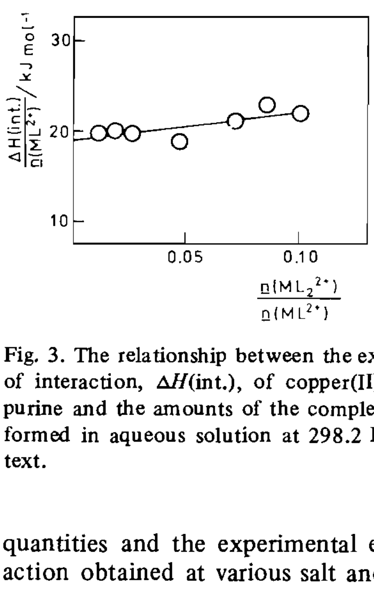

Fig. 3. The relationship between the experimental enthalpies of interaction, ΔH(int.), of copper(II) ion with 9-methylpurine and the amounts of the complexes, ML^{2+} and ML_2^{2+}, formed in aqueous solution at 298.2 K. See eqn. (2) in the text.

quantities and the experimental enthalpies of interaction obtained at various salt and ligand concentrations can thus be expressed by eqn. (1), where ΔH_1 and ΔH_2 denote the molar enthalpies of formation

$$\Delta H(\text{int.}) = n(ML^{2+})\Delta H_1 + n(ML_2^{2+})\Delta H_2 \qquad (1)$$

of 1:1 and 1:2 complexes, respectively, and $n(ML^{2+})$ and $n(ML_2^{2+})$ are the amounts of the complexes formed during the measurement of ΔH(int.). Transformation of eqn. (1) to eqn. (2) enables the calculation of ΔH_1 and ΔH_2 as the intercept and slope of

$$\frac{\Delta H(\text{int.})}{n(ML^{2+})} = \Delta H_1 + \frac{n(ML_2^{2+})}{n(ML^{2+})}\Delta H_2 \qquad (2)$$

the straight line of ΔH(int.)/$n(ML^{2+})$ *vs.* $n(ML_2^{2+})$/$n(ML^{2+})$.

The enthalpies of interaction observed at various concentrations of 9-methylpurines and 3d transition metal perchlorates are listed in Table IV together with concentrations of the 1:1 and 1:2 complexes prevailing in the final state of each measurement. The data refer to the ionic strengths that the interacting metal salt results in. The differences in the ionic strength have been taken into account in calculations of $[ML^{2+}]$ and $[ML_2^{2+}]$. Figure 3 shows an example of applying eqn. (2) to the data in Table IV. It is clearly seen that only ΔH_1 can be obtained with a reasonable accuracy. The concentration of the 1:2 complexes are, under the experimental conditions, too small to allow the determination of ΔH_2. However, the measurements cannot be carried out at higher ligand concentrations, since the enthalpies of the self-association of purine derivatives begin to interfere [22–24].

Table V summarizes the thermodynamic quantities for the formation of the 1:1 complexes considered above. We have suggested previously [18] that binding of 3d transition metal ions occurs competitively to N1 and N7 sites of 9-methylpurine, the stabilities of both types of complexes being of the same order. Methyl substituents at C2 and C8

TABLE IV. The Observed Enthalpies of Interaction between Some Divalent Metal Ions and 9-Methylpurines in Aqueous Solution at 298.2 K.[a]

Metal ion	$[M^{2+}]$[b] 10^{-3} mol dm^{-3}	$[L]$[b] 10^{-3} mol dm^{-3}	ΔH(int.) mJ	$[ML^{2+}]$[c] 10^{-3} mol dm^{-3}	$[ML_2^{2+}]$[c] 10^{-3} mol dm^{-3}
9-Methylpurine					
Co^{2+}	22.5	7.5	76	1.00	–
	20.0	10.0	85	1.18	–
	15.0	15.0	94	1.31	–
	10.0	20.0	80	1.15	–
	7.5	22.5	64	0.96	–
Ni^{2+}	25.0	5.0	138	2.00	0.01
	22.5	7.5	183	2.72	0.02
	20.0	10.0	216	3.24	0.04
	15.0	15.0	222	3.62	0.07
	10.0	20.0	207	3.15	0.09
	7.5	22.5	171	2.62	0.08
	5.0	25.0	120	1.90	0.07
Cu^{2+}	25.0	5.0	174	2.52	0.03
	22.5	7.5	242	3.43	0.06
	20.0	10.0	282	4.10	0.11
	15.0	15.0	301	4.59	0.22
	10.0	20.0	292	3.95	0.28
	7.5	22.5	260	3.25	0.28
	5.0	25.0	178	2.33	0.23
Zn^{2+}	22.5	7.5	40	0.72	–
	20.0	10.0	46	0.85	–
	15.0	15.0	50	0.94	–
2,9-Dimethylpurine					
Ni^{2+}	22.5	7.5	146	1.84	–
	20.0	10.0	168	2.18	–
	15.0	15.0	175	2.43	–
	10.0	20.0	145	2.13	–
	7.5	22.5	120	1.78	–
Cu^{2+}	25.0	5.0	162	2.12	0.05
	22.5	7.5	213	2.87	0.11
	20.0	10.0	249	3.34	0.18
	15.0	15.0	267	3.77	0.33
	10.0	20.0	222	3.24	0.42
	7.5	22.5	182	2.67	0.41
	5.0	25.0	130	1.92	0.34
8,9-Dimethylpurine					
Ni^{2+}	25.0	5.0	72	1.41	–
	22.5	7.5	96	1.91	–
	20.0	10.0	112	2.26	–
	15.0	15.0	121	2.52	–
	10.0	20.0	101	2.20	–
	7.5	22.5	88	1.84	–
	5.0	25.0	62	1.34	–
Cu^{2+}	25.0	5.0	104	1.95	0.04

(continued overleaf)

TABLE IV. *(continued)*

Metal ion	$[M^{2+}]$[b] 10^{-3} mol dm^{-3}	[L][b] 10^{-3} mol dm^{-3}	ΔH(int.) mJ	$[ML^{2+}]$[c] 10^{-3} mol dm^{-3}	$[ML_2^{2+}]$[c] 10^{-3} mol dm^{-3}
	22.5	7.5	132	2.64	0.08
	20.0	10.0	166	3.12	0.13
	15.0	15.0	178	3.46	0.24
	10.0	20.0	150	2.99	0.30
	7.5	22.5	121	2.47	0.30

[a] Obtained by mixing aliquots of 1.75 cm^3 of the appropriate metal(II) perchlorate and ligand solutions. [b] Total concentration in the final state. [c] Calculated by the equilibrium constants at different ionic strengths [18].

TABLE V. Enthalpies and Entropies for the Formation of 1:1 Complexes between Some Divalent Metal Ions and 9-Methylpurines in Aqueous Solution at 298.2 K.[a]

Metal ion	9-Methylpurine		2,9-Dimethylpurine		8,9-Dimethylpurine	
	$\Delta H^\ominus$/kJ mol^{-1}	$\Delta S^\ominus$/J K^{-1} mol^{-1}	$\Delta H^\ominus$/kJ mol^{-1}	$\Delta S^\ominus$/J K^{-1} mol^{-1}	$\Delta H^\ominus$/kJ mol^{-1}	$\Delta S^\ominus$/J K^{-1} mol^{-1}
Co^{2+}	−20.4 ± 0.4	−51 ± 3				
Ni^{2+}	−19.5 ± 0.5	−37 ± 5	−20.8 ± 0.7	−46 ± 3	−14.2 ± 0.3	−23 ± 3
Cu^{2+}	−18.9 ± 0.7	−31 ± 4	−21.8 ± 0.2	−43 ± 4	−15.2 ± 0.3	−23 ± 2
Zn^{2+}	−15.4 ± 0.3	−38 ± 4				

[a] At the ionic strength of 0.18 mol dm^{-3}.

retard sterically coordination to the adjacent nitrogen atoms, but facilitate inductively attachment to the other potential donor atoms. The former of these two factors plays a decisive role in determining the preferential binding site [18]. Accordingly, 2,9-dimethylpurine may be expected to form N7-bonded and 8,9-dimethylpurine N1-bonded complexes, 9-methylpurine exhibiting both types of coordination. The equilibrium data in Table V are consistent with this view. Dimethylpurines, having one of the favorable binding sites blocked, form slightly less stable complexes than 9-methylpurine.

The enthalpies obtained for the formation of 1:1 complexes between 9-methylpurines and 3d transition metal ions range from −14 to −22 kJ mol^{-1}, being thus of the same order as the value reported earlier [25] for the complexing of silver(I) ion with adenosine, *viz.* −23 kJ mol^{-1}. Complexing of 2,9-dimethylpurine is characterized by slightly more negative enthalpy changes than complexing of 8,9-dimethylpurine. In other words, binding to the N7 atom appears to be enthalpically more favorable than binding to the N1 atom. This enthalpy gain is, however, cancelled by the more negative entropy term, $T\Delta S^\ominus$. The enthalpies and entropies obtained for complexing of 9-methylpurine fall between the values that 2,9- and 8,9-dimethylpurines exhibit. This is expected considering that 9-methylpurine forms both N1- and N7-bonded complexes. The thermodynamic quantities for the formation of the 1:2 complexes cannot be determined exactly enough for the reasons mentioned before.

In summary, the present data lend further support to our proposal [18] that 3d transition metal ions bind competitively to N1 and N7 sites of 9-methylpurine. The latter interactions appear to show more favorable enthalpy changes, but less favorable entropy changes.

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