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Complexing of 3d Transition Metal Ions with 9-Substituted Purines. I. Binding Sites in Aqueous Solution

JORMA ARPALAHTI and HARRI LÖNNBERG

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

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Stability constants for cobalt(II), nickel(II), copper(II), and zinc(II) ions with 9-methylpurine and its 2-, 6-, and 8-methyl derivatives have been determined in aqueous solution at 298.2 K. All methyl substituents reduce the complexing ability of 9-methylpurine, the destabilizing effect of the 6-methyl group being far greater than that of the 2- or 8-methyl groups. The equilibrium data obtained are accounted for by competitive attachment of metal ions to N1 and N7 of 9-methylpurine. The downfield shifts that zinc(II) ions exert on the ^{1}H NMR signals of the purine protons are discussed in terms of this model.

Introduction

Complexing of metal ions with nucleic acids and their monomeric constituents has become one of the main topics in the research of bioinorganic chemistry, as described by several reviews in recent years [1–6]. The numerous heteroatoms in these ligands offer a great variety of potential binding sites, the hard Lewis acids being generally coordinated to the glycon and phosphate moieties and the soft acids to the nitrogen atoms of the base moieties [1, 4, 6]. The latter interactions are of particular interest, since certain platinum(II) antineoplastic agents are supposed to complex with purine and pyrimidine residues in the nucleic acids of tumor cells [7]. Application of various spectroscopic techniques, including Raman difference spectroscopy [4, 8], ^{1}H NMR relaxation [4, 6, 9], and ^{1}H, ^{13}C and ^{15}N NMR shift studies [4, 6, 8–16], has given valuable information about the structures of the complexes in solution. Most of the data reported refer to complexing of purine nucleosides. In adenosine, for example, N7 has been suggested to be the preferential binding site, though soft metal ions appear to interact also with N1 [1, 4, 6, 8, 16]. With 6-oxo-substituted nucleosides coordination occurs at N7 in acidic solutions and at N1 with displacement of a proton in basic solutions [1, 4, 6, 9–12, 15, 16]. While 6-substituted purine nucleosides have been extensively studied, few investigations have dealt with the complexing of the parent compound, 9-(β-D-ribofuranosyl)purine are coordinated simultures of the latter complexes are of interest in attempting to elucidate the factors that determine the binding behavior of purine nucleosides. ^{1}H NMR measurements have shown that both N1 and N7 of 9-(β-D-ribofuranosyl)purine are coordinated simultaneously to two different platinum atoms upon mixing the nucleoside and [Pt(dien)Cl]Cl in a 1:1 ratio [17]. The downfield shifts exerted by zinc(II) ions on the ^{1}H NMR signals of the purine protons of the unsubstituted purine riboside are also consistent with the view that the binding efficiencies of N1 and N7 are comparable [18]. The aim of the present study is to determine the preferential coordination sites of 3d transition metal ions in 9-substituted purines. The problem was approached by examining the effects that methyl groups at C2, C6 and C8, *i.e.* adjacent to the potential binding sites, have on the stabilities of the complexes of 9-methylpurine in aqueous solution. To obtain a quantitative estimation for the steric retardation caused by a methyl group next to the donor atom, the complexing abilities of 1-methyl- and 1,2-dimethylbenzimidazoles, having both only one unsubstituted heteroatom, are compared. The equilibrium data are employed to interpret the effects that diamagnetic metal ions have on the ^{1}H NMR spectra of the compounds investigated.

Experimental

Materials

9-Methylpurine and its 2-, 6-, and 8-methyl derivatives were prepared as mixtures of N7- and N9-isomers by treating the appropriate free purines with dimethyl sulfate in acetone [19]. Separation of the isomeric mixtures on a strong cation exchange resin

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TABLE I. Melting Points, Elemental Compositions and UV-Absorption Maxima of the 1-Substituted Benzimidazoles and 9-Substituted Purines Prepared.

Compound	M.p./°C	Elemental Composition[a]			UV_{max} (lg ε)/nm	
		C%	H%	N%	in acid[b]	in water
1-Methylbenzimidazole	59–60[c]	72.90	6.07	21.23		[d]
		(72.70)	(6.10)	(21.20)		
1,2-Dimethylbenzimidazole	111[e]	73.98	6.88	19.02		[d]
		(73.94)	(6.89)	(19.16)		
2,9-Dimethylpurine	116–118	56.68	5.50	37.73	265 (3.78)	268 (3.93)
		(56.74)	(5.44)	(37.81)		
6,9-Dimethylpurine	94–96	53.92	5.30	35.72	264 (3.85)	261 (3.91)
		(53.49)	(5.76)	(35.64)[f]	265 (3.81)[g]	262 (3.89)[g]
8,9-Dimethylpurine	123–124	56.81	5.39	37.67	263(3.87)	265 (3.96)
		(56.74)	(5.44)	(37.81)		
9-(Tetrahydro-2-pyranyl)-purine	139 dec.[h]	58.68	5.84	26.59	259 (3.79)	261.5 (3.87)
		(58.81)	(5.92)	(27.43)		

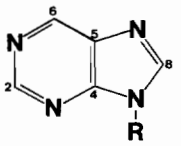
[a]Calculated values in parentheses. [b]In 0.2 mol dm^{-3} aqueous hydrogen chloride. [c]Lit. [28] 60–61 °C. [d]Agree with the values in lit. [28]. [e]Lit. [29] 110 °C. [f]For $C_7H_8N_4 \cdot \frac{1}{2}H_2O$. [g]Agree with the values in lit. [30]. [h]For the picrate.

loaded with Mg(II) ions gave pure N9-methylated purines [19]. Of the free bases employed as starting materials, the unsubstituted purine and its 6-methyl derivative were products of Sigma Chemical Company. 8-Methylpurine was prepared by heating 4,5-diaminopyrimidine (Sigma Chemical Company) with acetic acid anhydride [20]. 2-Methylpurine was synthesized as follows. Refluxing of acetamidine hydrochloride in ethyl cyanoacetate gave 4-amino-2-methyl-6-oxopyrimidine [21], which was further nitrosated according to Traube [22] and reduced to 4,5-diamino-6-oxopyrimidine [23]. The product was cyclized to 2-methyl-6-oxopurine with formamide [23], converted to the corresponding 6-mercaptopurine with phosphorous pentasulfide [24], and reduced to 2-methylpurine with Raney nickel [25]. All dimethylpurines were purified by sublimation at about 10 °C below their melting points at 2 kPa, and the sublimates were crystallized from hexane or carbon tetrachloride. 6,9-Dimethylpurine was observed to be hygroscopic. According to the thermogravimetric analysis (a Fischer thermobalance) the product contained half a mole of water, which was liberated at 70–90 °C. 9-(Tetrahydro-2-pyranyl)purine was prepared by heating purine in excess of 2,3-dihydropyran (Koch-Light Laboratories Ltd) containing a catalytic amount of *p*-toluene sulfonic acid. The unreacted vinyl ether was converted to 2-methoxytetrahydropyran with methanol to avoid polymerizations during the separation of the product. 9-(Tetrahydro-2-pyranyl)purine was crystallized from the solution as its picric acid salt and regenerated by extracting it in chloroform from an aqueous sodium hydroxide solution. Extraction of the crude product in boiling hexane yielded a colorless oil, which according to NMR spectra contained only one isomer. 1-Methylbenzimidazole was obtained by refluxing benzimidazole (Fluka A.G.) in methanolic potassium hydroxide [26] and 1,2-dimethylbenzimidazole by methylation of 2-methylbenzimidazole (Fluka A.G.) *via* phase transfer catalysis [27]. The products were crystallized from hexane to constant melting points.

Table I records the melting points, elemental compositions and UV-absorption maxima for the compounds prepared. The melting points were determined on a Büchi capillary melting point apparatus. The UV-spectra were recorded on a Cary 17 D spectrophotometer, the cell housing block of which was thermostated with water circulation from a Lauda thermostat. Table II summarizes the NMR chemical shifts for the purine derivatives. The spectra of the benzimidazole derivatives agreed with those reported in the literature [29, 31, 32]. The ^1H NMR spectra were recorded on a Jeol JNM PMX60 spectrometer and the ^{13}C NMR spectra on a Jeol FX60FT apparatus, using TMS as the external standard.

The ^{13}C NMR chemical shifts listed in Table II indicate that the purine derivatives prepared are N9-isomers. With each compound C4 and C5 exhibited signals at 150 and 132 ppm, respectively, as expected for N9-substituted purines [33]. In the corresponding N7-isomers C4 resonates at about 160 ppm and C5 at 125 ppm [19, 33]. The metal perchlorates were products of Fluka A.G. and G. Frederick Smith Chemical Company, and they were employed as received. Perchloric and formic acids were of analytical grade. Standard base solutions (Merck A.G.) were employed to check the concentrations of the acid solutions.

TABLE II. ^{1}H and ^{13}C NMR Chemical Shifts[a] for the 9-Substituted Purines Prepared.

Compound								
		δ(2)	δ(4)	δ(5)	δ(6)	δ(8)	δ(N9-CH_3)	δ(C2,6,8-CH_3)
9-Methylpurine[b]	^{1}H NMR:	s8.74			s8.89	s8.31	s3.83	
	^{13}C NMR:	153.9	153.3	135.2	149.6	150.9	32.5	
2,9-Dimethylpurine	^{1}H NMR:				s8.51	s8.11	s3.66	s2.54
	^{13}C NMR:	162.3	151.8	131.1	147.3	148.5	30.6	25.0
6,9-Dimethylpurine	^{1}H NMR:	s8.36				s8.13	s3.70	s2.49
	^{13}C NMR:	151.3	149.7	131.4	158.9	147.3	30.7	18.9
8,9-Dimethylpurine	^{1}H NMR:	s8.60			s8.65		s3.64	s2.57
	^{13}C NMR:	151.5	151.9	132.3	145.2	158.5	29.3	14.1
9-(Tetrahydro-2-pyranyl)purine[c]	^{1}H NMR:	s8.76			s8.96	s8.16		
	^{13}C NMR:	152.6	150.6	134.2	143.2	148.7		

[a]Taken as ppm from external TMS in D_2O. [b]Data from Ref. 19. [c]From internal TMS in $CDCl_3$. Shifts for the tetrahydropyran moiety: δ(H3',4',5', m) 1.7–2.1, δ(H6', m) 3.6–4.3, δ(H2', d–d) 5.6–5.8, δ(C3',4',5') 22.8, 24.9, 31.7, δ(C6') 68.8, δ(C2') 81.9.

TABLE III. Apparent Acidity Constants, K_a(app.), for the Monocations of 9-Substituted Purines in Aqueous Solutions of Various Metal Perchlorates at 298.2 K.[a]

Metal ion	$-\lg(K_a$ (app.)/dm^3 mol^{-1})				
	9-Methylpurine	2,9-Dimethylpurine	6,9-Dimethylpurine	8,9-Dimethylpurine	9-(Tetrahydro-2-pyranyl)purine
–	3.05 ± 0.03	3.84 ± 0.01	3.55 ± 0.01	3.51 ± 0.01	2.60 ± 0.03
Mn^{2+}	2.98 ± 0.02	3.80 ± 0.05	3.54 ± 0.02	3.48 ± 0.04	2.58 ± 0.05
Co^{2+}	2.73 ± 0.01	3.63 ± 0.02	3.51 ± 0.02	3.31 ± 0.01	2.37 ± 0.01
Ni^{2+}	2.38 ± 0.01	3.40 ± 0.01	3.50 ± 0.01	3.05 ± 0.02	2.17 ± 0.02
Cu^{2+}	2.12 ± 0.01	2.99 ± 0.02	3.36 ± 0.01	2.80 ± 0.02	1.78 ± 0.02
Zn^{2+}	2.80 ± 0.01	3.66 ± 0.01	3.51 ± 0.02	3.36 ± 0.01	2.48 ± 0.02

[a]$[M^{2+}]$ = 0.1 mol dm^{-3}. The ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate.

Determination of the Acidity Constants

A modified potentiostatic technique described earlier [18] was applied to the determinations of the acidity constants of the protonated purine and benzimidazole derivatives. The measurements were performed at 298.2 K in the absence and presence of the divalent metal ions studied. The ionic strength was generally adjusted to 1.0 mol dm^{-3} with sodium perchlorate. For comparison the acidity constant of the monocation of 9-methylpurine was also determined spectrophotometrically. The spectra of 1×10^{-4} mol dm^{-3} substrate solutions were recorded at different oxonium ion concentrations against the same solution having pH 7. The oxonium ion concentrations were adjusted with formic acid–sodium formate buffers in the pH range of 2.5–4.0 and with perchloric acid in more acidic solutions. Data from the literature [34] were employed to calculate the pH values of the buffers under the conditions employed. The spectrum of the completely protonated 9-methylpurine was obtained in 1.0 mol dm^{-3} perchloric acid.

Results and Discussion

Table III records the apparent acidity constants, defined by eqn. (1), for the monocations of some

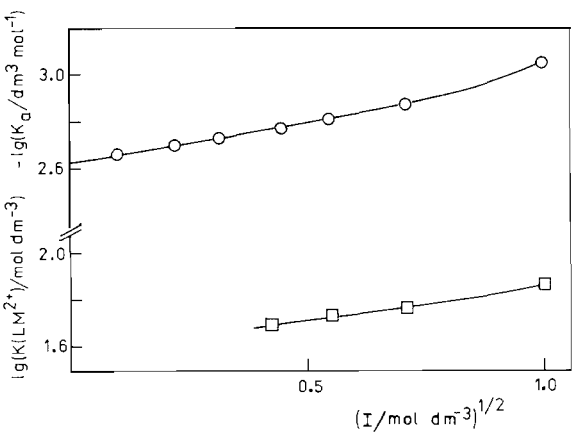


Fig. 1. The effect of ionic strength on the acidity constant of protonated 9-methylpurine (○) and on the stability constant of the corresponding copper(II) complex (□) at 298.2 K.

9-substituted purines in aqueous solutions of various 3d transition metal ions. The pK_a-values obtained

$$K_a(\text{app.}) = \frac{[H^+]([L(\text{tot.})] - [LH^+])}{[LH^+]} \quad (1)$$

for 9-methyl- and 6,9-dimethylpurines in the absence of complexing metal ions are somewhat greater than those reported earlier, *viz.* 2.5 [35] and 3.2 [30] at low ionic strengths at 293 K. At least part of the difference is, however, the consequence of different experimental conditions. As seen from Fig. 1, extrapolation of the acidity constant of protonated 9-methylpurine to zero ionic strength gives a pK_a-value of 2.6 in fairly good agreement with that in the literature. Furthermore, the value of 2.77 ± 0.08 obtained spectrophotometrically at the ionic strength of 0.1 mol dm^{-3} is in good accordance with the potentiostatic values, and indicates the reliability of the data in Table III. As described previously [18], the stability constants, $K(LM^{2+})$, for the 1:1 complexes between purine derivatives and metal ions can be calculated *via* eqn. (2) from the apparent acidity constants determined under conditions $[M^{2+}] \gg [L(\text{tot.})]$. Here K_a stands for the acidity

$$K(LM^{2+}] = \frac{[LM^{2+}]}{[L][M^{2+}]} = \frac{1}{[M^{2+}]}\left(\frac{K_a(\text{app.})}{K_a} - 1\right) \quad (2)$$

constant in the absence of complexing metal ions, and $[M^{2+}]$ is the equilibrium concentration of the free metal ion. The results obtained are listed in Table IV. As seen from Fig. 1, the stability constants respond to changes in the ionic strength in approximately the same manner as the acidity constants. With each ligand the complexing efficiencies of various metal ions obey the Irving–Williams order.

Inspection of the data in Table IV reveals that introduction of methyl substituents in 9-methylpurine decreases the stability of the metal ion complexes, the destabilizing effect of the 6-methyl group being far greater than that of the 2- or 8-methyl groups. Obviously the methyl groups retard complexing sterically, since their electropositive inductive effects facilitate attachment of metal ions, as can be seen from the increased basicity of dimethylpurines compared to 9-methylpurine. Comparison of the complexing abilities of 1-methyl- and 1,2-dimethylbenzimidazoles enables estimation of the influence that a methyl group adjacent to the donor atom exerts on the stabilities of the transition metal complexes of ligands related to imidazole. As seen from Table V, the stability constant for the nickel(II) complex of 1-methylbenzimidazole is about 25 times larger than that for the corresponding complex of 1,2-dimethylbenzimidazole. A similar stability difference is observed between the nickel(II) complexes of pyridine and 2-methylpyridine, which can be considered model compounds for the complexing of six-membered rings.

TABLE IV. Stability Constants, $K(LM^{2+})$, for the 1:1 Complexes of 9-Substituted Purines with 3d Transition Metal Ions in Aqueous Solution at 298.2 K.[a]

Metal ion	$\lg(K(LM^{2+})/mol\ dm^{-3})$				
	9-Methylpurine	2,9-Dimethylpurine	6,9-Dimethylpurine	8,9-Dimethylpurine	9-(Tetrahydro-2-pyranyl)purine
Mn^{2+}	0.2 ± 0.1	<0.2	<0.2	<0.2	<0.2
Co^{2+}	1.04 ± 0.07	0.80 ± 0.07	<0.2	0.78 ± 0.05	0.84 ± 0.08 (1.00)[b]
Ni^{2+}	1.56 ± 0.06	1.26 ± 0.03	<0.2	1.28 ± 0.04	1.24 ± 0.06 (1.31)
Cu^{2+}	1.88 ± 0.05	1.78 ± 0.04	0.74 ± 0.05	1.62 ± 0.03	1.76 ± 0.03 (1.50)
Zn^{2+}	0.9 ± 0.1	0.71 ± 0.06	<0.2	0.6 ± 0.1	0.5 ± 0.2 (0.70)

[a]See footnote a in Table III. [b]Values for the corresponding complexes of 9-(β-D-ribofuranosyl)purine [18].

TABLE V. Apparent Acidity Constants, K_a (app.), for the Monocations of some Nitrogen Bases in Aqueous Salt Solutions, and the Stability Constants for their Nickel(II) Complexes at 298.2 K.[a]

Compound	$[Ni^{2+}]$/mol dm^{-3}	$-\lg(K_a(\text{app.})/\text{dm}^3\ \text{mol}^{-1})$	$\lg(K(LM^{2+})/\text{mol dm}^{-3})$
1-Methylbenzimidazole	–	5.90 ± 0.04	
	0.1	4.68 ± 0.02	2.18 ± 0.08
1,2-Dimethylbenzimidazole	–	6.76 ± 0.04	
	0.1	6.56 ± 0.01	0.77 ± 0.09
Pyridine			1.92[b]
2-Methylpyridine			0.35[b]

[a]See footnote a in Table III. [b]From Ref. 36. Refers to ionic strength of 0.1 mol dm^{-3}.

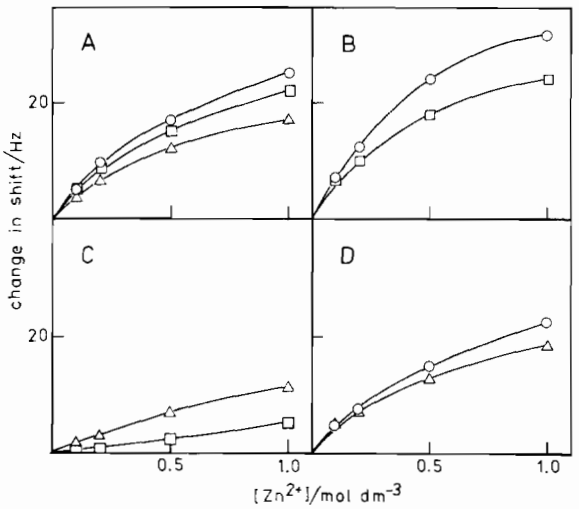


Fig. 2. The effect of zinc(II) ion on the ^{1}H NMR shifts of 9-methylpurine (A), 2,9-dimethylpurine (B), 6,9-dimethylpurine (C) and 8,9-dimethylpurine (D). Notation: 2H (△), 6H (○) and 8H (□).

Consequently, 2- and 8-methyl groups would be expected to form considerable steric obstacles to the coordination of metal ions at N1 and N7 of the purine ring, respectively. However, the complexing ability of 2,9- and 8,9-dimethylpurines is only slightly less than that of 9-methylpurine. In contrast, the stability constants for the complexes of 6,9-dimethyl- and 9-methylpurines exhibit the expected difference of about 1.3 logarithmic units. These observations can only be accounted for by competitive attachment of metal ions at N1 and N7 of 9-methylpurine. The 2-methyl group, for example, prevents binding to N1, but exerts practically no effect on binding to N7. The 8-methyl group, in turn, retards coordination to N7, and leaves N1 binding unaffected. In contrast, the 6-methyl group is sterically in the proximity of both N1 and N7 atoms, and therefore blocks both sites. Accordingly, the observed stability constant, $K(LM^{2+})$, for the complexes of 9-methylpurine may be expressed by eqn. (3),

$$K(LM^{2+}) = K_{N1}(LM^{2+}) + K_{N7}(LM^{2+}) \quad (3)$$

where $K_{N1}(LM^{2+})$ and $K_{N7}(LM^{2+})$ refer to formation of N1 and N7-bonded complexes, respectively. It seems reasonable to assume that the stability constants for 8,9-dimethylpurine approximate to the values of $K_{N1}(LM^{2+})$ and those for 2,9-dimethylpurine to the values of $K_{N7}(LM^{2+})$. Substituting the constants obtained with nickel(II) ion in eqn. (3) yields a value of 1.57 for $\lg(K(LM^{2+})/\text{mol dm}^{-3})$. This is in good agreement with the value determined experimentally for 9-methylpurine. If it is further assumed that the 6-methyl group decreases $K_{N1}(LM^{2+})$ and $K_{N7}(LM^{2+})$ by a factor of 25, which is the case with pyridines and benzimidazoles, the value of $\lg(K(LM^{2+})/\text{mol dm}^{-3})$ is diminished to about 0.1. Again the consistency with the experimental observations is reasonable.

In the preceding discussion N3 has been ignored as a possible binding site. However, the low complexing ability of 6,9-dimethylpurine argues strongly against N3-binding. Furthermore, as the data in Table IV indicate, replacement of the 9-methyl group with the more bulky tetrahydro-2-pyranyl or β-D-ribofuranosyl groups has no effect on the stabilities of the complexes. Evidently the distance between N9 and the coordination site must be large. Figure 2 shows that addition of zinc(II) perchlorate to the deuterium oxide solution of 9-substituted purines shifts the signals of all purine protons downfield. The shifts result partly from changes in the electrolyte composition, as shown by the influences of inert electrolytes such as sodium and tetramethylammonium salts. The latter effects are, however, less than 3 Hz. Comparison of the different sets of curves in Fig. 2 reveals that the magnitude of the

shifts at a given metal ion concentration correlates with the complexing ability of the ligands. However, the differences between the shifts of various protons of a given compound are small, and it appears highly doubtful that the coordination sites could be assigned on the basis of ^{1}H NMR data. It is generally accepted that adenosine, for example, forms N7-coordinated monodentate complexes, while protonation occurs at N1. A possible explanation for the difference in the binding behavior of 9-substituted adenines and purines is that the 6-amino group of the former compounds blocks sterically the N1 site more efficiently than the N7 site. Protonation is not susceptible to steric hindrances, and the electron-donating amino group makes the adjacent nitrogen atom the preferential protonation site. 9-Substituted purines contain no bulky substituents near N1 and N7 and the distribution of protons and metal ions between these sites is affected only by electronic factors.

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