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Complexing of 3d Transition Metal Ions with 9-Substituted Purines. III. The Effect of Polar Substituents on Binding Sites and Stabilities

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Abstract

Stability constants for Ni(II) and Cu(II) complexes of several 9-substituted purines bearing amino, chloro, methoxy, methyl and methylthio groups at C2, C6 or C8 were determined potentiostatically in aqueous sodium perchlorate at 298.2 K. The results were verified by distributing some of the ligands between chloroform and aqueous nickel(II) perchlorate solutions. The equilibrium data obtained were interpreted to indicate that binding to N1 and N7 occurs with comparable strength when C6 of the purine ring is unsubstituted. In contrast, with adenine derivatives N7 coordination seems to be favoured. The susceptibility of the complex formation to the basicity of the binding site is low.

Introduction

The multisite binding behaviour of nucleic acids and their monomeric constituents towards cations has received much attention in recent years [1–9]. The coordination properties of the nucleobase moieties are of particular interest, since certain platinum(II) compounds termed 'anti-neoplastic agents' are supposed to complex with purine and pyrimidine residues in the nucleic acids of malignant cells [10].

Interactions of 3d transition metal ions with purine nucleosides constitutes one of the more extensively studied problems in this field. Spectroscopic measurements [4, 6, 11–22] have given valuable information about the structures of the complexes in aqueous solution. However, little is known about the relative strengths of the various possible binding modes, for example N1 *vs.* N7 binding, and the factors that determine the binding properties. We have suggested previously [23] that 3d transition metal ions bind competitively to N1 and N7 of the unsubstituted 9-methylpurine. Very recently, examination of the linear relationships between the logarithmic stability and acidity constants of a variety of ligands led Kim and Martin [24] to conclude that the N1 and N7 sites of neutral adenosine bind metal ions with comparable strength. With inosine the distribution of the metal ions between the N1 and N7 sites is pH-dependent, the N7-metallation prevailing in acidic solutions [6, 16, 25].

The aims of the present study may be summarized as follows: to obtain additional evidence for the previously [23, 26] suggested binding properties of the 9-substituted purine ring; to examine the effects that polar substituents exert on the stability of the 3d transition metal complexes of 9-substituted purines; and to elucidate further the competitive attachment of metal ions to the N1 and N7 sites of 9-substituted adenines.

Experimental

Materials

6-Methoxy- and 6-methylthio-9-(β-D-ribofuranosyl)purines (Sigma) were used without further purification. N^6,N^6-Dimethyladenosine was prepared from inosine (Sigma) in three steps. Inosine was first acetylated to 2′,3′,5′-tri-O-acetylinosine [27], converted to the corresponding 6-chloro derivative [28] and then to N^6,N^6-dimethyladenosine by stirring the latter with a twentyfold molar excess of dimethylamine (40% aqueous solution, Merck A.G.) in methanol overnight at room temperature. The acetyl groups were simultaneously cleaved under the basic reaction conditions employed. The mixture was finally evaporated to dryness and the product crystallized from ethanol. ^{13}C NMR spectrum, LC behaviour and the melting point of the product were the same as those of a commercial sample (Sigma). All the other 9-substituted purines and adenines examined were prepared as described previously [29]. The metal perchlorates employed were products of G. Frederick Smith Company and Fluka A.G., and they were used as received. Chloroform (Merck A.G.) used in the distribution studies was of analytical grade.

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Titrimetric Measurements

A modified potentiostatic technique described earlier [30] was applied to the determination of the acidity constants of the purine derivatives.

Distribution Measurements

The equilibrations of the 9-substituted adenines between aqueous solutions of nickel(II) perchlorate, the concentration of which was varied from 0 to 0.12 mol dm^{-3}, and chloroform were performed in stoppered tubes (10 cm^3) at 298.2 K. The ionic strength of the aqueous phase was adjusted to 1.0 mol dm^{-3} with sodium perchlorate. In order to minimize the salting effects of the electrolytes to the distribution of the ligand between the two phases, the total concentration of the divalent cations in aqueous solution was adjusted to 0.12 mol dm^{-3} with calcium perchlorate. The participation of calcium(II) ions on the complex formation was assumed to be negligible: it has been shown [25] that calcium(II) does not form complexes of measurable strength with 9-substituted purines even if they contain oxo substituents, and the replacement of calcium(II) ions with magnesium(II) ions did not alter the distribution of the ligand as a function of the nickel(II) concentration.

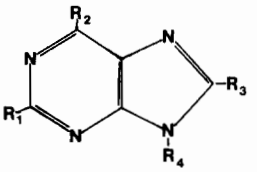
A series of tubes containing 3 cm^3 of organic and 2 cm^3 of aqueous phases were prepared and exactly the same amount of the ligand studied was added into each of these tubes. To avoid the interference of the protonation equilibria to the ligand distribution the oxonium ion concentration of all stock solutions was previously adjusted to 3×10^{-7} mol dm^{-3} or below. The tubes were equilibrated by continuous shaking for three days, after which the phases were separated by centrifugation. The water layer was removed by suction and a known sample (2 cm^3) from the organic layer was added into a tube containing 2 cm^3 of water. These tubes were again shaken overnight to transfer the solute back to the aqueous phase, centrifuged, and the concentration of the solute in the aqueous phase was determined by LC. The analyses were performed on a combined apparatus consisting of Altex 110 A pump, a variable wavelength UV-detector (Kratos Spectroflow 757), a Rheodyne injector and a commercial PP 103-5 column (HPLC-Technology, U.K.) packed with Spherisorb 5 ODS (5 μm). The column was thermostatted by water circulation to improve the reproducibility of the signals. Isocratic elution (0.8 cm^3 min^{-1}) with a mixture of an acetonitrile and acetic acid buffer (pH 4.3) was employed throughout. Peak heights were employed as the measure of the concentrations. The distribution coefficients were obtained by measuring the peak heights from both phases under conditions $[Ni^{2+}] = 0$.

Results and Discussion

Table I records the apparent acidity constants, defined by eqn. (1):

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

for the monocations of 9-substituted purines and adenines in aqueous solutions of various metal perchlorates. The structures of the compounds studied are depicted in Scheme 1. The acidity constants obtained for some compounds in this study tend to deviate about 0.5 logarithmic units from those reported in the literature (Table I). This difference can most probably be explained by the differences in the ionic strength. For comparison, the acidity constant of protonated 9-methylpurine is increased by 0.4 logarithmic units as the ionic strength is increased from 0.1 to 1.0 mol dm^{-3} [23]. The data in Table I reveal that the basicity of 9-substituted purines is more susceptible to polar substituents in position 2 than to those in position 8. This finding agrees with earlier observations, according to which protonation in 9-substituted purines and adenines occurs mainly at N1 [19, 36, 37, 38].



Compound	R_1	R_2	R_3	R_4
1	NH_2	H	H	CH_3
2	Cl	H	H	CH_3
3	CH_3O	H	H	CH_3
4	CH_3S	H	H	CH_3
5	H	H	NH_2	CH_3
6	H	H	Cl	CH_3
7	H	H	CH_3O	CH_3
8	H	H	CH_3S	CH_3
9	H	NH_2	H	CH_3
10	CH_3	NH_2	H	CH_3
11	H	NH_2	CH_3	CH_3
12	H	CH_3O	H	$C_5H_{10}O_5$
13	H	CH_3S	H	$C_5H_{10}O_5$
14	H	$(CH_3)_2N$	H	$C_5H_{10}O_5$

Scheme 1.

As described previously [22], 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:

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

TABLE I. Apparent Acidity Constants, K_a(app.), for the Monocations of Some 9-Substituted Purines and Adenines in Aqueous Solutions of Various Metal Perchlorates at 298.2 K.

Compound[a]		$-\lg(K_a(\text{app.})/\text{mol dm}^{-3})$		
		[b]	Ni^{2+} [c]	Cu^{2+} [c]
1	2-Amino-9-methylpurine	4.26 ± 0.03	3.68 ± 0.03	3.19 ± 0.03
2	2-Chloro-9-methylpurine	1.20 ± 0.05[d]	0.93 ± 0.05	0.77 ± 0.05
3	2-Methoxy-9-methylpurine	2.86 ± 0.03	2.33 ± 0.04	2.03 ± 0.04
4	9-Methyl-2-methylthiopurine	2.63 ± 0.03[e]	2.14 ± 0.04	1.86 ± 0.04
5	8-Amino-9-methylpurine	4.77 ± 0.08	4.08 ± 0.08	3.42 ± 0.08
6	8-Chloro-9-methylpurine	2.55 ± 0.03[f]	2.25 ± 0.03	2.15 ± 0.04
7	8-Methoxy-9-methylpurine	3.59 ± 0.03	3.07 ± 0.03	2.82 ± 0.03
8	9-Methyl-8-methylthiopurine	3.39 ± 0.03	2.91 ± 0.03	2.68 ± 0.03
9	9-Methyladenine	4.45 ± 0.03[g]	4.27 ± 0.03	4.00 ± 0.03
10	2,9-Dimethyladenine	5.17 ± 0.03	5.01 ± 0.03	4.76 ± 0.03
11	8,9-Dimethyladenine	4.66 ± 0.03	4.63 ± 0.03	4.39 ± 0.03
12	6-Methoxy-9-(β-D-ribofuranosyl)purine	1.27 ± 0.05[h]	1.19 ± 0.05	0.94 ± 0.05
13	6-Methylthio-9-(β-D-ribofuranosyl)purine	1.23 ± 0.05[i]	1.18 ± 0.05	1.03 ± 0.07
14	6-Dimethylamino-9-(β-D-ribofuranosyl)purine	4.18 ± 0.03[j]	4.16 ± 0.03	4.09 ± 0.03

[a]For the structures see Scheme 1. [b]In 1.0 mol dm^{-3} $NaClO_4$. [c]$[M^{2+}]$ = 0.1 mol dm^{-3}. The ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate. [d]In lit. [31]: 0.65 at 293.2 K, ionic strength not specified. [e]In lit. [32]: 2.11 at 293.2 K, ionic strength not specified. [f]In lit. [31]: 2.11 at 293.2 K, ionic strength not specified. [g]In lit. [33]: 3.99 in I = 0.05 mol dm^{-3} at 298.2 K. [h]In lit. [34]: 0.89 in I = 0.1 mol dm^{-3} at 298.2 K. [i]In lit. [35]: 0.78, temperature and ionic strength not specified. [j]In lit. [35]: 3.69, temperature and ionic strength not specified.

determined under conditions $[M^{2+}] \gg [L(\text{tot.})]$. Here K_a stands for the acidity 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 II. We have shown previously [23] that introduction of a methyl group in position 6 of 9-methylpurine decreases the complexing-ability of the parent compound to a much larger extent than a C2 or C8 bonded methyl group. Inspection of Table II reveals that the influences of amino, chloro, methoxy and methylthio substituents are analogous. For example, introduction of methoxy or methylthio groups in C2 (compounds **3** and **4**) or C8 (compounds **7** and **8**) of 9-methylpurine results in only slight decreases in the stabilities of metal ion complexes. The influences are actually about the same magnitude as those observed previously for methyl groups at corresponding sites. A chloro substituent (compounds **2** and **6**) prevents more efficient complexing, probably due to larger electronegativity. It is noteworthy that the destabilizing effects of all these substituents are moderate and seem almost equal for C2 and C8 bonded groups.

In contrast, when attached to C6 these groups decrease markedly the stabilities of the metal complexes. For example, in 9-(β-D-ribofuranosyl) purines the introduction of methoxy or methylthio groups in C6 (compounds **12** and **13**) reduces the stability of the nickel(II) complexes by a factor of at least 10, while these substituents at C2 or C8 in 9-methylpurines are destabilizing only by a factor of 1.5 and 1.8, respectively. These observations lend further evidence to our previous proposal that 3d transition

TABLE II. Stability Constants, $K(LM^{2+})$, for the 1:1 Complexes of Some 9-Substituted Purines and Adenines with Nickel(II) and Copper(II) Ions in Aqueous Solution at 298.2 K[a].

Compound[b]	$\lg(K(LM^{2+})/\text{dm}^3\ \text{mol}^{-1})$	
	Ni^{2+}	Cu^{2+}
c	1.56	1.88
1	1.45 ± 0.08	2.03 ± 0.07
2	0.9 ± 0.2	1.2 ± 0.2
3	1.38 ± 0.09	1.76 ± 0.08
4	1.33 ± 0.09	1.69 ± 0.08
5	1.6 ± 0.2	2.3 ± 0.2
6	1.0 ± 0.1	1.2 ± 0.1
7	1.36 ± 0.08	1.69 ± 0.07
8	1.31 ± 0.08	1.62 ± 0.07
9	0.7 ± 0.2	1.26 ± 0.09
10	0.6 ± 0.2	1.20 ± 0.09
11	<0.1	0.9 ± 0.1
12	0.3 ± 0.2	1.1 ± 0.2
13	<0.1	0.8 ± 0.2
14	<0.1	0.4 ± 0.2
d	1.31	1.50

[a]See footnote c in Table I. [b]For numeration see Table I. [c] For 9-methylpurine in I = 1.0 mol dm^{-3} at 298.2 K [23]. [d]For 9-(β-D-ribofuranosyl)purine in I = 1.0 mol dm^{-3} at 298.2 K [30].

metal ions bind approximately for the same extent to N1 and N7 of 9-substituted purines. A moderately bulky group at C2 sterically hinders metal ion coordination to N1, but has only an inductive influence on coordination to N7. The situation is reversed when the group is attached to C8. Accordingly, the effect on the observed complexing ability of the ligand remains slight. In contrast, the C6 substituent sterically prevents the binding of metal ions to both of these atoms, and hence diminishes drastically the complexing ability. It should be noted that the attachment of an exceptionally bulky substituent at C6, *e.g.* a $N(CH_3)_2$ group, restrains the complexation almost completely, as seen from the stabilities of the metal complexes of N^6,N^6-dimethyladenosine (Table II).

The amino group at C6 is less destabilizing than methyl, methoxy or methylthio groups. This results probably from two reasons: the amino group is not as bulky as the other groups studied, but the destabilization due to steric hindrances is partially compensated by the increased basicity of the ring nitrogens. It should be noted, however, that the amino group retards complexing considerably at C6, but not at C2 or C8. In fact, the stabilities of the nickel(II) complexes of 2- and 8-amino-9-methylpurines are almost equal to that of the nickel(II) complex of 9-methylpurine, and the corresponding Cu(II) complexes are even more stable than is the Cu(II) complex of 9-methylpurine.

On the basis of the preceding discussion it appears reasonable to assume that with 8-substituted 9-methylpurines both the protonation and complexation take place at N1. Consequently, comparison of the stability and acidity constants of these compounds elucidates the susceptibility of the 3d transition metal complexation to the basicity of the binding site. As seen from Fig. 1, the influence of polar substituents on the complexing ability is small compared to their effect on the basicity, the sensitivity with Cu(II) being slightly larger than with Ni(II). Evidently, the complex formation with 3d transition metal ions is not very sensitive for the electron density of the corresponding site. Steric obstacles, for example, appear to play a decisive role.

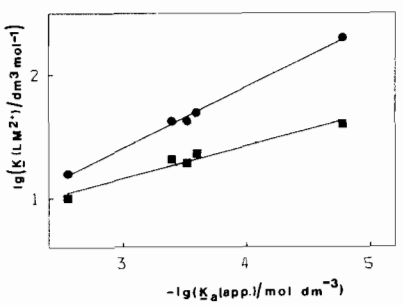


Fig. 1. The stability constants, $K(LM^{2+})$, for the Cu(II) (•) and Ni(II) (■) complexes of 8-substituted 9-methylpurines plotted against the acidity constant, K_a, of the protonated ligands in aqueous sodium perchlorate (1.0 mol dm^{-3}) at 298.2 K.

Table II also records the stability constants for the nickel(II) and copper(II) complexes of 2,9- and 8,9-dimethyladenines. Comparison of the complexing abilities of these ligands with that of 9-methyladenine indicates that the C8 methyl group retards the complex formation considerably, while the influence of the C2 bonded methyl group is hardly noticeable. The most straightforward explanation to this difference is that in 9-methyladenine coordination occurs predominantly to N7. This conclusion is consistent with several spectroscopic observations [13, 19, 20], but is not in complete agreement with the results of Kim and Martin [24], according to whom Ni(II) and Cu(II) ions are bound slightly more favorably to N1 than to N7 of adenosine.

The potentiometric method employed in the present investigation involves the basic assumption that complexing of the protonated ligand is negligible compared to the complexing of the neutral ligand. For this reason we determined the stability constants for the complexes of the adenine derivatives by an independent method. The ligands were equilibrated between chloroform and aqueous metal perchlorate solutions. The stability constants for the 1:1 complexes were calculated in the following way. When the total concentration of the ligand in aqueous phase is negligible compared to the total concentration of metal ion, $[M^{2+}(tot.,w)]$, the stability constant, $K(LM^{2+})$, can be expressed:

$$K(LM^{2+}) = \frac{[LM^{2+}(w)]}{[L(w)]\,[M^{2+}(tot.,w)]} \qquad (3)$$

by eqn. (3) where $[LM^{2+}(w)]$ and $[L(w)]$ denote the equilibrium concentrations of the complex and ligand in the aqueous phase, respectively. The total amount of the ligand, n{L(tot.)}, which was kept constant in the experiments, can be expressed by eqn. (4):

$$\begin{aligned} n\{L(tot.)\} &= V(org.)[L(org.)]_0 + V(w)[L(w)]_0 \\ &= V(org.)[L(org.)] + V(w)\{[L(w)] \\ &\quad + [LM^{2+}(w)]\} \end{aligned} \qquad (4)$$

Here V(org.) and V(w) denote the volumes of the organic and aqueous phases, respectively. The terms $[L(org.)]_0$ and $[L(w)]_0$ represent the equilibrium concentrations of the ligand in the absence of nickel(II) ions and the term [L(org.)] the equilibrium concentration in the presence of nickel(II) ions. Substitution of the distribution coefficient, K_d,

TABLE III. Stability Constants, $K(LM^{2+})$, for the 1:1 Complexes of 9-Substituted Adenines with Nickel(II) Ion in Aqueous Solution at 298.2 K[a].

Compound	$K(LM^{2+})/dm^3\ mol^{-1}$	K_d[b]	a[c]	b[d]	r[e]
9-Methyladenine	4.5 ± 0.2(0.65)[f]	6.8 ± 0.3	0.96 ± 0.01	3.7 ± 0.1	0.997
2,9-Dimethyladenine	4.2 ± 0.3(0.62)	3.4 ± 0.3	1.02 ± 0.01	2.9 ± 0.1	0.995
8,9-Dimethyladenine	0.9 ± 0.2(−0.05)	2.8 ± 0.3	1.00 ± 0.01	0.6 ± 0.1	0.977

[a]The ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate. [b]Distribution constant from eqn. (5). [c]Intercept for eqn. (6) by least-squares method. [d]Slope for eqn. (6). [e]Correlation coefficient for eqn. (6). [f]The values in parentheses refer to logarithmic units.

expressed by eqn. (5), and eqn. (3) in eqn. (4) gives (after minor manipulations) eqn. (6):

$$K_d = \frac{[L(w)]_0}{[L(org.)]_0} = \frac{[L(w)]}{[L(org.)]} \quad (5)$$

$$\frac{[L(org.)]_0}{[L(org.)]} = 1 + \left(\frac{K_d V(w)}{V(org.) + K_d V(w)}\right) K(LM^{2+}) \times [M^{2+}(tot.,w)] \quad (6)$$

representing a straight line, the slope of which enables the calculation of $K(LM^{2+})$.

Table III summarizes the stability constants obtained by eqn. (6) for the formation of nickel(II) complexes of the 9-substituted adenines examined. The satisfactory linearity of the plots shown in Fig. 2 over the whole concentration range studied ($0.02 < [Ni^{2+}] < 0.12$ mol dm^{-3}) and the intercepts close to unity lend additional support to the reliability of the method. In addition, the stability constants obtained by the distribution measurements are in agreement with the results determined potentiometrically. Since the stability constants obtained by the two independent methods are nearly equal, we believe that our equilibrium data are reliable.

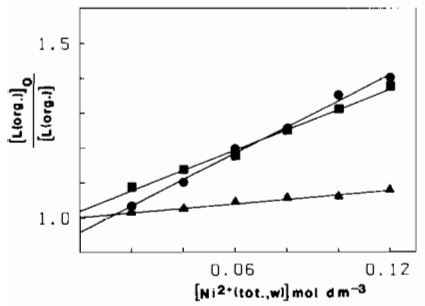


Fig. 2. Distribution of 9-methyladenine (•), 2,9-dimethyladenine (■) and 8,9-dimethyladenine (▲) between chloroform and aqueous solutions of nickel perchlorate at 298.2 K. Ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate. For the presentation of the data see eqn. (6).

The presented data are consistent with the earlier proposal of competitive attachment of 3d transition metal ions to N1 and N7 of 9-substituted purines. The complexing ability of these sites appear to be more sensitive to the steric nature of the adjacent substituents than to the basicity of the binding sites. For example, bulky groups at C6 may prevent the complex formation almost completely. In 9-substituted adenines the coordination of 3d transition metal ions appears to occur predominantly at N7, the N1 site being possibly more efficiently blocked by the amino group.

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