Complexing of 3d Transition Metal Ions with 9-Substituted Purines. IV. The Effect of Base-stacking on the Basicity and Complexing-ability

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Abstract

A number of 9-methylpurines were equilibrated between carbon tetrachloride or chloroform and aqueous solutions containing either nickel(II) perchlorate or N^6,N^6-dimethyladenosine. The equilibrium constants for the complex formation with nickel(II) ion and association with N^6,N^6-dimethyladenosine were calculated on the basis of the distribution data. The results, together with those obtained in the presence of both nickel(II) perchlorate and N^6,N^6-dimethyladenosine, are interpreted to indicate that stacking-association with the latter compound reduces the complexing-ability of 9-methylpurines. The protonation of guanosine in the presence of caffeine was examined potentiostatically and its association with caffeine studied by phase-solubility measurements. Association with caffeine was shown to lower the basicity of guanosine.

Introduction

Derivatives of nucleic acid bases exhibit an exceptionally strong tendency to associate in aqueous solution [1–15]. The association-ability correlates roughly with the polarizability of the π-electron system [5, 12–17], being thus more marked with purines than with pyrimidines [1, 2, 4, 9, 11, 18]. Most probably the interacting molecules are stacked vertically, *i.e.* perpendicular to the plane of the aromatic rings [1, 2, 5, 6, 19, 20]. Dipole-induced interactions have been suggested to be the driving force for the association [16], but hydrophobic bonding may also contribute [14, 15, 21–23].

Stacking interactions also influence the complexing of nucleic acid bases and their derivatives with metal ions. For example, the unexpectedly high stabilities of the 1:2 complexes involving a 3d transition metal ion and two xanthosine or hypoxanthine ligands have been repeatedly accounted by stacking of the coordinated nitrogen bases [24–27]. Likewise, stacking interactions have been suggested to stabilize the ternary mixed-ligand complexes comprising a 3d transition metal ion, a purine derivative and an aromatic ligand, which has been 2,2′-bipyridyl, 1,10-phenantroline, 5-sulfosalicylic acid, an aromatic amino acid or a pyrimidine derivative [24, 25, 28–31]. In ternary complexes of nucleotides the metal ion is bound to the phosphate group and the base moiety of the coordinated nucleotide molecule stacks with the other heteroaromatic ligand attached to the same central ion [32–39]. On the other hand, complexing with metal ions has been observed to enhance the self-stacking of nucleotides [40–42].

Knowledge about the relationships between the base-stacking and metal ion complexing is relevant, since most of the studies dealing with the metal complexes of nucleic acid constituents have been carried out at high ligand concentrations, where molecular interactions play an important role. We have previously presented equilibrium data for the complex formation between 3d transition metal ions and 9-substituted purines in aqueous solution [43–47]. The aim of the present study is to clarify to what extent these equilibria are affected by the presence of a co-solute that associates efficiently with the ligand under consideration, but does not complex significantly with the metal ion. For this purpose the apparent stability constants for the nickel(II) complexes of a variety of 9-methylpurines were determined at several concentrations of N^6,N^6-dimethyladenosine. The effect of base-stacking on the basicity of purine derivatives was examined by measuring the apparent protonation constants of guanosine in the presence of caffeine.

Experimental

Materials

Guanosine and caffeine were purchased from Sigma and were used as received. All the other purine derivatives were prepared as described previously [17, 45, 47, 48]. The metal perchlorates were products of G. Frederick Smith Company or Fluka A.G., and were employed without further

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purification. Chloroform and carbon tetrachloride were analytical reagents of Merck A.G. All solutions were made in distilled and degassed water.

Distribution Measurements

9-Methyladenine and its methyl derivatives were equilibrated between chloroform and aqueous solutions containing nickel(II) perchlorate and/or N^6,N^6-dimethyladenosine, as described earlier [47]. The concentration of nickel(II) perchlorate was varied from 0 to 0.12 mol dm^{-3} and that of N^6,N^6-dimethyladenosine from 0 to 0.074 mol dm^{-3}. The total concentration of divalent cations was adjusted to 0.12 mol dm^{-3} with calcium(II) perchlorate, and the ionic strength was further increased to 1.0 mol dm^{-3} with sodium perchlorate. As mentioned previously [47], calcium(II) ions do not interact markedly with the substituted purines investigated.

The equilibrations of 9-methylpurine and its methoxy and methyl derivatives were carried out analogously. However, carbon tetrachloride was used instead of chloroform, and the concentration of nickel(II) perchlorate was always less than 0.06 mol dm^{-3}.

The concentrations of the solutes were determined by LC from the organic phases only, since the presence of nickel(II) ions altered the shapes of signals obtained from the aqueous phases. The details of the LC analyses have been described earlier [47]. The retention times of the solutes and N^6,N^6-dimethyladenosine differed always by more than one minute. The concentrations in the aqueous phases were calculated with the aid of the volumes of the phases and the total amount of the solute added to the two-phase system.

Titrimetric Measurements

A modified potentiostatic technique (described previously [43]) was applied to the determinations of the apparent protonation constants of guanosine in aqueous solutions containing caffeine from 0 to 0.3 mol dm^{-3}. All titrations were performed at the ionic strength of 1 mol dm^{-3}, adjusted with sodium perchlorate.

Solubility Measurements

The solubility of guanosine in aqueous solutions of caffeine was determined in stoppered bottles, which were agitated mechanically. The concentration of caffeine was varied from 0 to 0.3 mol dm^{-3}, and the ionic strength was kept at 1 mol dm^{-3} with sodium perchlorate. Samples were withdrawn on successive days and filtrated through a 0.22 μm membrane. The concentration of the dissolved guanosine was determined by LC, as presented above. The solubility equilibrium usually settled within 3 days.

Spectrophotometric Measurements

The equilibrium constant for the protonation of caffeine was determined by recording its UV-spectrum in aqueous hydrogen chloride solutions, the concentration of which ranged from 0 to 5 mol dm^{-3}. The ionic strength was not adjusted. H_0-function was employed in the calculations. The apparatus used was a Cary 17D spectrophotometer.

The distributions, titrations, solubility measurements and spectrophotometric measurements were all carried out at 298.2 ± 0.2 K.

Results and Discussion

Association of 9-methylpurines with N^6,N^6-dimethyladenosine

Figure 1 shows examples of the distribution of 9-methylpurines between aqueous solutions of N^6,N^6-dimethyladenosine (called co-solute in the following)

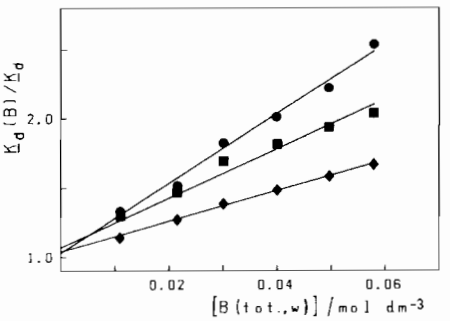

Fig. 1. Distribution of 9-methyladenine (●), 8-methoxy-9-methylpurine (■) and 9-methylpurine (♦) between aqueous solutions of N^6,N^6-dimethyladenosine and carbon tetrachloride or chloroform (see Table I). [B(tot.,w)] refers to the total concentration of N^6,N^6-dimethyladenosine in the aqueous phase, and $K_d(B)$ and K_d are the distribution coefficients in the presence and absence of N^6,N^6-dimethyladenosine, respectively.

and chloroform or carbon tetrachloride. The solutes are markedly transferred from the organic to the aqueous phase, when the concentration of the co-solute in the aqueous phase is increased. As indicated previously [17], these changes in the distribution behavior most probably result from the association of the solutes with the co-solute in the aqueous solution. The concentration of the co-solute in the organic phase remains always low, *i.e.* less than 2×10^{-3} mol dm^{-3} in chloroform and less than 2×10^{-5} mol dm^{-3} in carbon tetrachloride (distribution coefficients 22 and >3500, respectively). This fact, together with the low solute concentration ($<2 \times 10^{-3}$ mol dm^{-3}), suggests that the solute–co-solute interactions in the organic phase are of minor importance and do not significantly influence the distribution of the solutes. For comparison the

9-ethoxymethyl derivative of N^6,N^6-dimethyladenine has been shown to increase at the concentration of 2.5×10^{-2} mol dm^{-3} the solubility of purine in dichloromethane by less than 20% [17].

Association of a solute, L, with N^6,N^6-dimethyladenosine, B, is treated formally in the following as formation of a 1:1 associate. Consequently, the association constant, K(BL), is expressed by eqn. (1), where [L(w)], [B(w)] and [BL(w)] refer to the equilibrium concentrations of L, B and their associate, BL, in the aqueous phase. It should be noted, however, that owing to the self-association a minor proportion of the co-solute molecules are present as dimers and trimers in the concentration range studied [5]. The self-association of the solutes may be ignored, since their concentrations never exceed 2×10^{-3} mol dm^{-3} [17].

$$K(\mathrm{BL}) = \frac{[\mathrm{BL(w)}]}{[\mathrm{L(w)}]\,[\mathrm{B(w)}]} \quad (1)$$

As shown previously [17], eqn. (1) can easily be transformed to eqn. (2), where K_d(B) and K_d stand for the distribution coefficients of L between the aqueous and organic phases in the presence and absence of B, respectively. Since [L] is always negligible compared to [B(w)], the latter may be replaced by the corresponding total concentration, [B(tot.,w)]. Accordingly the slopes of the straight-lines presented in Fig. 1 are equal to the association constant, K(BL). The results obtained with all the compounds studied are collected in Table I. The satisfactory linearity of the plots and the intercepts close to unity lend some support to the assumptions made in the treatment of the experimental observations. With 2,9-disubstituted purines, however, the intercepts tend to deviate slightly from unity. The reason for this remains unknown. The association constants obtained in the present study correlate with those reported for the association of the same compounds with free purine [17].

$$\frac{K_d(\mathrm{B})}{K_d} = K(\mathrm{BL})[\mathrm{B(w)}] + 1 \quad (2)$$

Complexing of 9-Methylpurines with Nickel(II) Ion

Table II records the stability constants for the 1:1 complexes between nickel(II) ion and various 9-methylpurines. The values are based on the distribution measurements, analogous to those employed in the determinations of the association constants. Accordingly, the data in Table II refer to eqn. (3), where $K_d(M^{2+})$ denotes the distribution coefficient of L between the aqueous and organic phases in the presence of nickel(II) ions. The stability constants obtained are in agreement with those determined potentiometrically [47].

$$\frac{K_d(\mathrm{M}^{2+})}{K_d} = K(\mathrm{LM}^{2+})[\mathrm{M}^{2+}(\mathrm{tot.,w})] + 1 \quad (3)$$

Complexing of 9-Methylpurines with Nickel(II) Ion in the Presence of N^6,N^6-Dimethyladenosine

Figure 2 shows the influence of N^6,N^6-dimethyladenosine on the distribution of 9-methylpurine between aqueous solutions of nickel(II) perchlorate and carbon tetrachloride. The presence of N^6,N^6-dimethyladenosine in the aqueous phase clearly diminishes the influence that nickel(II) ions have on the distribution. We have shown previously that the logarithmic stability constant for the nickel(II) complex of N^6,N^6-dimethyladenosine is less than 0.1 [47]. Moreover, the distribution of the compound between the aqueous and organic phases is, within the limits of experimental errors, independent of the concentration of nickel(II) ion. Accordingly, the co-solute does not complex significantly with the nickel(II) ion. The equilibria prevailing in the aqueous phase may thus be expressed by eqns. (4)–(6). In the organic phase L exists solely as a free monomer. Consequently, the distribution coefficient,

TABLE I. Equilibrium Constants, K(BL), for the Association of Some 9-Substituted Purines with N^6,N^6-Dimethyladenosine in Aqueous Solution at 298.2 K[a].

Compound	K(BL) (dm^3 mol^{-1})	K_d[b]	b[c]	r[d]
1 9-Methylpurine	11.1 ± 0.3(2.9)[e]	69 ± 3	1.04 ± 0.01	0.999
2 2,9-Dimethylpurine	15.5 ± 0.8(6.7)	30 ± 1	1.11 ± 0.04	0.991
3 8,9-Dimethylpurine	12.8 ± 0.4(5.6)	33 ± 1	1.04 ± 0.01	0.998
4 2-Methoxy-9-methylpurine	17.8 ± 0.9(7.5)	13.1 ± 0.5	1.14 ± 0.03	0.995
5 8-Methoxy-9-methylpurine	14.9 ± 0.8(6.2)	3.7 ± 0.3	1.07 ± 0.02	0.996
6 9-Methyladenine	25.6 ± 1.2(11.7)	6.8 ± 0.3	1.03 ± 0.01	0.997
7 2,9-Dimethyladenine	30.0 ± 1.5(17.2)	3.4 ± 0.3	1.00 ± 0.02	0.9991
8 8,9-Dimethyladenine	28.6 ± 2.7(17.7)	2.8 ± 0.3	1.06 ± 0.04	0.993

[a]The ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate. [b]Distribution coefficient between the aqueous solution and carbon tetrachloride (compounds 1–5) or chloroform (compounds 6–8). [c]Intercept for eqn. (2) by least-squares method. [d]Correlation coefficient for eqn. (2). [e]The values in parentheses refer to the association constants with free purine in aqueous solution at 298.2 K [17].

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

Compound[b]	lg $K(LM^{2+})$ (dm^3 mol^{-1})	b[c]	r[d]
1	1.61 ± 0.02(1.56)[e]	0.93 ± 0.05	0.998
2	1.38 ± 0.02(1.26)	1.03 ± 0.01	0.9998
3	1.27 ± 0.02(1.27)	0.98 ± 0.01	0.9996
4	1.52 ± 0.02(1.38)	1.05 ± 0.03	0.991
5	1.33 ± 0.03(1.32)	0.99 ± 0.02	0.998
6	0.65[f]		
7	0.62[f]		
8	−0.05[f]		
g	<0(<0.1)		

[a]See footnote a in Table I. [b]For the enumeration see Table I. [c]Intercept for eqn. (3) by least-squares method. [d]Correlation coefficient for eqn. (3). [e]The values in parentheses obtained potentiostatically [45, 47]. [f]From ref. 47. [g]Refer to N^6,N^6-dimethyladenosine.

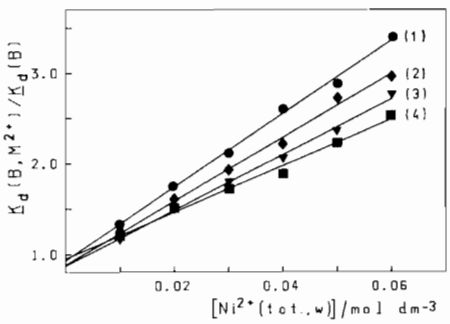

Fig. 2. Distribution of 9-methylpurine between aqueous solutions of nickel(II) perchlorate and carbon tetrachloride in the presence of N^6,N^6-dimethyladenosine. $[Ni^{2+}(tot.,w)]$ refers to the total concentration of Ni(II) ions in the aqueous phase, and $K_d(B,M^{2+})$ and $K_d(B)$ are the distribution coefficients in the presence and absence of Ni(II) ions at various concentrations of N^6,N^6-dimethyladenosine *viz.* 0(1), 0.02-(2), 0.04(3) and 0.074(4) mol dm^{-3}.

$K_d(B,M^{2+})$, observed for L in the presence of both B and Ni^{2+} may be presented by eqn. (7). Division by eqn. (2) yields after simple transformations eqn. (8). In other words, at a constant co-solute

$$L + M^{2+} \rightleftharpoons LM^{2+} \quad (4)$$

$$B + L \rightleftharpoons BL \quad (5)$$

$$BL + M^{2+} \rightleftharpoons BLM^{2+} \quad (6)$$

$$K_d(B,M^{2+}) = K_d\{1 + K(LM^{2+})[M(tot.,w)] + K(BL)[B(tot.,w)] + K(BLM^{2+})K(BL) \times [B(tot.,w)][M^{2+}(tot.,w)]\} \quad (7)$$

$$\frac{K_d(B,M^{2+})}{K_d(B)} = \frac{K(LM^{2+}) + K(BLM^{2+})K(BL)[B(tot.,w)]}{1 + K(BL)[B(tot.,w)]} \times [M^{2+}(tot.,w)] + 1 \quad (8)$$

concentration, $[B(tot.,w)]$, the ratio of $K_d(B,M^{2+})/K_d(B)$ is a linear function of $[M^{2+}(tot.,w)]$, and the slope of the plot enables the calculation of $K(BLM^{2+})$, *i.e.* the stability constant of the nickel complex of the associate BL. The results obtained at different co-solute concentrations are given in Table III.

TABLE III. Stability Constants, $K(BLM^{2+})$, for the 1:1 Complexes of Ni(II) Ions with the Heteroassociates Formed Between Some 9-Substituted Purines and N^6,N^6-Dimethyladenosine in Aqueous Solution at 298.2 K[a].

Compound[b]	lg $K(BLM^{2+})$(dm^3 mol^{-1})[c]			
	0.02[d]	0.04[d]	0.074[d]	e
1	0.96	0.94	0.88	0.93
2	0.89	0.90	0.88	0.89
3	0.65	0.62	0.65	0.64
4	1.05	1.07	1.03	1.05
5	1.07	1.05	1.04	1.05
6	0.26	0.28		0.27
7	0.38	0.34		0.36

[a]See footnote a in Table I. [b]For the enumeration see Table I. [c]Refer to eqn. (8). [d]The total concentration of N^6,N^6-dimethyladenosine (mol dm^{-3}) in the aqueous phase. [e]The mean.

The preceding discussion indicates that N^6,N^6-dimethyladenosine complexes extremely weakly with nickel(II) ions, but associates efficiently with purine derivatives. Accordingly, it appears reasonable to assume that the metal ion is coordinated in the complex BLM^{2+} to L only, while the base-stacking interactions are responsible for the attachment of B. The stability constants $K(LM^{2+})$ and $K(BLM^{2+})$ may thus be employed to elucidate the difference between the complexing-abilities of free and associated purine molecules. Comparison of the data in Tables II and III reveals that the stacking with N^6,N^6-dimethyladenosine reduces the stability constants of the nickel(II) complexes of various 9-methylpurines by 0.3–0.7 logarithmic units. The influence seems to be with alkyl-substituted purines slightly larger than with those bearing heteroatom substituents. As seen from Fig. 3, a rough inverse correlation appears to exist between the $\lg\{K(LM^{2+})/K(BLM^{2+})\}$ values and the bulk polarizabilities of the complexing ligands. The factors enforcing the

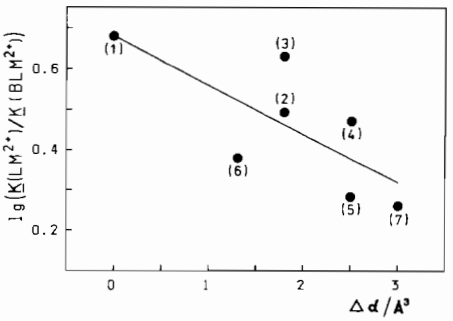

Fig. 3. The effect of the association of 9-substituted purines with N^6,N^6-dimethyladenosine on their complexing-ability, plotted against the polarizabilities of the same compounds. $\Delta\alpha$ is the polarizability subtracted by that of 9-methylpurine. The enumeration of the compounds refer to Table I.

stacking interactions thus may reduce the stability difference between the complexes LM^{2+} and BLM^{2+}. The available data are, however, too limited to allow any firm conclusions to be drawn.

Protonation of Guanosine in the Presence of Caffeine

The logarithmic equilibrium constant for the protonation of guanosine, L, has been reported to be 2.33 in aqueous sodium perchlorate (1 mol dm^{-3}) at 298.2 K [44]. As seen from Table IV, the presence of caffeine, B, reduces slightly the apparent protonation constant, defined by eqn. (9). The most obvious explanation for the observed diminution of $K(LH^+$, app.) is that association with caffeine lowers the

$$K(LH^+,\text{app.}) = \frac{[LH^+]}{[H^+]\{[L(\text{tot.})] - [LH^+]\}} \quad (9)$$

TABLE IV. Apparent Protonation Constants, $K(LH^+,\text{app.})$, of Guanosine in the Presence of Caffeine, B, in Aqueous Solution at 298.2 K[a].

[B(tot.)] (mol dm^{-3})	lg $K(LH^+,\text{app.})$ (dm^3 mol^{-1})	lg $K(BLH^+)$ (dm^3 mol^{-1})[b]
–	2.33[c]	
0.10	2.19 ± 0.03	1.96
0.15	2.13 ± 0.02	1.89
0.20	2.13 ± 0.02	1.97
0.25	2.11 ± 0.02	1.97
0.30	2.04 ± 0.03	1.86

[a]Refer to eqn. (9). The ionic strength adjusted to 1.0 mol dm^{-3} with sodium perchlorate. [b]Protonation constant for the associate between guanosine and caffeine. [c]From ref. 44.

basicity of guanosine. Application of the phase-solubility method described by Nakano and Igarashi [11] gave the value of 9.4 dm^3 mol^{-1} for the association constant, $K(BL)$, in aqueous sodium perchlorate (1 mol dm^{-3}). Consequently, equilibria (10)–(12) prevail under the experimental conditions, *i.e.* at $[H^+] \sim K(LH^+)^{-1}$.

$$L + H^+ \rightleftharpoons LH^+ \quad (10)$$

$$B + L \rightleftharpoons BL \quad (11)$$

$$BL + H^+ \rightleftharpoons BLH^+ \quad (12)$$

Caffeine is not significantly protonated at such low concentrations of oxonium ions, since UV-spectrophotometric measurements indicated the pK_a value of the monocation of caffeine to be about 0.3. Under the experimental conditions the total concentration of L is always small compared to that of B, and the equilibrium concentration of the latter may thus be approximated by its total concentration. When this is taken into account, eqn. (9) can be replaced by eqn. (13). Substitution of the known values of $K(LH^+,\text{app.})$, $K(LH^+)$ and $K(BL)$ in the

$$K(LH^+,\text{app.}) = \frac{[LH^+] + [BLH^+]}{\{[L] + [BL]\}[H^+]}$$

$$= \frac{K(LH^+) + K(BLH^+)K(BL)[B(\text{tot.})]}{1 + K(BL)[B(\text{tot.})]} \quad (13)$$

latter equation enables the calculation of $K(BLH^+)$ at different concentrations of caffeine. The results are listed in Table IV. Comparison of the values of $K(BLH^+)$ and $K(LH^+)$ indicates that the association of guanosine with caffeine decreases its basicity by about 0.4 logarithmic units. The influence is analogous to that exerted by N^6,N^6-dimethyladenosine on the stabilities of the nickel(II) complexes of 9-methylpurines. Evidently the involvement of π-electrons in the stacking interactions decreases the electron density at the ring nitrogens of guanosine, and hence lowers its basicity.

In summary, both the basicity and complexing-ability of 9-substituted purines are reduced by stacking-association with another neutral hetero-aromatic compound that is unable to form stable metal complexes. The influences on the acidity and stability constants range from 0.3 to 0.7 logarithmic units. These findings agree with the results of Sigel [34], according to which 3d transition metal complexes of 2,2'-bipyridyl associates with adenosine and inosine to a slightly lesser extent than the free ligand.

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