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Ternary Complexes in Solution**: Intramolecular Stack Formation in Mixed Ligand Complexes Containing Cu^{II}, 2,2'-Bipyridyl, and the 5'-Monophosphate of Inosine (IMP), Guanosine (GMP) or Adenosine (AMP)

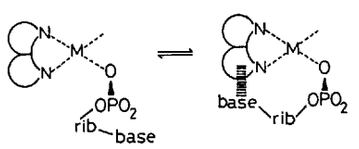
Salah S. Massoud and Helmut Sigel*

Abstract: Stability constants of mixed ligand Cu(bpy)(NMP) complexes (bpy = 2,2'-bipyridyl; $NMP^{2\ominus}$ = 5'-$IMP^{2\ominus}$, 5'-$GMP^{2\ominus}$, or 5'-$AMP^{2\ominus}$) were determined by potentiometric pH titrations in aqueous solution at $I = 0.1$M ($NaNO_3$) and 25°C. These ternary Cu(bpy)(NMP) complexes are more stable than the corresponding Cu(bpy)(R-MP) complexes, where R-$MP^{2\ominus}$ represents a phosphate monoester with a group R that is unable to participate in any kind of interaction within the complexes as, e.g., D-ribose 5'-monophosphate. This increased stability is attributed, in agreement with previous results, to intramolecular stack formation within the Cu(bpy)(NMP) complexes between the purine residue of the NMPs and the aromatic rings of bpy. The formation degree of the Cu(bpy)(NMP) species with the intramolecular stacks increases in the series, $IMP^{2\ominus}$ (72 ± 5%) < $AMP^{2\ominus}$ (81 ± 4%) ≈ $GMP^{2\ominus}$ (85 ± 3%). This order is different from that previously observed for the self-stacking tendency of nucleic base residues.

The Background

Nucleotides and their metal ion complexes play a key role among enzymic cofactors[2] and are therefore widely studied[3,4]. Our efforts to evaluate the factors that determine the recognition reactions of nucleic base residues focus on the following topics: (i) The metal ion coordinating properties of nucleotides[4], (ii) the self-association properties of nucleosides, nucleotides, and their metal ion complexes[5], (iii) the metal ion promoted hydrolysis of nucleoside 5'-triphosphates[6], and (iv) the extent of intramolecular ligand-ligand interactions in mixed ligand complexes containing nucleotides[7]. Information about item (i) is imperative for studies of items (ii) to (iv), and knowledge on (ii) and in part also (iii) is a prerequisite for investigations on (i) and (iv).

During research on intramolecular stack formation (topic (iv))[1,7,8] in mixed ligand complexes containing a divalent metal ion ($M^{2\oplus}$), a nucleoside monophosphate ($NMP^{2\ominus}$), and 1,10-phenanthroline (phen) or 2,2'-bipyridyl (bpy), the latter two ligands proved especially useful as second ligands; they are easy to handle and still provide generalizable information. For example, studies on the position of Equilibrium (1) for several M(bpy)(5'-NMP) or



(1)

M(phen)(5'-NMP) complexes revealed an increasing stacking tendency for the following nucleic base moieties: uracil ≲ cytosine ≲ thymine ≪ adenine[1,8]. Another interesting result is the dependence of the intramolecular aromatic-ring recognition on the position of the phosphate group at the ribose ring; the formation degree of the Cu(bpy)(AMP) species with the intramolecular stack increases for: 3'-$AMP^{2\ominus}$ < 5'-$AMP^{2\ominus}$ < 2'-$AMP^{2\ominus}$[1].

It is our present aim to quantify the stacking tendency of structurally different purine residues, and we report now the results of our first effort: For the title-nucleotides (Fig. 1)[9] stack formation in Cu(bpy)(NMP) decreases in the order 5'-$GMP^{2\ominus}$ ≈ 5'-$AMP^{2\ominus}$ > 5'-$IMP^{2\ominus}$. This result warrants special attention as the given order differs from that observed for self-stacking of the corresponding base residues: e.g., adenosine > guanosine > inosine or 5'-$AMP^{2\ominus}$ > 5'-$GMP^{2\ominus}$ ≈ 5'-$IMP^{2\ominus}$[5].

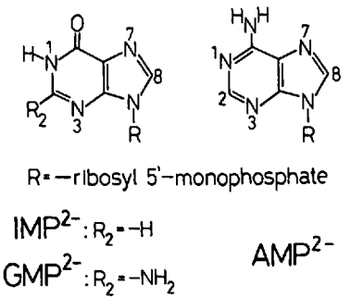


Fig. 1. Chemical structures of the nucleic base residues of the nucleoside 5'-monophosphates (NMPs), i.e. $IMP^{2\ominus}$, $GMP^{2\ominus}$, and $AMP^{2\ominus}$, considered in this study.

The Results

If the two species in Equilibrium (1) are designated as $Cu(bpy)(NMP)_{op}$ and $Cu(bpy)(NMP)_{st}$ the overall complex formation[10] is given by Equilibrium (2a)[1,8,11]:

$$Cu(bpy)^{2\oplus} + NMP^{2\ominus} \rightleftharpoons Cu(bpy)(NMP)_{op} \rightleftharpoons Cu(bpy)(NMP)_{st} \quad (2a)$$

$$K^{Cu(bpy)}_{Cu(bpy)(NMP)} = \frac{([Cu(bpy)(NMP)_{op}] + [Cu(bpy)(NMP)_{st}])}{[Cu(bpy)^{2\oplus}][NMP^{2\ominus}]} = \frac{[Cu(bpy)(NMP)]}{[Cu(bpy)^{2\oplus}][NMP^{2\ominus}]} \quad (2b)$$

A large formation degree of $Cu(bpy)(NMP)_{st}$ must be reflected in a high value for the experimentally accessible overall stability constant (Equation (2b))[11], in comparison with the stability of the open form, which is more difficult to assess:

$$K^{Cu(bpy)}_{Cu(bpy)(NMP)_{op}} = \frac{[Cu(bpy)(NMP)_{op}]}{[Cu(bpy)^{2\oplus}][NMP^{2\ominus}]} \quad (3)$$

However, the stability of this open isomer with a pure phosphate-coordination in dependence on the phosphate-group basicity is quantified by Equation (4)[8] [error limit within the pK_a range 5 to 7: ±0.027 (1σ)]:

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$$\log K^{Cu(bpy)}_{Cu(bpy)(NMP)_{op}} =$$

$$0.453 \times pK^{H}_{H(NMP)} + 0.103 \quad (4)$$

Indeed, the plot of log $K^{Cu(bpy)}_{Cu(bpy)(NMP)}$ versus $pK^{H}_{H(NMP)}$ given in Fig. 2 for the present and some previous[1,8] results, and a comparison with the regression line according to Equation (4) immediately shows that all the Cu(bpy)(NMP) complexes are more stable than expected for a simple phosphate coordination. Without any further mathematical treatment it is obvious from the vertical distances of the experimental points to the regression line that the conclusions summarized in the first section (The Background) are valid; especially the increasing stacking tendency of the purine moiety in Cu(bpy)(5'-NMP) follows very clearly: hypoxanthine ($IMP^{2\ominus}$) < adenine ($AMP^{2\ominus}$) ≈ guanine ($GMP^{2\ominus}$). A simplified structure for Cu(bpy)(5'-GMP)$_{st}$ is shown in Fig. 3.

A quantitative evaluation of the position of Equilibrium (1) is possible with Equation (5)[1,11]:

$$K_I = \frac{[Cu(bpy)(NMP)_{st}]}{[Cu(bpy)(NMP)_{op}]} = \frac{K^{Cu(bpy)}_{Cu(bpy)(NMP)}}{K^{Cu(bpy)}_{Cu(bpy)(NMP)_{op}}} - 1 = 10^{\log \Delta} - 1 \quad (5)$$

where

$$\log \Delta = \log K^{Cu(bpy)}_{Cu(bpy)(NMP)} - \log K^{Cu(bpy)}_{Cu(bpy)(NMP)_{op}} \quad (6)$$

It is probably helpful to emphasize that the constant $10^{\log \Delta}$ defines the position of Equilibrium (7), where R-$MP^{2\ominus}$ represents a phosphate monoester with a group R that is *not* suitable for any kind of interaction (e.g., the ribose moiety in D-ribose 5'-monophosphate), i.e. Cu(bpy) $(NMP)_{op} \triangleq$ Cu(bpy)(R-MP):

$$NMP^{2\ominus} + Cu(bpy)(R\text{-}MP) \rightleftharpoons Cu(bpy)(NMP) + R\text{-}MP^{2\ominus} \quad (7)$$

As the coordination spheres of $Cu^{2\oplus}$ on both sides of Equilibrium (7) are identical, the values for log Δ are indeed a true reflection of the extent of the intramolecular stack formation. The results from these evaluations, together with the equilibrium constants they are based on, are given in Table 1.

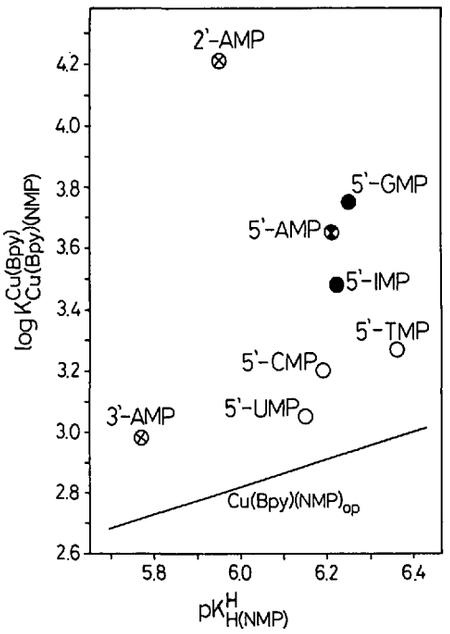

Fig. 2. Relationship between log $K^{Cu(bpy)}_{Cu(bpy)(NMP)}$ and $pK^{H}_{H(NMP)}$ for ternary Cu(bpy)(NMP) complexes in aqueous solution at I=0.1 M ($NaNO_3$) and 25°C, where $NMP^{2\ominus}$ equals (i) a pyrimidine-nucleoside 5'-monophosphate[8], i.e. 5'-$UMP^{2\ominus}$, 5'-$CMP^{2\ominus}$, and 5'-$TMP^{2\ominus}$ (○); (ii) an adenosine monophosphate[1], i.e. 2'-$AMP^{2\ominus}$, 3'-$AMP^{2\ominus}$ (⊗), and 5'-$AMP^{2\ominus}$ (⊗); or (iii) a purine-nucleoside 5'-monophosphate, i.e. 5'-$IMP^{2\ominus}$, 5'-$GMP^{2\ominus}$ (●), and 5'-$AMP^{2\ominus}$, (⊗) (cf. Table 1). The reference line represents the log K/pK_a relationship (see Equation (4) and text) for the open form of the Cu(bpy)(NMP) complexes (Equilibrium (1)), i.e. Cu(bpy)$(NMP)_{op}$, in which no intramolecular ligand-ligand interaction occurs.

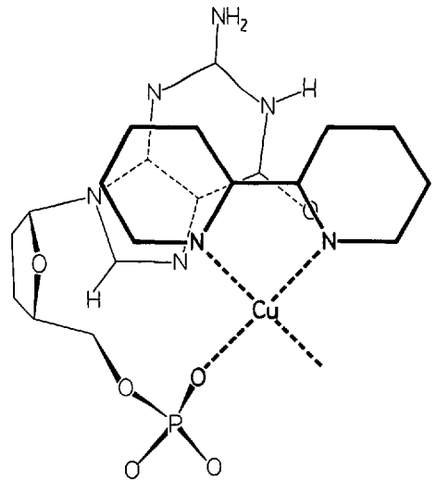

Fig. 3. Probable (schematic) structure of the species with an intramolecular stack (Equilibrium (1)) for Cu(bpy)(5'-GMP) in solution.

Table 1. Extent of intramolecular stack formation in ternary Cu(bpy)(5'-NMP) complexes as quantified by the intramolecular dimensionless equilibrium constant K_I (Equation (5)) and by the percentage of the stacked species (Equilibrium (1)), i.e. % Cu(bpy)$(NMP)_{st}$, together with the equilibrium constants determined in aqueous solutions for the H_2(NMP) and Cu(bpy)$^{2\oplus}$/$NMP^{2\ominus}$ systems, on which the evalution is based (see text) (I = 0.1 M, $NaNO_3$; 25°C)[a,b].

5'-$NMP^{2\ominus}$	$pK^{H}_{H_2(NMP)}$ [10a]	$pK^{H}_{H(NMP)}$ [10a]	log $K^{Cu(bpy)}_{Cu(bpy)(NMP)}$ [10a] (Eq. 2b)	log $K^{Cu(bpy)}_{Cu(bpy)(NMP)_{op}}$ [c] (Eq. 3)	log Δ (Eq. 6)	K_I (Eq. 5)	%Cu(bpy)$(NMP)_{st}$ [d] (Eq. 1)
$IMP^{2\ominus}$	1.30 ± 0.10	6.22 ± 0.01	3.48 ± 0.02	2.92 ± 0.08	0.56 ± 0.08	2.63 ± 0.69	72 ± 5
$GMP^{2\ominus}$	2.48 ± 0.04	6.25 ± 0.02[e]	3.75 ± 0.02	2.93 ± 0.08	0.82 ± 0.08	5.61 ± 1.25	85 ± 3
$AMP^{2\ominus}$	3.84 ± 0.02	6.21 ± 0.01	3.65 ± 0.02	2.92 ± 0.08	0.73 ± 0.08	4.37 ± 1.02	81 ± 4

[a] The error limits for the acidity and stability constants are three times the standard error of the mean value or the sum of the probable systematic errors, whichever is larger. The error limits for log Δ and the other two columns at the right were calculated according to the error propagation after *Gauss* by using the errors listed in the fourth and fifth column. – [b] The results for AMP are from Ref.[1]. – [c] Calculated with Equation (4) and the acidity constants of column three. – [d] Calculated according to %Cu(bpy)$(NMP)_{st}$ = 100·K_I/(1 + K_I). – [e] From S.S. Massoud, H. Sigel, *Bull. Chem. Soc. Ethiop. 2* (1988) 9.

Discussion

The results listed in Table 1 confirm the increasing stack formation in the Cu(bpy)(5'-NMP) complexes, $IMP^{2\ominus} < AMP^{2\ominus} \approx GMP^{2\ominus}$, and they show in addition that the formation degree of the stack in aqueous solution in all three cases is rather large. It may be added that X-ray crystal studies of $[Cu(H \cdot 5'\text{-}AMP)(bpy)(H_2O)]_2 \cdot (NO_3)_2 \cdot 6H_2O$[12], $[Cu(H \cdot 5'\text{-}AMP)(phen)]_2 \cdot (NO_3)_2 \cdot 8H_2O$[13], and of similar mixed ligand complexes[14] have proven the formation of intramolecular stacks also for the solid state.

It is remarkable that the intramolecular stack of Equilibrium (1) reaches within the error limits the same formation degree for Cu(bpy)(5'-GMP) and Cu(bpy)(5'-AMP). Indeed, the mentioned order warrants attention as it differs from that observed for the self-stacking tendency of the corresponding base residues (which occurs head-to-tail): inosine ($K = 3.3\,M^{-1}$) < guanosine ($8\,M^{-1}$) < adenosine ($15\,M^{-1}$)[5]. This observation indicates that in the stack formation donor-acceptor effects are involved because these evidently change in the two compared stacking processes. Furthermore, the results confirm earlier observations[4,5,7,15] that a metal ion-bridge facilitates stacking interactions.

All the mentioned effects certainly influence the recognition reactions of the base moieties in enzymic reactions of nucleotides, as well as those of nucleic acids with other substances. The occurence of nucleic base interactions with amino acid side chains[4,7] in enzymes is well-known[16], as is the intercalation of bpy, phen, and related ligands[17] into nucleic acids, especially into DNA.

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[9] The source of the NMPs is the same as previously, and the determinations of equilibrium constants via potentiometric pH titrations were carried out exactly as described[1,8].
[10] a) $Cu(bpy)^{2\oplus}$ is practically completely formed[8]. In the calculations for Equation (2) $H^{\oplus}$, $H_2(NMP)$, $H(NMP)^{\ominus}$, $NMP^{2\ominus}$, $Cu(bpy)^{2\oplus}$, and Cu(bpy)(NMP) are taken into account[1,8]. The acidity constants are based on direct pH-meter reading, i.e. they are defined for $H^{\oplus}$ activity (so-called «mixed» or Brønsted constants): $K^{H}_{H_2(NMP)} = [H^{\oplus}][H(NMP)^{\ominus}]/[H_2(NMP)]$ and $K^{H}_{H(NMP)} = [H^{\oplus}][NMP^{2\ominus}]/[H(NMP)^{\ominus}]$. – b) In the $Cu^{2\oplus}$ complexes of $IMP^{2\ominus}$, $GMP^{2\ominus}$, and $AMP^{2\ominus}$ macrochelate formation with N-7 of the purine moiety occurs[4,10c]; however, N-7 is released from the coordination sphere of metal ions upon formation of mixed ligand complexes[4]. – c) H. Sigel, S.S. Massoud, R. Tribolet, *J. Am. Chem. Soc. 110* (1988) 6857.
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Herstellung von $[(CH_3)_3Si]_2NSe_xN[Si(CH_3)_3]_2$ (x = 1,2) und neuen Se-S-N-Heterocyclen

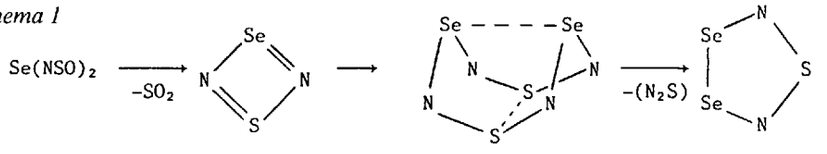
Alois Haas* und Jörg Kasprowski

Abstract: Reaction of $Se(NSO)_2$ with $TiCl_4$ yields the four-membered ring SeN_2S (**1**) which was isolated as the adduct $SeSN_2 \cdot TiCl_4$ (**2**). This adduct forms with AsF_5 (molar ratio 1:1) in SO_2 the ionic compound $[SeS_3N_5]^{\oplus}[AsF_6]^{\ominus}$ showing a cage structure for the cation (**3**). The covalent isomer (**4b**) of the ionic $[ClSe_2N_2S]^{\oplus}Cl^{\ominus}$ (**4a**) is obtained from $Se(NSO)_2$ and $POCl_3$. Lithium bis(trimethylsilyl)amid reacted with Se_2Cl_2 (molar ratio 2:1) to give the bis(disilylamido)-derivatives of Se_x, x = 1,2. The monoselenium derivative (**5a**) forms with $SeCl_4$ in good yields explosive Se_4N_4 and with SCl_2 a salt $\{SeS_2N_2Cl\}_2$ (**6**) of unknown structure..

Umsetzungen von Bis(sulfinylamido)-selen mit MF_5 (M = As, Sb, Nb) oder MCl_5 (M = P, Sb) führten zu den Cyclothia-di(selenazenium)-Kationen[1] $[Se_2N_2S]_2^{2\oplus}$, $[XSe_2N_2S]^{\oplus}$ (X = Cl, Br) und $[Se_2N_2S]^{2\oplus}$. Wir vermuteten, dass diese Fünfringe über die in Schema 1 angegebenen Zwischenstufen entstehen. Es ist nun gelungen, das postulierte Selenschwefeldinitrid (**1**) als Addukt $SeSN_2 \cdot TiCl_4$ bei der Umsetzung von $Se(NSO)_2$ mit $TiCl_4$ in CH_2Cl_2 gemäss Schema 2 zu isolieren. Das gelb-orange Pulver schmilzt unter Zersetzung bei 250 °C und wurde durch vollständige Elementaranalyse sowie IR- und Raman-Spektrum charakterisiert. Im Massenspektrum erscheinen neben den Fragmenten der Lewis-Säure die Bruchstücke $SeNS^+$, SeN^+, SN^+ und Se^+. Durch Röntgen-Pulveranalysen lässt sich zeigen, dass aus S_2N_2 und $TiCl_4$ hergestelltes $S_2N_2 \cdot TiCl_4$[2] mit dem homologen Addukt **2** isostrukturell ist. Einkristalle von **2** konnten bisher nicht erhalten werden, da es weder sublimiert noch in gebräuchlichen Solventien löslich ist.

Beim Versuch, $TiCl_4$ in **2** durch AsF_5 zu ersetzen, bildeten sich hellgelbe Kristalle der Zusammensetzung $SeS_3N_5[AsF_6]$, die bei 161–163 °C schmelzen. IR- und ^{19}F-NMR-spektroskopische Untersuchungen

Schema 1



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